Department of Molecular Medicine and Surgery
Colorectal Surgery Research Group
Karolinska Institutet
Stockholm, Sweden

COLON CANCER
ASPECTS ON SURGICAL TREATMENT AND COMPLETE MESOCOLIC EXCISION

Richard Bernhoff

Karolinska Institutet

Stockholm 2018

Published by Karolinska Institutet.
Printed by E-print AB
Layout by Christina Edberg

ISBN 978-91-7676-919-5

Colon cancer aspects on surgical treatment and Complete Mesocolic Excision

THESIS FOR DOCTORAL DEGREE (Ph.D.)

Publicly defended in Rolf Luft Auditorium, Karolinska University Hospital Solna

Friday February 2, 2018, 9:00 am

By

Richard Bernhoff

Principal Supervisor:
Professor Anna Martling
Karolinska Institutet
Department of Molecular Medicine and Surgery
Colorectal Surgery Research Group

Co-supervisor(s):
Professor Torbjörn Holm
Karolinska Institutet
Department of Molecular Medicine and Surgery
Colorectal Surgery Research Group

Senior Professor Anders Ekbom
Karolinska Institutet
Department of Medicine
Unit of Clinical Epidemiology

Associate Professor Annika Sjövall
Karolinska Institutet
Department of Molecular Medicine and Surgery
Colorectal Surgery Research Group

Opponent:
Associate Professor Eva Angenete
University of Gothenburg
Institute of Clinical Sciences
Department of Surgery

Examination Board:

Associate Professor Jacob Freedman
Karolinska Institutet
Department of Clinical Sciences, Danderyd Hospital

Professor Kenneth Smedh
Uppsala University
Centre for Clinical Research , County of Västmanland

Professor Richard Palmqvist
Umeå University
Department of Medical Biosciences

“Nothing surprises me, I’m a scientist”
Indiana Jones

CONTENTS

LIST OF SCIENTIFIC PAPERS 9

ABSTRACT 11

ABBREVIATIONS 13

BACKGROUND 15
- Basic Physiology and Anatomy 15
- Epidemiology 15
- Etiology 16
- Hereditary colorectal cancer 17
- Screening 18
- Staging 18
- Clinical presentatio 20
- Clinical Workup 20
- MDT-conference. 21
- Surgical treatment 21
- Complete Mesocolic Excision. 22
- Vascular anatomy of the right colon with importance for Complete Mesocolic Excision 25
- Minimally invasive surgery 26
- Adverse events 28
- Centralization of surgery 29
- Emergency presentation 29
- Pathology 30
- Adjuvant treatment 32
- Prognosis 32
- Swedish ColoRectal Cancer Registry (SCRCR) 33
- Stockholm Colon Cancer Project 33

AIMS OF THE THESIS 35

PATIENTS AND METHODS 37
- Paper I 37
- Paper II 37
- Paper III 38
- Paper IV 39

RESULTS 41
Paper I 41
Paper II 41
Paper III. 42
Paper IV 43

DISCUSSION 45

CONCLUSIONS 53

FUTURE PERSPECTIVES 55

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA 57

ACKNOWLEDGEMENTS 59

REFERENCES 63

LIST OF SCIENTIFIC PAPERS

I. Increased lymph node harvest in patients operated on for right-sided colon cancer: a population-based study.
R.Bernhoff , T.Holm, A.Sjövall, F.Granath, A.Ekbom, A.Martling
Colorectal Dis. 2012 Jun;14(6):691-6. doi: 10.1111/j.1463-1318.2012.03020.x.

II. Improved survival after an educational project on colon cancer management in the county of Stockholm – A population based cohort study.
R.Bernhoff, A.Martling, A.Sjövall, F.Granath, W.Hohenberger, T.Holm
Eur J Surg Oncol. 2015 Nov;41(11):1479-84. doi: 10.1016/j.ejso.2015.07.019. Epub 2015 Aug 14.

III. Complete Mesocolic Excision (CME) in right sided colon cancer does not increase severe short term postoperative adverse events.
R.Bernhoff, A.Sjövall, C.Buchli, F.Granath, T.Holm, A.Martling
Colorectal Dis. 2017 Nov 1. doi: 10.1111/codi.13950. [Epub ahead of print]

IV. Oncological outcomes after Complete Mesocolic Excision (CME) in right sided colon cancer - A population based study.
R.Bernhoff, A.Sjövall, T.Holm, A.Martling, C.Buchli
Manuscript

ABSTRACT

In rectal cancer, total mesorectal excision (TME), including surgery with dissection outside the mesorectal fascia, together with pre-operative radiotherapy improves survival. An educational effort on TME improved results in rectal cancer in Stockholm in the 1990's. The Stockholm Colon Cancer Project (SCCP) was an educational project on the management on colon cancer, launched in 2004, introducing Complete Mesocolic Excision (CME). CME is described as an en-bloc resection of a large part of the mesocolon with preservation of the mesocolic fascia and a proximal vascular ligature. The term 'CME' is relatively novel although the concept has been relevant since long ago. A partly synonymous term is D3-surgery, referring to the resection of centrally disposed lymph nodes. The overall aim of this thesis was to evaluate the effect of the introduction of CME on short- and long term outcome for patients with colon cancer. In **Paper I** all patients operated for right-sided colon cancer in the Stockholm area, between 1996 and 2009 were divided into three time periods. The number of analyzed lymph nodes increased significantly over the study period. The proportion of patients having less than 12 lymph nodes analyzed in the specimen decreased from 77.1% to 18.3% ($p<0.001$). Metastatic index (MI) (in lymph node positive patients) was 0.40 in period 1 and 2, compared to 0.25 in period 3 ($p<0.001$). In **Paper II** survival for patients diagnosed with right sided colon cancer before (2001-2003, n=819) and after (2006-2008, n=897) SCCP was studied. The proportion of patients having a tumor resection was larger in the earlier group, 96.6% compared to 91.2% the latter group ($p<0.001$). There were a larger proportion of patients having emergency tumor resection in the earlier time period and there was a significantly higher proportion of R0 resection in the latter group. The crude three year disease free survival among patients in TNM stage I-III who had their tumor resected was also significantly higher in the latter time period, 71.5% compared to 64.6% ($p=0.006$). In **Paper III** patients operated for right sided colon cancer between 2004 and 2012 was studied in a case-control study. Cases were patients that died within 90 days of surgery or had an emergency re-operation. Two controls per case were matched for sex, age-interval, TNM-stage and emergency surgery. Exposure was CME determined from surgical reports. The reports were classified as "CME" or "no CME" according to pre-defined criteria. The Odds Ratio (OR) for postoperative death or re-operation was 0.75 (95% CI: 0.50-1.13)($p=0.17$) for CME surgery compared to no CME surgery, suggesting CME is not associated with short term morbidity or mortality.

In **Paper IV**, all patients, electively operated for right sided colon cancer (stage I-III) in Stockholm between 2008 and 2012 were studied in a cohort study (n=1171). CME-exposure was determined in a similar way as in paper III. Five year relapse-free survival (RFS) was 73.6% in the "CME" group vs 63.5% in patients classified as "no CME". The multivariable adjusted model showed a significantly improved RFS for the "CME" group, Hazard Ratio (HR)=0.74 (95% CI: 0.58-0.94, $p=0.014$).

ABBREVIATIONS

AL	Anastomotic Leakage
ASA	American Society of Anesthesiologists
CEA	Carcinoembryonic antigen
CI	Confidence Interval
CME	Complete Mesocolic Excision
CRC	Colorectal Cancer
CT	Computed Tomography
CRM	Circumferential Resection Margin
DFS	Disease Free Survival
FAP	Familial Adenomatous Polyposis
FOBT	Fecal Occult Blood Test
GTH	Gastrocolic Trunk of Henle
HNPCC	Hereditary Nonpolyposis Colorectal Cancer
HR	Hazard Ratio
ICA	Ileocolic Artery
IMA	Inferior Mesenteric Artery
IRA	Ileo-Rectal Anastomosis
LCA	Left Colic Artery
LOS	Length of Stay
LVI	(extramural) Lympho Vascular Invasion
MCA	Middle Colic Artery
MDT	Multi-Disciplinary Team
MI	Metastatic Index
OR	Odds Ratio
OS	Overall Survival
PME	Partial Mesorectal Excision
RCA	Right Colic Artery
RCT	Randomized Controlled Trial
RFS	Relapse Free Survival
RGEV	Right Gastro-Epiploic Vein
SCCP	Stockholm Colon Cancer Project
SCRCR	Swedish Colorectal Cancer Registry
SMA	Superior Mesenteric Artery
SRA	Superior Rectal Artery
SRCV	Superior Right Colic Vein

BACKGROUND

Basic physiology and anatomy

the colon is a major part of the gastrointestinal tract. Its functions include re-uptake of fluids and electrolytes as well as storage and elimination of rest products of food. The colon is embryological derived from the midgut and the hindgut. At rest, 4.3% of cardiac output flows to the large intestine[1]. The vascular supply of the colon is, thru different vessels, derived from the abdominal part of the aorta. The superior mesenteric artery (SMA) departs from the aorta in the upper part of the abdomen. The SMA supplies the small bowel but is also the origin of the vessels supplying the ascending colon and the proximal two thirds of the transverse colon. The ileocolic artery (ICA) supplies the terminal ileum and the caecum. The right colic artery (RCA) supplies the ascending colon but is subject to anatomical variations, it is actually only present in 33-63% of individuals[2-4]. Thus, in many individuals the ascending colon and the right flexure are supplied from branches from the ICA and from the middle colic artery (MCA). The MCA arises from the SMA and supplies the proximal two thirds of the transverse colon. The distal part of the transverse colon and the descending colon are supplied from the left colic artery (LCA), which is a branch from the inferior mesenteric artery (IMA), in turn the last major branch of the aorta before it divides into the iliac arteries. The sigmoid colon has its arterial supply from the sigmoidal arteries which are branches from the superior rectal artery (SRA), the continuation of the IMA after its division from the LCA. The venous drainage follows the corresponding arteries. However, the venous drainage from the right colon has some complex anatomical features, important for surgical oncology as well as patient-safe surgery. Lymphatic drainage from the colon follows the vascular pattern.

Common definitions of the boundary between the colon and the rectum are the level of the sacral promontory or within 15 cm from the anal verge.

Epidemiology

Colorectal cancer (CRC) is a common disease in man. Globally it's the third most common cancer, causing approximatively 600 000 deaths yearly. The incidence varies regionally with Western Europe as an area of high incidence, together with Australia, New Zealand and North America. The lifetime risk of acquiring colon- or rectal cancer is in the United States between 5 and 6%. High incidence of CRC seems to be associated with "western lifestyle" and is

rising in many low- and middle-income countries whereas in highly developed countries rates are stabilizing or decreasing[5-7].

In Sweden, CRC is the third most common form of cancer, after prostate- and breast cancer. Between 2007 and 2011 there were in Sweden approximatively 6000 new cases of CRC yearly. About two thirds of them were colon cancer. The incidence rate of CRC in Sweden was 69/100 000 in 2015. In Sweden the age-standardized incidence of colon cancer has increased in recent decades, while rectal cancer has had an almost unchanged incidence. CRC is an uncommon disease in young people. Less than 5% of patients are under the age of 50 at the time of diagnosis, with a similar pattern for colon- and rectal cancer[8]. However, in non-Hispanic white people in the United States an increase in CRC has been noted, mostly in distal colon cancer and rectal cancer[9].

Etiology

It is a common accepted view that CRC is developed from neoplastic adenomas in the bowel mucosa. This is supported by the fact that colonoscopic polypectomy leads to a lower-than-expected incidence of CRC[10, 11]. The molecular pathway in the transformation from polyp/adenoma to cancer is complex. The steps required for the development of cancer often involve the mutational activation of an oncogene coupled with the loss of several genes that normally suppress tumor genesis[12].

Riskfactors

Many separate risk factors have been studied for determining a connection to the development of CRC. Smoking, a risk factor for numerous causes of illness but often not primarily mentioned when discussing CRC, has in two large meta-analyses been shown to be a risk factor for developing CRC[13, 14]. Alcohol consumption has in a study from 2004 been associated with a moderate, and dose dependent, risk-elevation for developing CRC[15], supported by later studies[14]. High intake of red and processed meat increases the risk of CRC[14, 16-18]. Obesity has also been found to be a risk factor for CRC[14]. Recently, a Danish study also noted that high body mass index (BMI) or being tall in childhood is associated with increased risk for colon, but not rectal, cancer[19]. An Israeli study showed that being overweight (85th weight-percentile) in adolescence was associated with an increased risk of subsequent colon cancer, whereas only obesity (95th weight-percentile)was associated with rectal cancer[20]. Diabetes, both type 1 and 2, is a risk factor for developing CRC[21, 22]. Also, sedentary behavior is a risk factor for colon, but not rectal, cancer[23].

Compared to the general population, and to patients undergoing appendectomy, non-surgical treatment for appendicitis is associated with an elevated risk for right sided colon

cancer, even after exclusion of patients diagnosed with colon cancer the first 12 months after the appendicitis diagnosis[24, 25].

Factors reducing the risk of colorectal cancer

Long term use of acetylsalicylic acid (Aspirin) has been shown to reduce the risk of developing colorectal adenomas as well as CRC[26-28]. Physical activity is strongly associated with a reduced risk of colon cancer (CC)[29]. Oral calcium supplementation has in a randomized controlled trial (RCT) been shown to reduce the risk of cancer disease in general, although the numbers were too small for CRC specifically[30]. In animal experimental studies, Vitamin D deficiency has been associated with cancer development and growth[31]. In population based studies, intake of calcium and dairy products has been shown having a protective effect against colon cancer[18, 32, 33]. There are studies showing that a high intake of dietary fibers reduces the risk of CRC[34, 35] proposedly by reducing constipation and bowel transit time, while other studies have not been able to confirm that connection[36]. The risk-reduction seen in some studies associated with high fiber intake may be attributed to intake of fruit and vegetables[35, 37]. Coffee consumption seems to be associated with a lower risk of CRC[38].

Hereditary colorectal cancer

The absolute majority of cases of CRC are so called sporadic. Hereditary CRC occurring due to known mutations and defects in certain genes accounts for about 5% of all cases of CRC[39, 40].

Familial Adenomatous Polyposis (FAP) is an autosomal-dominant disorder that is associated with mutations in the *APC* tumor suppressor gene. It has an approximate prevalence of 1 in 10,000 births and is characterized by the presence of hundreds or even thousands of colonic adenomatous polyps. Polyps occur at young age, often before 20. If the colon and rectum are not removed, the lifetime risk of CRC is >90%, often occurring before the age of 40. FAP accounts for less than 1% of cases of CRC[39, 41].

Lynch Syndrome, synonymous with *Hereditary Nonpolyposis Colorectal Cancer (HNPCC)*, is the most common hereditary CRC syndrome and is caused by inherited mutations affecting any of four DNA mismatch repair (MMR) genes. It accounts approximately for 2% to 3% of all CRCs. It is also an autosomal dominant, inherited disorder. The average patient age at cancer diagnosis is 45 years. Individuals with HNPCC have a high occurrence of synchronous and proximal colonic malignancies. Lynch syndrome also entails elevated risk for developing other malignancies, especially endometrial, but also ovarian, gastric, small intestine, or renal cancer[42-44].

Screening

Screening is testing for disease in apparently healthy people in order to detect disease in an early stage, enabling successful treatment. Different methods of screening for CRC includes Guaiac based faecal occult blood test (gFOBT), Faecal immunochemical tests (FIT) and detection of stool DNA. In the case of a positive test the patient is offered diagnostics, often a colonoscopy. Randomized studies have shown a possibility for lowering CRC-deaths by screening measures in a population[45, 46]. In 2003 the Council of the European Union issued recommendations for CRC screening and in Stockholm, Sweden, screening started in 2008 for individuals aged 60-69. Of those that during the first five years of screening program participated with Fecal Occult Blood Test (FOBT) 1.8% underwent screening-colonoscopy and 0.1% was eventually diagnosed with CRC[47]. Screening detected cancers have been found to be of lower stage and the patients having better prognosis[48-50].

Staging

Figure 1. *Cuthbert Dukes.*

In 1936 the British pathologist Cuthbert Dukes wrote a paper on classification of rectal tumors[51]. It became the widely accepted classification system for CRC, grading the disease into Dukes A, B, C or D. It has later been replaced by the TNM system where T stands for tumor, N for nodal-involvement and M for (distant) metastases.

