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Emergent colon cancer and postoperative complications

Risks and management

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LUND UNIVERSITY

DOCTORAL DISSERTATION

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Title and subtitle: Emergent colon cancer and postoperative complications - risks and management

Abstract:

Background:
10-30% of the colon cancer cases present as emergencies, of which 80% are caused by large bowel obstruction (LBO). To overcome the risks associated with emergency resection (ER) the patients can be managed with a staged preocedure or bridge to surgery (BtS). Data in these studies comes from the Swedish Colorectal Cancer Registry (SCRCR) which is proofed to have high validity.

Aims:

I. To evaluate the impact of postoperative complications after curative resection of colon cancer on long-term survival.
II. To compare short- and long-terms outcome after management of acute malignant large bowel obstruction with Bridge to Surgery or emergency resection.
III. To evaluate short- and long-term outcomes following emergent colon cancer surgery depending on sub-specialization of the operating team.
IV. To evaluate the validity of data from the Swedish Colorectal Cancer Registry.

Methods:
Study I-III were retrospective cohort studies of patients operated for colon cancer. Data on short-and long-term outcomes were analysed. In study IV, data from medical files of 700 was randomly selected patients opereated for CRC in 2015 was compared with data in the SCRC.

Main outcome measures: Paper I-III, 5-year overall and 3-year disease-free survival or recurrence-free survival. Postoperative mortality and morbidity. Validity of selected variables in the SCRCR.

Results: Postoperative complication is associated with decreased long-term outcome but not recurrence rate. 5-year overall survival is higher in patients managed with BtS compared with ER. Specialization of surgical team dit not impact short-or long-term survival. Agreement of histopathology and recurrence data in the SCRCR is high, whereas postoperative complication is not.

Importance:
The results of this thesis shows that postoperative complications need to be addressed and treated promptly in attempt to increase survival. BtS has better overall survival and lower stoma rate and may be considered as a primary alternative in the management of malignang LbO. Acute care surgeons treat patient with emergent colon cancer with same result on long-time survival as colorectal surgeons. The validity of data in the SCRCR is very good but care must be taken when interpreting information on postoperative complications.

Key words:

Colorectal cancer, postoperative complications, bridge to surgery, emergency surgery, specialization, survival, validity, cancer registry.

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MADE IN SWEDEN

To my wife Ingibjörg and my late brother Þórarinn, the smartest people in my life.

Table of Contents

List of Papers

I. **Arnarson Ö**, Butt-Tuna S, Syk I. Postoperative complications following colonic resection for cancer are associated with impaired long-term survival. Colorectal Dis. 2019;21(7):805-815. doi:10.1111/codi.14613

II. **Arnarson Ö**, Axmarker T, Syk I. Short- and long-term outcomes following bridge to surgery and emergency resection in acute malignant large bowel obstruction. Colorectal Dis. 2023;25(4):669-678. doi:10.1111/codi.16458

III. ***Arnarson Ö**, Syk I, Butt ST. Who should operate patients presenting with emergent colon cancer? A comparison of short- and long-term outcome depending on surgical sub-specialization. World J Emerg Surg. 2023;18(1):3. Published 2023 Jan 9. doi:10.1186/s13017-023-00474-y*

IV. **Arnarson Ö**, Moberger P, Sköldberg F, Smedh K, Birgisson H and Syk I *A validation of the Swedish Colorectal Cancer Register* Manuscript unpublished

Abbreviations

ASA	American Society of Anaesthesiologists
BMI	Body Max Index
BtS	Bridge to Surgery
DFS	Disease Free Survival
DS	Deviating stoma
CEA	Carino-Embryonic Antigen
CRC	Colorectal Cancer
CRT	Colorectal team
CD	Clavien Dindo
CI	Confidence Interval
CPH	Cox Proportional Hazard model
CT	Computed Tomography
ESGE	European Society of Gastrointestinal Endoscopy
EST	Emergency Surgical Team
FTR	Failure to Rescue
GST	General Surgical Team
HR	Hazard Ratio
ICU	Intensive Care Unit
LBO	Large bowel obstruction
MDT	Multi-disciplinary Team
OS	Overall Survival
OR	Odds Ratio
POC	Postoperative complications
RFS	Recurrence Free Survival
RCT	Randomized Clinical Trial
SCRCR	Swedish Colorectal Cancer Register
SEMS	Self-Expanding Metal Stent
TNM	Tumour Node Metastases
UICC	Union for International Cancer Control

Thesis at a glance

Paper	Aims	Study design	Outcomes	Conclusion
I	To analyse the impact of postoperative complications on long-term survival	Retrospective register-based national cohort study.	5-year overall and 3-year disease-free survival	Postoperative complications are associated with impaired long-term survival. They do not impact recurrence rate.
II	To compare short- and long-term outcomes after management of acute malignant bowel obstruction with bridge to surgery (BtS) or emergency resection (ER)	Retrospective register-based national cohort study	5-year overall and 3-year recurrence-free survival.	BtS is associated with higher overall 5-year survival. There is no difference in recurrence free survival or postoperative mortality rate. Overall complication rate is higher in patients managed with BtS.
III	Evaluate short- and long-term outcomes following emergent colon cancer surgery depending on specialization of the operating team	Retrospective register-based regional cohort study.	5-year overall and 3-year recurrence-free survival. Postoperative morbidity and mortality	There is no difference in short- or long-term outcome depending on surgical specialization. Stoma rate is higher in patients operated by emergency care surgeons
IV	To assess the validity of the Swedish Colorectal Cancer Register (SCRCR)	Validation study. Re-abstracted data from medical files was compared with data in the SCRCR	Exact agreement of non-missing data and the strength of that agreement.	Variables on histopathology and cancer recurrence showed almost perfect agreement whereas the agreement in postoperative complications was weaker.

Introduction

Colorectal cancer

Colorectal cancer (CRC) is the third most diagnosed cancer in Sweden with 6908 cases diagnosed in 2022. The incidence is equal between males and females for colon cancer but slightly higher in men regarding rectal cancer. 75% are over 65 years of age while 5% are under 50 years [1]. Five-year cancer specific survival in Sweden is 65% and correlated to cancer stage at diagnosis. Stage 1 has 95% survival compared to 20% for stage IV [2]. More than one half of all cases and deaths are attributable to modifiable or environmental risk factors, such as smoking, an unhealthy diet, high alcohol consumption, physical inactivity, and excess body weight [3]. It is estimated that heritability of colorectal cancer ranges from 12% - 35%[4].

Colorectal cancer is in earlier stages largely an asymptomatic disease and bowel symptoms usually occur at an advanced stage [5]. The patient typically presents with rectal bleeding, microcytic anaemia, altered bowel habits and chronic abdominal pain [6]. Onset of symptoms should prompt investigation in patients aged 50 or older [7].

Colonoscopy is the method of choice in diagnosing CRC as it allows thorough inspection of the mucosa and detection of lesions [5]. CT colonography can be used as a complementary imaging method for the diagnosis of polyps and colorectal cancer for example after incomplete or inadequate colonoscopy [8]. Imaging methods however are mostly used for accurate locoregional and distant staging [5, 9]. Carcinoembryonic antigen (CEA) concentration is usually checked at the time of diagnosis since an elevated concentration is associated with worse prognosis and might indicate residual disease if not normalised after surgery [10]. Screening of average-risk individuals is an effective method of preventing CRCR and reducing CRC-related deaths[11] and have many countries in Europe and North America initiated population-based screening programs[12].

Early CRC can often be resected endoscopically in an en-bloc manner[5]. For more advanced cancer, surgery with or without adjuvant chemotherapy, depending on cancer stage, is the cornerstone of treatment with curative intent. Radiotherapy with or without concomitant chemotherapy prior to surgery (neo adjuvant treatment) has become standard treatment for high-risk rectal cancers based on preoperative staging[13] and the trend is to also treat colon cancer with neoadjuvant chemotherapy, following the results presented from the FOXTROR trial [14].

Clinical and pathological staging is essential to determine the local and distant extent of disease, which in turn provides a framework for determining prognosis and therapy[15]. Pathological features can be divided into TNM stage, histological and molecular features. AJCC-UICC tumor node metastasis (TNM) staging is the most important pathological classification in most all international CRC guidelines[16, 17]. Histological features include tumor budding, perineural invasion and lymph node positivity and an example of molecular features include microsatellite instability (MSI) and Kirsten rat sarcoma virus (KRAS)[15]. Tumor stage in CRC independently and negatively influence survival. A higher T stage is associated with worse 5-year overall survival (OS) as well as relapse[18, 19]. Regional lymph node involvement is considered the second strongest predictor of outcome in CRC, after distant metastatic spread[18]. Five-year OS in node positive patients ranges from 30-60%, compared to 70-90% in node negative disease[20]. Recurrences rates in node positive CRC patients are around 30-35%, with the majority of recurrences occurring in the first three years following surgical resection [21]. A higher number of involved lymph nodes (pN) and low lymph node yield (<12) is associated with worse prognosis[22]. Studies have also shown that lymph node ratio may be better prognostic indicator than pN [23, 24]. Nodal involvement is an indication for adjuvant chemotherapy to reduce the risk of metachronous distant metastasis[17]. Adjuvant chemotherapy decreases the absolute risk of death by 10-20%[25] and risk of recurrence by 20-30% in node positive disease[21]. Around 25% of patients present with distant metastasis at diagnosis and is stage IV the strongest predictor of prognosis and outcome of colorectal cancer[26, 27].

Tumor size does not determine management in any international guidelines as its prognostication ability in CRC remains controversial. T-stage is determined by depth of tumor invasion through the layers of bowel wall rather than tumor size[28]. Smaller tumors with T4b infiltration and/or lymph node metastases may be associated with worse prognosis regardless of tumor size[29].

Colon cancer emergencies

Despite advancements in cancer prevention and early detection with incorporation of screening programs, the rate of colorectal cancer presenting with acute symptoms requiring urgent surgical treatment remains high or 10-30% according to most studies[30-34]. The tumors are typically of more advanced T stage and higher histologic grade[35, 36] and with higher proportion of patients presenting with liver metastasis compared to patients undergoing elective surgery[37, 38].

The most common cause of colon cancer emergency is bowel obstruction (70-80%), but also perforation and hemorrhage can demand emergent intervention[39, 40]. Emergency intervention is associated with high rates of morbidity and mortality partly due to the critical state of many of these patients[32, 37, 41]. Besides emergency surgery alone, functional health status, frailty, comorbidities such as cardiorespiratory, metabolic and renal diseases are all predictors and independent risk factors for postoperative morbidity and mortality[42, 43]. The 30-day and 90-day mortality rate is 5.5%-9.9% and 11.1%-21.0% after emergency resection [44-46] compared to 0.8%-1.1% and 1.7-3% after elective surgery respectively [46, 47]. In cases of perforation the mortality rate is 5% in contained intra-abdominal collection[48] with increase to 19-40.5%[48, 49] in case of diffuse faecal peritonitis.

Regarding long-term oncological outcomes, the results are more elusive. While some studies have identified emergency surgery as a negative predictive factor for recurrence and survival [32-34, 50], other studies have, especially after adjusting for baseline characteristics[30, 37, 51].

Presentation of complete bowel obstruction is often delayed by a gradual onset of symptoms. The patient usually complaints of difficulty with bowel movements and may have developed significant abdominal distension at presentation. Usual findings on examination are tenderness, abdominal distension and hyperactive or absent bowel sounds[52]. When perforation occur at the tumor site, peritoneal contamination is usually localised. Proximal perforation however can result in faecal contamination with diffuse peritonitis and septic shock. On examination the abdomen may be localised of diffusely tender with guarding or rebound tenderness[53]. A patient that presents with such late symptoms often have physiologic derangements, dehydration and electrolytes abnormalities, poor nutrition, and neglected comorbidities[40]. Management of emergent colorectal cancer is therefore challenging in terms of clinical severity, diagnostic and therapeutic options.

Diagnosis

Abdominal CT scan represents the imaging test of choice in current clinical practice. It provides the clinician with an optimal grade of information, particularly regarding the complications of cancer-related large bowel obstruction and staging of the neoplastic disease[53]. When there is a suspicion of bowel perforation, abdominal ultrasound or plain X-ray can be used instead to reduce mobilization of a critically ill patient and delay of treatment. Colonoscopy usually has a limited role in diagnosis of LBO mainly due to lack of availability in the emergency setting. In a stable patient it enables direct visualization of the tumor and to explore the various etiologies of obstruction as well as secure biopsies of the lesion if the treatment plan is a two stage strategi[53-55].

Treatment

In case of cancer-related colon perforation a prompt combined medical and surgical treatment is advised to control the source of sepsis. Obstruction situated in the right colon, between cecum and the splenic flexure, can be in most cased be safely treated with right hemicolectomy with primary ileocolic anastomosis. The rate of anastomotic leak in emergent circumstance is 0.5%-4.6% compared to 0.5-1.5% in elective ones according to studies[56]. In case of critically ill patient with impaired vital functions an appropriate initial management can be loop stomal or in case of haemodynamic failure and/or bowel perforation a right hemicolectomy with end-ileostomy[55].

