Incidence of Colorectal Cancer and Comparisons of Outcomes after Minimally Invasive and Open Surgery

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To my Family

Per aspera ad astra

- Seneca

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ABSTRACT

Aim Surgery remains the mainstay of treatment for colorectal cancer. The aim of this thesis was to determine the overall incidence of colorectal cancer in Sweden over time and to evaluate surgical treatment comparing minimally invasive surgery including laparoscopic and robot assisted laparoscopic surgery to open surgery.

Methods Paper I explores the overall incidence of colorectal cancer in Sweden over time. Papers II-IV report results from two population based cohort studies and a randomised controlled trial. The papers compare minimally invasive surgery including laparoscopic and robot assisted laparoscopic surgery to open surgery for colon and rectal cancer.

Results Paper I found a decrease in the overall incidence of colorectal cancer in Sweden in the last decade, whilst the incidence in patients under the age of 50 years continued to increase. Paper II demonstrated favorable short-term outcomes following laparoscopic surgery compared to open surgery for colon cancer. Paper III showed that minimally invasive surgery for rectal cancer was non-inferior to open surgery with regard to adequate cancer resection with advantageous short-term outcomes. There were no long-term difference in risk of bowel obstruction, incisional, or parastomal hernia comparing the surgical techniques in patients with rectal cancer as reported in paper IV.

Conclusion The overall incidence of colorectal cancer in Sweden has decreased in the last decade, despite an increase in the younger population. Surgical resection for colorectal cancer using minimally invasive technique is oncologically safe with favorable short-term outcomes compared to open surgery. No advantage was found following minimally invasive surgery for rectal cancer with regard to long-term risk of bowel obstruction, incisional and parastomal hernia.

Keywords: colorectal cancer incidence, colon cancer, rectal cancer, surgery

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SAMMANFATTNING PÅ SVENSKA

Tjock- och ändtarmscancer är den tredje vanligaste cancerformen internationellt och i Sverige. Den högsta incidensen för tjock- och ändtarmscancer återfinns i västvärlden med en lägre incidens i utvecklingsländer. Senare rapporter har angivit en minskning av incidensen i västvärlden av oklar anledning. Ålder är en välkänd riskfaktor för tjock- och ändtarmscancer men trots detta har en ökning på senare tid noterats i västvärlden hos individer under 50 år. Denna yngre del av populationen har också uppvisat ett mer avancerat tumörstadium vid tidpunkten för diagnos.

Den förbättrade överlevnaden som observerats hos patienter med tjock- och ändtarmscancer under de senaste fyra årtionden kan härledas till förbättringar inom kirurgisk teknik, cellgifts- och strålbehandling, särskilt för ändtarmscancer. Kirurgi är fortsatt grunden för botande behandling och traditionellt har kirurgi för tjock- och ändtarmscancer inneburit ett stort buksnitt, öppen kirurgi. På 90-talet infördes titthålskirurgin, den så kallade minimalinvasiva kirurgin, först den laparoskopiska kirurgin och senare även den robot assisterad laparoskopiska kirurgin. Trots att flertalet studier funnit tydliga korttidsfördelar inklusive minskad blödning, minskad postoperativ smärta och kortare återhämtning vid minimalinvasiv kirurgi jämfört med öppen teknik så utförs en stor andel av tjock- och ändtarmscancerkirurgi fortsatt med öppen teknik. Populationsbaserade studier från Tyskland och Norge har även pekat på en förbättrad korttidsöverlevnad efter laparoskopisk kirurgi jämfört med öppen kirurgi vid tjocktarmscancer. Laparoskopisk kirurgi vid ändtarmscancer uppvisade tidigt likvärdiga resultat med öppen kirurgi avseende långsiktiga cancerrelaterade resultat. Detta har senare ifrågasatts då två randomiserade studier inte kunnat bekräfta att laparoskopisk kirurgi inte är sämre än öppen kirurgi när det gäller att avlägsna tumören fullständigt. Det är inte känt om minimalinvasiv kirurgi minskar långtidsriskerna för sjukhusvård eller behovet för ytterligare kirurgi till följd av tarmvred, ärrbråck och bråck i anslutning till stomin.

Syfte Syftet med avhandlingen var att studera incidensen av tjock- och ändtarmscancer i Sverige samt att utvärdera kirurgisk teknik genom att jämföra minimalinvasiv kirurgi både laparoskopisk och robot assisterad laparoskopisk kirurgi med öppen kirurgi.

Metod Första studien är en populationsbaserad studie som undersöker incidensen av tjock- och ändtarmscancer i Sverige över tid. Studie två och tre är populationsbaserade studier som jämför minimalinvasiv och öppen kirurgi för tjocktarmscancer respektive ändtarmscancer med avseende korttidsresultat samt förmågan att avlägsna tumören fullständigt. COLOR II är en internationell randomiserad studie som jämför laparoskopisk och öppen kirurgi vid ändtarmscancer. I studie IV utvärderas de sekundära resultaten från COLOR II nämligen behovet av sjukhusvård och ytterligare kirurgi till följd av tarmvred, ärrbråck och bråck i anslutning till stomin. Jämförande laparoskopisk och öppen kirurgi vid ändtarmscancer.

Resultat Studie I fann att incidensen av tjock- och ändtarmscancer minskat i Sverige under det senaste årtiondet, trots en noterad ökning hos individer under 50 år. Studie II visade korttidsfördelar vid tjocktarmscancer inklusive minskad mortalitet samt en bättre förmåga att fullständigt avlägsna tumören vid laparoskopisk jämfört med öppen kirurgi. Studie III demonstrerade att minimalinvasiv kirurgi för ändtarmscancer är likvärdig öppen kirurgi i dess förmåga att fullständigt avlägsna tumören med fördelaktiga korttidsresultat. Vid jämförelsen av laparoskopisk och öppen kirurgi för ändtarmscancer i studie IV sågs ingen skillnad i behovet av sjukhusvård eller ytterligare kirurgi till följd av tarmvred, ärrbråck eller bråck i anslutning till stomin.

Slutsats Incidensen av tjock- och ändtarmscancer minskar i Sverige, trots en noterad ökning bland individer under 50 år. Sammantaget är minimalinvasiv kirurgi vid tjock- och ändtarmscancer i rutinsjukvård säker utifrån ett cancerperspektiv med flera korttidsfördelar. Minimalinvasiv kirurgi påverkar sannolikt inte det långsiktiga behovet av sjukhusvård eller ytterligare kirurgi till följd av tarmvred, ärrbråck eller bråck i anslutning till stomin.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Petersson J, Bock D, Martling A, Smedby KE, Angenete E, Saraste D.
Increasing incidence of colorectal cancer among the younger population in Sweden
BJS Open. 2020;4(4):645-658

II. Petersson J, Matthiessen P, Jadid KD, Bock 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(1):4335

III. Josefin Petersson, Peter Matthiessen, Kaveh Dehlaghi Jadid, David Bock, Eva Angenete.
Short-term results in a population based study indicate advantage for minimally invasive rectal cancer surgery versus open
Submitted manuscript