T-stage

TX – Primary tumor cannot be assessed

T0 - No evidence of primary tumor

Tcis - Carcinoma in situ: intraepithelial or invasion of lamina propria

T1 - Tumor invades submucosa

T2 - Tumor invades muscularis propria

T3 - Tumor invades through the muscularis propria into the pericolorectal tissues

T3a – Minimal invasion: <1mm beyond the borders of the muscularis propria

T3b – Slight invasion: 1-5mm beyond the borders of the muscularis propria

T3c – Moderate invasion: >5-15mm beyond the borders of the muscularis propria

T3d – Extensive invasion: >15mm beyond the borders of the muscularis propria

T4a - Tumor penetrates to the surface of the visceral peritoneum

T4b - Tumor directly invades or is adherent to other organs or structures

N-stage

NX - Regional lymph nodes cannot be assessed

N0 – No regional lymph node metastasis

N1 - Metastasis in 1-3 regional lymph nodes

N1a - Metastasis in 1 regional lymph node

N1b - Metastasis in 2-3 regional lymph nodes

N1c - Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis

N2 - Metastasis in 4 or more lymph nodes

N2a - Metastasis in 4-6 regional lymph nodes

N2b - Metastasis in 7 or more regional lymph nodes

M-stage

MX – Distant metastasis cannot be assessed

M0 - No distant metastasis

M1 - Distant metastasis

M1a - Metastasis confined to 1 organ or site

M1b - Metastases in more than 1 organ/site or the peritoneum

Table 1. *TNM-classification*[52].

The T, N and M entities are combined to a TNM-stage, shown slightly abbreviated in the table below.

Stage	T	N	M
0	Tis	0	0
I	1-2	0	0
II A	3	0	0
II B-C	4a-b	0	0
III	1-4	1-2	0
IV	1-4	0-2	1

Table 2. *Abbreviated staging for colon cancer*[52].

cTNM ('c' for clinical) is based on clinical findings and radiology. yTNM describes stage in patients whose first course of treatment consists of chemotherapy or radiation. pTNM ('p' for pathology) is based on clinical and radiological information, together with the information from the pathologists examination of the surgical specimen.

Clinical presentation

Often, early signs is non-specific but symptoms that should evoke suspicion of CRC are: anemia, blood in the stools or change of bowel habits[53]. General symptoms (including fatigue, weight loss and unknown fever) and anemia are more common in right-sided colon cancer whereas blood in stools and change in bowel habits are more commonly associated with left sided colon cancers[54-56]. Abdominal pain, change of bowel habits and acute symptoms are more common in higher disease stage, TNM-stage > II[54]. More than 80% of non-screening diagnosed patients had in a study anemia *or* visible blood in stools[54].

Clinical Workup

The tumor is often diagnosed at a colonoscopy where a tissue sample is taken from the tumor. An alternative to colonoscopy is computed tomography of the colon (CT-colon) with the obvious disadvantage of inability to take tissue samples from a tumor. The patient is then often admitted for a computed tomography (CT) of the thorax and abdomen in the search for systemic disease or locally advanced cancer. The accuracy for pre-operative CT in staging of colon cancer was in a review 67%, 69% and 95% respectively for T, N and M stage[57]. Magnetic Resonance Imaging (MRI) can be used for pre-operative staging of colon

cancer with at least as good accuracy as CT but more resource consuming[58]. The biochemical tumor marker Carcinoembryonic antigen (CEA) has if used for diagnostic purposes both low sensitivity and specificity. CEA is merely used for baseline for future follow up and detection of relapse and as a marker for advanced disease. CEA is a useful marker for metastatic relapse and has also been found to be a pre-operative prognostic marker in colon cancer stage II[59, 60].

MDT-conference

The principle to discuss individual patients at a Multi-Disciplinary Team (MDT)-conference has been mostly developed regarding rectal cancer. More recently also colon cancer patients are more frequently discussed, not only post-operative, but also pre-therapeutic. In clinical practice, at these often weekly meetings, individual patients are discussed by present surgeons, radiologists, oncologists, pathologists and contact-nurses. Typically the first MDT-meeting is held after the clinical workup is finished and the conference suggests a treatment for the patient. Regarding colon cancer, the most common decision at the pre-therapeutic MDT-conference is curatively intended surgery. Other possible decisions include neo-adjuvant chemotherapy, palliative chemotherapy or palliative surgery. Often the patient is discussed at a second MDT-meeting after surgery and the pathologist's report of the specimen is highlighted and adjuvant treatment is perhaps recommended.

There are no randomized studies on the effect on outcome for patients discussed (or not) at an MDT. Patients with rectal cancer are more frequently discussed at MDT-conferences than patients with colon cancer[61]. In the case of rectal cancer, being discussed at an MDT means increased probability for the patient to receive neo-adjuvant treatment[62] and at surgery having a negative circumferential resection margin (CRM)[63]. Contemporary guidelines advices that "all patients with CRC should be treated within a framework of MDT-conferences"[53].

Surgical treatment

Curative treatment for colon cancer includes resection of the tumor-bearing bowel segment. There are standard types of operations, depending on the location of the tumor. The types of standard resections are based on the knowledge of lymphatic drainage and lymph node anatomy.

Right sided hemicolectomy is the standard type of operation for cancers in the caecum, the ascending colon, the hepatic flexure and in the proximal part of the transverse colon. In the case of a distal transverse cancer a so called "extended right sided hemicolectomy" can be done. The procedure includes division of the ICA, the RCA (if present) and the MCA, or at least its right branch. An anastomosis between the terminal ileum and the transverse colon

is made.
Resection of the transverse colon is an oncologically limited type of operation for a malignancy in the transverse colon. Left sided hemicolectomy is the procedure for cancers in the left flexure or the descending colon. It includes division of the LCA and a transverso-sigmoidal anastomosis.
In the common case of cancer in the sigmoid colon, left-sided hemicolectomy or sigmoidal resection is done. The level of the vascular tie is often dependent of the extent of the bowel resection. If the cancer is situated in the distal sigmoid, or in the recto-sigmoidal junction, the upper part of the rectum is also removed, a so called PME, partial mesorectal excision. Colectomy, sub-total or total, is justified in the case of synchronous tumors in the colon or in patients with FAP or Lynch syndrome. Colectomy can also be advocated if the patient has had CRC earlier in life. If the rectum can be spared, the bowel-continuity can be accomplished with an ileo-rectal anastomosis (IRA). If not, a pelvic reservoir can be an alternative, especially in young patients[53].

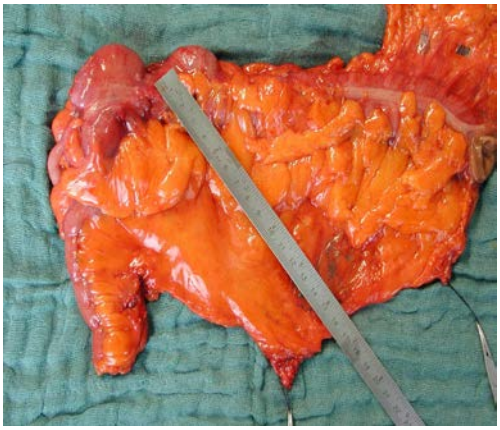

Figure 2. *CME-specimen from right sided hemicolectomy. Photo by Prof Werner Hohenberger.*

Complete Mesocolic Excision

Complete Mesocolic Excision (CME) was first described by Professor Werner Hohenberger, University of Erlangen, Germany[64]. A similar description, but named ‘mobilization along anatomical planes’ comes from Professor Lesley Bokey, Sydney, Australia[65].
The main background reasoning with CME is that the lymphatic spread of a colon carcinoma follows the lymphatic vessels along the arteries and veins in the mesentery. These vessels are embedded in the mesentery, which is covered by a thin visceral fascia, like an envelope. If this visceral, peritoneal fascia is not breached, tumour spread will be, in theory, less likely. On the medial/front side of the mesocolon the peritoneal fascia is visible like a very thin, shiny surface. On the back/lateral side, this plane lies onto the retroperitoneal surface. The plane between the back side of the colon mesentery and the retroperitoneal area is sometimes called

the fascia of Toldt[66].
CME is applicable to left and right sided colectomies but here, and often elsewhere, mainly described and discussed for right sided hemicolectomies. The reason for this is probably that the anatomy is more challenging on the right side, both regarding the blood-vessels as well as other present organs such as the pancreas and the duodenum.
One major part of a CME-operation is to separate the mesocolic/visceral fascia from the retroperitoneal surface in an embryologic plane. In the case of a right sided hemicolectomy, Hohenberger describes mobilization of the duodenum with the pancreatic head (Kocher's maneuver) and the mesenteric root up to the origin of the superior mesenteric artery. Then, the uncinate process of the pancreas, with the mesopancreas and part of the duodenum is separated from the mesentery, ensuring access to the mesenteric vein.
The other main component of a CME is the central vascular ligation (CVL). When the central vascular anatomy is exposed the operation includes a central tie and division of the supplying arteries, and veins, ensuring a large resected portion of the mesocolon, containing many lymph nodes. In the case of a cancer in the caecum or in the ascending colon, the ICA and the RCA (if existing) and the corresponding vein(s) are divided where they originate from the SMA and the SMV. The right branch of the MCA should be divided after its division. If the colon cancer is situated in the right flexure, in the transverse colon or in the left flexure, a more proximal division of the MCA is advocated.
For tumors of the left colon, the splenic flexure is mobilized. The mesocolon of the descending colon and the sigmoid are dissected off the retroperitoneal plane leaving the prerenal fat, the ureter, the vesicular or ovarian vessels covered. The greater omentum is detached from the transverse colon for full exposure of the lesser sac and subsequent division of the transverse mesocolon at the lower edge of the pancreas. The LCA is divided[64, 65].
In Japanese literature colon resection for malignancies with dissection of lymph nodes near the SMA or SMV is called "D3-resection"[67].

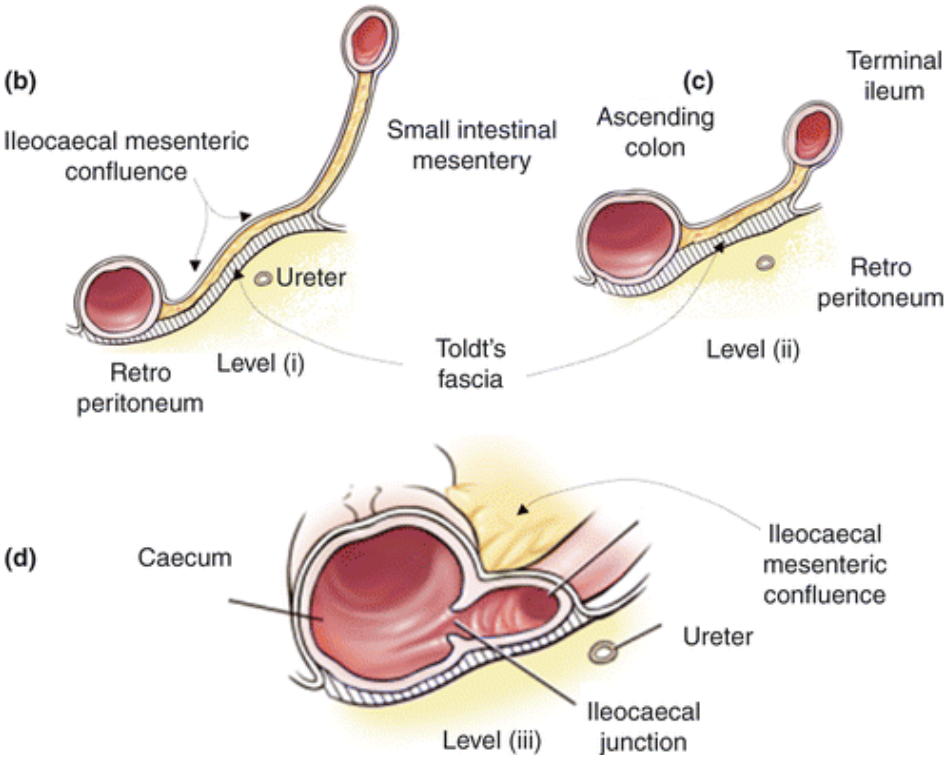

***Figure 3**. Cross sectional view of the right colon and its mesentery. Reprint with permission[66].*

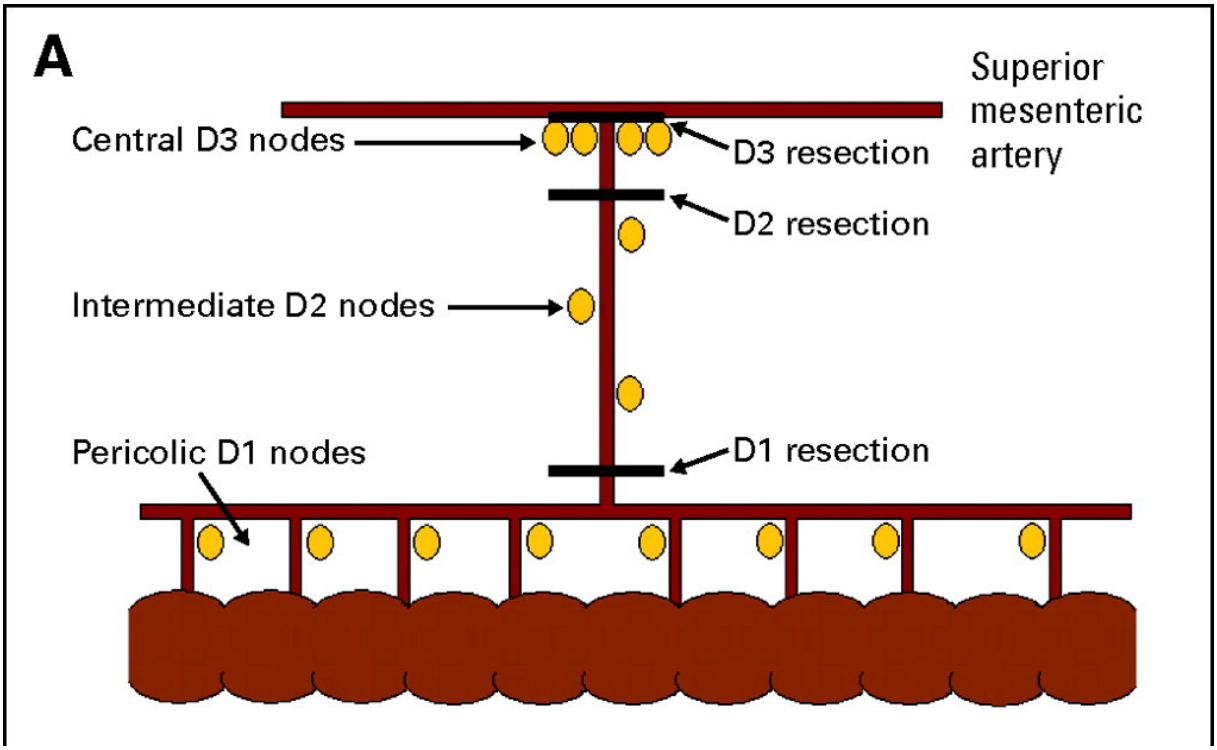

***Figure 4.** Schematic view of the Ileocolic Artery and corresponding lymph nodes. Reprint with permission[67].*

Vascular anatomy of the right colon with importance for Complete Mesocolic Excision

Surgical challenges when handling a right sided cancer includes dissection close to the pancreas and the duodenum and a more complex vascular anatomy in the area of, or behind, the hepatic colonic flexure, with close relation to the pancreatic head and the duodenum. Several authors have performed cadaver dissections in order to study the vascular anatomy related to surgery of the right colon. In those studies, the ICA is always present, always arises from the SMA and can pass both anteriorly or posteriorly to the SMV[2-4.] Common is the description of a venous gastrocolic trunk anterior to the head of the pancreas, sometimes referred to as the Gastrocolic Trunk of Henle (GTH), that drains the confluence of the Superior Right Colic Vein (SRCV) and the right gastroepiploic vein (RGEV) and in turn draining into the SMV[68, 69]. The GHT is subject to extensive anatomical variations[2]. Well known for colorectal surgeons are the troublesome bleedings that can occur in the area of the right flexure/pancreatic head. This is often caused by excessive traction during surgery. These bleedings often comes from the SRCV which may be torn and retracted under the uncinate process of the pancreas. As mentioned above, the RCA is absent in many humans and therefore the SRCV has no corresponding artery and may therefore be difficult to anticipate during surgery[68]. The MCA inevitable arises from the SMA. The MCV drains into the SMV but in about 25% of individuals it does not convert into one stem before entering the SMV[2].