The higher incidence of left sided LBO compared to the right side is explained by the luminal discrepancy where the diameter of the colon is narrowest between the splenic flexure and the rectosigmoid junction[55] as well as the more fluid consistency of the bowel contents in the right colon. Treatment options of left colonic obstruction are related to both the general and local consequences of the obstruction and to the operative risk of the patient. There are two main treatment options. Direct resection of the tumor and a two-stage procedure where the bowel is decompressed at an initial intervention, either with a diverting stoma (DS) or placement of self-expanding endoluminal metal stent (SEMS). Secondary final resection surgery is performed electively after the patient's physiological status has optimized and after staging of the neoplasia[57]. This method is also called Bridge to Surgery (BtS) and effectively delays surgery and therefore aiming at reducing the operative risk that is associated with emergent surgery.

Emergency resection.

Most patients that need intervention for acute colon cancer undergo emergency resection (ER), which objective is to simultaneously achieve a radical tumor resection and resolving the emergency problem. The surgeon can choose to either perform anastomosis if the bowel segments are healthy and non-distended[58], or defer from restoring bowel continuity, a practice most used in high-risk patients[59]. Hartmann´s procedure is currently the most common operation performed for distal colon carcinomas emergencies[54, 60]. Resection of the tumor is completed by proximal colostomy and closure of the distal colonic segment. It is a safe method and eliminates the risk of anastomotic leak[59, 61, 62]. Studies have also demonstrated its feasibility of emergency resection following standard oncologic principles of high ligation of the vascular pedicle, retrieval of at least 12 regional lymph nodes and en bloc resection of adjacent tissues for negative margins[34, 63]. However, studies have shown that 35-44% of patients never underwent restoration of continuity, due to advanced disease, complications from treatment and poor performance status[64, 65]. Hartmann´s procedure is by many considered the treatment of choice for older patients with high ASA scores, advanced obstructions and patients with underlying medical comorbidies[54, 66].

In case of ischemia in the right colon or a mural laceration and subsequent risk of perforation a subtotal or total colectomy with ileocolic (or ileorectal) anastomosis can be performed. This method has the advantage of performing an anastomosis in a well vascularized terminal ileum and also removing any synchronous cancer which can be present in about 7% of cases[55, 67]. Resection and primary anastomosis (RPA) is feasible in appropriately selected patients as it can reduce length of stay and number of operations with similar rates of morbidity and mortality[68, 69]. Studies have shown the rate of anastomotic leak in emergency settings to be 2.2% to 15.8%[69, 70] compared to 1.9%-8%[41, 71] in elective colon resection and there is good evidence supporting that the presence of feces in the large bowel does not influence the rate of anastomotic leak[72, 73]. There has been an increasing trend towards one-stage resections for left-sided obstruction, despite the lack of strong evidence and the choice seems generally depend on the individual surgeon's judgment[53]. It is important that the advances of RPA are weighted together with the potentially catastrophic result from anastomotic leak in a fragile patient. Many parameters, related to both the surgeon and the patient should therefore be considered before deciding to perform an anastomosis[53, 68, 69]. Hartmann´s procedure could be more appropriate for high-risk patients in an emergency setting by unspecialized surgeons.

Bridge to Surgery

Many patients who present with acute malignant LBO have a deteriorated physical condition after several days of reduced intake and vomiting before presentation. ER is associated with high risk of mortality and morbidity, especially in elderly and frail patients[74]. BtS is a concept of staged approach toward a definitive oncologic resection. Initial decompression overcomes the risks of ER by addressing the immediate problem of colonic obstruction and allows for optimization of the clinical condition of the patient. Furthermore, accurate tumor staging can be achieved, and neo-adjuvant treatment can be considered if indicated[75]. BtS can also facilitate a laparoscopic resection with primary anastomosis[76]. Decompression of the colon can be accomplished either by a stoma or placement of a self-expandable metal stent (SEMS).

DS has been the historical BS approach before the introduction of SEMS. Loop colostomy is an established treatment options for obstructing distal carcinoma. The obstruction is managed in the first stage with the creation of a proximal loop colostomy. In the second stage, the tumor is resected, and the stoma reversed. Alternatively, colostomy reversal can be performed as a third stage. Lopp ileostomy is usually discouraged, because the presence of a competent ileocecal valve may prevent adequate alleviation of the distal obstruction[40]. Loop colostomy can be appropriate in cases of locally advanced tumors invading adjacent organs limiting the feasibility of a proper oncologic resection in an emergency situation[40]. The literature comparing DS and ER is scarce but a few studies have shown either no difference[77] or lower postoperative mortality and better 3-year overall survival in patients operated with diverting stoma[76].

SEMS

Self-expandable metal stent for the management of acute large bowel obstruction was first described in 1990 by Tejero and co-workers[78]. It has since then seen growing use as palliation for malignant LBO as well as bridge to surgery. SEMS are composed of a radiopaque, woven, metal mesh with a cylindrical shape that exerts self-expansion forces. Unexpanded stent is collapsed and can fit through the channel of an endoscope. When in place it expands through a deployment device placed at the end of the SEMS and are held in place against the bowel wall by friction. The stent may be coated to prevent tumor from growing into the stent although studies have shown higher incidence of stent failure due to migration in coated stents[79]. Uncoated stents are therefore mostly used in large bowel obstructions.

After determination of the location and nature of the obstruction, a colonoscopy is performed. Visualization of the site of obstruction provides the opportunity for tissue biopsy. If the colonoscope is easily passed through the site of obstruction, there is an increased risk for stent migration[80]. Stent should not be placed in patients with perforation, intra-abdominal abscess, intestinal ischemia and coagulopathy. Placement of stents within 3-4 cm of the anal sphincter is not advocated because of risk of bleeding, pain and incontinence[81]. Placement of SEMS is a complex procedure especially if colon cannot be prepped before the intervention, if the obstruction is complete and if the tumor is located within a flexure or area of angulation[82].

Complications related to SEMS placement are mainly migration, perforation and bleeding and can be divided into early and late. Studies have shown overall complication rate of up to 25%[83]. Perforation, a serious complication associate with high mortality rate, has an median rate of 4,5%[84]. Colonic stenting should therefore be performed by endoscopist who demonstrate a good expertise and some studies recommend a minimum number of procedures[85].

Studies have reported better clinical outcomes of SEMS placement compared with ER, including lower postoperative morbidity, lower rate of stoma formation and shorter hospital stay[86, 87]. Other studies have shown technical success rate of 85-96.2%[83, 84] and that resection with primary anastomosis as a one-step surgery was successful in 60%-85% of patients[88-90]. It is though advisable that benefits of delaying surgery must be weighed against the risk of stent complications[82].

There have been concerns that stent induced perforation and tumor manipulation could lead to dissemination of tumor cells, with negative impact on oncologic outcome[91, 92]. Studies on outcomes of SEMS as BtS have shown conflicting results, with the main concerns that it may jeopardize oncological and survival outcomes in those with curable disease[83, 93, 94]. A meta-analysis and a retrospective observational study with propensity score matched comparison of BtS and ER reported increased rate of overall recurrence in BtS compared to ER[95, 96]. Other studies have reported no significant difference in overall recurrence rates[44, 97]. It has also been shown that the use of SEMS compared to ER is safe regarding short-term outcomes[98-101].

The results of previous studies on outcome comparing BtS and ER are heterogenous and based on small non-randomized population, often single center studies. Regarding meta-analyses that only included randomized controlled trial, it has been suggested that pooling of small RCTs may be underpowered and unreliable mostly because of study and publication bias[102]. Meta-analysis of observational studies only, still show conflicting results regarding outcome of BtS and ER. Perhaps the last story has not been told and there is still a need for cohort studies describing the use of SEMS and outcome in daily practice.

Ultimately, the best management of colon cancer emergencies must be tailored to each specific scenario and care must be individualized to the patient, the experience of the surgeon and the resources available at the facility.

Postoperative complications

A postoperative complication (PC) can be defined as any deviation from the normal postoperative course[103]. Studies estimate that 7-28% of patients undergoing major surgery will experience a postoperative complication[104-106] and that overall postoperative mortality rate varies from 0.79-5.7%[107]. Further, there is a strong inverse relationship between hospital volume and mortality[108]. In colorectal surgery, studies have shown overall mortality rate from 1-16.4% with morbidity rates as high as 35%[109]

Complications can occur after any operation and surgeons must be versed in anticipating, recognizing, and managing them. The spectrum of these complications ranges from the relatively minor, such as a small postoperative seroma, to the catastrophic, such as postoperative myocardial infarction or anastomotic leak. The management of these complications also spans a spectrum from nonoperative strategies to those requiring an emergent return to the operating room.

A classification of POC was first proposed in 1992 by Clavien et al. in an effort to standardize reporting of postoperative complications[103]. The classification system was later improved by recommendations from Dindo et al. in 2004[110]. Grading of surgical complications before the suggestion of the Clavien-Dindo (CD) classification lacked standardization and relied on subjective terminology such as mild, moderate and severe[110]. This limited the impact of evidence-based medicine in improving surgical outcomes because of difficulty in the interpretation of data. CD classification is today widely used in scientific literature as well as quality registries. It groups complications based on the level of intervention required to resolve them[110], and benefits from simplicity and ease of use, both of which contribute its to high inter-rater reliability[35]. It has been validated for use in many specialties due to strong correlation with key outcome measures including length of stay and postsurgical quality of life[111, 112]. CD classification system grades complications from I to IV (Table 1) where grade I requires minor deviations from the planned postoperative course and grade V indicates the death of a patient resulting from surgical complications.

Table 1. Clavien-Dindo classification system of postoperative complications.

Grade	Definition
I	Deviation from normal postoperative course without need for pharmacological treatment or surgical intervention
II	Requiring pharmacological treatment, including transfusion or total parenteral nutrition
III	Requiring surgical, endoscopy, or radiological intervention
IIIa	Intervention under general anesthesia
IIIb	Intervention not under general anesthesia
IV	Life-threatening complication requiring management in ICU
IVa	Intervention under general anesthesia
IVb	Multiorgan dysfunction
V	Death

Numerous patient factors have been found to increase the risk of postoperative complications. Many of these factors are associated with poor functional status and overall poor health [109] such as dependent functional status, American Society of Anesthesiologists (ASA) class III-V, older age and residual neurological sequela after stroke[106]. Overall frailty has been found to be associated with PC[104]. Frailty is defined as a clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with every day or acute stressors is compromised[113]. A study of patients over 65 years of age demonstrated a 2.54-fold increased risk in frail patients as compared with robust patients[114]. It has been shown that patients that improve their functional status with pre- rehabilitation are less likely to experience complications which required ICU admission or reoperation [115].

PC account for a large financial burden in the form of additional health care expenses especially when a patient requires Intensive Care Unit (ICU) treatment, reoperation or readmission[116]. While the incidence of PC is correlated to the complexity of the surgery, the economic cost depends on the type and severity of the complication and are due mainly to prolonged hospitalization[117]. Patient death due to postoperative complications has a negative economic effect. A cost analysis study showed that hospital costs due to patient death were significantly higher than the costs of CD grade I-IIIb complications although lower than those associated with grade IV[118].

According to one study do 15.4% of all hospital related injuries or complications happen in the surgical wards in Sweden, although the rate of postoperative complications was unknown. 51.7% of the injuries lead to delayed hospital discharge and 5.8% of the injuries were permanent or lead to patient death. It was concluded that 62.5% of the total injuries were preventable and the extra cost of hospital care estimated to be around 1.4 milliard SEK if only delayed discharge was taken into count[119]. Another study from Linköping hospital in 2009 showed that 23% of all patients admitted to the surgical ward for more than 5 days suffered injuries or complications and the rate of POC was 30%[120]. According to the SCRCR, the annual rate of postoperative complications after colorectal surgery in Sweden is approximately 28% in the past 10 years of which 8% were graded as severe[121].

Failure to rescue (FTR) is defined as death after a complication. While patient characteristics may predict adverse postoperative occurrences, hospital characteristics may ultimately be responsible for preventable deaths after those occurrences take place[122]. Ghaferi et al analyzed hospital characteristics associated with decreased FTR rates. Hospital with more than 200 beds, teaching status, high hospital technology and increased nurse to patient ratios were associated with reduced FTS rates after pancreatectomy[123]. Also, studies have shown significant difference between low and high FTR rates in hospitals with a closed ICU model and a greater proportion of board-certified intensivists[124]. To reduce FTR it is important to promote a safety culture that promotes time-critical communication and effective management of postoperative complications [125].

Surgical specialization

Mortality, surgical complications, and frequent re-hospitalization are related to the quality of care and are important quality indicators. Studies have shown that hospital volume is related to surgical outcomes due to differences in perioperative morbidity and mortality for patients treated at high-volume versus low-volume facilities for different surgical procedures[126-129]. The volume-outcome relationship has become relevant in regards of preventing postoperative complications. Measures of surgical quality have the potential of development and implementation of quality improvement protocols. Similarly to the high hospital volume, high volume surgeons have significantly better outcomes than low volume surgeons in terms of better short term outcomes as well as hospital costs for many procedures[130, 131]. Therefore, a higher-volume hospitals and surgeons that are more experienced could be a superior combination and have a greater likelihood of post-surgery success for different surgical procedures. High volume centers may have better infrastructure, more resources and wider specialist and technology-based services and greater resources for dealing with postoperative complications. These factors in combination with skill and experience of the individual surgeon can affect the outcome of care[132]. In cancer surgery volume-outcome relationships may, besides focusing on measures of surgical safety such as morbidity and mortality, also focus on quality measures such as disease free and overall survival. An association between volume and outcome has been reported for esophagectomy, pancreatectomy and liver resection [133-135].