IV. Petersson J, Koedam TW, Bonjer HJ, Andersson J, Angenete E, Bock D, Cuesta MA, Deijen CL, Fürst A, Lacy AM, Rosenberg J, Haglind E; COlorectal cancer Laparoscopic or Open Resection (COLOR) II Study Group.
Bowel Obstruction and Ventral Hernia After Laparoscopic Versus Open Surgery for Rectal Cancer in A Randomized Trial (COLOR II)
Ann Surg. 2019;269(1):53-57

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ABBREVIATIONS

TME	Total mesorectal excision
CME	Complete mesocolic excision
COLOR II	Colorectal cancer Laparoscopic or Open Resection II
ICD	International Classification of Diseases
TNM	International standard for cancer staging
ASA	American Society of Anaesthesiologists
R1	Presence of tumour cells at resection margin
BMI	Body mass index

INTRODUCTION

COLORECTAL CANCER

Colorectal cancer is the third most common cancer internationally and in Sweden.[1,2] In 2020, the age standardized rate for colorectal cancer was 19.5 per 100 000 in the world and 23.9 per 100 000 in Europe.[3] Colorectal cancer is partly preventable with modification of risk factors along with detection and removal of precancerous lesions.[4-6] The mainstay treatment for colorectal cancer is surgery and the improved survival over the last four decades can be attributed to improvements in surgical technique together with radiation and chemotherapy treatment, especially in rectal cancer.[7-9]

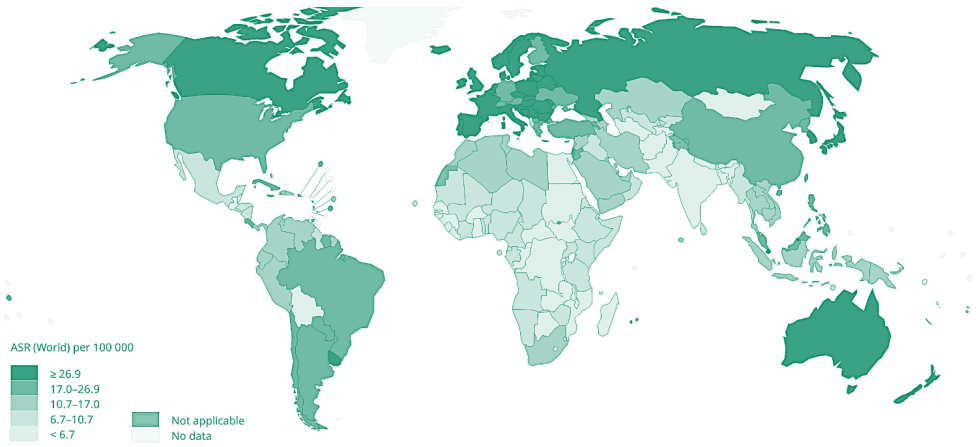

Figure 1. Estimated age-standardized incidence rates (World) in 2020, colorectal, both sexes, all ages. Data source: GLOBOCAN 2020F. Graphic available at IARC (http://gco.iarc.fr/today), World Health Organization.

INCIDENCE OF COLORECTAL CANCER

The incidence rates of colorectal cancer are highest in the developed and industrialized countries, with the highest rates seen in Australia/New Zealand and in European regions (40.6 per 100 000 in males). Lower rates have been documented in developing countries, 4.4 per 100 000 in females in African regions and Southern Asia.[10] The incidence in the developed world is reported to be decreasing. It is not clear whether this can be partly attributed to introduction of bowel screening programs, or if there are other explanations. In Sweden the national bowel screening program was first introduced in 2022, whereas other countries including Australia and the UK started their programs in 2006.
The overall risk of colorectal cancer is known to increase with age, but more recent studies have demonstrated an increase in the incidence in the younger population, in particular of rectal cancer.[11-14] The younger population has also been reported to present with more advanced tumour stages.[15,16] Overall, a change in localization of colorectal cancers with an increasing shift from left to right side with increased age has also been described.[17,18]

SURGICAL TREATMENT

Principles of oncological resection

The overall 5 year survival rate in Sweden for colon cancer is 64% in men and 68% in women and for rectal cancer 66% in both men and women.[19] The surgical management of both colon and rectal cancer has improved over the last 40 years. The principles for an oncological resection include sufficient resection margin, central ligation of vessels and a specimen containing a minimum of 12 lymph nodes.[20-22] In the mid 1980s, the concept of total mesorectal excision (TME) was introduced after reports of improved oncological outcomes including decreased local recurrence.[7,23,24] The technique involves a dissection along embryological planes, removing mesorectum with an intact block of the tumor along with the lymphatic node drainage. Despite the fact that high grade

evidence was not available at the time when TME was introduced, it was quickly accepted and widely implemented by surgeons in light of it being a more straightforward operation with encouraging oncological results. The TME technique has since demonstrated improved local recurrence and survival in cohort studies.[7,23,25] At around the same time, rectal cancer treatment further improved with the introduction of radiotherapy, demonstrating reduced local recurrences and improved survival in randomised controlled trials.[25-27]

For colon cancer, a similar concept called complete mesocolic excision (CME) has more recently been introduced. [28] Publications of a case series and a single center cohort study in the mid 2000s suggested that CME may reduce the 5-year recurrence rate from 6.5% to 3.6% in selected cases.[8,29] Despite these findings, no high grade evidence to support the use of CME for colon cancer has been published.[30,31]

Laparoscopic surgery for colon cancer

Laparoscopic surgery was introduced for colon cancer in the early 1990s and studies have demonstrated oncological short- and long-term outcomes comparable to open surgery with the advantage of less bleeding and enhanced recovery following laparoscopic surgery.[32-38] Well established advantages following laparoscopic surgery include reduced blood loss, pain and length of hospital stay.[32,39,40] Improved quality of life during the first postoperative month has also been reported.[41] Recently, a few population-based studies have suggested improved short-term morbidity and mortality following laparoscopic surgery compared to open surgery for colon cancer.[42-45] A quarter of patients with colon cancer present with Stage IV cancer, these patients are frequently excluded in studies.[37,41] Also, the treatment of T4 tumors by laparoscopic surgery lacks high grade evidence, with the latest meta-analysis from 2013 based exclusively on retrospective studies.[42,46,47] Prospective, controlled studies should be undertaken in order to evaluate minimally invasive surgical techniques for T4 tumours.

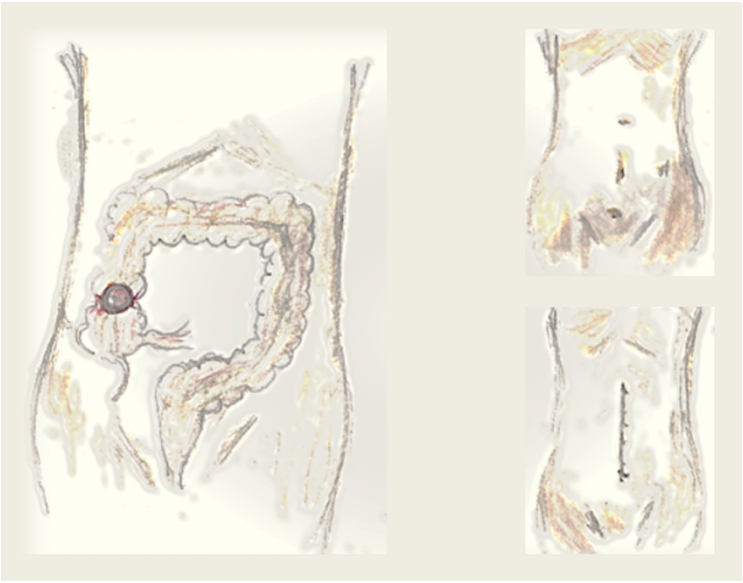

Figure 2. Laparoscopic (top right) vs open (bottom right) surgery for right sided colon cancer (left). Author's own figure.