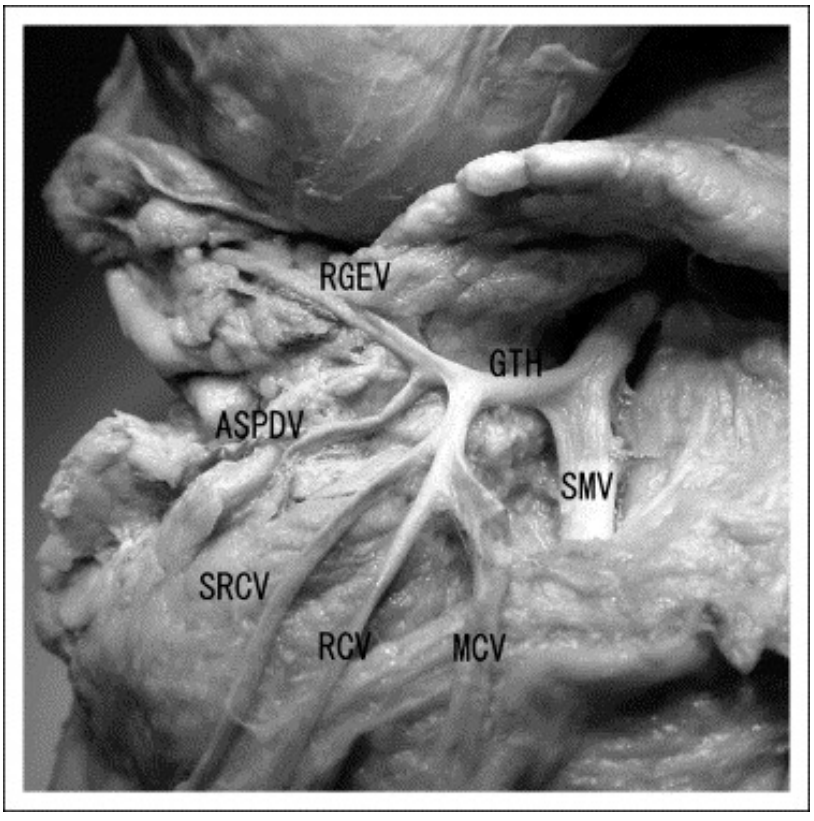

Figure 5. *Photo of right colic venous anatomy. Reprint with permission[68].*

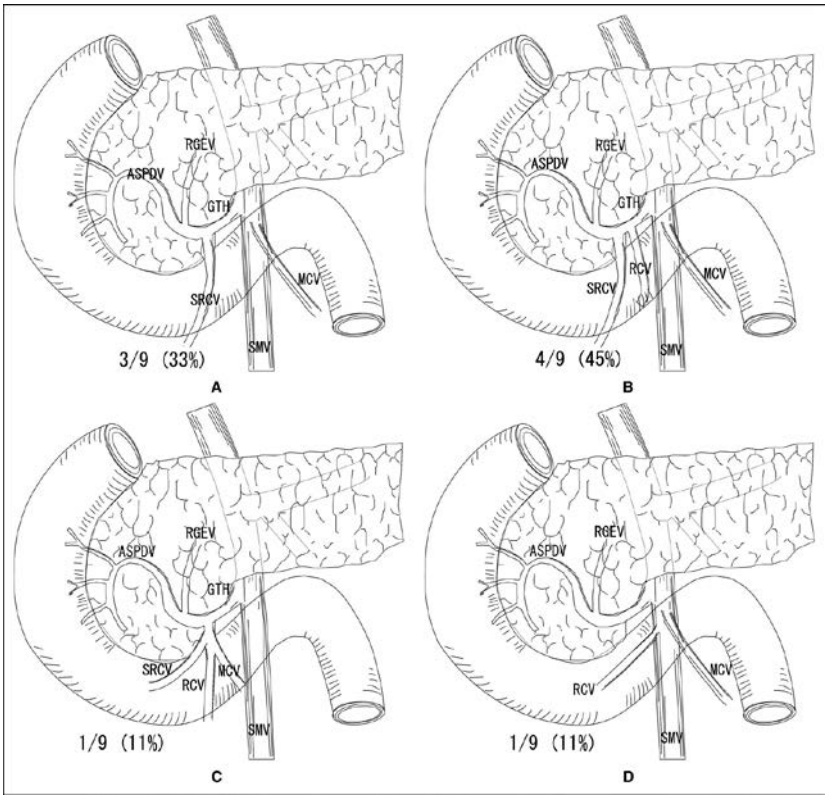

Figure 6. *Venous variations. Reprint with permission*[68].

Minimally invasive surgery

Laparoscopic resections for colon cancer started to develop in the early 1990's. Both short and long term outcomes have been studied in randomized controlled trials (RCT's). The COLOR trial investigated 1248 patients that were randomized to open or laparoscopic resection for right- or left sided colon cancer. The laparoscopic operations took longer time but resulted in less blood loss. There were no differences in pTNM stage, lymph node yield or positive resection margins. The laparoscopically operated patients resumed digestive- and bowel functions quicker, were able to leave the hospital earlier and needed less analgesics postoperatively. Serious complications, both surgical and non-surgical did not differ between the groups[70]. In the long term follow up of the COLOR trial there were no differences in 3- or 5-year disease free survival (DFS) or overall survival (OS) and no difference in the frequency of hospitalization for bowel obstruction, depending on whether the patient had undergone laparoscopic or open surgery. The study could not, due to its non-inferiority design, rule out that laparoscopic surgery for colon cancer is not inferior to open surgery[71, 72].

In the randomized CLASSIC trial patients operated laparoscopically did not have positive margins in a higher frequency and tumor- and nodal stage were similar[73].

The COST trial was a randomized multi-center study with 872 patients undergoing open or laparoscopic resections for colon cancer. There was no difference in cancer recurrence after 4 years or in 5y OS[74, 75]. A meta-analysis of the COST, COLOR and CLASSIC studies

concluded that laparoscopic surgery for colon cancer is oncologically safe[76].
In a retrospective study from 2013, patients operated with a laparoscopic colorectal resection had a lower risk both for being admitted to hospital for bowel obstruction and for being operated for obstructing adhesions[77].
It is nowadays considered that laparoscopic resection for colon cancer has short term benefits and no obvious long term disadvantages, compared to open surgery. Laparoscopic colonic resections are more expensive than the open counterpart if looking at the costs for the operation and the healthcare system. Some of those costs are however regained when looking at society costs including for example sick-leave[78]. However there are patients and situations were laparoscopy according to many surgeons is not a method of choice, for example an abdomen with massive adhesions from previous surgery, locally advanced T4 tumors and an emergency situation with obstructed or perforated bowel. Many surgeons with experience from laparoscopic colonic resections are also of the opinion that tumors located in the flexures or in the transverse colon are not perfectly suitable for laparoscopic resection although shown feasible[79, 80].
In Sweden, the proportion of resections for colon cancer performed with laparoscopy has, compared to other European and Nordic countries, been low but has increased after 2010[81] although many patients probably eligible for laparoscopic surgery are still operated with open surgery[82].

Robotic surgery
Robot assisted laparoscopic surgery was introduced in the previous decade. When referred to a "robotic" operation one usually means a laparoscopic operation where two or more ports/instruments are operated by the robotic system but controlled by a human surgeon at the console in the operating room a few meters from the patient. Typically, a second surgeon/assistant is operating conventional laparoscopic instruments bedside. Often mentioned benefits with robot assisted laparoscopic surgery are superior high-definition view, improved ergonomics and ability to work with high precision in confined spaces.
An early established area of use for the robotic system was prostatectomy for prostate cancer. Robot assisted laparoscopic radical prostatectomy seems to be oncologically safe[83].
In a prospective non-randomized comparison between open retro pubic radical prostatectomy and robot assisted laparoscopic prostatectomy (the LAPPRO-study) the authors concludes that there was no difference in urinary leakage and a modest benefit for robot assisted laparoscopy regarding erectile dysfunction[84]. Robot assisted laparoscopic radical prostatectomy is more expensive than open retro pubic radical prostatectomy[85, 86].
Robotic assisted laparoscopic colorectal resection surgery has also been established. In the case of rectal cancer there are several studies comparing robotic assisted laparoscopic surgery with conventional laparoscopic surgery. Robot assisted laparoscopic surgery is according to the majority of these studies associated with longer operating time[87-89]. There

are no differences in short term oncological parameters such as lymph node yield or positive margins[88-91]. The robotic operations seem to be converted to open surgery to a lesser extent and there is less short term serious complications associated with robot assisted laparoscopic operations than conventional laparoscopic surgery[87, 92]. There are no studies comparing robotic surgery for rectal cancer to open surgery but laparoscopic surgery for rectal cancer is oncologically equivalent to open surgery[93].
Robot assisted laparoscopic right hemicolectomy for cancer has also been demonstrated feasible[94], yielding less blood loss and shorter time to first post-operative flatus but longer operation time and is more expensive[95].

Adverse events

Resection surgery for colon cancer is vitiated with complications. Complications of any kind have been reported in more than one in four patients undergoing colorectal resection surgery[96]. Major postoperative complications include wound infection, anastomotic leakage (AL), ileus and bleeding[97]. Pre-operative, patient related risk-factors for encountering complications in general, non-thoracic surgery includes American Society of Anesthesiologists (ASA) grading >2, emergency surgery and congestive heart failure[98]. In laparoscopic colorectal surgery male gender, ASA>2 and age >=75 have been found to be risk factors for complications[99].
In segmental colonic resection with formation of an anastomosis, AL is a specific and feared complication. It is associated with morbidity, mortality, prolonged hospital stay and suffering. In order to heal properly, the anastomosis must be tension-free and have an adequate blood supply[100]. In an AL, the integrity of the anastomosis is for some reason compromised and intraluminal bowel contents and/or fluid is displaced out into the peritoneal cavity, causing inflammation, sepsis and later abscesses. The condition is often revealed within a week from the index operation but sometimes later[101]. Typically, the patient's condition is worsened with ileus, abdominal pain, fever, rising inflammatory parameters and sometimes hemodynamic instability. Abdominal CT scan has a high sensitivity for detecting AL[101], but sometimes the diagnosis is made upon re-laparotomy. There is no universal definition of AL[102]. The frequency of AL after colonic resections (not involving anastomoses to the rectum) has been found to be 1-4% and short term mortality after AL 6-16%[101, 103, 104]. Male gender is a risk factor for AL[103-105], as is smoking, alcohol consumption and ASA>2[100]. Regarding obesity and steroid use and risk for AL, data points in different directions[100]. In a Cochrane review from 2011, based on six studies, of which at least four contained cancer resections, there was a lower frequency of AL after stapled ileocolic anastomoses[106]. In contrary, a large Swedish population based study, showed that hand-sewn ileocolic anastomoses had a lower leakage rate than stapled[107]. A recent study found an increased risk for AL with stapled anastomosis in right sided hemicolectomy[108].

Even adjusted for disease stage, age and 30-day mortality AL is negatively associated with overall survival and cancer specific survival[103, 104, 109].

Centralization of surgery

Treatment for colon cancer is nowadays a complex procedure with many components. There has been a debate in Sweden and in other countries regarding centralization, in other words that treatment for a specific condition should be given in fewer hospitals. The foremost argument for centralization is higher caseloads for individual surgeons and teams, proposedly leading to better short- and long term results. Other argued pros with centralization includes ability to introduce new technology and methods, improved conditions for teaching, research and learning, better conditions for MDT-conferences and better abilities to treat patients with advanced co-morbidities.
Arguments against centralization of colon cancer treatment comprises lack of evidence that high volume yields better results, consequences for other specialties and patients, more difficult to recruit and keep, surgeons and also the argument that both information technology and transport logistics make smaller hospitals coming closer to larger centers.

In a Danish study of AL after resections for colon cancer, patients were included over a period of 7.5 years. During the study, the number of hospitals performing resections for colon cancer decreased from 48 to 28 without a decrease in the frequency of AL[105]. A Swedish study showed improved 5-year overall survival after surgery for rectal cancer in a region when surgery for those patients was centralized from four to one hospital and a dedicated colorectal unit was formed[110]. The same group also reported improved results after surgery for sigmoid tumors after the above described centralization[111]. Another Swedish study showed that patients operated for rectal cancer where a surgeon operating at least 12 such operations a year participated had a better outcome[112]. A Cochrane review from 2011 concludes that high-volume hospitals and, especially, high-volume- and specialized colorectal surgeons is associated with better long term OS[113]. In the Stockholm area, the number of hospitals surgically treating CRC, have the last decade decreased from eight to five, while the population at the same time is increasing.

Emergency presentation

The definitions of “emergency” presentation and acute operation are heterogeneous. The proportion of patients that have their colon tumor resected emergently is high, often reported to be over 20%. Emergency resection of a colon cancer is associated with poor outcome, both in the short and in the longer perspective. In the long term, emergency

presentation or operation carries a worse prognosis, even after exclusion for early post-operative deaths and adjustment for sex, age and stage[114-117].

Pathology

More than 90% of colon tumors are adenocarcinomas. Mucinous cancer is a subtype of adenocarcinoma where more than 50% of the tumor consists of mucin producing epithelium and "pools" of mucin. It accounts for about 10-15% of all CRC's. Signet ring cells carcinoma, named by its appearance in microscopic view, is rare, representing maybe 1% of all CRC's and has worse prognosis. Mucinous cancers presents in later stages but stage-adjusted they don't have worse prognosis than ordinary adenocarcinomas. Some but not all studies show that patients with mucinous cancers are younger[118, 119].

When the bowel specimen, including the tumor, has been resected it is sent to the pathology department. It can be sent fresh or fixed in formalin. Macroscopic evaluation and photographing is recommended. Tumor site and planes of surgery is evaluated and the surgical planes are dyed with ink. The mesocolon is dissected for lymph nodes. To facilitate the finding of lymph nodes, fat clearing agents can be used[120]. Samples for microscopic evaluation is taken and evaluated for T-stage, clear resection margins, tumor deposits, extramural lympho-vascular invasion (LVI) and peri-neural invasion[53, 121].
CRM has been defined for rectal cancer specimens. It is defined as the shortest distance from the tumor border to the resection margin. 1 mm or less is defined as a positive CRM. More than 1 mm is defined as a negative CRM. Positive CRM is associated with inferior outcome in rectal cancer[122, 123]. The term CRM is much less used in colon cancer although microscopically radical surgery is as important for tumor clearance and survival[124, 125].

Lymph node yield

One of the crucial factors for prognosis and possible adjuvant treatment is the examination of lymph nodes from the colonic mesentery. Already in 1909 Jamieson and Dobson described the necessity of removing relevant lymph nodes at surgery for colon cancer[126]. If the examined lymph nodes contain tumor cells the patient is graded as at least N1 and thereby pTNM stage III. This has implications both regarding prognosis as well the decision to offer the patient adjuvant chemotherapy. Studies regarding the relationship between the number of analyzed lymph nodes and the probability of a false negative classification of node positive disease show that the adequate number is depending on T-stage. According to Wu et al, the statistical number of required analyzed nodes to correctly diagnose the N-stage with 80% confidence is for T1-tumors three nodes, for T2-tumors eight nodes and for T3-tumors 24 nodes[127]. In table 3 the probability for the patient *not* having lymph node

metastases is shown, in relation to T-stage and the number of examined, healthy lymph nodes[128].

Nodes /stage	1	5	8	10	12	15	18	20	25
T1	91.5	96.3	97.5	98.0	98.3	98.7	98.9	99.0	99.2
T2	84.5	92.9	95.2	96.1	96.7	97.4	97.8	98.1	98.5
T3	60.8	78.9	84.9	87.4	89.3	91.3	92.8	93.5	94.9
T4	47.9	68.9	76.9	80.5	83.2	86.2	88.4	89.5	91.7

Table 3. *Probability of true N0-stage related to number of analysed non-metastatic lymph nodes. Reprint with permission[128].*

pT1 and pT2 tumours carries a relatively low risk of lymph node metastases[128, 129]. There are Japanese studies on lymph node metastases patterns, mentioning findings in central, D3 lymph nodes in less than 6% of specimens[130].
The minimum number of lymph nodes that the pathologist need to examine in order to correctly classify the patient as N0 or N+, has been debated. In Sweden, as well as in the United States and in Germany, there are guidelines suggesting a minimum of 12 examined lymph nodes as a marker for quality in colon cancer surgery[53, 131, 132]. There are more lymph nodes retrieved from younger patients and more nodes from right sided cancers compared to left side[131, 133]. In a study of more than 7000 surgically resected CRC patients Morris et al describes many factors influencing the numerical lymph node yield such as tumor characteristics, patient age, calendar year and degree of specialization of surgeons and pathologists[134]. Both in node-negative and node-positive colon cancer, the number of analyzed lymph nodes removed at surgery are influencing survival. Low numbers are associated with a worse prognosis[135-138]. The number of metastatic lymph nodes divided by the number of analyzed nodes has been named Metastatic Index (MI), Index of Metastases or Lymph Node Ratio. Lower numbers are associated with a better prognosis[139, 140]

Stage migration
When more lymph nodes are analyzed by the pathologist, the probability to find a node containing cancer cells increases. An effect of stage migration is that the characteristics of

patient groups are altered. If the hypothetical last lymph node examined in a specimen contains cancer cells, that patient is moved from stage I-II to stage III. In theory, a patient with high risk for relapse within stage I-II is instead placed in stage III and there maybe representing a relatively early case. This may actually improve survival both groups (I+II and III) and is sometimes described as the Will-Rogers phenomenon[131, 141].

Adjuvant treatment

Stage III colon cancer patients benefit from adjuvant chemotherapy with improved DFS and OS[142]. In stage II adjuvant treatment is debatable. Many stage II patients have a prognosis similar to stage I. However there are some prognostic factors entailing worse prognosis in stage II. These include T4, bowel perforation or occlusion, high grade tumor (low differentiated) or LVI. Patients with these attributes probably benefits from adjuvant chemotherapy[143]. In colon cancer, LVI is associated with local recurrence but not impaired OS[144].