The relationship between hospital volume-outcome in colorectal cancer surgery has previously been unclear[136] but recent studies point toward more favorable outcomes for patients treated with by high-volume surgeons or in high-volume hospitals in regard to both short- and long-term outcome[137-140]. In the past decades there has been a trend towards organized clinical units of surgeons with a special interest in and professional activity focused on specifically coloproctology and have several studies have shown improved outcomes from fully trained colorectal surgeons[141-144].

Limited conclusion however can be drawn from the literature concerning the role of colorectal specialization in regards to outcomes in colon cancer emergencies although recent studies point to the favor of colorectal surgeons compared to general surgeons regarding short term outcome[142, 144] but more elusive regarding oncologic outcomes[145].

General surgeons in Sweden that specialize in colorectal surgery are encouraged to take the accreditation exam through the European Union of Medical Specialists. Today 188 surgeons in Sweden are accredited colorectal surgeons[146]. There are two types of high-volume hospitals in Sweden: university hospitals and county hospitals. The surgical department at the university hospitals are often highly specialized and take referrals from other regions while the county hospitals perform high volume surgery of standard cases, and often take referrals from the university Hospital that do not require highly specialized treatment. These hospitals usually have a dedicated surgical ward with specially trained nurses as well as accredited colorectal surgeons. The smaller low-volume hospitals usually don´t have this division into specialties and the rate of accredited colorectal surgeon may be lower although all surgeons treating patients with colorectal disease are encouraged to take the accreditation exam. There has been a shift in hospital volume in Sweden the past 15 years. The volume of colon cancer operation at some of the university hospitals has decreased but increased in the county hospitals. Part of the reason for this is that university hospitals are operating more rectal cancer and probably other highly specialized surgery. The number of hospitals performing surgery for colon and rectal cancer has also decreased by 17% (58 to 48) and for rectal cancer by 28% (47 to 34) between 2009 and 2022[121].

Patients requiring emergency surgery represent a distinct population with a unique physiology compared with patients requiring similar but elective operations[147, 148]. Acute care surgeons provide time-sensitive care for both trauma and non-trauma surgical emergencies and has acute care surgery become widely accepted as a surgical specialty encompassing three areas of surgical practice: trauma surgery, emergency general surgery and surgical critical care[149-151]. The association of Swedish Emergency Surgery and Traumatology was formed in 2017 with the intent to promote the development of emergency and trauma surgery[152]. A three-year accreditation program has been founded and includes 9 weeks of courses over a three-year period and requires a minimum count of various types of emergency operations. European accreditation emergency and trauma surgery[153] is also available although it is unclear how many Swedish surgeons have taken the exam. It is thus clear that the field of emergency surgery is growing in Sweden and Europe.

The few available studies on surgical specialization on outcome after colorectal cancer surgery in Sweden have shown better outcomes for patients operated by colorectal surgeons in elective cases[154] but not after operation for acute colon cancer[155]. It is therefore clearly a need for more research regarding the impact of surgical subspecialization on outcome after emergent colon cancer surgery in Sweden.

Cancer registries

A clinical register is defined as "an organized system that uses observational study methods to collect uniform data to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves predetermined scientific, clinical, or policy purposes[156]. Clinical registries serve many purposes including: describing the course of disease and care patterns; understanding variations in treatment and outcomes; determining clinical- or cost effectiveness of services and products; monitoring safety; and measuring quality of care[157]. Cancer registries receive and collect data about cancer patients. They are population-based registries that record all cancer cases in a defined population. Cancer registries are designed to determine cancer patterns among various populations or sub-populations, monitor cancer trends over time, guide planning and evaluation of cancer control efforts, help prioritize health resource allocations, and to advance clinical, epidemiological, and health services research. Cancer registries maintain data on all patients diagnosed and/or treated for cancer[158]. Cancer quality registries collect more specific information, including stage of cancer, treatment, prognostic characteristics and patient outcomes[159]. The Swedish colon cancer registry is a nationwide quality registry launched in 2007 and later merged with the Swedish Rectal Cancer Registry, which started in 1997, forming the Swedish Colon Cancer Registry (SCRCR). All invasive colorectal cancers except autopsy findings are registered prospectively by surgeons, radiologist, pathologist, and oncologist. The register has a coverage of more than 99% of all patients registered compared with the Swedish Cancer Registry[160]. Recorded data include basic patient characteristics, preoperative staging, neoadjuvant therapy, surgery, pathology, postoperative complications, and adjuvant therapy. Follow-up data is registered at one, three and five years after surgery including date of recurrence diagnosis. Data on survival is linked to the Swedish Cause of Death registry. The SCRCR has shown to have a high degree of completeness and validity[160, 161].

Clinical research based on registry data usually are observational cohort studies that are longitudinal and aim to collect data on both the exposure(s) to therapy and the outcome(s) of interest. These studies are dependent on the accuracy and completeness of collected clinical data[162]. While registry studies usually are retrospective the data inputted into the cancer registry itself is done prospectively. Registry studies can therefore be less affected by the bias often connected to retrospective studies such as recollection bias, poor inter-rater reliability and unavailability of data for many subjects[163]. Registry based cohort studies with "real life data" are invaluable tool in measuring the impact of introduced treatment and methods in clinical practice in a population compared to RCT that have the inherent risk of selection bias.

Aims of the thesis

This thesis investigates impact of post operative complications on outcome after colon cancer surgery, outcome after treatment of emergent colon cancer with bridge to surgery technique as well as outcome depending on subspecialization of the surgical team treating the patient. As the thesis relies on registry data a validation of the Swedish Colorectal Cancer Registry was performed.

Specific aims:

I. To analyze the impact of postoperative complications after curative resection of colon cancer on long term outcomes.

II. To compare short- and long-terms outcome after management of acute malignant large bowel obstruction with Bridge to Surgery or emergency resection.

III. To evaluate short- and long-term outcomes following emergent colon cancer surgery depending on specialization of the operating team.

IV. To evaluate the validity of data from the Swedish Colorectal Cancer Registry by a validation process.

Methods

Paper I

This was of retrospective design and based on a national cohort of prospectively registered patients between 2007 and 2009. SCRCR was used to identify patients eligible for inclusion. All patients with stage I-III colon cancer were evaluated for inclusion. Patients that were not radically resected according to both macroscopically by the surgeon and microscopically according to the pathology report were excluded.

Paper II

This was of retrospective design and based on the same population as in paper I. All patients with malignant large bowel obstruction were evaluated for inclusion. All patients that underwent emergent resection (ER) were included in the ER group. Patients that were, with curative intent, treated with temporary decompression of colon prior to definitive resection surgery were included in the BtS group. Data on complications and length of stay regarding the decompression procedure in the BtS group was retrieved from medical files, but all other data regarding operation and follow up came from SCRCR.

Paper III

This was of retrospective design and based on a regional cohort of prospectively registered patients between 2011 and 2016 in the southern region in Sweden. SCRCR was used to identify patients eligible for inclusion. All patients that underwent emergent colon cancer resection were included. Data on which operating team treated the patient was retrieved and the cohort was divided into three groups: Treatment by Colorectal team (CRT), Emergency surgical team (EST) or General surgical team (team).

Paper IV

To evaluate validity of the SCRCR re-abstracted data from medical records were compared to the reported data in the SCRCR. A two-stage cluster sampling plan was used to randomly select 700 cases of colorectal cancer diagnosed in 2015. The re-abstracted data was entered into a specially designed module, blinded for earlier registered data, in the National Information for Cancer Care (INCA) platform and subsequently merged with the originally recorded data to calculate exact data agreement. Exact agreement corresponds to the proportion of cases which data recorded in the SCRC is the same as in the validation data set. Only non-missing data was included in the calculation of exact agreement.

Statistical analysis

The variables in this thesis were typically considered non-parametric. Continuous data was expressed as mean with standard deviation (paper I) or as median and range (paper II and III). Categorical data was expressed as numbers and proportion in percentage. For group comparison, Pearson´s chi-square test was used for categorical data and Kruskal-Wallis test (paper I&III) or Mann-Whitney U test (paper II) for continuous data. Kaplan-Meier curves were used to describe overall, disease-free and recurrence-free survival and analyzed using the log-rank test to determine the statistical significance of differences (paper I-III). The Cox proportional regression analysis was used to calculate hazard ratios for survival and recurrence adjusted for potential confounders. A p-value less than 0.05 was considered statistically significant and the 95% confidence interval is presented when appropriate. In paper IV, Cohen´s Kappa (k) coefficient was used to calculate the strength of agreement. The cut-off values according to Landis and Koch were used for qualitative interpretation of the kappa coefficients, i.e. κ = 0–0.20 (slight agreement); 0.21–0.40 (fair agreement); κ = 0.41–0 .60 (moderate agreement); κ = 0.61–0 .80 (substantial agreement) and κ = 0.81-1.0 (almost perfect agreement). For numerical variables the Pearson´s correlation coefficient was used. Statistical analysis analyses were performed using SPSS (IBM SPSS version 25, Armonk, NY, USA). Kaplan–Meier figures were generated with STATA Statistical Software: Release 13 (StataCorp LP, College Station, Texas, USA).

Postoperative complications

Clavien-Dindo grading classification system was not incorporated into the SCRCR until 2010. For study I and II all postoperative complications were therefore arranged into two categories, severe and non-severe, where severe complications included anastomotic leakage, sepsis, intra-abdominal infection, any complication requiring reoperation or unplanned admission to the intensive care unit. All other complications were considered as non-severe. In study III complications were graded according to the Clavien-Dindo classification.

Survival analysis

Survival analysis concerns the follow-up in time of individuals from an initial exposure until a discrete event. It can be used to describe and compare survival of one or more group of patients. In randomized clinical trials it is used to compare the occurrence of outcomes in patients receiving different treatments to establish which is the most effective[164]. In observational research, as is in the case of this thesis, exposure is observed instead of intervention.

Survival analysis is used when considering the occurrence in a population of a binary outcome or event that’s either present or absent, for example death or cancer recurrence. This event is also called dependent variable whereas the exposure is called independent variable. Censoring is a concept that applies subjects in the cohort who never suffer the event of interest. In this thesis it applies to patients that are lost to follow up or are alive and/or have not been diagnosed with cancer recurrence. Survival time is the interval between the start of follow-up for that subject until the occurrence of the event of interest or until censored. In this thesis, follow-up starts on the day of operation.

Kaplan-Meier is the most widely used survival analysis technique in randomized controlled trials and observational research. It considers at different points the number of patients remaining in the cohort and the cumulative number of events that have occurred up to that point. The incidence rate as function of time is calculated by putting the observation in ascending order of time until occurrence. Baseline observation of each patient is set as time 0 (figure 1). After arranging all data points, the incidence rate is calculated at each occurrence of the event, followed by survival curve estimation. Kaplan-Meier survival analysis is used to test for significant differences between survival curves and in median or mean survival time and therefore useful in studies focusing on survival time, i.e. time to the occurrence of the event of interest. The most used method of comparing two or more Kaplan-Meier curves is the log-rank method[165, 166].

In paper I overall survival (OS) and disease-free survival (DFS) was used as survival endpoints. OS was measured from the date of surgery to death of any cause whereas DFS was measured from date of surgery to death of any cause or cancer recurrence. In paper II and III OS and recurrence-free survival (RFS) were calculated, where RFS was measured from date of surgery to cancer recurrence.

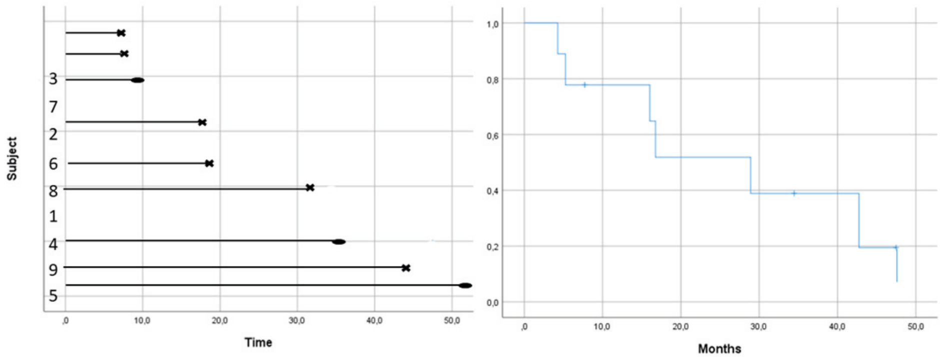


Figure 1. Data arranged for Kaplan-Meier analysis. Observations are rearranged to start at zero. Events are denoted "X" and censored data are denoted "O". Data from the figure on the left produces survival curve on the figure to the right generated using the Kaplan-Meier methodology.