Minimally invasive surgery for rectal cancer

Rectal cancer surgery is well recognised to be technically difficult, as it entails performing a sharp dissection deep down a narrow pelvis to achieve adequate cancer resection. The use of different surgical techniques can make this more or less difficult and may therefore affect oncological outcome. Laparoscopic surgery for rectal cancer was introduced in the 1990s, with advantageous short term benefits such as less blood loss, reduced pain and shorter length of hospital stay compared to open surgery.[39,48-51] Initial randomised controlled trials comparing laparoscopic and open technique demonstrated no differences in short- and long-term oncological outcomes including locoregional recurrence and disease-free and overall survival.[34,52,53] COLOR II, the largest randomised controlled trial demonstrated non-inferiority for the primary endpoint of locoregional recurrence at three years.[54] Some uncertainty was later raised, when two trials were unable to show non-inferiority comparing laparoscopic with open surgery in terms of 'successful' resection, an outcome solely based on pathology results. It is

not well established how this composite outcome correlates with clinically relevant outcomes such as local recurrence and disease-free survival.[55,56] No difference was revealed at 2 years in terms of local recurrence, disease free survival or overall survival, though neither study was powered to assess non-inferiority at the two year mark.[57,58] More recently, a randomised controlled trial designed to assess for non-inferiority with regard to three year disease free survival comparing laparoscopic and open surgery for low rectal cancer demonstrated no difference in short term pathologic and surgical outcomes.[59] Overall, studies have demonstrated no significant differences in long-term oncological outcomes comparing laparoscopic and open surgery and a recent population based register study did report non-inferiority following laparoscopic surgery.[60-63]

Long-term surgical outcomes following colorectal surgery

Long-term surgical outcomes following colorectal surgery include the risk of bowel obstruction, incisional hernia and parastomal hernia, all of which are associated with significant morbidity.[64,65] Laparoscopic abdominal surgery has been reported to decrease the risk of bowel obstruction compared to open. [66-70] It has also been reported to decrease the risk of incisional hernia compared to open surgery.[71-73] Studies available include all types of abdominal surgery, a mix of colorectal cancer surgery or only colon cancer surgery. Reports from randomised controlled trials and studies following rectal cancer surgery are few. Furthermore, the formation of a stoma, which is not infrequently needed during rectal cancer surgery, presents the possibility for a parastomal hernia to develop. It is not known whether using laparoscopic or open surgery changes the subsequent risk of developing a parastomal hernia.

AIM

The overall aim of this thesis is to estimate the overall incidence of colorectal cancer in Sweden over time and to evaluate the introduction of minimally invasive surgery compared to open surgery for colorectal cancer.

Specific aims were:

I. Investigate the overall incidence of colorectal cancer in Sweden over time, including age and sex-specific trends in a population based setting.
II. To compare laparoscopic surgery with open surgery in a routine health care setting regarding short-term mortality, morbidity and completeness of cancer resection for colon cancer.
III. Determine if minimally invasive surgery is non inferior to open surgery for rectal cancer with regard to adequacy of cancer resection in a routine health care setting.
IV. Evaluate the risk of bowel obstruction, incisional and parastomal hernia following laparoscopic versus open surgery for rectal cancer in the setting of a randomised controlled trial, Colorectal cancer Laparoscopic or Open Resection II (COLOR II).

PATIENTS AND METHODS

LEVEL OF EVIDENCE

Traditionally, surgical practice has been based on an understanding of mechanisms of disease guided by personal clinical experience and individual surgical expertise. Within the hierarchy of evidence, this correlates to the lowest grade of evidence: an idea or an opinion. In the surgeons' attempt to provide patients with the best level of care, evidence based surgery has evolved. The randomised controlled trial has become the gold standard for determining causality and efficacy of a new intervention. To ensure safety when introducing a new technique, randomised controlled trials tend to exclude high risk patient groups, thereby leaving more homogenous groups to be compared. Too strict inclusion criteria reduces outcome variability, but it may also limit generalisability. The highest level of evidence is obtained from a review or meta- analyses including high quality randomised controlled trials. In some situations, it may be difficult to perform a randomised controlled trial. Observational analytic studies are most suitable if randomisation of the intervention or exposure is not feasible, or if the research question focuses on unintended effects of interventions. For example, if the existing evidence for an intervention is perceived as sufficient by doctor or patient, then one or both parties may not accept randomisation to what is perceived as an inferior intervention. Prospective comparative studies can be used in these instances including cohort-studies or case-control studies and well-designed prospective cohort studies can provide good evidence. Observational cohort studies from population based high quality registers can act as a complement to randomised controlled trials, providing generalisability but lack in internal validity and vice versa. Use of modern statistical methods such as multivariable regression, propensity score matching and inverse probability weighted regression analysis can reduce the risk of confounding. To ascertain causality from observational studies replication of results is necessary. In the end, surgical practice is still based on and guided by clinical experience and surgical expertise.

However, we need no longer rely solely on the clinical experience or surgical expertise of only a few surgeons. Rather, we are able to base our decision making on the collaborated results provided by the surgical community within a scientific framework - known as evidence based surgery.

STUDIES AND STUDY DESIGNS

This thesis is based on four different studies, three of these studies are population based and the data used have been retrieved from the Swedish Colorectal Cancer Registry, the Swedish Cancer Register and the National Patient Register. Data from the randomised controlled trial was collected in clinical record forms during follow-up. One study is descriptive and the three others are analytical, including one randomised controlled trial and two observational cohort studies.

Paper I

Paper I is a descriptive epidemiological population-based study reporting the overall incidence of colorectal cancer in the population of Sweden including the age and sex-specific trends.

The primary outcome was overall colorectal cancer incidence over time including age- and sex-specific incidence. The secondary outcomes tumour localisation and tumour stage were analysed over time and specific for age and sex.

For this study we extracted data for all patients diagnosed with colorectal adenocarcinoma from the Swedish Cancer Register, a national register to which all malignant tumours have been mandatory reported to since 1958. Through benchmarking the Swedish Cancer Register has been assessed to have an underreporting of about 4 %.[74] The study-period included was 1970-2016. Tumour location was recorded as reported by the International Classification of Diseases
(ICD) code. Localization was categorized as proximal: from caecum including splenic flexure (153.0 and 153.1), distal: from descending colon including sigmoid (153.2 and 153.3), and lastly rectal: from rectosigmoid including rectum (154.0). The following locations were excluded:

appendix, anus and unspecified. Synchronous tumours were not included and in patients with metachronous tumours only the first tumour was included. Age was categorized into three groups: 0-49 years, 50-74 years and 75 years or more. Tumours were staged according to the TNM classification based on clinical TNM if available or otherwise by pathology TNM. Tumour stage data was available for analyses 2007-2016, this data was extracted both from the Swedish Cancer Register and the Swedish Colorectal Cancer Registry to minimize missing values.