Prognosis

Patients with colon cancer constitutes a heterogeneous group where prognosis varies, depending on many factors. Survival can be measured in different ways. Often DFS or OS have been used as endpoints. Relapse free survival (RFS) and time to event (TTE) are examples of surrogate markers for survival[145]. In a Swedish material published in 2013, there was an actuarial, crude, three year OS of 62.7% and for patients undergoing elective tumor resection three year relative survival was 83,7%[146]. In the long-term follow up of the COLOR trial (stage I-III, elective resection) the three year DFS was approximatively 75% and five year OS was approximatively 74%[71].

Patients in stage I have a good prognosis with long term survival exceeding 90%[71, 147].

Non-high-risk stage II patients have a prognosis almost as advantageous as those of stage I[143].

In an adjuvant treatment study, five year DFS was for high risk stage II patients 79,9%-83,7% and in stage III 58,9%-66,4%, varying with chemotherapy regime[142].

Stage IV, although a heterogeneous condition, entails a bad prognosis. A French study, albeit 20 years old, on patients having liver resection for metastases, three year actuarial OS was 44% and at five years 28%[148].

Stage is a strong marker for DFS as well as OS. There is a strong correlation between three years DFS and five years OS[71, 149]. As in the study of many other diseases, age is a very prominent factor for both OS and DFS and in colon cancer age is also associated with worse cancer specific survival[150, 151].

In summary, colon cancer stage I-II has good prognosis, stage III has a mediocre prognosis and stage IV has as a group, in spite of vast achievements the last decades, bad prognosis.

Swedish ColoRectal Cancer Registry (SCRCR)

The Swedish ColoRectal Cancer Registry (SCRCR) is a national registry with prospectively registered data on colon cancer and rectal cancer. The SCRCR has data on rectal cancer since 1995 and colon cancer since 2007. In the Stockholm region there is a regional registry with data on colon cancer since 1997. The SCRCR contains numerous variables including treating hospital, age, sex, dates for diagnosis and operation, tumor location, pre-treatment staging, neo-adjuvant treatment, type of surgery, length of hospital stay, short term morbidity, post-operative staging, dates for MDT-conferences, adjuvant treatment, relapse and recurrence. Information regarding death is available through linkage to the Cause of Death registry. Information on other malignancies is available through linkage to The Swedish Cancer Registry. Linkage to other registries is enabled by the Swedish personal number, unique for every individual. The SCRCR has been validated and has a patient coverage of >99% and a coverage in terms of correctly registered variables of >90% and a high validity[152, 153]. Surgical complications are under-reported although re-operations seems adequately reported[154].

Follow up

The national Swedish guidelines recommend a follow-up of five years after treatment for colon cancer stratified on pathological stage[53]. All patients have their CEA-level measured preoperatively and 1, 3 and 5 years postoperatively. CT scan of the thorax and the abdomen should according to the guidelines be performed after one and three years postoperatively at a minimum. After complete, preoperative colonoscopy an endoscopic follow-up is recommended three to five years postoperatively. Postoperative chemotherapy is recommended for patients with pathological stage III disease or stage II disease with risk factors. Time to local recurrence, distant metastases or death is registered prospectively in SCRCR. Registration of local recurrence is underreported in SCRCR in case of synchronous finding of distant metastasis during follow-up. Relapse includes therefore the events of local recurrence and/ or systemic disease. The date of death is registered in SCRCR based on the official Civil Registry.

Stockholm Colon Cancer Project

In 2004 an educational project, similar to the TME-project (described in ‘discussion’), was launched. It was called the Stockholm Colon Cancer Project (SCCP) and the aim was to introduce the MDT-concept and CME surgery in colon cancer. The target group was surgeons, radiologists, oncologists and pathologists treating patients with CRC in the Stockholm area. Recurrent meetings were held annually including lectures, discussions and live demonstration-surgery with domestic and international surgeons demonstrating CME-surgery. Also specimens from colon cancer were demonstrated and discussed. At these

meetings it was also emphasized that emergency resection of colon cancer entails poorer prognosis and should be avoided if possible.

AIMS OF THE THESIS

Overall aim

To evaluate the introduction of CME in clinical practice and the impact on short- and long term outcome for patients with for colon cancer.

Specific aims

Paper I

To assess the number of lymph nodes in the specimen and MI after surgery for right sided colon cancer in the Stockholm area between 1996 and 2009.

Paper II

To assess the impact of the SCCP on survival for patients diagnosed with right sided colon cancer in the county of Stockholm.

Paper III

To assess the association between CME and serious short term adverse events.

Paper IV

To evaluate the effect of CME on oncological outcomes after surgery for right sided colon cancer.

PATIENTS AND METHODS

Paper I

All patients surgically treated for adenocarcinoma in the caecum, the ascending colon or the hepatic flexure, in the Stockholm area, between January 1st 1996 and December 31st 2009 were included in the study. Data on patient characteristics, tumor location, stage, type of surgery, specimen data (including lymph node status) were collected from the SCRCR. The study period was divided into three groups, based on the calendar year in which they were operated, Period 1 (1996-1999), Period 2 (2000-2004) and Period 3 (2005-2009). Parameters studied were age, sex, tumor location, tumor stage, emergency or elective operation, number of lymph nodes analyzed by the pathologist, number of metastatic lymph nodes. Among lymph node positive patients, mi was calculated by dividing the number of metastatic lymph nodes by the number of examined lymph nodes.

Differences in the distribution of qualitative variables with respect to time period and other categorical variables were assessed using the chi-square test. The number of lymph nodes and mi, with respect to dichotomous variables were compared using Wilcoxon two-sample test and, for variables with more than two categories, using the Kruskal-Wallis test.

Paper II

The Stockholm colon cancer project (SCCP) has been described in the background to this thesis. All patients diagnosed with adenocarcinoma in the caecum, the ascending colon or the hepatic flexure during two time periods before and after the start of the SCCP (January 1st 2001 to December 31st 2003 (Group 1) and January 1st 2006 to December 31st 2008(Group 2)) were included in the study. Data were obtained from the SCRCR regarding age, sex, tumor stage (TNM), whether the tumor had been resected or not, type of surgery, emergent or planned surgery, neoadjuvant and adjuvant treatment, failure events (local recurrence, distant metastases and death) and survival times. Survival between the two groups and between different pTNM-stages were compared.

Proportions were compared using the Chi-square test. Differences in patient age between the groups were compared with the Students t-test. OS was calculated from the date of diagnosis. DFS was calculated from the date of tumor resection and patients were considered to be at risk until the diagnosis of local recurrence, metastases or death from any cause. Survival was measured using the Kaplan-Meier method and differences between the two groups were assessed with the Log-Rank test. Death specific hazards modelling was performed using Cox's proportional hazards regression including potential confounding factors. Hazard ratios (HR) were calculated along with 95% confidence intervals (CI) and were analyzed statistically by means of likelihood ratio tests.

Paper III

All patients operated for adenocarcinoma in the caecum, ascending colon or the hepatic flexure, between January 1st 2004 and December 31st 2012 were the study base for this nested case-control study. Patients that died within 90 days of tumor resection or had an emergency re-operation within 30 days or within hospital stay were identified as cases. Two controls per case were randomly selected from the study base and matched for sex, age-interval, TNM-stage and emergency vs. elective surgery.

Exposure was defined as CME. Exposure status was determined from original surgical reports, blinded for surgeon's name(s), date of surgery, patient age, sex and hospital and whether the patient was a case or a control. Two colorectal surgeons each read all the surgical reports. The reports were classified as "CME", "no CME" or "CME unclear" according to pre-defined criteria.

1	Dissection of the mesocolon from the duodenum and the head of pancreas
2	Visualization of the superior mesenteric vein
3	Ligation of the ileocolic or right colic vessels at the level of the superior mesenteric vein
4	Ligation of the right branch of the middle colic vessels at its origin or central ligation of the middle colic vessels
5	Integrity of the mesocolon and the resected bowel segment

Table 4. *Criteria for classifying a surgical report as CME.*

Reports classed as "CME unclear" or with discordance between the reviewers were re-assessed by both the initial reviewers and a third colorectal surgeon, all three blinded to the initial assessment.

Comparison between the groups (cases and controls) was made with Wilcoxon Rank-sum test (continuous variables) and Fisher's exact test (dichotomous variables). Crude odds ratios (OR) with exact CI were calculated for the combined outcome (reoperation or short-term mortality) and for both outcomes separately. Conditional logistic regression was used to account for individually matched sets of cases with two controls. The confounding effect of matching variables and ASA was assessed by comparison between basic and adjusted conditional logistic regression models.

Paper IV

All patients, operated for adenocarcinoma in the caecum, the ascending colon or the hepatic flexure, in the Stockholm County from January 1st 2008 until December 31st 2012 were identified in the SCRCR. Patients registered as emergent colonic resections or with synchronous systemic were excluded. Local recurrence, metachronous systemic disease and survival were compared between patients treated with or without CME surgery. The exposure to CME surgery was assessed from original surgical reports, anonymized regarding surgeon(s) names, date of surgery and hospital. Two colorectal surgeons classified the reports independently according to five predefined criteria as shown in table 4.

The surgical reports were classified into the following three categories, “CME”, “CME uncertain” and “no CME”. Reports with discordance regarding CME status between the two reviewers were assessed by a third colorectal surgeon, blinded to the result of the initial assessment, to reach a majority decision on the classification of CME surgery. If all three reviewers took a different standpoint the report was classed as “CME uncertain”.

Statistics

For comparisons of the three groups of CME surgery, Kruskal-Wallis tests (continuous variables) and Fisher’s exact tests (categorical variables) were used. Time to relapse or death was analysed with the Kaplan-Meier method and groups compared with log-rank tests. For the analysis of relapse, patients were censored at the time of death or last follow-up. Local or systemic recurrence and death of any cause were the events in the analysis of relapse-free survival (RFS). Death of any cause was the event in OS. Patients were censored at the time of last follow-up in survival analysis. The assumption of proportional hazards was assessed for RFS and OS with “log-log” plots and on the basis of Schoenfeld residuals. Cox regression was then used to assess the prognostic and confounding effect of covariates in uni- and multivariable models. Age (dichotomized at median age of 75 years), gender, ASA-class, pTNM-stage and adjuvant treatment were included in multivariable models.

RESULTS

Paper I

3536 patients were operated in Stockholm for right sided colon cancer during the study period. There were more women than men operated in the study, 57% compared to 43% but no difference within the three time periods. There were fewer patients having their colon cancer resected in an emergency operation during the last period of the study, 14.9% compared to 17.4% and 20.7% in period 1 and 2 respectively ($p<0.001$). The number of analyzed lymph nodes rose from seven (mean) in period 1 to 11 in period 2 and 18 in period 3 ($p<0.001$). The proportion of patients having less than 12 lymph nodes analyzed in the specimen was 77.1% in period 1, 55.8% in period 2 and 18.3% in period 3 ($p<0.001$). The mean number of metastatic lymph nodes increased from two in period 1 to four in period 3 ($p<0.001$). MI was 0.40 in period 1 and 2, compared to 0.25 in period 3 ($p<0.001$). MI decreased with an increasing number of analyzed lymph nodes. Patients were more likely to be staged as pTNM stage III if more than five lymph nodes were detected in the specimen ($p<0.001$). Men were more likely to have five or less lymph nodes analyzed and women were more likely to have >11 lymph nodes analyzed ($p=0.008$).

Paper II

During the two time periods, 1716 patients were diagnosed with right sided colon cancer, 819 patients in Group 1 and 897 patients in Group 2. There were more women than men in both groups.

The proportion of patients having a tumor resection was larger in Group 1, 96.6% compared to 91.2% in Group 2 ($p<0.001$). There were a larger proportion of patients having emergency tumour resection in Group 1. Group 2 had a larger proportion of patients with stage I disease. There was a significantly higher proportion of R0 resection in Group 2.

There were a crude OS at three years after diagnosis of 61.3% in Group 2 vs 56.0% in Group 1 ($p=0.025$). The crude three year disease free survival among patients in TNM stage I-III who had their tumor resected was also significantly higher in Group 2, 71.5% compared to 64.6% in Group 1 ($p=0.006$).

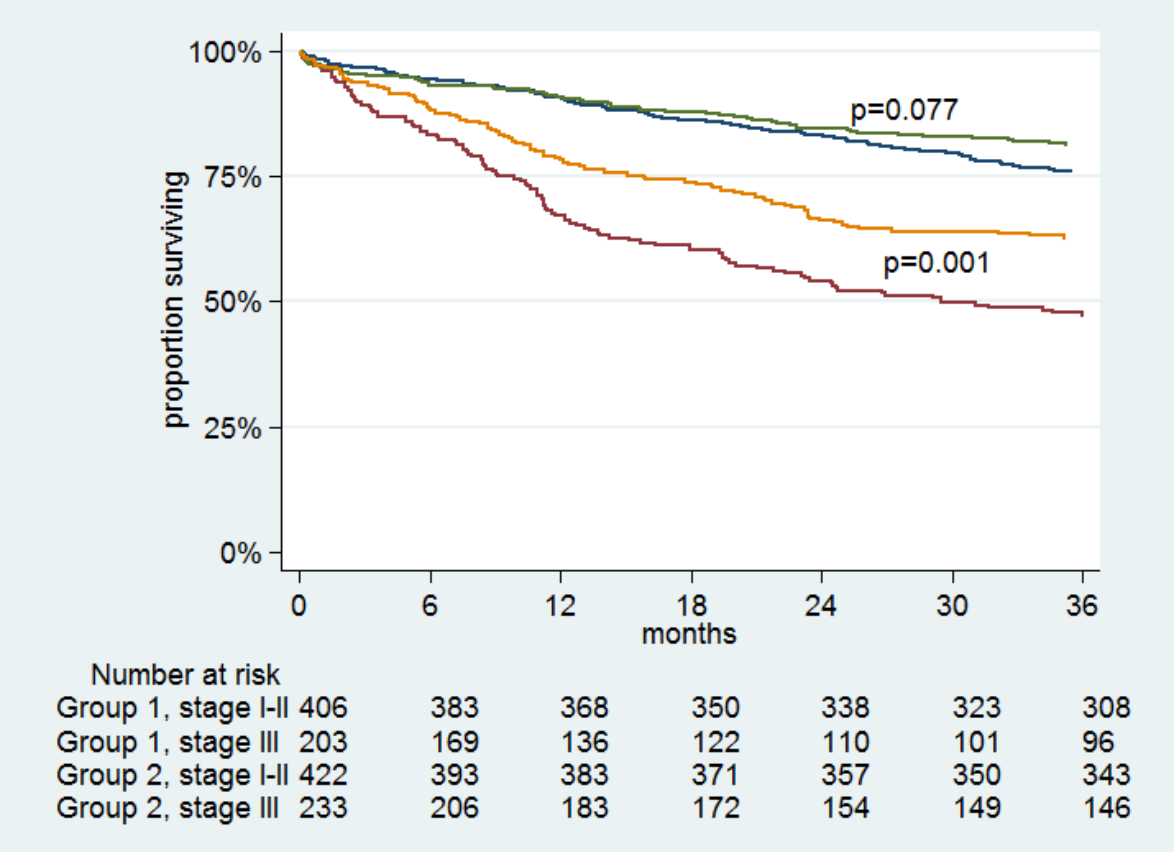

Figure 7. *DFS in patients with pTNM stage I-II and III within Group 1 and 2.*

In a multivariable analysis patients in Group 2 had a HR for DFS of 0.79 (95% CI: 0.64.0.97)(p=0.022) compared to patients in Group 1. Other factors entailed with a HR for a worse DFS was emergency surgery and age > 69 years.

Paper III

During the study period 2464 patients were operated for right-sided colon cancer in the Stockholm County. After exclusion of patients with distant metastases, unknown disease stage or unknown date of surgery 2070 patients remained. Of these, 240 patients died within 90 days after surgery and/or were re-operated and were therefore included as cases. 480 individually matched controls were randomly selected from the SCRCR. The surgical reports could not be retrieved in four cases and in seven controls. The matching process resulted in a similar distribution of age, sex, tumour stage and proportions of emergent versus elective procedures among cases and controls. ASA score was available in 69% of the patients. ASA 3-4 was significantly higher among cases than controls; 62.1% versus 42.4% (p<0.01). After reassessment of the group “CME unclear” and those where the two reviewers initially disagreed, a binary CME status was agreed for all 236 cases and 473 controls. The proportion

of CME-surgery was 14.8% (35 of 236) in cases and 19.5% (92 of 473) in controls.
The crude OR for short-term mortality or re-operation following CME-surgery was 0.72 (95%CI 0.47-1.10; p=0.15) compared to no CME-surgery. In the unadjusted conditional logistic regression model, OR for postoperative death or re-operation was 0.75 (95% CI: 0.50-1.13; p=0.17) for CME surgery compared to no CME surgery. The adjusted models showed no evidence for relevant confounding by matching factors or ASA. When the study period was divided into three time-periods, OR for postoperative death or re-operation was 0.51 (95% CI: 0.26-1.01; p=0.05) for CME surgery compared to no CME surgery in the last third of the study. In hospitals operating more than 100 patients in the study, OR for postoperative death or re-operation was 0.61 (95% CI: 0.35-1.06; p=0.08) for CME surgery compared to no CME surgery.