Multivariate survival models can be used where there is a desire to quantify the size of relative differences between groups, where the existence of strong prognostic indicators could be biasing the results, or where there is a desire to quantify the impact of other prognostic indicators. Multivariate survival analyses are very useful in observational studies such as in this thesis where the nature of the data means there are likely to be confounding variables, a variable that can both impact exposure and outcome without being in the causal pathway. The most widely used technique is the Cox Proportional Hazard Model (CPH). The technique works by modelling the hazard function or a subject´s risk of suffering the event of interest at any given time during the follow-up. The CPH model is based on two main assumptions: 1) the survival function is an exponential function and 2) the hazard ratio for the two compared groups is constant throughout the study period. The null hypothesis for comparison of two survival curves is that the hazard ratio (HR) for the two groups is 1[165]. In the CPH regression model, result is derived from the comparison between the risk levels of the occurrence and non-occurrence influenced by a variable which could affect the outcome[167]. The result is an estimate of the hazard ratio of that variable and is calculated as the corresponding regression coefficient in the regression model. If the hazard ratio of a variable is greater than 1 and poses statistically significance, that variable contributes to increasing the probability of occurrence of the event.

Missing values

In any study design, especially cohort studies, with routinely collected data, missing values are unfortunately unavoidable. There are three main types of missing data: missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR)[168]. With MCAR the underlying reasons for data being missing are independent of known and unknown patient characteristics. Patient characteristics will, therefore, be similar between subjects with and without missing data. MAR is a usual reason for data being missing in clinical research and are often related to several known patient characteristics. The third type, MNAR, is the most complicated type of missing data as here the underlying reason for data being missing are related to unknown patient characteristics. The most common methods of dealing with missing data is so called complete case analysis, where patients with missing data are excluded from the analysis. This not only leads to a smaller sample size and therefore may reduce statistical power, but it can also lead to biased results. Another method is mean substitution where missing observations for a certain variable are replaced by the average of observed data for that variable in other patients. This can also lead to biased results when the patients with missing data have different patient characteristics compare with those with available data[168, 169]. Multiple imputation is another method of handling missing data by estimating and replacing values many times. It fills in missing values by generating plausible numbers derived from distributions of and relationships among observed variables int the data set[170].

In study I-III in this thesis the rate missing values is reported and is generally low and assumed to be MAR. Variables with missing value were therefore included in all analyses except in Paper II where multiple imputation was used for ASA score because of high rate of missing data in the ER group.

Ethical considerations

Ethical approval for study I-III was granted by The Regional Ethical Review Board in Lund and by the Swedish Ethical Committee for study IV. Data extraction from the SCRCR (paper I-III) and review of medical records (paper IV) were conducted in accordance with these approvals. Owing to the retrospective design of the studies, no treatment intervention was made.

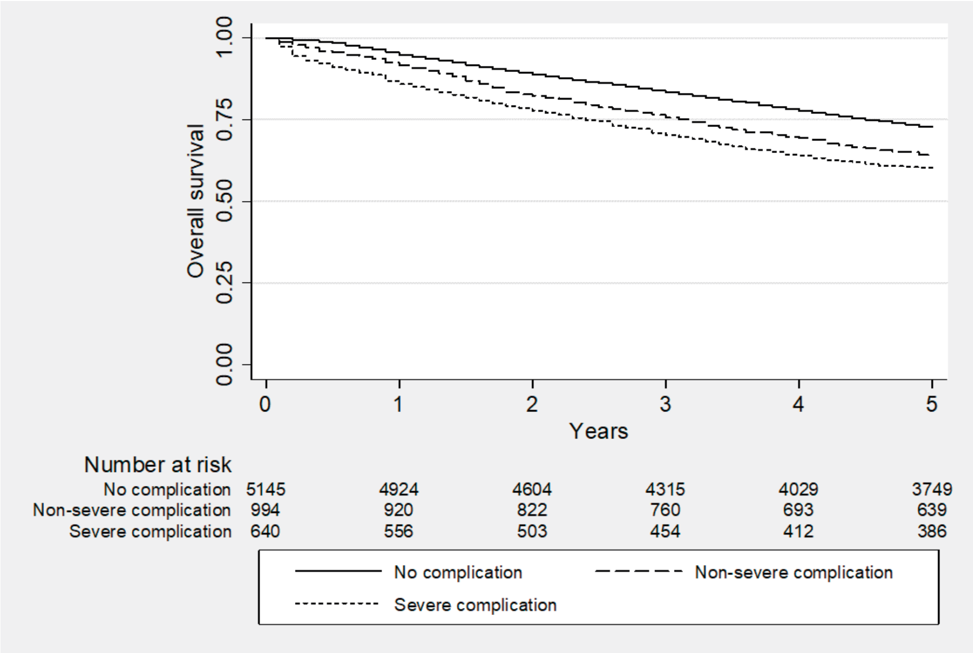
Results

Paper I

A total of 6779 patients were included in the study. Of these, 76% had no complications, 15% had non-severe complications and 9% had severe complications. Patients that suffered postoperative complications were older, had higher ASA score and more frequently men. 80.3% of the patients with severe complications underwent reoperation.

The 5-year overall survival rate was 60.3%, 64.2% and 72.8% in patients in the severe-complication group, non-severe complication group and no complication group respectively (*p*=<0.05). The 3-year disease-free survival rate was 66.8%, 70.9% and 77.8% respectively (*p*=<0.05), (Figure 2). There was no significant difference in recurrence rate between the groups, ranging from 13.0% - 14.6% even though significantly fewer patients who suffered postoperative complications received adjuvant chemotherapy.

Both severe and non-severe complications were found to be risk factors for decreased 5-year OS in a multivariate Cox proportional analysis after adjusting for potential confounders (HR 1.34, 95% CI 1.13-1.59 and HR 1.17 95% CI 1.10-1.34 respectively). Similarly, patients in the complication groups had higher risk of impaired 3-year DFS (HR 1.37, 95% CI 1.14-1.64 and HR 1.24, 95% CI 1.06-1.45), (Table 2).



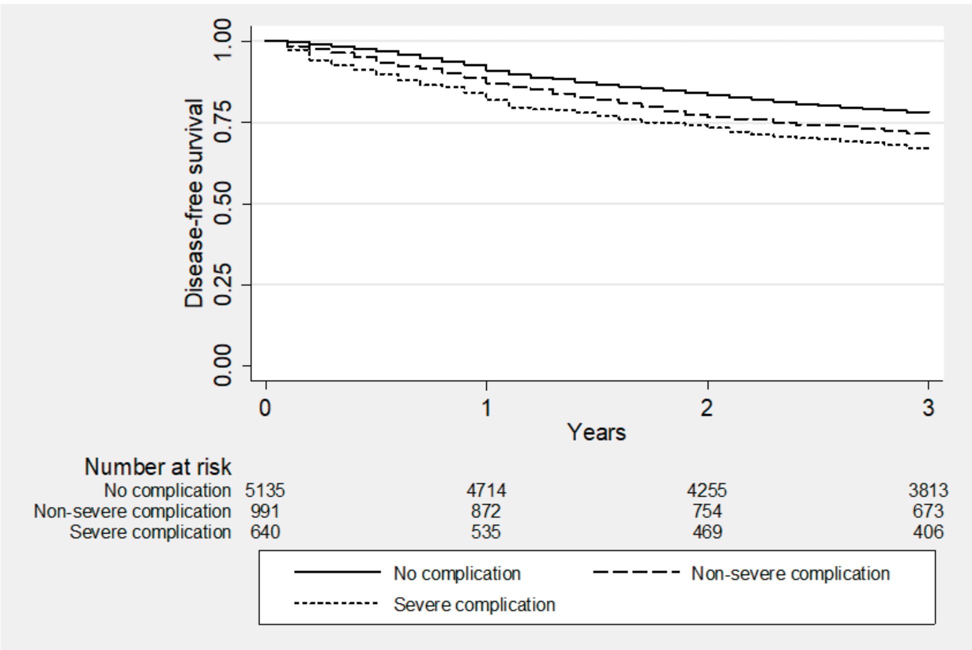
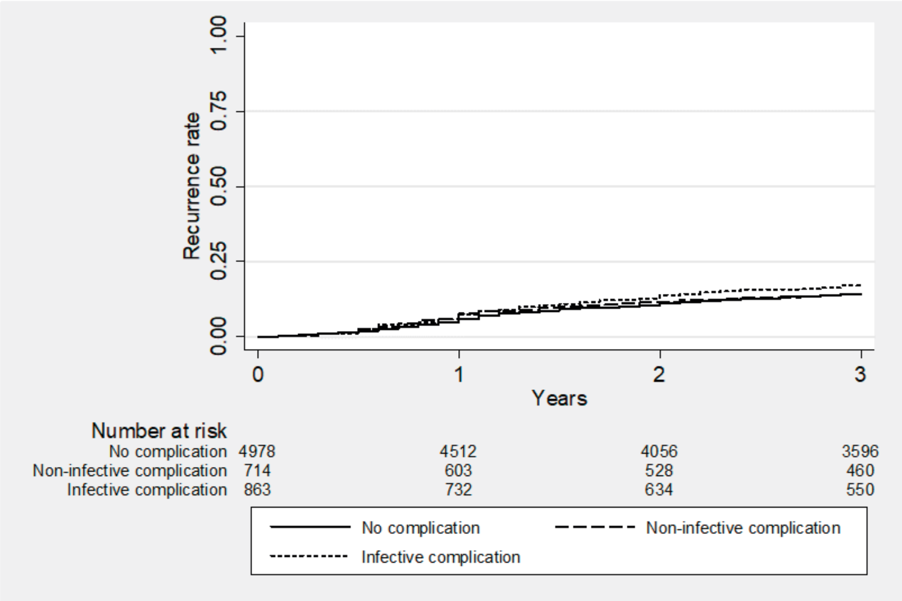


Figure 2. Kaplan-Meier survival estimates for 5-year overall and 3-year disease-free survival stratified by severity of postoperative complications within 30 days after resection for colon cancer

Table 2. COX proportional hazard regression analysis of factors associated with 5-year overall and 3-year disease free survival.

	5-year overall survival		3-year disease free survival	
	Univariate HR (CI 95%)	Multivariate HR (CI 95%)	Univariate HR (CI 95%)	Multivariate HR (CI 95%)
Gender				
Female	1.00	1.00	1.00	1.00
Male	1.2 (1.10–1.30)	1.32 (1.20–1.47)	1.2 (1.06–1.38)	1.24 (1.10-1.40)
Age category				
≤65	1.00	1.00	1.00	1.00
66-80	1.76 (1.54–2.00)	1.65 (1.41–1.94)	1.26 (1.11–1.43)	1.34 (1.40-1.56)
>80	4.04 (3.54–4.60)	3.28 (2.76–3.90)	2.12 (1.85–2.42)	2.03 (1.71-2.41)
BMI				
<18	1.00	1.00	1.00	1.00
18-25	0.50 (0.37–0.67)	0.47 (0.35-0.64)	0.68 (0.47-0.99)	0.68 (0.47- 1.00)
>25	0.41 (0.30–0.55)	0.43 (0.17-0.59)	0.61 (0.42-0.88)	0.64 (0.44-0.94)
ASA score				
I-II	1.00	1.00	1.00	1.00
III	2.57 (2.35–2.82)	1.91 (2.70–2.14)	1.96 (1.77–2.17)	1.60 (1.42-1.82)
IV	4.26 (3.48-5.22)	2.90 (2.25-3.74)	3.30 (2.64-4.13)	2.49 (1.88-3.29)
Emergent surgery				
No	1.00	1.00	1.00	1.00
Yes	2.04 (1.84-2.26)	1.65 (1.42-1.91)	2.39 (2.14–2.67)	1.93 (1.66-2.26)
Tumor grade				
High/moderate	1.00	1.00	1.00	1.00
Low	1.50 (1.35–1.66)	1.23 (1.08-1.39)	1.48 (1.32–1.67)	1.16 (1.02-1.35)
T stage				
1-2	1.00	1.00	1.00	1.00
3	1.42 (1.25–1.6)	1.09 (0.94-1.27)	1.71 (1.47–1.98)	1.33 (1.10-1.60)
4	2.60 (2.23–3.02)	2.00 (1.66-2.43)	3.44 (2.89–4.09)	2.32 (1.87-2.90)
N stage				
0	1.00	1.00	1.00	1.00
1-2	1.81 (1.66–1.98)	2.00 (1.81-2.27)	2.2 (1.20–2.43)	2.07 (1.83-2.34)
Adjuvant chemotherapy				
No	1.00	1.00	1.00	
Yes	0.67 (0.49-0.9)	0.66 (0.55-0.79)	0.95 (0.83-1.09)	
Postoperative complication				
None	1.00	1.00	1.00	1.00
Non-severe	1.42 (1.26-1.59)	1.17 (1.01-1.34)	1.39 (1.22–1.58)	1.24 (1.06-1.45)
Severe	1.68 (1.47-1.92)	1.34 (1.13-1.59)	1.65 (1.43–1.91)	1.37 (1.13-1.64)

A subgroup analyses showed a difference in recurrence rate between groups of patients with infective complication compared to those without complications (15.2% vs 13.2%, log rank p=0.02) (figure 3). Multivariate analysis did not however show any increased risk of recurrence (HR 1:19, 95% CI 0.98-1.44)



Figur 3. Kaplan-Meier survival estimates for recurrence rate stratified by infective and non-infective complications.