Paper II

Paper II is a population-based study comparing laparoscopic to open surgery for colon cancer using population based register data with the primary outcome being short-term mortality. Secondary outcomes were morbidity and adequacy of cancer resection All patients diagnosed with right sided and sigmoid colon cancer stage I-IV were included from the Swedish Colorectal Cancer Registry from 1st January 2012 through to 31st December 2018 who went on to have a surgical resection. Data regarding all available possible confounders were also retrieved from the register. We also used data from the National Patient Register to assess morbidity. Robotic assisted laparoscopic surgery has been recorded separately in the Swedish Colorectal Cancer Registry since 2014. Robotic laparoscopy was infrequently used for colon cancer surgery and therefore we decided to analyse the laparoscopic and robotic assisted laparoscopy groups together. Owing to the fact that transverse and descending colon cancers are less common and that cancers at these locations are subject to less standardised resections these cancers were not included in this study. Subgroup analyses including Stage I-III were also performed.

Paper III

Paper III is a population based study examining if minimally invasive surgery is non-inferior to open surgery for rectal cancer with regard to adequacy of cancer resection in a population based setting. The secondary outcomes included 30- and 90-day mortality, anastomotic leak and re-operation within 30 days, 30- and 90-day re-admission, length of

stay, positive distal resection margin and less than 12 lymph nodes in the surgical specimen.
Data from the Swedish Colorectal Cancer Registry and the National Patient Register was used and included all patients diagnosed with rectal cancer 1st January 2012 to 31st December 2018 who underwent curative abdominal surgery including, all cancer stages. Locally resected rectal cancers were not included. Robotic surgery was registered in the Swedish Colorectal Cancer Registry since 2014. Robot and laparoscopic surgery were analysed as one group and subgroup analyses were performed comparing robotic and open surgery 2014 to 2018.

Paper IV

Paper IV is the 5 year follow up of the secondary endpoints: bowel obstruction, incisional hernia and parastomal hernia in the open-label, randomised non-inferiority trial: COLOR II. The primary endpoint for COLOR II was 3-year local recurrence. Thirty centres from Belgium, Canada, Denmark, Germany, the Netherlands, South Korea, Spain and Sweden participated and accrued 1044 patients.
In COLOR II all consecutive patients with rectal cancer stage cT1-cT3 without evidence of metastatic disease, who were suitable for elective surgery and who consented to participate were included and randomised. The rectum was defined as within 15 cm from anal verge. Only patients aged 18 years and older were eligible for inclusion. Exclusion criteria were: cT4 tumours, T3 tumours within 2mm of mesorectal fascia, T1 tumours that were locally excised, rectal cancer other than adenocarcinoma, history of other malignancy except basal cell carcinoma or in-situ carcinoma of the cervix uteri, signs of acute bowel obstruction, synchronous colorectal tumour, familial adenomatous polyposis, hereditary non-polyposis colorectal cancer, active Crohn's or active ulcerative colitis, absolute contraindication to general anaesthetic or pneumoperitoneum, American Society of Anaesthesiologists (ASA)classification >III and pregnancy. Randomisation ratio was 1:2 favouring laparoscopy. Patients were randomly assigned centrally using a list of randomisation numbers generated by the trial statistician implemented by the use of internet. Patients were stratified according to

participating centre, resection type and preoperative radiotherapy. Patients and clinicians were not blinded to treatment assignment. Data were recorded in clinical record forms and kept centrally in the coordinating centre in Halifax, Canada.

OUTCOME MEASURES

Paper I

The primary outcome was overall colorectal cancer incidence over time. This included age- and sex-specific incidence. We decided not to include cancers reported prior to 1970, as we were not able to validate the correct inclusion of only colorectal adenocarcinomas, therefore the study-period was set to 1970-2016. Synchronous tumours were not included so as not to inflate the incidence of colorectal cancers by location. Similarly, in patients with metachronous tumours, we recorded only the first tumour. Tumour localization and tumour stage at the time of diagnosis were also analysed by age and sex over time. We decided to use similar classification as previous studies with regard to tumour localization and age to facilitate comparability between studies.

Paper II and III

The primary outcome in paper II was 30-day mortality. Registry-based studies had recently suggested a decreased 30-day mortality following laparoscopic compared to open surgery for colon cancer. The 30 day mortality is a validated outcome measure used to assess risk, evaluate surgical safety and provide a benchmark in reporting. However, with improving perioperative care and life sustaining therapies, reports have shown that mortality after colectomy can come later than is often assumed. It has been suggested that 90 day mortality more accurately captures the true postoperative mortality rate, especially in the comorbid population.[75] We included 90-day mortality as a secondary outcome in both papers.

In paper III, the primary outcome was incomplete resection defined as positive circumferential resection margin and positive resection margin.

Two recent randomised controlled trials were not able to confirm non-inferiority comparing laparoscopic and open surgery with regard completeness of resection. The primary outcome in the American and Australian randomised trials was a composite outcome based on pathology results, including an assessment of positive margins and the quality of the mesorectal fascia. Validated long-term outcomes for rectal cancer include overall survival, cancer free survival and local recurrence. Whilst positive circumferential resection margin and positive resection margin are not as clearly validated, both outcomes are recognised as important negative prognosticators for local recurrence and long-term survival of rectal cancer.[76-78] In the Swedish Colorectal Cancer Registry, the definition of circumferential resection margin is <1 mm resection margin and negative resection margin is defined as no tumour cells in the margin of resection. Both of these were available for analysis from the Swedish Colorectal Cancer Registry for the time period of interest, whereas mesorectal fascia quality was not.

Both papers II and III evaluated whether the specimen contained sufficient number of lymph nodes (>12), as it also is an independent prognostic factor in colorectal cancer. [21,22]

Paper IV

The randomised controlled trial COLOR II was designed and powered for the primary outcome of 3-year local recurrence. The secondary outcomes included the risk of bowel obstruction, incisional and parastomal hernia five years after laparoscopic and open surgery for rectal cancer. The secondary outcomes are all associated with risk of morbidity affecting quality of life.[79] Bowel obstruction, incisional and parastomal hernia may also require health care, including challenging stoma care and surgical re-interventions.

A statistical analysis plan clearly defining the primary outcomes was agreed upon prior to the analyses in this COLOR II sub-study. A hernia at a previous stoma site was considered an incisional hernia. Perineal hernias following abdominoperineal resection were not included as incisional hernia. Parastomal hernias were defined as a hernia at an active

stoma site. Each endpoint was scored positive if reported in a clinical record during yearly follow up for 5 years. Admissions and re-operations were included if recorded for each endpoint.

METHODOLOGICAL CONSIDERATIONS

Choosing the primary outcome

The aim of clinical research is threefold: to improve patient outcomes, population health and cost. Outcome measures therefore need to be of clinical, biological or economic importance preferably to the patient, the health provider and society. Outcomes should also be well-defined, measurable, validated, comparable and reproducible.