Paper IV

During the study period 1542 patients were operated for right-sided colon cancer in nine different hospitals in the Stockholm County. After exclusion of patients with systemic disease, emergency surgery or missing data regarding hospital, surgical report or systemic disease, 1171 patients could be analysed.
In 727 patients (62.1%), both colorectal surgeons agreed in the classification of CME status. The third colorectal surgeon assessed the remaining 444 surgical reports. The final classification of surgical reports was “CME” in 357 (30.5%), “CME uncertain” in 273 (23.3%) and “no CME” in 541 (46.2%). Median age was lower for patients with surgical reports classified as “CME” compared to the groups classified as “CME uncertain” and “no CME” (72 vs 75 vs 77 years respectively, p<0.001) and had a lower ASA-score (p<0.001). The proportion of laparoscopic resections were lower in the “CME” group (5.4% vs 11.7% and 17.2% respectively, p<0.001). The three categories of CME surgery did not differ statistically regarding proportion of R0-resections (95.8 to 97.8%), 30-day mortality (1.4 to 2.8%) or risk for reoperation (8.1 to 10.0%). The distribution of pTNM-stage was different (p<0.001) with the highest proportion of stage III disease in the “CME” group (38.7%) and the highest proportion of stage I disease in the “no CME” group (24.8 %). The median number of analyzed lymph nodes was highest among patients with “CME” (n=20) and lowest in the “no CME” group (n=16) (p<0.001). Patients in the “CME” group were followed for 66 months (median)(range 0-107 months), the patients in the “CME uncertain” group for 65 months (0-106) and the patients in the “no CME” group for 61 months (0-107). Five year RFS was 73.6% in the “CME” group vs 72.4% in the “CME uncertain” group vs 63.5% in the “no CME” group. Five year OS was 76.1% in the “CME” group vs 76.1% in the “CME uncertain” group vs 65.8% in the “no CME”.

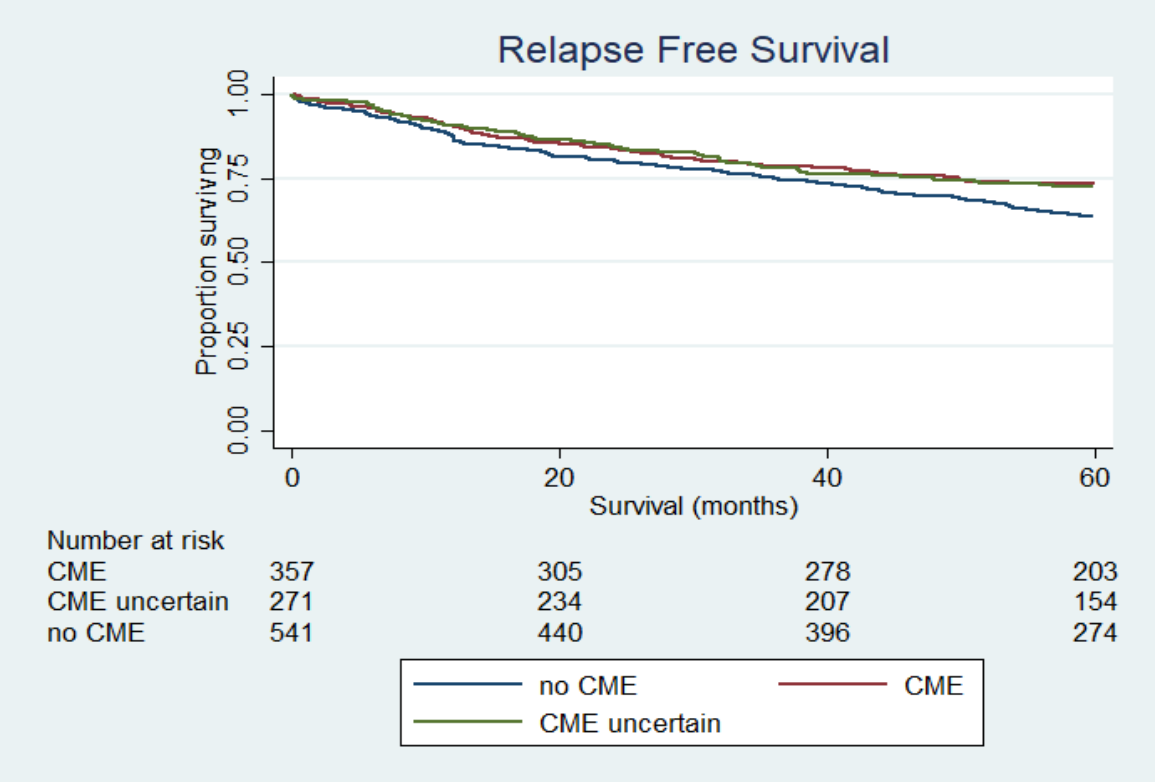

Figure 8. *Five year RFS after surgery for right sided colon cancer (p=0.062 (Log-Rank test))*

The univariable Cox regression analysis showed improved RFS for patients with surgical reports classified as “CME” HR=0.64 (CI: 0.51-0.81, p<0.001) and “CME uncertain” HR=0.76 (CI: 0.60-0.96, p=0.023). Age, ASA and pathological stage changed the unadjusted HRs of CME status by more than 10% and were considered as confounders. The final model, adjusted for age, gender, ASA, laparoscopic technique, adjuvant chemotherapy and pTNM-stage showed a significantly improved RFS for “CME” HR=0.74 (95% CI: 0.58-0.94, p=0.014) and a trend to improved RFS for “CME uncertain”, HR=0.80 (95% CI: 0.63-1.03, p=0.078).

DISCUSSION

In the 1980's surgical treatment of rectal cancer went through a paradigm shift with the introduction of the TME concept[155, 156]. This concept included dissection and mobilization of the rectum along an embryonal plane, behind the mesorectum, respecting the mesorectal fascia. In studies this was proven leading to improved results in terms of local recurrence and OS[157, 158]. In Stockholm the TME-concept was introduced in an educational project in 1994[158]. This project compromised workshops, discussions, lectures and video-based live surgery sessions. A majority of surgeons in Stockholm at that time treating patients with rectal cancer attended and many had the opportunity to assist in the operating theatre. In a five year follow up of patients operated during 1995 and 1996 the results were gratifying. Compared to historical controls, patients operated within the "TME-project" had a rate of local recurrence of 8%, compared to earlier 19-22%. 5-year cancer specific survival was 77% compared to 66%[159].

Historically, prognosis for rectal cancer has been inferior to the prognosis for colon cancer. Coincident in time with the introduction of TME, the prognosis for rectal cancer improved faster than the one for colon cancer and this was ascribed the introduction of TME-surgery and pre-operative radiotherapy[160].

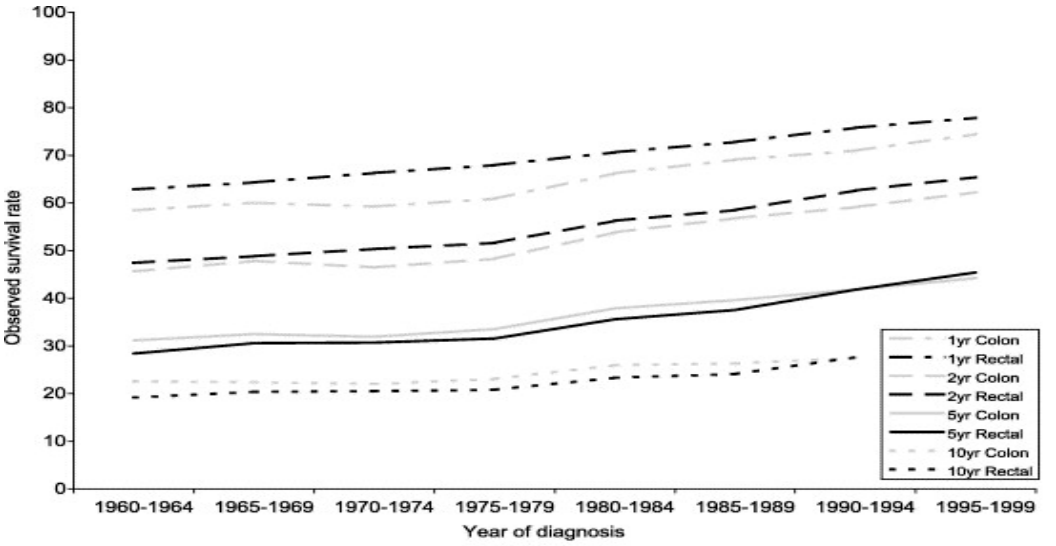

Figure 9. *Observed survival-rates in colon- and rectal cancer in Sweden. Reprint with permission[160].*

The concept of TME is largely based on the concept of embryonal layers. This concept has also been translated into the practice of colon cancer management.
In Australia, Bokey et al describes the introduction of a new technique in the early 1980's with "precise dissection along anatomic planes, facilitating an operation that will not compromise or breach the fascial envelope of the colon and it's mesentery"[65]. Further, Bokey describes the aim of the surgery as: "...to perform a bloodless extra fascial dissection with minimal handling of the tumour and to remove the entire specimen as an 'intact package' without disrupting the embryological tissue planes, thus minimizing the potential for surgical transection of the tumour. These techniques also entailed ligation of the lymphovascular bundle at the origins of the relevant principal named vessels."[161] It is also since approximatively the same time frame that Hohenberger describes the evolvement of CME in Erlangen[64].
It has been questioned if CME is a new surgical technique or merely an old technique that has gained attention and been refined lately[162]. More than a century ago Jamieson et al wrote: "The ideal operation consists in removing a considerable length of gut on each side of the growth, the primary glands, together with the vessels running to the from the gut, and the tissues in which these vessels lie, i.e. the so-called lymphatic area." He also wrote, regarding surgery for neoplasms in the right colon: "The artery and vein are ligated and divided close to the superior mesenteric artery"[126].

Introduction of a more or less new surgical technique raises justifiable questions. When TME was introduced criticism was endured in the beginning and Professor RJ Heald was disbelieved when presenting new figures with low frequencies of local recurrence. There is a risk that a new surgical technique is introduced first and evaluated later. A new technique may look good, feel good and have eloquent advocates. For example, laparoscopic cholecystectomy was introduced in the second half of the1980's and became the method of choice without scientific evidence. The introduction of laparoscopic cholecystectomy increased the frequency of bile duct injuries[163, 164]. The comparison between open and laparoscopic cholecystectomy came later with small randomized studies of varying external validity during the first half of the 1990's[165]. Laparoscopic appendectomy has also been introduced widely as a standard treatment for acute appendicitis. There are benefits in certain patient groups but in general the advantages over open appendectomy are small and the operation takes longer time and is more expensive[166]. In Sweden, robot assisted laparoscopic surgery has been introduced for a number of surgical procedures even though the scientific evidence for clear advantages are absent[167]. In the last decade CME has been introduced and implemented as a more or less new surgical technique. The need to evaluate what this has meant for surgical treatment of colon cancer was the background for this work.

Randomized trials?

There are, yet, no RCT's between CME and standard resection for colon cancer.

It might be possible to randomize between D2 and D3 surgery or, in other words, between CVL and non-CVL. However there would be cases where the surgeon intra-operatively suspects for example D3 lymph node metastases and if that particular patient is randomized to D2 surgery the patient has to be excluded from the study. This would of course introduce bias. There are other hypothetical peri-operative events, findings and decisions that would exclude patients and causing bias. There might also be increasingly difficult to inform and discuss the possible differences with the patients since there are several papers included in, and discussed within this thesis showing a long term advantage with CME-surgery. In order to design and conduct a RCT between an old a new (surgical) treatment, there must be an unawareness of which treatment is the best. There must not be strong opinions or beliefs in the new treatment being better (or worse). There must be 'equipoise', i.e. there must be substantial uncertainty about the relative value of one treatment versus another. This can be applied to the individual surgeon or to the collective of informed surgeons[168-172].

How do we know if CME-surgery has been performed?

In the absence of RCT's, there have been different efforts to evaluate CME compared to conventional colonic resection surgery for cancer.

Firstly, there are published single-center case series. In these, there are sometimes few, dedicated surgeons operating the patients. There are authors presenting very impressive results[64, 173] although the grade of scientific evidence in case-series types of studies is considered low[174].

Secondly, the comparison of different time-periods has been made, with the assumption that CME has been introduced in between the periods, among others in our paper II. Comparison with an historical control-group is a known weakness of study design. It is difficult to know to what degree the assumption that CME is not done in the early period and that it is done in the late period is correct. There might also be other parameters that have changed between the time periods and that one fails to adjust for in the statistical analysis, for example changing chemotherapy guidelines and centralization of treatment.

Another potential method is to compare hospitals were CME is implemented with others where CME is proposedly not practiced. This approach was used by Bertelsen, Storli and West[175-177]. It has maybe an advantage over comparison of time periods, in the sense that there might have been instructions and guidelines promoting the use of CME at the "CME hospital(s)". Otherwise this method may suffer from the same type of bias as the comparison of time periods.

Moreover, there are interesting attempts on evaluating whether CME has been done by radiological examinations post-operatively. In a Danish study the patients were examined with CT Angiography two days post-operatively and the stump of the ICA was measured.

Munkedal et al found that the mean length of the remaining ICA stump after right sided hemicolectomy was 31mm and a trend towards a negative correlation between the length of the arterial stump and the number of lymph nodes in the specimen ($p=0.06$)[178]. In a Norwegian study, patients that were x-rayed on suspicion of AL also had the arterial stump measured. The average radiological, post-operative, length of the ICA stump was 24mm[179]. In a study from Leeds, Kaye et al found that the ICA-stump after right-sided hemicolectomy was in average 28.1mm[180]. The disadvantages with these studies are size, the Danish and the Norwegian study contains 52 and 18 patients respectively. The consistent conclusion of these post-operative radiological evaluations is that the ICA-stump is longer than expected indicating that the vascular tie in many cases are not so high/central.

Finally, in the present studies (paper III & IV) we retrospectively evaluated surgical reports. Two of the authors of paper III and IV read almost 1900 surgical reports describing right sided hemicolectomy. This has the advantage of looking into individual patients surgical procedures, hopefully evaluating the surgical procedure only. We found that it was often difficult to determine from a surgical report whether CME has been performed or not. “CME” or “no CME” was almost never stated in the report. Also, we noted that many surgical reports were of low quality. Vital information was often missing, unnecessary information was taking up large amount of text and it was in some cases unfortunately apparent that the surgeon’s anatomical knowledge was unsatisfactory, alternatively there were an inability to describe the anatomy. Another drawback of this method is that the reading of a surgical report is done by a human and the assessment is therefore inevitable colored by the reader’s subjective impression, even though we used a checklist as described in paper III and IV. This might introduce misclassification as a bias, however probably non-differential since the surgical reports were blinded. It is our impression that we might have judged the reports too strict, thereby classifying too few as CME. This would bias the effects of CME towards no difference and since our results in both paper III and IV points towards positive effects of CME, this may not be a problem, in this case.

There are no studies on pathology-specimen, assessing whether CME has been done or not. West et al has studied specimens from a CME-center (Erlangen) and compared them with specimens from a non-CME-center (Leeds). They found that the specimens from Erlangen contained more lymph nodes and that the surgical dissection was carried out in the mesocolic plane to a greater extent in Erlangen. This study, however, did not have as an aim to determine if CME had been done or not, judging from the specimen, and the pathologists evaluating the specimens were not blinded to whether the specimen was a CME-specimen or not[176]. From Denmark there are also a studies comparing time-periods and pathological specimens showing that educational efforts resulted in specimens with a higher proportion of dissection along the mesocolic plane and removal of more mesentery and a greater lymph node yield[181, 182].

Laparoscopic CME

It has been disputed whether it is possible to do a CME laparoscopically. There are no studies comparing long term outcome after open and laparoscopic CME. However there are studies on feasibility regarding laparoscopic D3 and CME surgery[183, 184]. Regarding specimen parameters Gouvas et al found in a non-randomized study of 90 laparoscopic and open operations no significant differences in distance between bowel wall or number of lymph nodes in the specimens[185]. In contrary West et al showed, when comparing specimens from open and laparoscopic CME, a lower number of lymph nodes after laparoscopic CME but a similar rate of mesocolic plane dissection[186].

In our paper IV, 144 patients (12.3 %) of the examined operations were laparoscopically performed. Of these, 19 (13.2 %) were classed as CME, 32 (22.2 %) were classed as uncertain CME and 93 (64.6 %) as no CME.

Lymph node yield

Lymph node yield has been shown to be of importance in colon cancer surgery[135, 138]. In paper I we showed that the lymph node yield increased over time in the region, coincident in time with introduction of CME. Also in paper IV, CME or "CME uncertain" was associated with a higher number of analyzed lymph nodes compared to "no CME".

Bertelsen compared two time-periods in one hospital before and after CME-implementation and showed that the mean number of analyzed lymph nodes increased from already high 24.5 to 26.7 ($p=0.009$)[187]. When comparing CME-hospital and non-CME-hospitals, there were a median of 34 vs. 19 ($p<0.001$) lymph nodes in favor of the CME-hospital[188]. Storli et al in Norway noted no statistical significant difference in lymph node yield between a CME hospital and non-CME hospitals[177]. In the comparison of specimens between Erlangen and Leeds, there were more lymph nodes in the CME-specimens from Erlangen, median 30 vs. 18 ($p<0.001$)[176]. In a patient series in Erlangen the proportion of colon cancer specimens where the pathologist examined at least 12 lymph nodes, rose from 85% to 100% over a period of three decades[189].