Paper II

A total of 542 patients were treated with decompression of the colon by means of SEMS or diverting stoma and with the intention of later curative resection surgery. After review of medical files and implementation of exclusion criteria, 143 patients were included in the bridge to surgery (BtS) group, of which 43.4% were decompressed by the use of SEMS and 56.6% by diverting stoma. 1302 patients underwent emergent resection (ER) because of malignant large bowel obstruction and constituted the ER group (Figure 4).

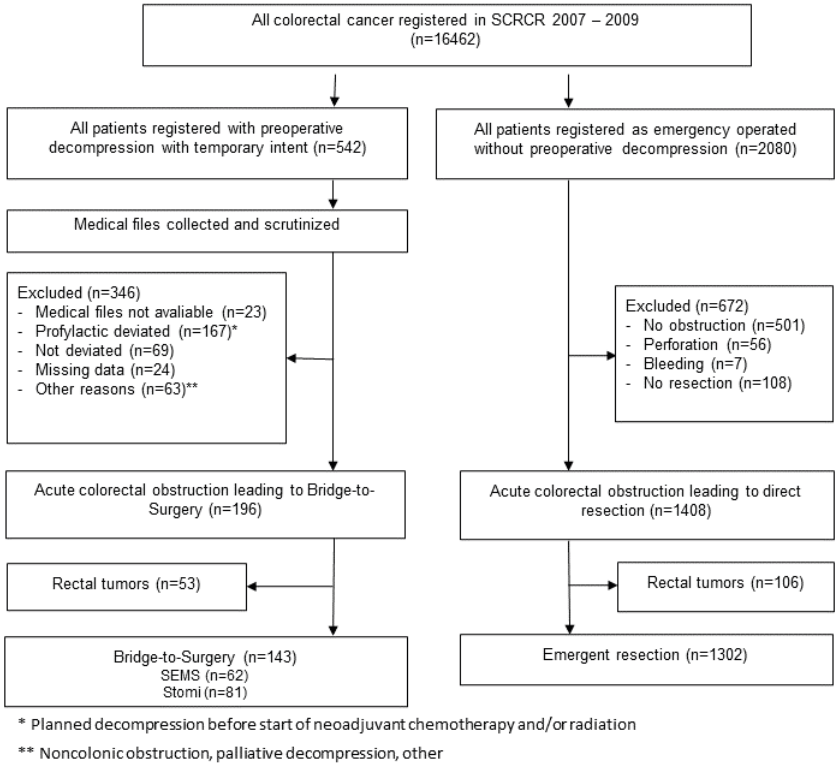


Figure 4. Study flow chart

88.8% of the tumors in the BtS group were located in the left colon compared to 47.7% in the SEMS group ($p<0.05$). Six patients (4.2%) in the BtS group did not undergo planned resection due to deterioration or advanced disease. There were more patients with metastasized disease in the ER group, i.e., 26.6% vs. 18.9% ($p<0.05$). Table 3 shows further tumor and patient characteristics.

Table 3. Patient and tumor characteristics

	Bridge to surgery N=143		Emergency resection N=1302		
	n	%	n	%	*p*-value*
Gender					<0.05
Female	59	41.3	659	50.6	
Male	84	58.7	643	49.4	
Age					<0.05
<65	48	33.6	308	23.7	
65-74	43	30.1	351	27.0	
75-84	41	28.7	418	32.1	
>85	11	7.7	225	17.3	
ASA score					0.31
1-2	94	65.7	784	60.2	
3	39	27.3	393	30.2	
4	9	6.3	51	3.9	
Missing	1	0.7	74	5.7	
Tumor location					
Right colon	8	5.6	508	39.0	<0.05
Transverse colon	8	5.6	173	13.3	
Left colon	127	88.8	621	47.7	
pT stage					
T1-T3	92	64.3	900	69.1	0.55
T4	45	31.5	392	30.1	
TX	6	4.2	10	0.8	
pN stage					
N0	61	42.7	512	39.3	
N1-2	75	52.4	762	58.5	0.29
NX	6	4.2	26	2.0	
Missing	1	0.7	2	0.2	
cM stage					
M0	115	80.4	953	73.2	<0.05
M1	27	18.9	346	26.6	
Missing	1	0.7	3	0.2	
Preop staging#	128	89.5	571	43.9	<0.05

*Chi^2-test. #CT scan of thorax and abdomen

The 5-year OS rate was higher in the BtS group compared with the ER group (53.8% vs 37.4%, *p*<0.05). Patients in the ER group had higher risk of 5-year mortality in a multivariate regression (HR = 1.4, 95% CI 1.1-1.9). There was however no difference in the 3-year recurrence-free survival rate or hazard risk for recurrence (74.8% vs 74.5%, *p*=0.4 and HR=1.1, % CI 0.7-1.6). In a subgroup analysis of left-sided tumors only, the 5-year OS was still higher in the BtS group (57.5% vs 43.6% *p*<0.05) and also the risk of 5-year mortality (HR=1.5, CI 1.1-2.2). There was still no difference in the risk of recurrence (HR 1.1, 95% CI 0.7-1.7) (Figure 5 & Table 4).

Postoperative mortality rate was higher in the ER group (7.3% vs 0.7%, $p<0.05$) whereas the postoperative morbidity rate was higher in the BtS group (46.9% vs. 35.9%, $p<0.05$).

In patients with left sided tumors, the rate of permanent stoma after 3-years was higher in the ER group compared to BtS group (34.9% vs. 17.4%, $p<0.05$).

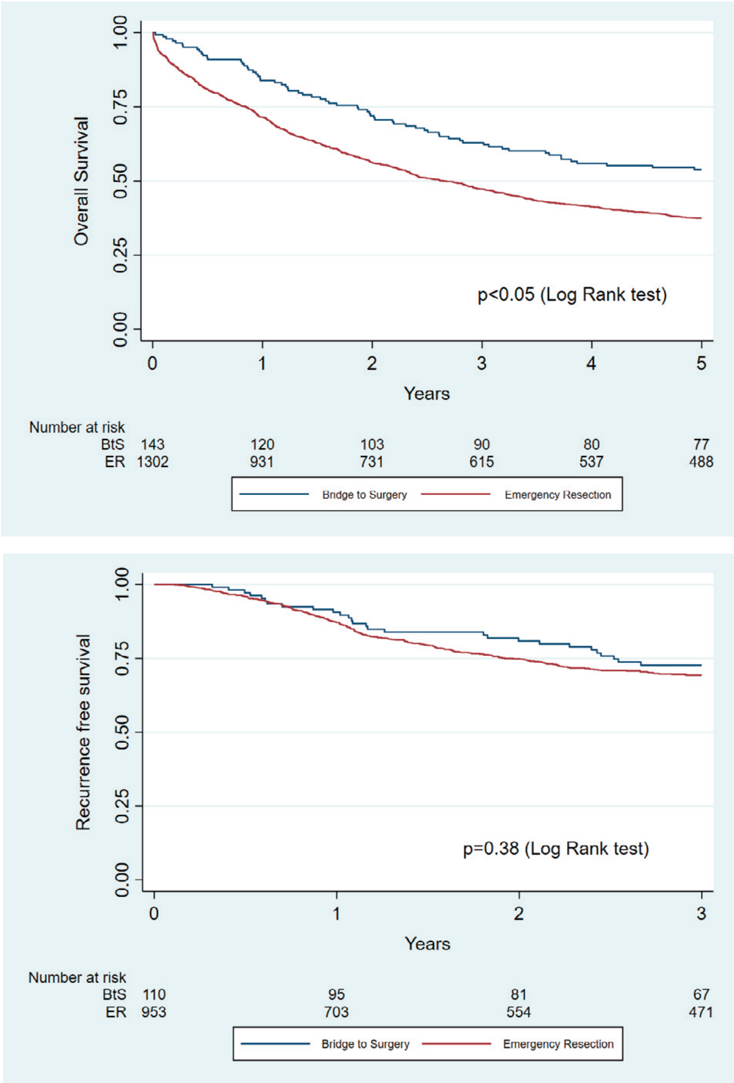


Figure 5. Five-year OS and 3-year recurrence-free survival in acute malignant large bowel obstruction stratified on bridge-to-surgery (BtS) and emergent resection (ER).

Table 4. Mortality and recurrence rates. COX proportional hazard model.

	Treatment group			Univariate		Multivariate	
		n	n(%)	HR	95% CI	HR	95% CI
5-year overall mortality			Death				
All tumors	BtS	143	66 (46.2)	Ref.		Ref.	
	ER	1302	815 (62.6)	1.64	1.27-2.11	1.44	1.10-1.90[a]
Left-sided tumors	BtS	127	54 (42.5)	Ref.		Ref.	
	ER	621	350 (56.4)	1.54	1.15-2.05	1.53	1.14-2.06[b]
3-year recurrence			Recurrence				
All tumors	BtS	110	28 (25.5)	Ref.		Ref.	
	ER	953	243 (25.5	1.18	0.80-1.74	1.10	0.70-1.57[c]
Left-sided tumors	BtS	99	24 (24.2)	Ref.		Ref.	
	ER	484	109 (22.5)	1.09	0.70-1.70	1.12	0.71-1.74[d]

[a] Adjusted for gender, age, ASA score, TNM stage and tumour location; [b] Adjusted for gender, age, ASA score and TNM stage; [c]Adjusted for gender, age, ASA score, TN stage and tumour location; [d]Adjusted for gender, age, ASA score and TN stage. OS: overall survival; RFS: recurrence free survival

Paper III

A total of 699 patients who underwent emergent colon resection were identified, after exclusion of patients with missing data on exposure variable (operating team), the cohort consisted of 656 patients of which 319 were operated by colorectal team (CRT), 210 by emergency surgical team (EST) and 127 by general surgical team (GST). Patient demography and tumor characteristics are presented in table 5.

Notably more patients in the EST group had ASA score of 3 or 4 compared to CRT and GST (53.8% vs 43.9% and 40.9% respectively, $p<0.05$). Large bowel obstruction was the most common indication of surgery in all groups (80.8%, 73.8% and 76.4%, $p=0.08$). Although all tumors were colon cancers and there was no difference in right or left sided tumors 11 patients in CRT underwent anterior resection.

Table 5. Patient and tumor characteristics stratified on specialization of operating team.

	CRT n=319		EST n=210		GST n=127		*p*-value
Gender							
Male	147	(46.1)	111	(52.9)	61	(48.0)	.31
Female	172	(53.9)	99	(47.1)	66	(52.0)	
Age							
<66	77	(24.1)	52	(24.8)	27	(21.3)	.75
66-80	149	(46.7)	91	(43.3)	60	(47.2)	.70
>80	93	(29.2)	67	(31.9)	40	(31.5)	.77
ASA score							
ASA 1-2	175	(54.9)	80	(38.1)	74	(58.3)	< 0.05
ASA 3	126	(39.5)	92	(43.8)	40	(31.5)	< 0.05
ASA 4	14	(4.4)	21	(10.0)	12	(9.4)	< 0.05
Missing	4	(1.3)	17	(8.1)	1	(0.8)	-
Indication for surgery							
Obstruction	261	(80.8)	155	(73.8)	97	(76.4)	.08
Bleeding	13	(4.1)	9	(4.3)	4	(3.1)	.87
Perforation	36	(11.3)	29	(13.8)	19	(15.0)	.50
Other	9	(2.8)	17	(8.1)	7	(5.5)	< 0.05
Tumor location							
Right colon	119	(37.3)	89	(42.4)	58	(45.7)	.22
Transverse colon	34	(10.7)	17	(8.1)	16	(12.6)	.39
Left colon	166	(52.0)	104	(49.5)	53	(41.7)	.14
T stage							
T1-T2	13	(4.1)	6	(2.9)	7	(5.5)	.48
T3	137	(42.9)	89	(42.4)	56	(44.1)	.95
T4	167	(52.4)	114	(54.3)	64	(50.4)	.78
TX	2	(0.6)	1	(0.5)	0	(0.0)	-
N stage							
N0	106	(33.2)	72	(34.3)	56	(44.1)	.06
N1-2	211	(66.1)	136	(64.8)	68	(53.5)	< 0.05
Missing	2	(0.6)	2	(1.0)	3	(2.4)	-
M stage							
M0	246	(77.1)	164	(78.1)	97	(76.4)	.93
M1	73	(22.9)	45	(21.4)	27	(21.3)	.09
Missing	0	(0.0	1	(0.5)	3	(2.4)	-

CRT: colorectal team; EST: emergency surgical team; GST: general surgical team

Five-year OS did not differ depending on operating team (48.3%, 45.7% and 42.5% in the CRT, EST and GST groups respectively; p=0.57). Neither was there any difference in 3-year RFS in M0 patients (Figure 6). Multivariate analysis showed no difference in impact of surgical specialization on 5-year OS or 3-year RFS (Table 6).