The primary outcome in the first paper, overall colorectal cancer incidence, is well-defined, measurable, validated, comparable and reproducible. It is of clinical importance, firstly as it informs health care professionals and patients to be vigilant in the diagnosis in younger patients. Secondly, it calls for exploration of the underlying causes as to why there is an increase in the incidence of colorectal cancer in the younger population. Thirdly, the incidence of a disease dictates the demand of health care in a population. Understanding the change in incidence of a disease will help inform planning, budgeting and monitoring mechanisms. For potentially preventable and curable diseases such as colorectal cancer, this also includes primary preventative strategies such as diet and lifestyle modification as well as secondary preventative population bowel screening to remove precancerous polyps.

Thirty day mortality is often used as a primary outcome. Though clearly a clinically meaningful and well-defined outcome, it is also a crude measure. Mortality is becoming increasingly uncommon following elective surgery and with fewer observations, comparisons become more difficult and less certain. Hence, other outcome measures might be more suitable to assess improvements in care and to evaluate outcomes important to patients. Anastomotic leak and re-operations at 30-days were included as

secondary outcomes and to further expose the extent of care needed, we also included length of stay and re-admission. All these outcomes are important from a societal point of view, as they require ongoing health care with increased cost.

Positive circumferential resection margin and presence of tumour cells at resection margin are both well-defined and measurable outcomes. Both are recognised to be associated with important long-term outcomes, including local recurrence and long-term survival. However, the reliability of pathological outcomes in a population-based study where pathology is reported on by a large number of different pathologists may present a weakness. The validity of such a proxy measure for local recurrence and long-term survival may contain flaws in its ability to accurately reflect the long-term outcomes that matters to the patient, the health provider and the society. However, in the absence of available long-term data following the introduction of new techniques and bearing in mind the expenses and the efforts involved in performing prospective trials similar proxy measures may still play a role.

Bowel obstruction, incisional and parastomal hernia are clinically important outcomes to patients, health providers and society and were used as primary outcomes. With improved survival, the number of patients living with complications related to colorectal cancer surgery increases. Long-term surgical complications including bowel obstruction, but perhaps more so incisional and parastomal hernias are difficult to measure, as these complications often are managed at home by patients without health care involvement.[80] They do however still have a substantial impact on patients' long-term quality of life.[79]

Internal and external validity

The validity of the results from a study is dependent on the internal validity of the study. The study design can include different strategies to avoid the risk of selection bias and confounders such as randomisation, block randomisation (balancing the groups), stratification, blinding of patients and assessors and standardization of treatment protocols. A well

designed randomised controlled trial is able to control for confounders by establishing two groups of patients with balanced characteristics. However, randomised controlled trials are expensive, time consuming and require homogenous comparative groups to be able to determine causative relations. They therefore often inadvertently end up with a narrow patient selection, which subsequently results in reduced external validity. For study results to be useful in the everyday clinical setting, they need to have external validity, results need to be generalisable and applicable to the population who are to receive the treatment. Strategies used to increase external validity in a randomised controlled trial include: inclusion from several centres and countries, wide inclusion criteria and registration of eligible non-included patients. Well-designed observational studies based on large population-based high quality registers can with the use of statistical methods act as a complement to randomised controlled trials, as they reflect an unselected population. Low frequency events often require careful consideration in larger population based studies. The quality of observational studies is dependent on the quality of the register data. However, despite careful planning and statistical adjustments, complete elimination of selection bias and residual confounding cannot be guaranteed in observational studies and as such, interpretation of outcomes must be approached with caution. To determine true causality from an observational study is therefore as a general rule not possible, but requires multiple high quality observational studies.

In Study IV, several strategies were used to ascertain internal validity. Primarily, the use of central randomisation to ensure similar groups and avoid introduction of known and unknown biases. Stratification was used to balance the allocations with regard to the participating centre, resection type and preoperative radiotherapy. Blinding of researchers, patients and staff was not possible, since scarring would reveal which surgery had been performed. The randomisation took place after the collection of baseline data, but well before the date of the surgery to ensure the logistics surrounding laparoscopic surgery, including the availability of a laparoscopically trained surgeon. In theory "sham surgery" with additional skin incisions to ensure uniform scarring for all could be

performed, but this would cause additional trauma and risks to all study participants. The inability of masking introduces the possibility for researchers, patients and staff to consciously and unconsciously influence outcome. Standardisation within the study is another strategy to increase internal validity. For study IV, participating clinics were required to submit five unedited recordings of laparoscopically performed rectal cancer resections for assessment along with corresponding pathology reports to quality certify recruiting surgeons and centres. There were no further standardisation of treatment protocols in this study.

Similarly, other strategies were used to increase the external validity such as including patients from different countries and from many centres. This widens the population included and thereby increases generalisability and subsequently reduces the risk of biases that can be introduced by single centres and single populations. All eligible non-included patients were registered in a screening log in order to control for the risk of selection bias.

Study I, II and III are all population based studies combining data from several high quality national registers. The internal validity of these studies are based on the completeness and the validity of the register. Regular external validations of registers is one way to assess and ensure the validity. The reliability in both the Swedish colorectal cancer registry and the National Patient Register has been deemed as high.[74,81]

Non-inferiority vs superiority

A non-inferiority trial is used when the new treatment may have other known advantages over existing treatment and hence we do not need to prove that the new treatment is better than the existing one – we need to prove that is not unacceptably worse - non-inferior and safe in other aspects. Failing to confirm non-inferiority does not imply inferiority. Results from randomised controlled trials had reported conflicting results with regard to oncological outcomes comparing laparoscopic surgery with open for rectal cancer. However, there were well established favorable short-term outcomes therefore a non-inferiority method was chosen.

An important part of a non-inferiority trial is to decide the margin of clinical significance, also called non-inferiority margin. This margin signifies how much worse the new treatment should be allowed to be compared to the old treatment. In other words, if the mean difference (and its 95% confidence interval) between laparoscopic surgery and open surgery is within the set non-inferiority margin, then laparoscopic surgery is non-inferior to open surgery. In paper III non-inferiority was assessed by risk difference analyses with 95% confidence intervals. Estimation of the non-inferiority margin is based on the effect of the intervention compared to no treatment as reported in previous trials. Since there is not data available from studies comparing the standard intervention with no intervention, another way of determining a non-inferiority margin is using a Delphi consensus. We used predefined non-inferiority margin of 2.4% for circumferential resection margin as suggested by the Delphi consensus, consisting of rectal cancer experts worldwide and for involved resection margin (R1) we used the cumulative figure they suggested for circumferential resection margin and distal resection margin 4%.
A superiority trial is similar to a non-inferiority trial, but now we want to prove that there is a difference between the two treatment groups. The stipulated null hypothesis is: There is no difference between the two groups. In the superiority trial we then set out to reject the null hypothesis. In other words, if the mean difference (and its 95% confidence interval) between laparoscopic surgery and open surgery is not 0 then laparoscopic surgery is significant different to open surgery; $\mu_1-\mu_0\neq 0$.