Is CME associated with short term adverse events?

In paper III we found that CME is not associated with short term, serious adverse events manifesting in death or emergency re-operation. Especially in high-volume hospitals and in the later part of the study period this was more salient.

Bertelsen et al found that CME was associated with more intra-operative organ injuries in the CME group. This was mainly because of injuries to other parts of the colon, the spleen and the SMV. Also pulmonary failure and sepsis was more common in the CME group. There were no statistical significant differences in 30- or 90-day mortality between CME-hospital and non-CME-hospitals in this Danish study. Any difference in re-laparotomy is not stated but there were no difference in surgical complications Clavien-Dindo grade IIIb[175]. In our

paper III we chose not to include specified surgical or non-surgical adverse as an outcome since it is underreported in the SCRCR[154]. Storli reported a lower (not significant) short term mortality after CME, compared to the patients operated in the non-CME hospitals[177]. Another Norwegian study has investigated whether dissection of D3 lymph nodes may cause damage to the superior mesenteric autonomous nerve plexus, causing diarrhea. They found an increased number of bowel movements among patients operated with a D3 resection, although not affecting quality of life[190].

CME and long term outcome

In paper II we found that both crude OS and DFS among resected patients in stage I-III was significantly higher after CME had been discussed, taught and, to an unknown extent, implemented in the region. In paper IV we found that patients operated for right sided colon cancer where the surgical report contained essential steps of CME surgery had a survival benefit.

In accordance with our findings, Bertelsen found that four year DFS was 85.8% at a CME hospital and 75.9% in three other hospitals not performing CME. This figures were confirmed when the population was compared with propensity score matching. In this study the positive effect of CME was most prominent in stage I-II[188]. In contrary in our paper II, the survival benefit was more pronounced in stage III in the later time period after the introduction of the CME concept. Storli in Norway reports a three year DFS of 82.1 versus 74.3 % ($p = 0.026$) when one CME hospital was compared to two non-CME hospitals. In this study only patients in stage I-II were included[177]. Bokey et al reports a 5-year OS of 76.2% and a cancer specific survival of 89.8%, among radically resected patients in stage I-III[161]. In an update of the Erlangen-results in 2016, a gradually increasing (statistically not significant) OS from 72.8 to 78.3%, and a cancer related survival rising from 78.9 to 90.6 ($p<0.001$) from 1978 to 2009 were reported. Consistent with our paper II, improvement over time was in Erlangen most pronounced in pTNM stage III[189]. Hohenberger and Bokey both reports excellent outcomes although these are studies from single centers. In a study by Adamina et al 52 consecutive patients with right sided colon cancer underwent laparoscopic CME and there were no local recurrences and four (7.7 %) distant metastases after 38 months of follow up[191].

These studies support CME but cannot define what specific components of CME surgery that is crucial for the observed improved oncological outcome.

Why do CME seem to be associated with better long term outcome?

One central part of CME is the central vascular ligation with the aim of a greater lymph node yield. This has been addressed in several publications. A very large Japanese population based study included patients operated for T3 and T4 colorectal cancer and compared D3 to D2 operations. On purpose they included patients operated before 1995 in an attempt to avoid confounding of newer chemotherapy agents. After propensity score matching they found a

significant benefit for OS for D3-operation (HR =0.81 (95 % CI: 0.74-0.89)[192]. The Danish study mentioned above noted a negative correlation (although statistically not significant) between the length of the remaining vascular pedicle in vivo and the number of lymph nodes in the specimen[178]. West et al compared specimens from two centres in Japan and one in Germany (Erlangen) and found that the Japanese specimens showed a smaller lymph node yield and where shorter in terms of bowel length, although there was no difference in the distance from the bowel wall to the vascular tie and no difference in the number of metastatic lymph nodes[67]. This implicates that the width of the mesenteric specimen (and the length of the resected bowel) plays a role in terms of lymph node numerical but not obviously in oncological outcome. A Swedish study supports this finding by showing no survival benefit of longer bowel resections, however without data on the length of the vascular pedicle[193]. The second central part of CME is dissection along embryonal planes. Two studies have investigated the relationship between mesocolic plane dissection and outcome. West et al showed a better outcome in pTNM-stage III patients where dissection had been in the mesocolic plane compared to the muscularis propria plane (HR=0.50, 95% CI:0.26-0.98)[194]. An Italian study showed similar results and also that respecting the mesocolic plane resulted in a higher frequency of R0 resections[195]. However, neither of these studies has adjusted for microscopically radical resection in a multivariable analysis.

In conclusion, two papers in this thesis, II and IV, imply that CME is associated with advantages regarding long term survival. This is supported by a number of other studies. It is not clear which specific part of the surgical concept included in CME that is responsible for the observed better oncological outcome. Consistent with the studies mentioned above, the CVL may entail better staging and resection of central metastatic lymph nodes, which may benefit some patients with advanced tumors. Furthermore, in our paper IV there were less missing data on preoperative radiology in the CME group, maybe suggesting a more thorough workup. This may be an indication that CME is included in a more thorough and dedicated care for colon cancer patients, resulting in overall improved results. Even so, there are reasons to believe that precise, meticulous surgery is important in oncologic surgery.

CONCLUSIONS

Overall conclusions

Prognosis for patients operated for right sided colon cancer in Stockholm has improved the last two decades. CME is feasible, safe and associated with good long term outcome and may be part of the improved results.

Specific conclusions

Between 1996 and 2009, lymph node yield in surgery for right sided colon cancer increased together with a decrease in MI. During the same period the proportion of emergency tumor resections decreased.

After the introduction of SCCP, the prognosis for patients diagnosed with right sided colon cancer was improved.

CME for right sided colon cancer does not seem to be associated with serious short term adverse events leading to death or emergency re-operation.

Patients with right sided colon cancer operated with CME had a better long term oncological outcome.

FUTURE PERSPECTIVES

The papers included in this thesis, and other papers, shows advantages with CME. Simultaneously, in Stockholm and in Sweden, a low proportion of patients have been operated with minimally invasive methods for colon cancer. It is likely that this proportion will increase the coming years. As described above, laparoscopic CME is feasible. One dimension lacking in laparoscopic surgery is the possibility to palpate central part s of the colonic mesentery and thereby judging the eventuality of lymph node metastases. On the other hand an advantage with laparoscopic surgery is that many operations, depending on local routines, are recorded and possible to evaluate afterwards. This would render another dimension in evaluating whether CME has been conducted or not.

Another aspect that warrants studying is the connection between pre-operative staging and the selection of patients for CME. As mentioned above, T1 and T2 tumors carry a low risk of central, D3, metastases. CT cannot optimally foresee the T-stage of the tumors, neither lymph node metastases. Is MRI a future alternative in the preoperative evaluation of colon cancer patients?

Already today many parameters are prospectively recorded in the patients file and in the SCRCR. Perhaps prospective registration of CME or not CME could be made mandatory in the surgical report to facilitate future research on the topic.

Post-operative morbidity and mortality is high in surgery for CRC. Part of the explanation is probably that about 50% of the patients are older than 70 years. In one hospital in Stockholm there is, since some years ago, a project on peri-operative care of patients that are old and/or co-morbid. This focuses on identifying high risk patients before surgery for CRC. High risk patients are identified either by a web-based risk-calculator or by the anesthesiologist at a pre-op visit. In high risk patients, not only peri-operative monitoring and fluid-management is included but also meticulous care the first days post-operatively. Preliminary this has improved short-term results among old and co-morbid patients but warrants further studies. Since complications (such as AL) has impact both on short- and long term outcome in CRC-surgery, it is probably an area where studies are warranted to further improve the prognosis for patients with CRC.

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Complete Mesocolic Excision (CME) är en ny operationsmetod för tjocktarmscancer där man följer anatomiska, embryonala skikt och bevarar ytan av tjocktarmsmesenteriet intakt samt att man delar till- och frånförande blodkärl mycket centralt nära avgångar från stora kropsspulsådern. Syftet är att minska risken för spridning av tumörceller i bukhålan och att ta bort och analysera ett stort antal lymfkörtlar, vilket är viktigt för prognos och för beslut om eventuell behandling med cellgifter. Det finns inga randomiserande studier som jämfört CME mot traditionell kirurgi. Det finns dock enskilda centra som praktiserat CME och uppvisat mycket goda resultat. Den nya operationsmetoden CME introducerades i Stockholm 2004. Det har funnits farhågor att CME skall leda till allvarliga komplikationer på kort sikt då operationsmetoden innebär att man dissekerar nära bukspottkörteln, tolvfingertarmen samt stora, centrala blodkärl. Syftet med detta avhandlingsprojekt var att utvärdera introduktionen av CME och dess effekt på kort och lång sikt för patienter med tjocktarmscancer.

I **delarbete 1** visade vi att antalet lymfkörtlar analyserade av patolog efter kirurgi för högersidig tjocktarmscancer ökade mellan åren 1996 och 2009.

I **delarbete 2** visade vi en bättre överlenad hos patienter som diagnosticerats med högersidig tjocktarmscancer 2006-2008 jämfört med 2001-2003.

I **delarbete 3** undersökte vi om CME ledde till allvarliga komplikationer på kort sikt, manifesterade i dödsfall inom 90 dagar efter operationen eller akut omoperation. Detta utvärderades i form av en s.k. fall-kontroll studie där CME utgjorde exponering och död eller akut omoperation utgjorde utfallet. Huruvida patienter exponerats för CME eller inte bedömdes från operationsberättelser. Vi fann att 14.8% av fallen opererats enligt CME jämfört med 19.5% av kontrollerna, vilket tolkas som att CME inte ökade risken för akut om-operation eller död på kort sikt.

I **delarbete 4** bedömdes operationsberättelser hos alla patienter som opererats för högersidig tjocktarmscancer i Stockholm under åren 2008-2012. 30.5% av patienterna bedömdes ha opererats enligt CME. Efter fem års uppföljning var återfallsfri överlevnad i den gruppen som opererats enligt CME 73.6% jämfört med 65.8% i gruppen som bedömts inte opererats enligt CME. Sammanfattningsvis visar denna avhandling att CME verkar vara associerat med förbättrad långtidsöverlevnad och inte verkar vara behäftad med några uppenbara nackdelar på kort sikt.

ACKNOWLEDGEMENTS

I would like to thank the following individuals, who, *in one way or another*, have contributed to this thesis:

My main supervisor **Anna Martling**, for making this possible, for sharing your knowledge, time, money and contagious good spirit and for showing leadership.

Torbjörn Holm, co-supervisor, for sharing your knowledge, experience and expertise, not only in science but also in surgery and clinical work and for your ability to look at things from a different perspective.

Annika Sjövall, co-supervisor, for sharing your knowledge, for your loyalty, hard work and on-time delivery and for reading almost 1900 surgical reports without to many complaints.

Christian Buchli, my friend and co-author, for your ability to look at difficult issues in a straight forward way, for your professional help with statistics and writing, for taking me to the Swiss alps and for the discussions around surgery, football, hockey, politics, life, children… and yes, research!

Also, jointly, Anna, Torbjörn, Annika and Christian, for your lovely sense of humor and all the laughs through the years. Some say that humor is a sign of intelligence.

Anders Ekbom, my co-supervisor, for your contributions to study design, for your warm and generous attitude and for being the man behind "Forskarskolan" (Karolinska Institutet's research school for clinicians within epidemiology).

Fredrik Granath, co-author and statistical advisor, for sharing your impressive knowledge in biostatistics.

Werner Hohenberger, co-author and inspirer. For your generosity and contributions in the field of colorectal cancer treatment.

Christina Edberg, Research Group administrator, for among many other things, with the layout of this thesis and for having a kind answer to most questions.

Tongplaew ”Toom” Signomklao, data-manager at the SCRCR, for delivering data on which these studies are made of and for help with data collection in paper IV.

Ann-Britt Wikström, administrator at the institution for calming and quick administrative help.

Dan Kornfeld and Christian Kylander, my current head of section and department respectively, for creating a positive and progressive atmosphere and for being understanding and supportive.

Per ”Pelle” Nilsson, my former head of section, for being that and for putting words on why working with colorectal surgery: “…challenging surgery and great comradeship”. **Johan Dalén**, my collegue and clinical mentor, for introducing me to colorectal surgery, for your humor and for being a rock. **Louis “Ludde” Riddez** and **Henrik Iversen**, for always showing kind interest in this project and asking me uncomfortable questions.

David Edler and **Deborah “Debbie” Saraste**, for arranging research group seminars, contributing to a scientific atmosphere.

Madelene Ahlberg and **Malin Lehander** for help with data collection in paper III.

Karl-Patrik Jonsson and **Thomas Marmolin** with colleagues and staff at Kungsholmsdoktorn, for giving me the opportunity to look into the fantastic speciality of family medicine. I will never forget that.

Caroline Staff for kind help with the dissertation-application. **Jesper Magnusson** and **Frida Lédel** for moral support and practical advices towards the completion of this thesis.

Colleagues and friends at Capio S:t Göran Hospital, Karolinska University Hospital, Danderyds Hospital and Ersta Hospital, who through the years have been supportive, contributed with scientific discussions and made clinical work fun, none forgotten and especially **Claes Anderin**, **Ulf Gustafsson** and **Filip Strömberg** for your support, consolation, humor and your view on the world we live in and life in general.

Gunilla Bernhoff, my dear mother, for your support, for always being there (on my side) and for your “it’ll be ok”-attitude. **Albert Bernhoff**, my father, for, probably without knowing it himself, long ago (in a galaxy far away), inspiring me to study medicine. My brother **Hans Bernhoff** for your friendship, humor and for inspiring to a scientific attitude and way of thinking. My sister **Gabriella Bernhoff** for linguistic help.

My children **Gustav**, **Alexander**, **Alice** and **Agnes**, and my dear wife **Ulrika Bernhoff**. It is for me, obviously, very hard to put words on how much you mean to me. You all make me very proud and privileged.

REFERENCES

1. Sidhu P, Peng HT, Cheung B, Edginton A. Simulation of differential drug pharmacokinetics under heat and exercise stress using a physiologically based pharmacokinetic modeling approach. Can J Physiol Pharmacol. 2011;89(5):365-82.

2. Kuzu MA, Ismail E, Celik S, Sahin MF, Guner MA, Hohenberger W, et al. Variations in the Vascular Anatomy of the Right Colon and Implications for Right-Sided Colon Surgery. Dis Colon Rectum. 2017;60(3):290-8.

3. Shatari T, Fujita M, Nozawa K, Haku K, Niimi M, Ikeda Y, et al. Vascular anatomy for right colon lymphadenectomy. Surg Radiol Anat. 2003;25(2):86-8.

4. Ignjatovic D, Sund S, Stimec B, Bergamaschi R. Vascular relationships in right colectomy for cancer: clinical implications. Tech Coloproctol. 2007;11(3):247-50.

5. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683-91.

6. Jackson-Thompson J, Ahmed F, German RR, Lai SM, Friedman C. Descriptive epidemiology of colorectal cancer in the United States, 1998-2001. Cancer. 2006;107(5 Suppl):1103-11.

7. http://globocan.iarc.fr [

8. http://www.socialstyrelsen.se/statistik/statistikdatabas.

9. Siegel RL, Jemal A, Ward EM. Increase in incidence of colorectal cancer among young men and women in the United States. Cancer Epidemiol Biomarkers Prev. 2009;18(6):1695-8.

10. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med. 1993;329(27):1977-81.

11. Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. Cancer. 1975;36(6):2251-70.

12. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988;319(9):525-32.

13. Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. JAMA. 2008;300(23):2765-78.

14. Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. Int J Cancer. 2009;125(1):171-80.

15. Cho E, Smith-Warner SA, Ritz J, van den Brandt PA, Colditz GA, Folsom AR, et al. Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. Ann Intern Med. 2004;140(8):603-13.

16. Chan DS, Lau R, Aune D, Vieira R, Greenwood DC, Kampman E, et al. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. PLoS One. 2011;6(6):e20456.

17. Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. Int J Cancer. 2006;119(11):2657-64.

18. Vieira AR, Abar L, Chan DSM, Vingeliene S, Polemiti E, Stevens C, et al. Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. Ann Oncol. 2017;28(8):1788-802.

19. Jensen BW, Gamborg M, Gogenur I, Renehan AG, Sorensen TIA, Baker JL. Childhood body mass index and height in relation to site-specific risks of colorectal cancers in adult life. Eur J Epidemiol. 2017.

20. Levi Z, Kark JD, Katz LH, Twig G, Derazne E, Tzur D, et al. Adolescent body mass index and risk of colon and rectal cancer in a cohort of 1.79 million Israeli men and women: A population-based study. Cancer. 2017.

21. Harding JL, Shaw JE, Peeters A, Cartensen B, Magliano DJ. Cancer risk among people with type 1 and type 2 diabetes: disentangling true associations, detection bias, and reverse causation. Diabetes Care 2015;38:264-270. Diabetes Care. 2015;38(4):734-5.