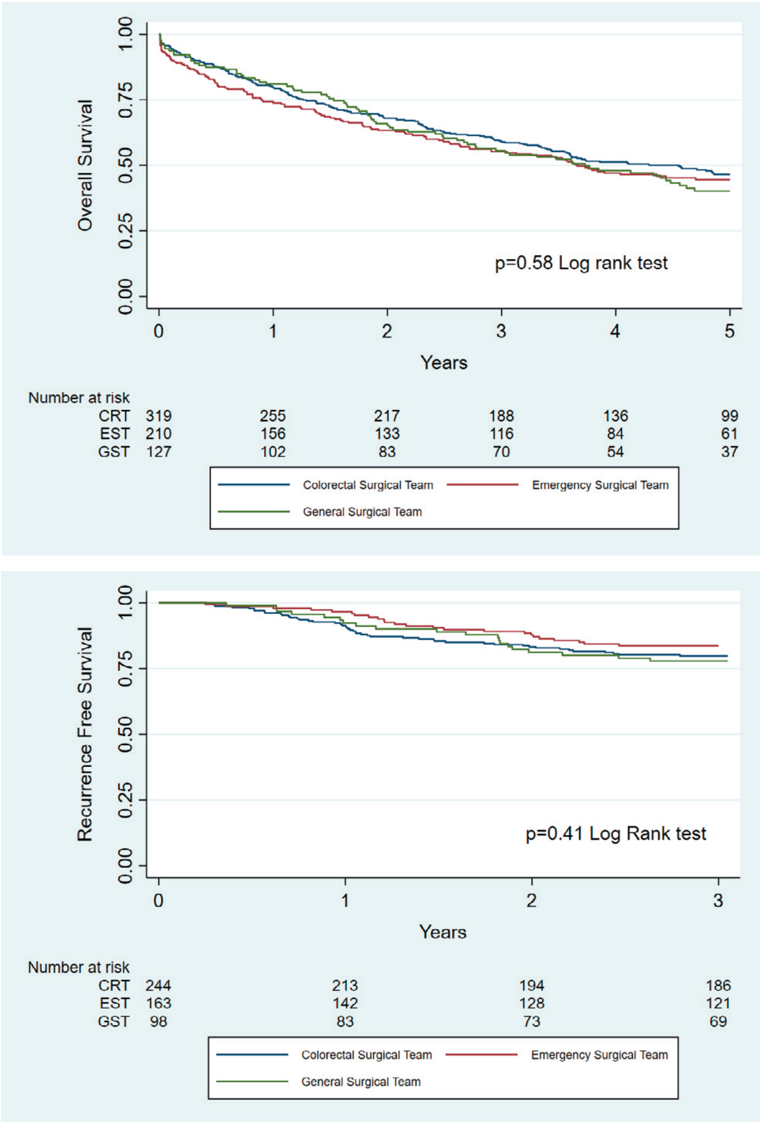


Figure 6. Kaplan-Meier survival estimates for overall survival and recurrence free survival (M0 only) stratified by specialization of the surgical team.

There was no difference in the rate of postoperative complications or mortality between the groups (35.5%, 35.9% and 30.7% in CRT, EST and GST respectively, p=0.53). Surgical specialization was not predictive for ninety-day mortality in a multivariate logistic regression analysis (Table 7). The use of diverting ileostomy was higher in the CRT group but in turn also higher rate of stoma reversal.

Permanent stoma rate at three years was higher in the EST group compared with CRT and GST (34.5% vs 24.3% and 23.9%, *p*=0.12).

Table 6. Multivariate COX proportional hazard model. Hazard ratios (HR) for 5-year overall mortality and recurrence within 3 years following emergent resection of colon cancer.

	5-year mortality			Recurrence within 3-years		
	HR	95% CI	p value	HR	95% CI	*p* value
Age						
<65	1.0			1.0		
65-74	1.2	(0.8-1.6)	.4	1.2	(0.7-2-1)	.52
75-84	1.8	(1.3-2.5)	.00	1.0	(0.6-1.8)	.95
>85	3.6	(2.5-5.1)	.00	0.5	(0.2-1.3)	.15
ASA score						
1-2	1.0			1.0		.90
3	1.8	(1.4-2.3)	.00	1.0	(0.6-1.5)	.50
4	4.0	(2.8-5.9)	.00	1.4	(0.5-3.7)	.60
T-stage						
1-2	1.0			1.0		
3	1.4	(0.7-3.0)	.34	1.1	(0.3-4.6)	.90
4	2.4	(1.1-4.9)	0.2	1.4	(0.3-5.9)	.70
N-stage						
0	1.0			1.0		
1-2	1.6	(1.2-2.1)	<0.05	2.9	(1.7-4.9)	<0.05
M-stage						
0	1.0					
1	2.9	(2.3-3.7)	.00			
Surgical specialisation						
CRT	1.0			1.0		
EST	1.0	(0.7-1.3)	.88	0.7	(0.4-1-1)	.15
GST	1.2	(0.9-1.6)	.24	1.3	(0.8-2.2)	.36

CST: colorectal team; EST: emergency surgical team; GST: general surgical tea

Table 7. Logistic regression of 30- and 90-day mortality.

	30-day mortality			90-day mortality		
	OR	(95% CI)	p-value	OR	(95% CI)	*p*-value
Surgical specialization						
CRT	Ref.			Ref.		
EST	1.4	(0.6-3.1)	.41	1.0	(0.5-2-0)	.96
GST	1.1	(0.4-2.9)	.89	0.8	(0.3-1.8)	.60

Adjusted for age, ASA score, M-stage (90-day only), indication for surgery.

There was no difference in the rate of radical resection between the three groups (90.9%, 85.2% and 89.8% respectively, *p*=0.12). Even though the patients in the GST group had lower count lymph node evaluation (mean 22.8, S.D 11.9) compared to the other groups it was well over the minimum of 12 recommended by UICC.

Paper IV

Of the 700 cases selected for validation one was accidentally omitted from the validation and therefore excluded from the study. Thus, a total of 699 cases were validated. Follow-up data for 3 patients was not available because of emigration and therefore excluded from the follow-up analysis. Seven cases were excluded from the validation of histopathology because of missing pathology reports.

Median agreement of histopathology variables was 93.4% with median Cohen´s kappa of 0.85 and can be therefore regarded as almost perfect agreement. Tumor grade, tumor budding and Quirke´s TME assessment had a substantial agreement of 89.5% (k=0.73), 89.2% (k=0.67) and 91.0% (k=0.74) respectively (Table 8).

The variable "postoperative complication" had a substantial agreement of 84.3% (k=0.61) (Table 8). There was a total of 370 registered complications in 273 patients and a large variation of registered events in each group of complication. Cardiovascular complication had only 29 registered events divided over five sub-type variables and neurological complications had only four registered events. Of the total registered complication, 25% were postoperative infections, 7.8% cardiovascular, 1.1% neurological, 35.6% surgical and 29.7 "other complications". After exclusion of cardiovascular and neurological complications variables due to few registered events, the median agreement of the main complication variables was 72.9 (range 69.2-82.1) (Table 8). Crosstabulation of postoperative complications and variables are shown in table 9. When postoperative complications were divided into non-severe and severe according to Clavien-Dindo grade the agreement was 93.0% (k=0.75) for severe complications (CD IIIb-V) and 59,7% (k=0.32) for non-severe complications (CD II- IIIa). Because of few registered events in many sub-type variable calculation of Cohen´s kappa coefficient was not meaningful and only agreement in crosstabulations are presented.

The agreement of cancer recurrence was almost perfect or 95.7% (k=0.86) whereas the agreement of local and distant recurrence was moderate and fair (93.6%, k=0.5 and 80.0%, k=0.26 respectively). The dates of local and distant recurrence were almost perfect with a pearson´s coefficient of r=0.9. (Figure 7).

Table 7. Pathology report data. Comparison of original data in the Swedish Colorectal Cancer Registry and re-abstracted data from medical files.

	Missing values in the SCRCR	Missing values in re-abstracted data	Missing values in both sources	Exact agreement (non-missing records) (%)	Cohen´s Kappa score (*k*)	Pearson´s coefficient (*r*)
Adenocarcinoma	0/696	1/696	0/696	99.6	N/A	
Quirke TME classification	98/216	76/216	58/216	91.0	0.74	
T-stage	4/692	4/692	1/692	96.7	0.95	
T1-stage	9/692	6/692	4/692	91.1	0.85	
T3-stage	26/346	0/346	0/346	97.8	0.95	
T4-stage	6/132	0/132	0/132	90.0	N/A	
N-stage	6/670	12/670	3/670	97.2	0.97	
Number of Examined lymph nodes	9/692	14/692	5/692	98.2		0.94
Number of positive lymph nodes	14/692	17/692	6/692	94.8		0.97
Microscopically radical resection	7/692	24/692	5/692	95.9	0.43	
Mucinous tumor	3/692	23/692	1/692	92.5	0.75	
Perineural invasion	4/692	12/692	1/692	95.1	0.86	
Vascular invasion	12/692	24/692	11/692	94.4	0.87	
Tumor grade	2/692	15/692	0/692	89.5	0.73	
LRM	52/692	37/692	24/692	79.9		0.87
CRM	54/692	42/692	33/692	88.2		0.82
Tumor budding	8/692	18/692	1/692	89.2	0.67	
count	17/80	10/80	5/80	96.6		0.97

Table 8. Postoperative complication data. Comparison of original data in the Swedish Colorectal Cancer Registry and re-abstracted data from medical files.

	Missing values in the SCRCR	Missing values in re-abstracted data	Missing values in both sources	Exact agreement (non-missing records) (%)	Cohen´s Kappa score (*k*)
Postoperative complications	*0/699*	*11/699*	*0/699*	*84.3*	*0.61*
Postoperative Infection	N/A	N/A	N/A	72.9	0.24
Surgical complications	N/A	N/A	N/A	82.1	0.63
Other complications	N/A	N/A	N/A	69.2	0.18
Intensive care	0/699	1/699	0/699	97.4	0.76
Reoperation	0/699	1/699	0/699	96.7	0.80

Table 9 Crosstabulation of postoperative complication variables stratified on type of complications.

Medical records	SCRCR		
Postoperative complications	No	Yes	Total
No	415	34	449
Yes	74	165	239
Total	500	199	11

Exact agrrement: 84.3%

Medical records	SCRCR		
Cardiovascular	No	Yes	Total
No	244	8	252
Yes	13	8	21
Total	257	16	273

Exact agreement: 92.3%

Medical records	SCRCR		
Postoperative infection	No	Yes	Total
No	175	18	193
Yes	56	24	80
Total	231	42	273

Exact agreement: 72.3%

Medical records	SCRCR		
Surgical complications	No	Yes	Total
No	141	8	149
Yes	41	83	124
Total	182	91	273

Exact agreement: 82.1%

Medical records	SCRCR		
Neurological	No	Yes	Total
No	269	2	271
Yes	2	0	2
Total	271	2	273

Medical records	SCRCR		
Unspecified complications	No	Yes	Total
No	163	42	205
Yes	42	26	68
Total	205	68	273

Exact agreement 69%

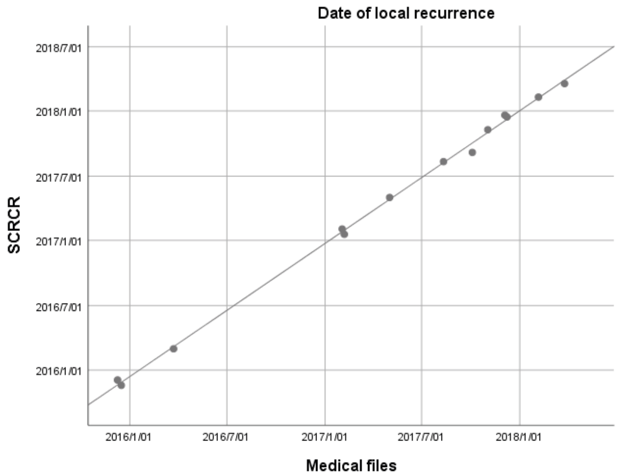
Table 10. Crosstabulation of registered complications in agreement stratified on non-severe (CDII-IIIa) and severe (IIIb-V) postoperative complications.

Medical records	SCRCR		
CD II-IIIa	No	Yes	Total
No	44	40	84
Yes	70	119	189
Total	114	159	273

Exact agreement: 59.7%, ***k***=0.32

Medical records	SCRCR		
CD IIIb-5	No	Yes	
No	219	5	224
Yes	14	35	49
	233	40	273

Exact agreement: 93.0%, ***k***=0.75



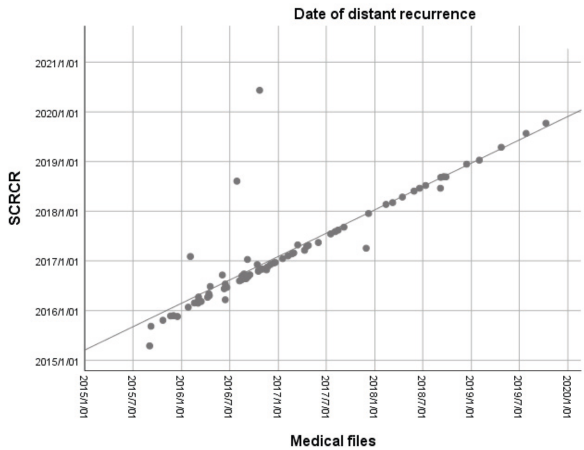


Figure 7. Correlation of non-categoric follow-up data

Discussions

Paper I

The hypothesis was that systemic inflammation resulting in immunologic suppression caused by resection surgery and magnified by postoperative complications could stimulate tumor growth leading to cancer recurrence[171, 172]. Study I showed that postoperative complications are clearly associated with lower overall survival but not the recurrence rate. A subgroup analysis showed however a higher recurrence rate in patients with infective complications compared with those who did not. This may suggest that infective complications through immune suppression is associated with higher recurrence rate although it was not supported by a multivariate analysis. A likely explanation for reduced overall and disease-free survival in patients that suffer post operative complications is deterioration of their health due to sequela from POC and not cancer recurrence. A contributing reason for the absence of any difference in recurrence rate could be that death is a competing event, as death may have occurred before patients with POC were diagnosed with recurrence. Delayed or lower rate of adjuvant chemotherapy might be another reason for the association between POC and survival, which has been shown in other studies[173, 174].