STATISTICAL CONSIDERATIONS

Missing data

One of the challenges in clinical studies is missing data. It has been suggested that <5% missing means little bias whereas >20% present a serious risk for bias.[82] In population based studies, the completeness of the register is of vital importance and strongly influences the quality of the study; not all variables are equally well reported. Regular external

validations of registers is one way to assess and ensure the validity. We were able to combine the register data from different registers based on the unique Swedish identification number to minimise the amount of missing data. Missing data in a randomised controlled trial can reduce the power and the efficiency of the study, but it can also bias the outcome partly because patients who are lost to follow up have a different prognosis compared with patients who complete the study. The missing data at the 5 year follow up in COLOR II was well below 20 % and it was evenly distributed across the two groups. In this paper, if a patient was lost to follow up in one group it would benefit that group as no further events would be recorded for that patient. We decided to use time as an offset variable, accounting for the time the patient was at risk for an event to reduce the effect of loss to follow up.

Cumulative incidence vs incidence density

The cumulative incidence method uses the number of patients diagnosed with colorectal cancer in a year divided by the population on the 31 December previous year. The numerator (number of patients diagnosed with colorectal cancer per year) was rather small in comparison to the denominator (Sweden's population) and hence this approach was considered a reasonable approach to estimate the incidence. In a dynamic population, where the number of patients at risk vary and the numerator is larger incidence density will more accurately estimate the incidence. It uses the average population - time at risk as denominator. We estimated the incidence using cumulative incidence and reported as number of patients per 100 000 and age-adjusted for the European Standard Population (1976). We also estimated the incidence by calculating the incidence density and found the discrepancies between the two approaches to be minimal in our study.

Randomisation

Since laparoscopic surgery was a novel technique for rectal cancer, the ratio of the randomisation was set to 1:2. This allowed a larger sample size in the laparoscopic group and subsequently increased the power to

detect adverse events related to the new technique. Furthermore, laparoscopic surgery was known to have a learning curve and a larger sample size in the laparoscopic arm provided the potential to reduce the effect of a learning curve on the outcome.

Intention to treat vs per protocol analysis

Intention to treat analysis simply means that one analyses patients as they were randomised. In COLOR II some patients underwent open surgery when no laparoscopic surgeon was available. Similarly, patients who were randomised to open underwent laparoscopic surgery by their "own choice" in violation of the study protocol.
In per protocol analysis, patients are analysed in accordance with the treatment they received. In a non-inferiority study, cross-overs between the two arms is more likely to attenuate differences meaning that the as treated analysis will provide a more cautious result compared to the intention to treat analysis. Whereas in a superiority study, the per protocol analysis will provide a greater difference in the results. The results in the randomised trial remained similar in the as treated analysis. In COLOR II intention to treat analysis were performed, as treated analysis were also reported on.

Multiple hypothesis testing

The risk of incorrectly rejecting the null hypothesis (type I error) when testing a hypothesis is set at a certain sensitivity e.g., 5%. The more hypothesis tests performed, the more likely one is to incorrectly reject a null hypothesis. An increased number of analyses will decrease the power of the results. There are several statistical methods used for dealing with multiple hypothesis testing. The Holm's procedure is one of them. It involves ordering the hypothesis by their p-values, starting with lowest p-value and comparing these to the determined significance level/number of hypothesis, then subsequently rejecting it if p-value is lower. Then repeating this process using the remaining $k-1$ hypotheses and a

threshold of $\alpha/(k-1)$. This is again repeated until the selected p-value is not smaller. At this point all remaining hypotheses should be accepted.

Confounding in observational studies

Observational studies including register studies always carry the risk of bias due to the nonrandom assignment to treatment. Without randomisation, treatment groups may be unbalanced and specific patient characteristics associated with both the treatment and the outcome may be more common in one group which may influence and confound the true treatment effect.

There are multiple statistical methods that can be used to reduce bias such as multivariable regression, stratification, propensity score matching and inverse probability treatment weighted regression analysis. In Paper II and III, inverse probability treatment weighted regression analysis was used. This involves two steps, firstly the propensity scores for all patients are calculated. The propensity scores provided the probability ranging from 0 to 1 that a patient will undergo minimally invasive surgery based on their baseline characteristics. All covariates that correlate to treatment and outcome need to be included to reduce confounding.[83] The potential confounders in Paper II and III were identified by using directed acyclic graphs.[84] Propensity scores where then used to perform inverse probability treatment weighted regression analysis. In comparison to propensity score matching, inverse probability treatment weighted analysis enables the use of most patients included in the study. This increases the effective sample size and allows for analyses of studies with small number of events or large number of confounders. [85]

ETHICAL APPROVALS

Ethical approval for study I was obtained from the regional ethics committee (Stockholm; dnr 2016/1145-31/2, 2017/43-32, 2017/2295-32, 2017/1753-32). Study II and III adhered to the Declaration of Helsinki. Individual informed consent was waived since both studies were of observational nature, ethics approval were obtained from the regional

ethics committee (Uppsala, Dnr 2018/129 and Dnr 2019/01787). For study IV, the participating centers obtained institutional review board approval, in accordance with local regulations. Patients provided written informed consent. The trial is registered with ClinicalTrials.gov, number NCT00297791.

RESULTS

PAPER I

The first paper displayed an overall increase in the incidence of colorectal cancer in Sweden from 1970 to 2006 which was followed by a decrease over the last decade from 2006 to 2016 (Average annual percentage change -0.55%, 95% CI: -1.02, -0.07).

The incidence of all colorectal cancer including proximal, distal and rectal was found to be increasing in the younger population, more so in women than men. The greatest increase of colon cancer was seen in women under 50 years of age between 1995 and 2005 with an average annual percentage change of 2.30% (95% CI: 0.09, 4.56) compared to 0.04% (95% CI: -1.35, 1.44) and -0.67% (95% CI: -1.62, 0.28) in women aged 50-74 and 75 years or more respectively. The incidence of rectal cancer in the younger population increased from 1990 onwards in both sexes. Women displayed a higher annual increase than men in the last decade, 2.01% (95% CI: -1.46, 5.61) compared to 0.20% (95% CI: -2.25, 2.71).

The study also revealed that patients younger than 50 years were more likely to present with a more advanced cancer stage compared to older patient groups for both colon (<50 years: 66.2%, 50-74 years: 57.6% and ≥75 years: 49.6 %) and rectal cancer (<50 years: 61.2%, 50-74 years: 54.3% and ≥75 years: 51.3%).

PAPER II

The second paper included 13683 patients from the Swedish Colorectal Cancer Registry diagnosed with colon cancer 2012-2018 who subsequently underwent elective colonic resection.

The study results indicated clear advantages for laparoscopic surgery compared to open surgery in routine health care setting but there was no

difference in the primary outcome of 30-day mortality: laparoscopic surgery (0.9%) and open surgery (1.3%) (OR 0.89, 95% CI 0.62-1.29, P=0.545).The weighted analyses however found an increase in the 90-day mortality associated with open surgery, P<0.001.

The study also demonstrated reduced number of re-operations and re-admissions as well as a 2.9 days shorter length of stay following laparoscopic surgery(P <0.001). R1 resections were significantly less common following laparoscopic surgery both in the unweighted and weighted analysis, P=0.004 and P<0.001 respectively. Subgroup analyses including only cancer stage TNM I-III demonstrated similar results.