22. Yuhara H, Steinmaus C, Cohen SE, Corley DA, Tei Y, Buffler PA. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? Am J Gastroenterol. 2011;106(11):1911-21; quiz 22.

23. Schmid D, Leitzmann MF. Television viewing and time spent sedentary in relation to cancer risk: a meta-analysis. J Natl Cancer Inst. 2014;106(7).

24. Enblad M, Birgisson H, Ekbom A, Sandin F, Graf W. Increased incidence of bowel cancer after non-surgical treatment of appendicitis. Eur J Surg Oncol. 2017.

25. Song H, Abnet CC, Andren-Sandberg A, Chaturvedi AK, Ye W. Risk of Gastrointestinal Cancers among Patients with Appendectomy: A Large-Scale Swedish Register-Based Cohort Study during 1970-2009. PLoS One. 2016;11(3):e0151262.

26. Larsson SC, Giovannucci E, Wolk A. Long-term aspirin use and colorectal cancer risk: a cohort study in Sweden. Br J Cancer. 2006;95(9):1277-9.

27. Chan AT, Giovannucci EL, Schernhammer ES, Colditz GA, Hunter DJ, Willett WC, et al. A prospective study of aspirin use and the risk for colorectal adenoma. Ann Intern Med. 2004;140(3):157-66.

28. Giovannucci E, Egan KM, Hunter DJ, Stampfer MJ, Colditz GA, Willett WC, et al. Aspirin and the risk of colorectal cancer in women. N Engl J Med. 1995;333(10):609-14.

29. Boyle T, Keegel T, Bull F, Heyworth J, Fritschi L. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. J Natl Cancer Inst. 2012;104(20):1548-61.

30. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr. 2007;85(6):1586-91.

31. Tangpricha V, Spina C, Yao M, Chen TC, Wolfe MM, Holick MF. Vitamin D deficiency enhances the growth of MC-26 colon cancer xenografts in Balb/c mice. J Nutr. 2005;135(10):2350-4.

32. Slattery ML, Sorenson AW, Ford MH. Dietary calcium intake as a mitigating factor in colon cancer. Am J Epidemiol. 1988;128(3):504-14.

33. Wu K, Willett WC, Fuchs CS, Colditz GA, Giovannucci EL. Calcium intake and risk of colon cancer in women and men. J Natl Cancer Inst. 2002;94(6):437-46.

34. Cummings JH, Bingham SA, Heaton KW, Eastwood MA. Fecal weight, colon cancer risk, and dietary intake of nonstarch polysaccharides (dietary fiber). Gastroenterology. 1992;103(6):1783-9.

35. Trock B, Lanza E, Greenwald P. Dietary fiber, vegetables, and colon cancer: critical review and meta-analyses of the epidemiologic evidence. J Natl Cancer Inst. 1990;82(8):650-61.

36. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Stampfer MJ, Rosner B, et al. Dietary fiber and the risk of colorectal cancer and adenoma in women. N Engl J Med. 1999;340(3):169-76.

37. Terry P, Giovannucci E, Michels KB, Bergkvist L, Hansen H, Holmberg L, et al. Fruit, vegetables, dietary fiber, and risk of colorectal cancer. J Natl Cancer Inst. 2001;93(7):525-33.

38. Giovannucci E. Meta-analysis of coffee consumption and risk of colorectal cancer. Am J Epidemiol. 1998;147(11):1043-52.

39. Stoffel EM, Mangu PB, Gruber SB, Hamilton SR, Kalady MF, Lau MW, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. J Clin Oncol. 2015;33(2):209-17.

40. Kanth P, Grimmett J, Champine M, Burt R, Samadder NJ. Hereditary Colorectal Polyposis and Cancer Syndromes: A Primer on Diagnosis and Management. Am J Gastroenterol. 2017.

41. Haggitt RC, Reid BJ. Hereditary gastrointestinal polyposis syndromes. Am J Surg Pathol. 1986;10(12):871-87.

42. Burt RW, DiSario JA, Cannon-Albright L. Genetics of colon cancer: impact of inheritance on colon cancer risk. Annu Rev Med. 1995;46:371-9.

43. Rijcken FE, Hollema H, Kleibeuker JH. Proximal adenomas in hereditary non-polyposis colorectal cancer are prone to rapid malignant transformation. Gut. 2002;50(3):382-6.

44. Vasen HF, Blanco I, Aktan-Collan K, Gopie JP, Alonso A, Aretz S, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut. 2013;62(6):812-23.

45. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996;348(9040):1472-7.

46. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996;348(9040):1467-71.

47. Blom J, Kilpelainen S, Hultcrantz R, Tornberg S. Five-year experience of organized colorectal cancer screening in a Swedish population - increased compliance with age, female gender, and subsequent screening round. J Med Screen. 2014;21(3):144-50.

48. Courtney ED, Chong D, Tighe R, Easterbrook JR, Stebbings WS, Hernon J. Screen-detected colorectal cancers show improved cancer-specific survival when compared with cancers diagnosed via the 2-week suspected colorectal cancer referral guidelines. Colorectal Dis. 2013;15(2):177-82.

49. Parente F, Marino B, DeVecchi N, Moretti R, Lecco Colorectal Cancer Screening G, Ucci G, et al. Faecal occult blood test-based screening programme with high compliance for colonoscopy has a strong clinical impact on colorectal cancer. Br J Surg. 2009;96(5):533-40.

50. Parente F, Vailati C, Boemo C, Bonoldi E, Ardizzoia A, Ilardo A, et al. Improved 5-year survival of patients with immunochemical faecal blood test-screen-detected colorectal cancer versus non-screening cancers in northern Italy. Dig Liver Dis. 2015;47(1):68-72.

51. Dukes C. Histological Grading of Rectal Cancer: (Section of Pathology). Proc R Soc Med. 1937;30(4):371-6.

52. Sobin L, Gospodarowicz M, Wittekind C, al. e. TMN Classification of Malignant Tumours, ed 7. 2009.

53. Nationellt Vårdprogram för Tjock- och Ändtarmscancer. Regionala Cancercentrum i Samverkan; 2016.

54. Alexiusdottir KK, Moller PH, Snaebjornsson P, Jonasson L, Olafsdottir EJ, Bjornsson ES, et al. Association of symptoms of colon cancer patients with tumor location and TNM tumor stage. Scand J Gastroenterol. 2012;47(7):795-801.

55. Benedix F, Kube R, Meyer F, Schmidt U, Gastinger I, Lippert H, et al. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. Dis Colon Rectum. 2010;53(1):57-64.

56. Majumdar SR, Fletcher RH, Evans AT. How does colorectal cancer present? Symptoms, duration, and clues to location. Am J Gastroenterol. 1999;94(10):3039-45.

57. Leufkens AM, van den Bosch MA, van Leeuwen MS, Siersema PD. Diagnostic accuracy of computed tomography for colon cancer staging: a systematic review. Scand J Gastroenterol. 2011;46(7-8):887-94.

58. Rollven E, Holm T, Glimelius B, Lorinc E, Blomqvist L. Potentials of high resolution magnetic resonance imaging versus computed tomography for preoperative local staging of colon cancer. Acta Radiol. 2013;54(7):722-30.

59. Spindler BA, Bergquist JR, Thiels CA, Habermann EB, Kelley SR, Larson DW, et al. Incorporation of CEA Improves Risk Stratification in Stage II Colon Cancer. J Gastrointest Surg. 2017;21(5):770-7.

60. Duffy MJ. Carcinoembryonic antigen as a marker for colorectal cancer: is it clinically useful? Clin Chem. 2001;47(4):624-30.

61. Segelman J, Singnomklao T, Hellborg H, Martling A. Differences in multidisciplinary team assessment and treatment between patients with stage IV colon and rectal cancer. Colorectal Dis. 2009;11(7):768-74.

62. Palmer G, Martling A, Cedermark B, Holm T. Preoperative tumour staging with multidisciplinary team assessment improves the outcome in locally advanced primary rectal cancer. Colorectal Dis. 2011;13(12):1361-9.

63. Burton S, Brown G, Daniels IR, Norman AR, Mason B, Cunningham D, et al. MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins? Br J Cancer. 2006;94(3):351-7.

64. Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. Colorectal Dis. 2009;11(4):354-64; discussion 64-5.

65. Bokey EL, Chapuis PH, Dent OF, Mander BJ, Bissett IP, Newland RC. Surgical technique and survival in patients having a curative resection for colon cancer. Dis Colon Rectum. 2003;46(7):860-6.

66. Culligan K, Coffey JC, Kiran RP, Kalady M, Lavery IC, Remzi FH. The mesocolon: a prospective observational study. Colorectal Dis. 2012;14(4):421-8; discussion 8-30.

67. West NP, Kobayashi H, Takahashi K, Perrakis A, Weber K, Hohenberger W, et al. Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. J Clin Oncol. 2012;30(15):1763-9.

68. Jin G, Tuo H, Sugiyama M, Oki A, Abe N, Mori T, et al. Anatomic study of the superior right colic vein: its relevance to pancreatic and colonic surgery. Am J Surg. 2006;191(1):100-3.

69. Yamaguchi S, Kuroyanagi H, Milsom JW, Sim R, Shimada H. Venous anatomy of the right colon: precise structure of the major veins and gastrocolic trunk in 58 cadavers. Dis Colon Rectum. 2002;45(10):1337-40.

70. Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol. 2005;6(7):477-84.

71. Colon Cancer Laparoscopic or Open Resection Study G, Buunen M, Veldkamp R, Hop WC, Kuhry E, Jeekel J, et al. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. Lancet Oncol. 2009;10(1):44-52.

72. Scholin J, Buunen M, Hop W, Bonjer J, Anderberg B, Cuesta M, et al. Bowel obstruction after laparoscopic and open colon resection for cancer: results of 5 years of follow-up in a randomized trial. Surg Endosc. 2011;25(12):3755-60.

73. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, et al. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet. 2005;365(9472):1718-26.

74. Clinical Outcomes of Surgical Therapy Study G, Nelson H, Sargent DJ, Wieand HS, Fleshman J, Anvari M, et al. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med. 2004;350(20):2050-9.

75. Fleshman J, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart RW, Jr., et al. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. Ann Surg. 2007;246(4):655-62; discussion 62-4.

76. Bonjer HJ, Hop WC, Nelson H, Sargent DJ, Lacy AM, Castells A, et al. Laparoscopically assisted vs open colectomy for colon cancer: a meta-analysis. Arch Surg. 2007;142(3):298-303.

77. Burns EM, Currie A, Bottle A, Aylin P, Darzi A, Faiz O. Minimal-access colorectal surgery is associated with fewer adhesion-related admissions than open surgery. Br J Surg. 2013;100(1):152-9.

78. Janson M, Bjorholt I, Carlsson P, Haglind E, Henriksson M, Lindholm E, et al. Randomized clinical trial of the costs of open and laparoscopic surgery for colonic cancer. Br J Surg. 2004;91(4):409-17.

79. Kim MK, Lee IK, Kang WK, Cho HM, Kye BH, Jalloun HE, et al. Long-term oncologic outcomes of laparoscopic surgery for splenic flexure colon cancer are comparable to conventional open surgery. Ann Surg Treat Res. 2017;93(1):35-42.

80. Kim MK, Lee IK, Kye BH, Kim JG. Procedural difficulty differences according to tumor location do not compromise the clinical outcome of laparoscopic complete mesocolic excision for colon cancer: a retrospective analysis. Oncotarget. 2017;8(38):64509-19.

81. Matthiessen P. Laparoskopisk kolorektal kirurgi inte längre en ful ankunge. Läkartidningen. 2016;Sect. 113.

82. Janson M, Edlund G, Kressner U, Lindholm E, Pahlman L, Skullman S, et al. Analysis of patient selection and external validity in the Swedish contribution to the COLOR trial. Surg Endosc. 2009;23(8):1764-9.

83. Rajan P, Hagman A, Sooriakumaran P, Nyberg T, Wallerstedt A, Adding C, et al. Oncologic Outcomes After Robot-assisted Radical Prostatectomy: A Large European Single-centre Cohort with Median 10-Year Follow-up. Eur Urol Focus. 2016.

84. Haglind E, Carlsson S, Stranne J, Wallerstedt A, Wilderang U, Thorsteinsdottir T, et al. Urinary Incontinence and Erectile Dysfunction After Robotic Versus Open Radical Prostatectomy: A Prospective, Controlled, Nonrandomised Trial. Eur Urol. 2015;68(2):216-25.

85. Hohwu L, Borre M, Ehlers L, Venborg Pedersen K. A short-term cost-effectiveness study comparing robot-assisted laparoscopic and open retropubic radical prostatectomy. J Med Econ. 2011;14(4):403-9.

86. Bolenz C, Freedland SJ, Hollenbeck BK, Lotan Y, Lowrance WT, Nelson JB, et al. Costs of radical prostatectomy for prostate cancer: a systematic review. Eur Urol. 2014;65(2):316-24.

87. Scarpinata R, Aly EH. Does robotic rectal cancer surgery offer improved early postoperative outcomes? Dis Colon Rectum. 2013;56(2):253-62.

88. Park JS, Choi GS, Lim KH, Jang YS, Jun SH. Robotic-assisted versus laparoscopic surgery for low rectal cancer: case-matched analysis of short-term outcomes. Ann Surg Oncol. 2010;17(12):3195-202.

89. Kwak JM, Kim SH, Kim J, Son DN, Baek SJ, Cho JS. Robotic vs laparoscopic resection of rectal cancer: short-term outcomes of a case-control study. Dis Colon Rectum. 2011;54(2):151-6.

90. Bianchi PP, Ceriani C, Locatelli A, Spinoglio G, Zampino MG, Sonzogni A, et al. Robotic versus laparoscopic total mesorectal excision for rectal cancer: a comparative analysis of oncological safety and short-term outcomes. Surg Endosc. 2010;24(11):2888-94.

91. Baek JH, Pastor C, Pigazzi A. Robotic and laparoscopic total mesorectal excision for rectal cancer: a case-matched study. Surg Endosc. 2011;25(2):521-5.

92. Baik SH, Kwon HY, Kim JS, Hur H, Sohn SK, Cho CH, et al. Robotic versus laparoscopic low anterior resection of rectal cancer: short-term outcome of a prospective comparative study. Ann Surg Oncol. 2009;16(6):1480-7.

93. Bonjer HJ, Deijen CL, Abis GA, Cuesta MA, van der Pas MH, de Lange-de Klerk ES, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Engl J Med. 2015;372(14):1324-32.

94. Trastulli S, Desiderio J, Farinacci F, Ricci F, Listorti C, Cirocchi R, et al. Robotic right colectomy for cancer with intracorporeal anastomosis: short-term outcomes from a single institution. Int J Colorectal Dis. 2013;28(6):807-14.

95. Rondelli F, Balzarotti R, Villa F, Guerra A, Avenia N, Mariani E, et al. Is robot-assisted laparoscopic right colectomy more effective than the conventional laparoscopic procedure? A meta-analysis of short-term outcomes. Int J Surg. 2015;18:75-82.

96. Longo WE, Virgo KS, Johnson FE, Oprian CA, Vernava AM, Wade TP, et al. Risk factors for morbidity and mortality after colectomy for colon cancer. Dis Colon Rectum. 2000;43(1):83-91.

97. Kirchhoff P, Clavien PA, Hahnloser D. Complications in colorectal surgery: risk factors and preventive strategies. Patient Saf Surg. 2010;4(1):5.

98. Leung JM, Dzankic S. Relative importance of preoperative health status versus intraoperative factors in predicting postoperative adverse outcomes in geriatric surgical patients. J Am Geriatr Soc. 2001;49(8):1080-5.

99. Kirchhoff P, Dincler S, Buchmann P. A multivariate analysis of potential risk factors for intra- and postoperative complications in 1316 elective laparoscopic colorectal procedures. Ann Surg. 2008;248(2):259-65.

100. Kingham TP, Pachter HL. Colonic anastomotic leak: risk factors, diagnosis, and treatment. J Am Coll Surg. 2009;208(2):269-78.

101. Hyman N, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: it's later than you think. Ann Surg. 2007;245(2):254-8.

102. Bruce J, Krukowski ZH, Al-Khairy G, Russell EM, Park KG. Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. Br J Surg. 2001;88(9):1157-68.

103. McArdle CS, McMillan DC, Hole DJ. Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. Br J Surg. 2005;92(9):1150-4.

104. Walker KG, Bell SW, Rickard MJ, Mehanna D, Dent OF, Chapuis PH, et al. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Ann Surg. 2004;240(2):255-9.

105. Krarup PM, Jorgensen LN, Andreasen AH, Harling H, Danish Colorectal Cancer G. A nationwide study on anastomotic leakage after colonic cancer surgery. Colorectal Dis. 2012;14(10):e661-7.

106. Choy PY, Bissett IP, Docherty JG, Parry BR, Merrie A, Fitzgerald A. Stapled versus handsewn methods for ileocolic anastomoses. Cochrane Database Syst Rev. 2011(9):CD004320.