Our finding is supported by recent studies. Warps et al found that POC was associated with lower five-year OS, being stronger for non-surgical complications than surgical complications[175]. In line with our findings of higher recurrence rate in patients with postoperative infections, Klaver et al. showed that postoperative infection is independently associated with intra-abdominal recurrence in patients with T4 colon cancer (HR 1.8; 95CI. 1.13-2.97)[176].

There are a few limitations in the study. First and foremost is selection bias. We choose to define seriousness of complications by its type since Clavien-Dindo grading classification had not been incorporated into the registry in the study period. There is therefore possibility that some severe complications were in fact non-severe. The study is based on registry data and the results dependent on its validity. As paper IV shows, low grade complications are often under reported and therefore it is likely that more than few patients in the no-complication group should be in one of the other groups though mostly in the non-severe group. There was no data available that supported the degree of infective complications such as CRP or neutrophil count to help determining the degree of infective complications.

Therefore, there is a risk of selection bias regarding the infective complications in the subgroup analysis. Further, there was no information on patients' functional status or comorbidity index. Complications, especially non-surgical, are probably more likely to occur in patients with preexisting comorbidities, which makes it difficult to determine the relative contribution of preexisting comorbidities and POC to the reduced survival probability.

Paper II

The main finding in this study was that 5-year overall survival was higher in patients treated with bridge to surgery compared to patients who underwent emergent resection of colon cancer. The difference was supported by multivariate analysis showing that patients in the ER group had significantly higher mortality risk. There was no difference in recurrence rate or risk of recurrence between the two groups.

Interpreting the literature regarding the efficacy of SEMS as a bridge to surgery is challenging because of conflicting results. The most common outcome measure in the randomized controlled trials (RCT) was perioperative outcome with short-term follow up and most of the studies included small samples of patients and presented high heterogeneity of methods and population characteristics[177].[178, 179]

The few comparative studies on effectiveness on diverting stoma as BtS have shown decreased postoperative mortality and improved 3-year overall survival rate with BtS[76] whereas another showed no difference in short term outcome[77]. It has also been shown that 5-year OS and 3-year DFS in patients managed either with SEMS or diverting stoma was comparable[180]. We therefore chose to merge the two BtS methods, SEMS and diverting stoma, and compare it with emergent surgery, irrespective of technique.

Results regarding safety of SEMS and its impact on long-term survival have also been conflicting. Initial studies showed high rate of perforations with negative impact on survival in a potentially curable CRC. There were also concerns that tumor manipulation could lead to increased locoregional recurrence rate. In fact, updated ESGE guidelines in 2014 recommended against the use of SEMS in the management of malignant LBO with curative intent[181]. Since then, more studies have shown that the use of SEMS is in fact safe and efficient in both curative and palliative [182] cases. In 2020 new ESGE guidelines were introduced, recommending stenting as a bridge to surgery to be discussed, within a shared decision-making process, as a treatment option in patients with potentially curable left-sided obstructing colon cancer as an alternative to emergency resection[183]. The result from this thesis supports that decision making.

In the recent years studies have shown increased use of SEMS as bridge to surgery in the management of malignant LBO[100]. This trend has not been seen in Sweden and since 2009 the rate of preoperative decompression with SEMS in M0 patients that later underwent resection surgery, has been around 0.5%[46]. Perhaps when more studies become available further supporting the evidence for better survival in BtS treated patients the use of SEMS will increase again. As mentioned previously the use of SEMS depends on availability and competence of the endoscopist and is therefore not necessarily an option in every hospital. Studies have shown that the short-term morbidity is lower in patients treated with SEMS vs. diverting stoma although there is no difference in postoperative mortality[184, 185]. With that in mind, perhaps it is advisable to choose SEMS over diverting stoma when possible but knowing that a diverting stoma is a reasonable option when SEMS is not an alternative. In 2022, 70% and 80% of all elective resections for colon and rectal cancers respectively were performed with minimal invasive techniques compared to 30% for both cancers in 2014[46]. Distended bowel may hamper laparoscopy and emergency resection is therefore usually conducted with open approach[57]. ER frequently concludes with stoma formation that negatively impacts patient quality of life[57]. BtS is associated with higher rate of laparoscopic resection[186, 187] as well as primary anastomosis and lower stoma rates, shown in this study and by others[97, 178, 188]. Therefore, BtS should be seen as a valid treatment option in the management of malignant colonic obstruction, not only for unstable patients or the elderly and frail, but for all patients.

Paper III

The main finding of this study was that surgical specialisation in hospitals in Southern Sweden did not impact short- or long-term outcome after emergent resection for colon cancer. Furthermore, there was no difference in the rate of radical resection and the number of examined lymph nodes was acceptable in all three study groups. These results are reflected by a similar oncological outcome in the three groups. The result contrasts with other studies that have reported a negative impact of hospital and surgeon volume on postoperative morbidity and mortality[126, 130, 189] while yet other studies in fact showed no difference[190, 191]. It is probably more likely hospital factors rather than specialisation and volume that have impact on survival such as the structure surrounding the management of critically ill patients and postoperative complications including the quality of intensive care units. In Sweden the education and training of personnel of all surgical and perioperative specialities is uniform. Any difference in competence and availability of resources across the hospitals is thus unlikely and therefore also the failure to rescue rates. The volume and production of elective colorectal surgery has increased in the last decade as well as technological advancement with the introduction of laparoscopic and robotassisted surgery and thus leading to more centralization. At the same time the need for specialization in emergency care surgery has risen to provide time sensitive and quality care to all patients with acute surgical conditions. As emergency surgery accounts for 9% of all colorectal cases in Sweden, and even higher in many other countries, it may be unreasonable that all these patients are treated by surgeons with colorectal specialization. It is therefore important to build a strong team around the patient with colorectal cancer emergency consisting of trained emergency care personnel, including anaesthesiology personnel to promptly address critical situations. The results in this thesis indicate that patients treated by emergency care teams do not have any worse outcome compared with patients treated by CRC surgeons.

Paper IV

The first three papers relied on data from the SCRCR and is therefore imperative for the result that the data is valid. The validation study in paper IV showed high validity of histopathology data and data regarding recurrence rate in the and the rate of missing data was low. The agreement of postoperative complications reported in SRCRC and re-abstracted data from medical files was generally low, especially regarding non-surgical complications and non-severe complications (Clavien-Dindo 2-3a). The reason in many cases was mostly due to under reporting in the SCRCR. For example, there were 80 postoperative infections reported by the validator compared to 42 in the SCRC. Many complication variables had few registered events which leads to inequality in the crosstabulation, especially where the alternative is only “yes or no”. Kappa is affected by the prevalence of the finding under consideration. For rare findings very low kappa values may not necessarily reflect low rates of overall agreement. The date of recurrence had a high correlation. Definition of date for recurrence is written in the list of description for SCRCR variables and this result indicates that it is clear and easy to follow. The agreement of local and distant recurrence was however weak, perhaps because only one site was registered when in fact, they both had occurred. To improve validity of the variables that showed inferior agreement, some measure can be implemented, for example more strict variable definition, better training in using the Clavien-Dindo system and stressing out the importance of registration of all metastases.

Methodological considerations

Studies I-III are observational cohort studies based on data from SCRCR. In a cohort study the participants usually do not have the outcome of interest to begin with but are selected based on the exposure status of each participant. They are followed over time to evaluate the outcome of interest. Over the period of follow-up, some of the exposed individuals will develop the outcome and some unexposed will also develop the outcome. In a cohort study the outcomes in these two groups are compared. In a retrospective cohort study, the data are collected from records, in this thesis from the SCRCR. Even though the outcomes have already occurred the study starts with the exposure and other variables at baseline, and at the end of follow-up period the outcome is measured. In a prospective cohort study the exposure of interest is selected and the patients are then classified as exposed or unexposed. These patients are followed and information on other variables that are important for the study such as confounding variables, is collected. The outcome of interest is then assessed in these individuals. Some of the strengths of cohort studies is that the outcome has not occurred at the time of the exposure, so the time to event is well defined. A cohort study helps to study multiple outcomes in the same exposure, in this thesis complications, recurrence or death. A prospective cohort study is designed with specific data collection methods and has the advantage of being tailored to collect specific exposure data and may be more complete than retrospective study. This is important to maintain uniformity in the measurement of exposure and outcomes. This is also useful for exposures that may require subjective assessment, for example surgeons' registration of his or her assessment of macroscopically radicality of the resection. The limitation of a retrospective cohort design is that the outcome variables are collected before the study has been initiated. Thus, the measurements may not be very accurate or according to the studies´ requirements as the investigator has limited control over the data collection. In addition, some of the exposures may have been assessed differently for various members of the cohort. For example, in the studies in this thesis, data is registered by many doctors of different specialities, surgeons, pathologists, radiologists, and oncologists without regards to the actual study. Therefore, a validation of quality register such as SCRCR is important to ensure the quality of the data.

Confounding and Internal validity

A confounding variable (or a confounder) is an extraneous variable associated with the response and the explanatory variable. In other terms, confounding is when a third variable influences the observed relationship between the response and explanatory variable. Managing confounding is important, as confounding can completely change the relationship between the response and explanatory variables and hence can compromise internal validity. If the values of potential confounding variables are recorded, their impact can be managed. However, sometimes the values of the confounding variables are not recorded. Failure to acknowledge unknown confounder can lead to wrong conclusions. To avoid unknown confounder, sometimes a large amount of data is collected about the individuals in the study and tested.

The internal validity of a study is the extent to which the observed difference in outcomes between the study groups can be attributed to the intervention/exposure rather than other factors. An internally valid study is one designed to focus on the relationship between the response and explanatory variables, and eliminating other influences such as confounders, bias and chance. Studies with high internal validity show that changes in the response variable can confidently be related to changes in the explanatory variable in the group that was studied; the possibility of other explanations has been minimised. Since treatments (or exposure) are not imposed in observational studies as in experimental studies, random allocation of treatments (exposure) is not possible. Confounding is thus always a potential threat to internal validity in observational studies. It is therefore important to manage confounding to maximise internal validity. Another threat to internal validity is that the groups being compared are initially different. To check this, the baseline characteristics of the individuals in the groups can be compared. The groups being compared should be as similar as possible, so that any differences in the outcome cannot be attributed to pre-existing difference in the groups.

Challenges of the studies in this thesis

The main threats for the internal validity of paper I-III are bias and confounding. Selection bias is a systematic error in sampling, selection, or allocation methods. Factors that determined whether an individual was exposed could result in difference in factors in the comparison groups that can affect the outcome. Confounding by indication is a form of selection bias, which occurs when exposure preferentially occurs in groups of patients based on their underlying risk profile. In paper I the cohort was divided into three groups regarding their exposure (postoperative complication): those without postoperative complications, those with non-severe and those with severe complications. There is a good probability that some patients in either of the complication groups belonged to one of the other, as well as other patients not suffering any complications but erroneously registered as such. There is in that way risk for selection bias. In paper II, the selection bias is more likely to be a confounding by indication as many patients selected for management with BtS might have had certain characteristics that differed from emergency resected patients. There is in that way a presence of incomparability between these groups. Thus, selection of exposure (BtS) is confounded with patient factors, which are also related to the outcome. Such factors include the degree of the colonic obstruction, for example patients with total obstruction were unlikely to be selected for management with SEMS as a BtS. The location and length of the tumor is another factor. Critically ill patients may have been selected for decompression with stoma instead of resection or vice versa undergoing emergency resection while not considered a candidate for BtS. In paper III there is also risk for selection bias. The selection of the patients into the exposure groups is strongly dependent on the validity of the data, that is the registration of the variable "operated by colorectal team or emergency team" is correct. Otherwise, there is a risk that patients were selected to a wrong group. Another selection bias is that without doubt many patients were managed by EST team because of their critical status, and perhaps also because of the presumed uncomplicated nature of the obstruction. Whereas the symptoms of the patients selected to CRT group weren´t as acute as in patients managed by EST or had more advanced or complicated obstruction that necessitated CRT competence.

Methods to reduce confounding and improve the comparability of exposure and control groups in observational studies can be done in the design phase and includes restriction where inclusion is restricted to certain category of confounders. This can limit generalizability. Matching enhances equal representation of subjects with certain confounders among study groups. The effect of the variable on outcome cannot therefore be evaluated. In the analysis phase confounding can be controlled by stratification or regression. The latter method was used in studies I-III. Regression analysis estimates the association between one or more explanatory variables (exposure, predictive or risk factors) on a response/outcome variable (mortality or cancer). An explanatory variable is also called indirect or covariate variable. A multivariate regression model can be used to attempt to assess the independent relationship between exposure and outcome while adjusting for various explanatory variables including potential confounders. In paper I-III the association between the exposure/treatment (complication, BtS vs ER and specialization of the surgical team) and outcome (death or recurrence) regression was done using Cox proportional Hazard analysis. Identification of covariates and potential confounders included in the multivariate model was based on a univariate association of clinical characteristic to the outcome variable. Building a regression model can be challenging. Including too many or irrelevant confounders and not include all relevant confounders for example hidden confounders, may result in residual confounding and loss of precision of the model. In this thesis, available characteristics that are known to be predictive of the outcome or potential confounders from other studies, were used to build the multivariate model such as age, gender, and TNM stage. There are for certain a few possible confounders not adjusted for in the model and thus impacting its precision. For example, information on medical comorbidity was not available although high ASA score can be associated with high comorbidity score.