Paper III

The third paper included a total of 9464 patients diagnosed with rectal cancer from the Swedish Colorectal Cancer Registry between 2012 and 2018 who underwent elective surgical resection with curative intent.
The study did not show any difference in terms of the primary outcomes circumferential resection margin <1 mm or R1 comparing minimally invasive surgery with open surgery. The results were similar for the adjusted unweighted and weighted analyses circumferential resection margin <1mm: minimally invasive surgery 3.7% and open surgery 5.4%, risk difference -1.8%, 95% CI: -2.79%, -0.86% and R1: minimally invasive surgery 2.9% and open surgery 4.6%, risk difference -1.7%, 95% CI: -2.51%, -0.85%.
Secondary outcomes suggested reduced mortality, length of stay and re-admissions at 30 and 90 days following minimally invasive surgery compared to open surgery in both the weighted and unweighted regression analyses.
Minimally invasive surgery was performed in 38% of cases between 2012 and 2019. Its use increased throughout the study time with a decrease in conversion rate from 20% in 2012 to 12% in 2019.
The results of this study indicate that minimally invasive surgery for rectal cancer in a population based setting is non-inferior to open surgery at

achieving adequate cancer resection with advantageous short-term outcomes.

PAPER IV

The fourth paper reported on data from the 1044 patients included in the international multicenter, randomised controlled trial COLOR II was analysed. Median follow up was 61 months.

No difference was found in the risk of developing bowel obstruction comparing the laparoscopic group 12.5% to the open group 11.9%; relative risk 1.00 (95% CI: 0.69–1.43), P=1.000. Nor was there a difference in the risk of developing bowel obstruction requiring re-admission (10.1% versus 9.2%, P=1.000) or re-operation (7.9% vs 6.1%, P=1.000).

With regard to the risk of developing an incisional hernia the study did not find a difference between the open and laparoscopic groups (18.7% vs 17.0%, P=1.000). Neither was there a difference in the risk of developing parastomal hernia (17.4% vs 9.3%, P=0.066). However, body mass index (BMI) >30 was found to significantly increase the risk for both incisional and parastomal hernia.

DISCUSSION AND FUTURE PERSPECTIVES

This thesis addresses the incidence of colorectal cancer in Sweden over time and evaluates outcomes following colorectal cancer resection comparing laparoscopic and open surgery.

INCIDENCE OF COLORECTAL CANCER

The incidence of colorectal cancer in Sweden decreased in the last decade, but there was an increase in the incidence of colorectal cancer in the younger population including proximal, distal and rectal cancers. Younger patients were more likely to present with a more advanced cancer stage which may in part be due to delayed presentation. Younger age has been reported to be associated with an increased time to presentation.[86]

A full explanation for the incidence trends observed are not easily provided. Risk factors for colorectal cancer are multifactorial, both inherited and acquired including ingestion of processed meats and red meats, low fruit and vegetable diet, sedentary lifestyle, obesity, smoking and moderate or high alcohol consumption. Primary prevention for colorectal cancer includes raising health awareness regarding these risk factors as this may help decrease the incidence of colorectal cancer. Bowel screening programs are part of so-called 'secondary prevention' and may reduce colorectal cancer by removing already existing precancerous polyps.[87-89] However, screening was first introduced in 2008 and only in one of six health regions. It is therefore unlikely to explain the decrease in overall colorectal cancer incidence seen in Sweden after 2006. National screening was not introduced in Sweden until 2022. Smoking may in part offer an explanation for the overall decrease in colorectal cancer incidence noted. Smoking has decreased substantially across the Swedish population over a similar period, except amongst younger women. The concurrent increase in the incidence of obesity and intake of processed and red meat in the younger population in Sweden

can to some extent explain the increased incidence of colorectal cancer in this group.[90-92] The pathogenesis of colorectal cancer is too multifaceted for there to be a simple explanation of the observed trends in colorectal cancer incidence. However, recent publications concerning the younger population have reported an increase in several other obesity related cancers.[93] It is not clear how big a role obesity, along with the associated sedentary lifestyle and obesogenic diet play with regard to the increase in colorectal cancer incidence in younger people. Future studies are needed to assess dietary and lifestyle modifications aimed to decrease obesity and their effects upon colorectal cancer incidence. Considering the worldwide increase in obesity among the younger population, the future burden of colorectal cancer might increase as these younger cohorts age. Therefore, prevention of colorectal cancer may need to include not only bowel screening programs but also interventions aimed to combat obesity along with promoting a healthy diet and lifestyle. It is unclear what role future medical and surgical interventions aimed at combating obesity might have on the incidence of colorectal cancer.

SURGICAL TREATMENT

Laparoscopic surgery for colon cancer

Improved short-term mortality following laparoscopic surgery compared to open surgery has previously been reported in register based studies.[43,45,94] The exclusion of emergency surgery from these studies likely provides an explanation as to why the overall mortality was lower than previously reported in population-based studies. This may also explain why there was no difference in 30-day mortality between the groups. In comparison with previous studies, the detailed data available in the Swedish Colorectal Cancer Registry enabled more refined adjustments of potential confounders.

Differences in less common complications that are associated with one of the techniques, such as wound dehiscence and small bowel obstruction may only be demonstrated in large population based studies. This may

provide an explanation as to the lower rate of reoperations noted in the laparoscopic compared to the open group. Additional analysis of complications using the Clavien Dindo classification would have been of interest to further assess morbidity if reliable data had been available.

The lower rate of readmission found in the laparoscopic group compared to the open may be secondary to previously known reduced rates of infectious, cardiac and pulmonary complications associated with laparoscopic surgery. This reduction may be more pronounced in this study, which includes more comorbid patients. It would be of importance to investigate whether the reduced rate of R1 resection following laparoscopic compared to open surgery actually translates into clinically relevant long-term cancer free survival. A subgroup analysis of T4 tumours would have been of interest, but was not performed as it would have constituted a post hoc analyses and as such, would have increased the probability of a false-positive finding. With regard to selection bias, the indication for laparoscopic or open surgery was not available and neither was hospital or volume effects (both known to impact short-term outcomes in colorectal cancer surgery).[95,96] The use of statistical methods with multiple adjustments helped to decrease bias, but residual confounding may still have been present.

In conclusion, the findings of this study are likely to reflect how favorable laparoscopic surgery is compared to open surgery in the short-term when applied to a real-world population including all stages of colon cancer.

Whereas the survival of rectal cancer has continued to improve over the last several decades, little improvement has been seen for colon cancer. To identify optimal surgical technique and best use of chemotherapy for colon cancer in order to improve long-term outcomes, there is a need for new research leading to high level evidence. And although complete mesocolic excision (CME) has been suggested to improve survival in colon cancer, there is no high grade evidence available to support this. Systematic reviews have also failed to show survival benefits.[8,29,31] CME surgery results in an extended lymphadenectomy, which in itself has been

reported to improve 5-year survival in retrospective and prospective cohort studies. CME will also upstage some patients from node negative to node positive, meaning they will receive adjuvant chemotherapy which may also influence survival. How big of a role CME plays in itself is not known. CME is a more technically challenging resection and risks include bleeding and damage to the superior mesenteric vein and potential small bowel ischemia. Only one randomised controlled trial has compared laparoscopic to open CME surgery and found laparoscopic CME surgery to be non-inferior to open surgery with regard to 5-year overall survival. It is not clear if CME will play a role in the future of colon cancer surgery. Prospective studies designed as superiority trials, preferably in combination with randomised controlled trials are needed to ascertain safety and potential benefits. Further studies to assess the safety of performing CME using minimally invasive technique including laparoscopic and robot assisted laparoscopic surgery will then also be required. If so, the future of colon cancer surgery may, like rectal cancer surgery, call for a more specialised and more individualised treatment approach.