Conclusion

The studies in this thesis show that:

- ❖ Patients who suffer postoperative complications after curative colonic resection for cancer have impaired 5-year overall survival. Postoperative complications do not affect cancer recurrence rate. When complications occur, early detection and prompt treatment may increase survival.
- ❖ Bridge to surgery is associated with higher 5-year overall survival compared with emergent resection. There is no difference recurrence rate between the groups. Postoperative mortality rate was higher in the ER group while morbidity rate was higher in the BtS group. BtS is a safe and efficient method in management of patients with acute malignant large bowel obstruction without compromising oncologic outcome. Its use, especially in centers with endoscopic capabilities for SEMS placements, may be recommended in selected cases.
- ❖ There is no difference in outcome after emergent colon cancer surgery depending on specialization of the surgical team. Management of this patient group by emergency care surgical team should not be discouraged.
- ❖ The validity of SCRCR regarding histopathology and cancer recurrence is good. The validity of postoperative complications needs to be addressed.

Future perspective

The incidence of colorectal cancer continues to rise as well as the demand for high quality service and improved survival. Elective cases are nowadays primarily performed laparoscopically which have improved postoperative outcome and shortened the length of stay. The population is getting older and with their frailty and medical comorbidities setting further press on the health care. The frail and sick are more likely to suffer postoperative complications and have decreased long-term survival. Implementation of system to identify a lurking complication like early warning scale (NEWS) helps to avoid a mild complications become a severe one. As well as direct line to intensive care unit team for early assessment and management. Hospitals that have special intermediate wards to treat patients with non-surgical complications and septicemia can further insure better outcomes of these patients. Acute care surgical team including personal from all disciplines needed to manage emergency surgical cases is necessary to provide best care in modern healthcare. Acute care surgeon must be well versed in all emergency settings including trauma and also trained in damage control colorectal surgery. A good understanding of principles in management of colorectal emergencies is crucial for good outcome. A fast diagnosis and right decision based on evidenced based knowledge of available treatment options is equally as important. This thesis has shown that postoperative complications have detrimental effects on long-term survival. Perhaps many of the severe complications could have been avoided with right intervention and perhaps right treatment to begin with. BtS is a valid method for large bowel obstructions, especially in the critical ill patient. This thesis showed that it is associated with better long-term overall survival than emergency surgery. The cohort was based on patients diagnosed in 2007-2009 so there is a need for further studies before introducing recommendation of its use in clinical practice. Both the technique and SEMS have improved in the past decade. The use of SEMS has increased significantly in other specialties especially upper GI and biliary surgery so the morbidity and technical failure rate may have improved since. A well designed prospective randomized study should be welcomed, focusing on short term outcome to begin with. Outcome measures should be clinical and technical success rate, procedure and postoperative morbidity and mortality. As well as rate of laparoscopic recession and permanent stoma. To further assess the impact of postoperative complications on survival there is also need for a well-designed study with special focus on patient and operative, perioperative care inclusive laboratory, and of course, correct classification and grading of complication. Such a study could help identify patients group in high risk of suffering complications and identify instances in the chain of patients care that needs to be addressed or improved. Regarding specialization of surgical team and to confirm (or not) the finding of this thesis, a single center (Malmö) prospective observational study on outcome of all emergency colon cancer can easily be designed and performed.

Populärvetenskaplig sammanfattning

Cancer i tjock- och ändtarm (kolorektal cancer) är den tredje vanligaste cancerformen i Sverige och varje år drabbas omkring 8000 svenskar av sjukdomen. Medelåldern vid diagnos är 73 år för koloncancer och 70 år för rektalcancer. Endast 5% är under 50 år. Koloncancer är lika vanlig hos män som hos kvinnor, men rektalcancer är vanligare hos män. Den relativa överlevnaden (i jämförelse med befolkningen utan kolorektal cancer i Sverige) är ca. 68% efter 5 år. Vanliga symptom är diarré eller förstoppning, blod i avföringen, buksmärta samt ofrivillig viktnedgång. Det är vanligt att inte ha några symptom när cancern är i ett tidigt stadie av cancern. Risken för kolorektal cancer kan minskas med att äta hälsosamt, vara fysiskt aktiv, rökfrihet och begränsat alkoholintag. Screening är viktig för att kunna upptäcka sjukdomen tidigt då överlevnaden är beroende av tumörstadium. Screening för kolorektal cancer infördes 2020 i Sverige och erbjuds alla personer i åldern 60–74 år med test av blod i avföringen. Vid positivt test följs provtagningen upp med en koloskopi för mer definitiv diagnos. Det säkraste sättet att bota kolorektal cancer är att operera bort tumören och de omkringliggande lymfkörtlar. Behandling av ändtarmscancer kombineras ofta med strål- och cellgiftsbehandling före operation. I många fall ges cellgiftsbehandling efter operationen för att minska risken för återfall.

Postoperativa komplikationer (skador till följd av kirurgi) efter kolorektal cancerkirurgi är tyvärr inte ovanliga. De kan indelas i kirurgiska och icke kirurgiska. De vanligaste kirurgiska komplikationerna är sårinfektioner och djupa infektioner i bukhålan. Icke-kirurgiska komplikationer kan till exempel vara lunginflammation och blodpropp. Postoperativa komplikationer graderas från I-V enligt ett system som heter Clavien-Dindo. Graden beror på typen av ingrepp som behöv för att behandla komplikationen. Till exempel vid Grad II har man behandlat med läkemedel. Vid grad IIIb har patienten behövt genomgå ett ingrepp som krävt sövning, ofta en ny operation. Vid grad IV har patienten vårdats på intensivvårdsavdelningen och vid grad V har patienten avlidit till följd av komplikationen. Grad IIIb-V benämns ofta för allvarliga komplikationer, medan de övriga för milda. I Sverige drabbas ungefär 20% av milda komplikationer efter kirurgi för kolorektal cancer och 8% av allvarliga. Femtio-tre patienter av 4947 som genomgick kirurgi för kolorektal cancer i Sverige 2022 avled inom 30 dagar efter operation till följd av komplikationer, en andel på 1.1%. De flesta av dem som avled hade opererats akut.

Ungefär 10–30% som drabbas av kolorektal cancer söker vård med akuta symptom. I de flesta fall har tumören ett avancerat stadie, och har ofta spridit sig till andra organ. Nio procent av de patienter som genomgick kirurgi för kolorektal cancer i Sverige 2022 opererades akut. Den vanligaste orsaken till akut operation är en förträngning i tarmen orsakad av tumören så att avföringen inte kan passera förbi. Patienter som opereras akut har högre risk för att drabbas av komplikationer och död efter ingreppet jämfört med patienter som genomgår en planerad operation. De har också högre risk för att dö inom 5 år. I vissa fall väljer man att istället för att operera bort tumören, att endast lägga ut tarmen som påse på magen (stomi) eller lägga en metallstent (vävt metallrör) inuti tjocktarmen som öppnar upp förträngningen. Denna metod kallas för ”Bridge To Surgery” (BtS) och används först och främst för patienter vars tillstånd är så allvarligt att de löper en högre risk för död och komplikationer om de genomgår en akut operation där tumören tas bort. Den används också i de fall tumörväxten är så avancerad att den har vuxit igenom tarmväggen mot omgivande organ. Metoden möjliggör en noggrann kartläggning av tumören och planering av operation när patientens tillstånd har förbättrats. Operationen kan då utföras av en kirurg som är specialiserad i operationer av kolorektal cancer då akuta operationer ofta utförs av kirurger som har en annan specialisering.

Ett kvalitetsregister ska underlätta uppföljning och utvärdering av hälso- och sjukvårdens resultat och kvalitet. Ett nationellt kvalitetsregister inom cancerområdet innehåller individbaserade uppgifter om diagnos, behandlingar och resultat. Det Svenska Kolorektala Cancerregistret (SCRCR) samlar information om patienter som opereras för kolorektal cancer. Det rör sig om patientinformation som ålder, kön och vikt, detaljerad information om operationen och efterföljande vårdförlopp, samt resultat av den mikroskopiska undersökningen av tumören. Information av efterbehandling och långtidsuppföljning registreras också.

Arbete 1

Syftet med studien var att undersöka huruvida komplikation efter operation för tjocktarmscancer påverkar patienternas överlevnad både i form av eventuell kortare livstid samt risk för att få tillbaka cancern. Patienter som genomgått operation för tjocktarmscancer i botande syfte men som efter operationen drabbades av komplikationer av olika grad. Uppgifter som användes vid studien hämtades från registret för tjock- och ändtarmscancer. 6779 patienter som opererades mellan 2007 och 2009 ingick i studien.

Resultatet visade att 73% av de patienter som klarade sig utan att drabbas av komplikation överlevde i 5 år efter operationen jämfört med 60% som drabbades av en allvarlig komplikation. Patienter som drabbas av livshotande komplikation hade

34% högre risk för att dö inom 5 år efter operationen jämfört med patienter som inte fick någon komplikation. Däremot fanns det ingen skillnad mellan grupperna avseende hur många som fick tillbaka cancern vilket tyder på att komplikation inte är kopplat till högre risk för cancer-återfall.

Arbete 2

Syftet med arbete 2 var att undersöka hur behandling av akut upptäckt koloncancer med BtS påverkade kort- och långsiktigt utfall. 143 patienter valdes i bridge to surgery gruppen och behandlades antingen med stent (43%) eller stomi (57%). De jämfördes med 1302 patienter som genomgick en akut operation där tumören opererades bort. Den totala överlevnaden fem år efter operationen var 53.8% i BtS gruppen jämfört med 37.4% i den akut opererade gruppen. Patienter som opererades akut hade 1.4 gånger högre risk att dö inom 5 år än patienterna som behandlades med BtS-metoden. Däremot sågs ingen skillnad i risken för återfall av sjukdomen. Större andel patienter i akuta gruppen hade kvar sin stomi 3 år efter operationen (34.9% mot 17.4%).

Arbete 3

Syftet med detta arbete var att undersöka om specialisering inom kirurgi kunde påverka utfallet efter akut kirurgi för koloncancer. Av 656 patienter, behandlades 319 av team med specialisering i kolorektal kirurgi, 210 av team med specialisering i akutkirurgi och 127 patienter av ett team utan specialisering men består av kirurger ofta med en lång kirurgisk erfarenhet. Resultatet visade ingen skillnad fem års överlevnaden eller frekvensen av återkomst av cancer. Det fanns inte heller någon skillnad i postoperativa komplikationer eller död efter trettio dagar efter operationen mellan grupperna. En högre andel av de patienter som opererades av akut-kirurger hade sin stomi kvar 3 år från operationen jämfört med patienter opererade av kolorektal-eller allmän-kirurger.

Arbete 4

All data från de övriga arbetena kommer från SCRCR. Resultat blir aldrig bättre än den data som används i studien. Det är därför viktigt att data som registreras i SCRCR är pålitliga. Vi genomförde en så kallad valideringsstudie där data från

SCRCR jämfördes med data från patienternas journaler. 700 patienter som blev opererade på 12 sjukhus i Sverige år 2015 blev slumpmässigt utvalda för validering. Resultaten visade mycket god överensstämmelse avseende den mikroskopiska undersökningen av tumören, med en medianöverenstämmelse på 93.4%. Däremot var överensstämmelsen av postoperativa komplikationer sämre. Det var vanligt att den som utförde valideringen inte var överens med den som registrerade uppgifterna i SCRCR 2015. Oftast rörde det sig om lindriga komplikationer där överenstämmelsen av allvarliga komplikationer var bättre. Överensstämmelsen avseende registreringen av cancer-återfall var mycket god, 95.7%.

Slutsatsen av de fyra arbetena studier är att det är viktigt att upptäcka postoperativa komplikationer tidigt och initiera en snar behandling. På det sättet kan en eventuellt allvarlig komplikation undvikas och med överlevnaden förbättras. Man bör överväga att behandla patienter med akut hinder i tjocktarmen enligt metoden BtS för bättre överlevnad och minskad risk för permanent stomi. Akut- och allmän-kirurg kan operera patienter med akut presenterande koloncancer med samma utfall som en kolorektal-kirurg, både i avseendet långtidsöverlevnad samt frekvensen av canceråterfall. Validiteten av data från det Svenska Kolorektalcancer Registret har mycket god överensstämmelse avseende mikroskopisk undersökning av tumören och uppgift om canceråterfall men sämre avseende postoperativa komplikationer, speciellt de lindriga.

Errata

Paper I

Conclusion should read: Complications after colonic resection for cancer are associated with impaired 5-year overall survival and 3-year disease-free survival, mainly via mechanisms other than cancer recurrence.

Paper III

In the table text in table 2 it should read 5-year overall survival instead of mortality.

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