Minimally invasive surgery for rectal cancer

Minimally invasive surgery for rectal cancer was non-inferior to open surgery in terms of complete cancer resection and demonstrated favorable short-term outcomes when performed in routine health care. The rates of positive circumferential resection margin and distal resection margin in this study were comparable to those reported in randomised trials, but lower than rates reported in previous population based studies.[50,51,56,97,98]. It is notable that randomised trials generally include a higher proportion of low rectal cancers compared to population based studies, which are known to be associated with positive resection margins.[99] However, this study included T4 tumours, frequently excluded in randomised controlled trials. It also included a higher proportion of patients who had received radiotherapy and a higher proportion of abdominoperineal resections, all known to increase the risk of a positive circumferential resection margin.[100] Other risk factors for an inadequate resection include N-stage 1-2 and high BMI.[99] [101] N-stage was similar

compared to other studies, whereas BMI was lower in comparison to trials from other western countries, reflective of the Swedish population. Overall, comparisons of studies are difficult, not only due to differences in patient and tumour characteristics but also with regard to variations in the use of preoperative radio and chemotherapy.
The reduced length of stay, mortality and re-admissions at 30 and 90 days following laparoscopic surgery compared to open surgery have previously been reported in large cohort and population based studies.[44,51,56,97] The conversion rate in the minimally invasive surgery group was higher than in randomised trials, though lower figures were noted over time. The decrease in conversions coincided with more frequent robot assisted laparoscopic resections and subgroup analyses demonstrated a lower rate of conversion in the robot assisted laparoscopic group. Similar findings have been reported amongst the secondary short-term outcomes from a recent randomised controlled trial comparing laparoscopic with robot assisted laparoscopic surgery for low and middle rectal cancer.[102] However, an earlier randomised controlled trial, ROLARR, using conversion to open as the primary outcome did not show a significant difference in conversion rate, comparing the two surgical techniques.[103] Subsequent explorative analysis accounting for learning effects within the ROLARR trial indicate a decreased conversion rate in the robot assisted arm.[104] This suggests that the initial results may have been confounded by more inexperienced surgeons. The reason for the lower conversion rate seen after robot assisted laparoscopic compared to laparoscopic surgery in Paper III cannot easily be deduced. One possible explanation is the learning curve associated with robotic surgery. However, there is no consensus as to whether robotic surgery provides a shorter learning curve compared to laparoscopic surgery as high quality studies are scarce.[105,106]

Robotic assisted surgery is increasingly being used in colorectal cancer surgery. For rectal cancer, it has been introduced despite its inability to demonstrate improved outcomes for adequacy of resection and conversion rate and with an increased cost to the health system.[103,107]

Long-term surgical risks following colorectal surgery

The risk of bowel obstruction, incisional and parastomal hernia following rectal cancer resection did not differ between laparoscopic and open surgery in the long-term follow up of 1044 patients included in the randomised controlled trial COLOR II.

Bowel obstruction has been reported to be lower following laparoscopic surgery in meta- analyses and population based studies. This study included only rectal cancer surgery. In contrast to other abdominal surgery, rectal cancer resection results in a large de-peritonealised area in the pelvis, irrespective of surgical technique. One hypothesis is that this pelvic de-peritonealised area causes the majority of adhesions following rectal cancer surgery and these adhesions in turn lead to an increase in the risk of small bowel obstruction. This hypothesis offers an explanation of both the higher risk of bowel obstruction reported in this study, with only rectal cancer, compared to previous studies and the lack of difference between the two groups. Bearing in mind that conversion rate in COLOR II was 16%, we also performed as-treated analysis with similar findings. Lastly, since COLOR II was not powered to assess for significance with regard to the secondary endpoints reported in this study, these results may be underpowered. In fact, differences between surgical techniques as to less frequent long-term surgical complications including bowel obstruction can be difficult to demonstrate. These may only become apparent in meta-analyses and larger population-based studies of high quality.

Overall rates of incisional and parastomal hernia found in this study are comparable to existing literature. However, the reported risks of developing both incisional and parastomal hernias vary considerably across publications. No difference was found between the two groups with regard to incisional hernia. However, this study was not power calculated to show a difference in incisional hernias. It is worth noting that a population-based study found a reduced risk in incisional hernia

following laparoscopic surgery for rectal cancer.[108] It was noted that there were numerically less frequent incisional hernias when a Pfannenstiehl, right or left sided lower abdominal incision was used. This is in line with results from previous studies.[109] The risk of incisional and parastomal hernia was increased in patients with a BMI >30 in both the laparoscopic and open group. BMI is known to be a risk factor for developing both incisional and parastomal hernias. Population based studies and metanalyses have demonstrated a decrease in both incisional hernia and small bowel obstruction following laparoscopic compared to open surgery.[72,108]

Regarding the role of robot assisted laparoscopic surgery for colon cancer, a metanalysis indicated improved short-term outcomes compared to laparoscopic surgery, but the level of evidence available is of low quality.[110] With regard to parastomal and incisional hernia, evidence has suggested that performing an intracorporeal anastomosis and enabling the extraction of the specimen through a Pfannenstiehl incision may reduce the risk of incisional hernias after colon cancer resection. However, this can be performed using laparoscopic technique without any additional benefits contributed by robotic assisted laparoscopic surgery. Overall, no high grade evidence has been published to support the use of robotic assisted laparoscopic surgery for colorectal cancer. As health care professionals, we should aim to ensure that the introduction of new surgical techniques are guided by high level evidence and patient centered care rather than allow this to be driven by the interests of surgeons or industry.

CONCLUSIONS

The overall incidence of colorectal cancer has decreased in Sweden over the last decade. There is an increase in the incidence of colorectal cancer in individuals under 50 years of age. The younger population group are more likely to present with a more advanced cancer stage. It is therefore of great importance to raise awareness of the increasing incidence of colorectal cancer in the younger population, both amongst health care professionals and the greater public in order to aid prompt recognition and treatment.

Laparoscopic surgery for colon cancer is advantageous compared to open surgery with regard to short-term clinical outcomes with significantly fewer R1 resections. Minimally invasive surgical resection for rectal cancer offers favorable short-term outcomes compared to open surgery without compromising the oncological resection. Health care services should strive to provide a significant proportion of colorectal cancer surgery using minimally invasive surgical techniques. This does not yet include robotic assisted techniques due to higher costs without proven additional benefit.

Minimally invasive surgery may not affect the long-term risks of bowel obstruction, incisional or parastomal hernia following rectal cancer resection. Further research to better understand the underlying mechanisms of small bowel obstruction and hernia formation is needed to understand how they can be reduced.

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