107. Gustafsson P, Jestin P, Gunnarsson U, Lindforss U. Higher frequency of anastomotic leakage with stapled compared to hand-sewn ileocolic anastomosis in a large population-based study. World J Surg. 2015;39(7):1834-9.

108. European Society of Coloproctology collaborating g. The relationship between method of anastomosis and anastomotic failure after right hemicolectomy and ileo-caecal resection: an international snapshot audit. Colorectal Dis. 2017.

109. Docherty JG, McGregor JR, Akyol AM, Murray GD, Galloway DJ. Comparison of manually constructed and stapled anastomoses in colorectal surgery. West of Scotland and Highland Anastomosis Study Group. Ann Surg. 1995;221(2):176-84.

110. Khani MH, Smedh K. Centralization of rectal cancer surgery improves long-term survival. Colorectal Dis. 2010;12(9):874-9.

111. Birgisson H, Smedh K. Effects of centralization of colorectal surgery on the outcome of patients with distal sigmoid colonic cancer. Dig Surg. 2009;26(2):169-75.

112. Martling A, Cedermark B, Johansson H, Rutqvist LE, Holm T. The surgeon as a prognostic factor after the introduction of total mesorectal excision in the treatment of rectal cancer. Br J Surg. 2002;89(8):1008-13.

113. Archampong D, Borowski D, Wille-Jorgensen P, Iversen LH. Workload and surgeon's specialty for outcome after colorectal cancer surgery. Cochrane Database Syst Rev. 2012(3):CD005391.

114. Jestin P, Nilsson J, Heurgren M, Pahlman L, Glimelius B, Gunnarsson U. Emergency surgery for colonic cancer in a defined population. Br J Surg. 2005;92(1):94-100.

115. Gunnarsson H, Jennische K, Forssell S, Granstrom J, Jestin P, Ekholm A, et al. Heterogeneity of colon cancer patients reported as emergencies. World J Surg. 2014;38(7):1819-26.

116. McArdle CS, Hole DJ. Emergency presentation of colorectal cancer is associated with poor 5-year survival. Br J Surg. 2004;91(5):605-9.

117. Hogan J, Samaha G, Burke J, Chang KH, Condon E, Waldron D, et al. Emergency presenting colon cancer is an independent predictor of adverse disease-free survival. Int Surg. 2015;100(1):77-86.

118. Kang H, O'Connell JB, Maggard MA, Sack J, Ko CY. A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. Dis Colon Rectum. 2005;48(6):1161-8.

119. Green JB, Timmcke AE, Mitchell WT, Hicks TC, Gathright JB, Jr., Ray JE. Mucinous carcinoma--just another colon cancer? Dis Colon Rectum. 1993;36(1):49-54.

120. Cawthorn SJ, Gibbs NM, Marks CG. Clearance technique for the detection of lymph nodes in colorectal cancer. Br J Surg. 1986;73(1):58-60.

121. Quirke P, Palmer T, Hutchins GG, West NP. Histopathological work-up of resection specimens, local excisions and biopsies in colorectal cancer. Dig Dis. 2012;30 Suppl 2:2-8.

122. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet. 1986;2(8514):996-9.

123. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol. 2008;26(2):303-12.

124. Sjovall A, Holm T, Singnomklao T, Granath F, Glimelius B, Cedermark B. Colon cancer management and outcome in relation to individual hospitals in a defined population. Br J Surg. 2007;94(4):491-9.

125. Averbach AM, Jacquet P, Sugarbaker PH. Surgical technique and colorectal cancer: impaction on local recurrence and survival. Tumori. 1995;81(3 Suppl):65-71.

126. Jamieson JK, Dobson JF. VII. Lymphatics of the Colon: With Special Reference to the Operative Treatment of Cancer of the Colon. Ann Surg. 1909;50(6):1077-90.

127. Wu Z, Qin G, Zhao N, Jia H, Zheng X. Assessing the adequacy of lymph node yield for different tumor stages of colon cancer by nodal staging scores. BMC Cancer. 2017;17(1):498.

128. Gonen M, Schrag D, Weiser MR. Nodal staging score: a tool to assess adequate staging of node-negative colon cancer. J Clin Oncol. 2009;27(36):6166-71.

129. Kanemitsu Y, Komori K, Kimura K, Kato T. D3 Lymph Node Dissection in Right Hemicolectomy with a No-touch Isolation Technique in Patients With Colon Cancer. Dis Colon Rectum. 2013;56(7):815-24.

130. Sondenaa K, Quirke P, Hohenberger W, Sugihara K, Kobayashi H, Kessler H, et al. The rationale behind complete mesocolic excision (CME) and a central vascular ligation for colon

cancer in open and laparoscopic surgery : proceedings of a consensus conference. Int J Colorectal Dis. 2014;29(4):419-28.

131. Markl B. Stage migration vs immunology: The lymph node count story in colon cancer. World J Gastroenterol. 2015;21(43):12218-33.

132. Forum NQ. National Voluntary Consensus Standards for Quality of Cancer Care. 2009.

133. Ahmadi O, Stringer MD, Black MA, McCall JL. Influence of age and site of disease on lymph node yield in colorectal cancer. N Z Med J. 2014;127(1395):31-40.

134. Morris EJ, Maughan NJ, Forman D, Quirke P. Identifying stage III colorectal cancer patients: the influence of the patient, surgeon, and pathologist. J Clin Oncol. 2007;25(18):2573-9.

135. Le Voyer TE, Sigurdson ER, Hanlon AL, Mayer RJ, Macdonald JS, Catalano PJ, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. J Clin Oncol. 2003;21(15):2912-9.

136. Norwood MG, Sutton AJ, West K, Sharpe DP, Hemingway D, Kelly MJ. Lymph node retrieval in colorectal cancer resection specimens: national standards are achievable, and low numbers are associated with reduced survival. Colorectal Dis. 2010;12(4):304-9.

137. Wong JH, Lum SS, Morgan JW. Lymph node counts as an indicator of quality at the hospital level in colorectal surgery. J Am Coll Surg. 2011;213(2):226-30.

138. Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst. 2007;99(6):433-41.

139. Moug SJ, Oliphant R, Balsitis M, Molloy RG, Morrison DS, West of Scotland Colorectal Cancer Managed Clinical N. The lymph node ratio optimises staging in patients with node positive colon cancer with implications for adjuvant chemotherapy. Int J Colorectal Dis. 2014;29(5):599-604.

140. Jestin P, Pahlman L, Glimelius B, Gunnarsson U. Cancer staging and survival in colon cancer is dependent on the quality of the pathologists' specimen examination. Eur J Cancer. 2005;41(14):2071-8.

141. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med. 1985;312(25):1604-8.

142. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009;27(19):3109-16.

143. Andre T, Sargent D, Tabernero J, O'Connell M, Buyse M, Sobrero A, et al. Current issues in adjuvant treatment of stage II colon cancer. Ann Surg Oncol. 2006;13(6):887-98.

144. Hogan J, Chang KH, Duff G, Samaha G, Kelly N, Burton M, et al. Lymphovascular invasion: a comprehensive appraisal in colon and rectal adenocarcinoma. Dis Colon Rectum. 2015;58(6):547-55.

145. Punt CJ, Buyse M, Kohne CH, Hohenberger P, Labianca R, Schmoll HJ, et al. Endpoints in adjuvant treatment trials: a systematic review of the literature in colon cancer and proposed definitions for future trials. J Natl Cancer Inst. 2007;99(13):998-1003.

146. Kodeda K, Nathanaelsson L, Jung B, Olsson H, Jestin P, Sjovall A, et al. Population-based data from the Swedish Colon Cancer Registry. Br J Surg. 2013;100(8):1100-7.

147. Van Cutsem E, Dicato M, Wils J, Cunningham D, Diaz-Rubio E, Glimelius B, et al. Adjuvant treatment of colorectal cancer (current expert opinion derived from the Third International Conference: Perspectives in Colorectal Cancer, Dublin, 2001). Eur J Cancer. 2002;38(11):1429-36.

148. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer. 1996;77(7):1254-62.

149. Sargent DJ, Wieand HS, Haller DG, Gray R, Benedetti JK, Buyse M, et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol. 2005;23(34):8664-70.

150. Latkauskas T, Rudinskaite G, Kurtinaitis J, Janciauskiene R, Tamelis A, Saladzinskas Z, et al. The impact of age on post-operative outcomes of colorectal cancer patients undergoing surgical treatment. BMC Cancer. 2005;5:153.

151. van Leeuwen BL, Pahlman L, Gunnarsson U, Sjovall A, Martling A. The effect of age and gender on outcome after treatment for colon carcinoma. A population-based study in the Uppsala and Stockholm region. Crit Rev Oncol Hematol. 2008;67(3):229-36.

152. Pahlman L, Bohe M, Cedermark B, Dahlberg M, Lindmark G, Sjodahl R, et al. The Swedish rectal cancer registry. Br J Surg. 2007;94(10):1285-92.

153. Jorgren F, Johansson R, Damber L, Lindmark G. Validity of the Swedish Rectal Cancer Registry for patients treated with major abdominal surgery between 1995 and 1997. Acta Oncol. 2013;52(8):1707-14.

154. Gunnarsson U, Seligsohn E, Jestin P, Pahlman L. Registration and validity of surgical complications in colorectal cancer surgery. Br J Surg. 2003;90(4):454-9.

155. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? Br J Surg. 1982;69(10):613-6.

156. Heald RJ. The 'Holy Plane' of rectal surgery. J R Soc Med. 1988;81(9):503-8.

157. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. Lancet. 1993;341(8843):457-60.

158. Martling AL, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. Lancet. 2000;356(9224):93-6.

159. Martling A, Holm T, Rutqvist LE, Johansson H, Moran BJ, Heald RJ, et al. Impact of a surgical training programme on rectal cancer outcomes in Stockholm. Br J Surg. 2005;92(2):225-9.

160. Birgisson H, Talback M, Gunnarsson U, Pahlman L, Glimelius B. Improved survival in cancer of the colon and rectum in Sweden. Eur J Surg Oncol. 2005;31(8):845-53.

161. Bokey L, Chapuis PH, Chan C, Stewart P, Rickard MJ, Keshava A, et al. Long-term results following an anatomically based surgical technique for resection of colon cancer: a comparison with results from complete mesocolic excision. Colorectal Dis. 2016;18(7):676-83.

162. Kontovounisios C, Kinross J, Tan E, Brown G, Rasheed S, Tekkis P. Complete mesocolic excision in colorectal cancer: a systematic review. Colorectal Dis. 2015;17(1):7-16.

163. Archer SB, Brown DW, Smith CD, Branum GD, Hunter JG. Bile duct injury during laparoscopic cholecystectomy: results of a national survey. Ann Surg. 2001;234(4):549-58; discussion 58-9.

164. Shea JA, Healey MJ, Berlin JA, Clarke JR, Malet PF, Staroscik RN, et al. Mortality and complications associated with laparoscopic cholecystectomy. A meta-analysis. Ann Surg. 1996;224(5):609-20.

165. Keus F, de Jong JA, Gooszen HG, van Laarhoven CJ. Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis. Cochrane Database Syst Rev. 2006(4):CD006231.

166. Sauerland S, Jaschinski T, Neugebauer EA. Laparoscopic versus open surgery for suspected appendicitis. Cochrane Database Syst Rev. 2010(10):CD001546.

167. Carlsson P SR, Theodorsson E. Robotassisterad kirurgi ökar - trots osäker kostnadseffektivitet. Läkartidningen. 2016;113:1-5.

168. Johnson N, Lilford RJ, Brazier W. At what level of collective equipoise does a clinical trial become ethical? J Med Ethics. 1991;17(1):30-4.

169. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med. 1987;317(3):141-5.

170. Fries JF, Krishnan E. Equipoise, design bias, and randomized controlled trials: the elusive ethics of new drug development. Arthritis Res Ther. 2004;6(3):R250-5.

171. Djulbegovic B, Lacevic M, Cantor A, Fields KK, Bennett CL, Adams JR, et al. The uncertainty principle and industry-sponsored research. Lancet. 2000;356(9230):635-8.

172. Cook C, Sheets C. Clinical equipoise and personal equipoise: two necessary ingredients for reducing bias in manual therapy trials. J Man Manip Ther. 2011;19(1):55-7.

173. Cho MS, Baek SJ, Hur H, Soh Min B, Baik SH, Kyu Kim N. Modified complete mesocolic excision with central vascular ligation for the treatment of right-sided colon cancer: long-term outcomes and prognostic factors. Ann Surg. 2015;261(4):708-15.

174. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ. 2001;323(7308):334-6.

175. Bertelsen CA, Neuenschwander AU, Jansen JE, Kirkegaard-Klitbo A, Tenma JR, Wilhelmsen M, et al. Short-term outcomes after complete mesocolic excision compared with 'conventional' colonic cancer surgery. Br J Surg. 2016;103(5):581-9.

176. West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. J Clin Oncol. 2010;28(2):272-8.

177. Storli KE, Sondenaa K, Furnes B, Nesvik I, Gudlaugsson E, Bukholm I, et al. Short term results of complete (D3) vs. standard (D2) mesenteric excision in colon cancer shows improved outcome of complete mesenteric excision in patients with TNM stages I-II. Tech Coloproctol. 2014;18(6):557-64.

178. Munkedal DLE, Rosenkilde M, Nielsen DT, Sommer T, West NP, Laurberg S. Radiological and pathological evaluation of the level of arterial division after colon cancer surgery. Colorectal Dis. 2017;19(7):O238-O45.

179. Spasojevic M, Stimec BV, Gronvold LB, Nesgaard JM, Edwin B, Ignjatovic D. The anatomical and surgical consequences of right colectomy for cancer. Dis Colon Rectum. 2011;54(12):1503-9.

180. Kaye TL, West NP, Jayne DG, Tolan DJ. CT assessment of right colonic arterial anatomy pre and post cancer resection - a potential marker for quality and extent of surgery? Acta Radiol. 2016;57(4):394-400.

181. Sheehan-Dare GE, Marks KM, Tinkler-Hundal E, Ingeholm P, Bertelsen CA, Quirke P, et al. The Effect of a Multidisciplinary Regional Educational Programme on the Quality of Colon Cancer Resection. Colorectal Dis. 2017.

182. West NP, Sutton KM, Ingeholm P, Hagemann-Madsen RH, Hohenberger W, Quirke P. Improving the quality of colon cancer surgery through a surgical education program. Dis Colon Rectum. 2010;53(12):1594-603.

183. Mori S, Baba K, Yanagi M, Kita Y, Yanagita S, Uchikado Y, et al. Laparoscopic complete mesocolic excision with radical lymph node dissection along the surgical trunk for right colon cancer. Surg Endosc. 2015;29(1):34-40.

184. Feng B, Sun J, Ling TL, Lu AG, Wang ML, Chen XY, et al. Laparoscopic complete mesocolic excision (CME) with medial access for right-hemi colon cancer: feasibility and technical strategies. Surg Endosc. 2012;26(12):3669-75.

185. Gouvas N, Pechlivanides G, Zervakis N, Kafousi M, Xynos E. Complete mesocolic excision in colon cancer surgery: a comparison between open and laparoscopic approach. Colorectal Dis. 2012;14(11):1357-64.

186. West NP, Kennedy RH, Magro T, Luglio G, Sala S, Jenkins JT, et al. Morphometric analysis and lymph node yield in laparoscopic complete mesocolic excision performed by supervised trainees. Br J Surg. 2014;101(11):1460-7.

187. Bertelsen CA, Bols B, Ingeholm P, Jansen JE, Neuenschwander AU, Vilandt J. Can the quality of colonic surgery be improved by standardization of surgical technique with complete mesocolic excision? Colorectal Dis. 2011;13(10):1123-9.

188. Bertelsen CA, Neuenschwander AU, Jansen JE, Wilhelmsen M, Kirkegaard-Klitbo A, Tenma JR, et al. Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a retrospective, population-based study. Lancet Oncol. 2015;16(2):161-8.

189. Merkel S, Weber K, Matzel KE, Agaimy A, Gohl J, Hohenberger W. Prognosis of patients with colonic carcinoma before, during and after implementation of complete mesocolic excision. Br J Surg. 2016;103(9):1220-9.

190. Thorsen Y, Stimec B, Andersen SN, Lindstrom JC, Pfeffer F, Oresland T, et al. Bowel function and quality of life after superior mesenteric nerve plexus transection in right colectomy with D3 extended mesenterectomy. Tech Coloproctol. 2016;20(7):445-53.

191. Adamina M, Manwaring ML, Park KJ, Delaney CP. Laparoscopic complete mesocolic excision for right colon cancer. Surg Endosc. 2012;26(10):2976-80.

192. Kotake K, Mizuguchi T, Moritani K, Wada O, Ozawa H, Oki I, et al. Impact of D3 lymph node dissection on survival for patients with T3 and T4 colon cancer. Int J Colorectal Dis. 2014;29(7):847-52.

193. Olofsson F, Buchwald P, Elmstahl S, Syk I. Wide excision in right-sided colon cancer is associated with decreased survival. Scand J Surg. 2013;102(4):241-5.

194. West NP, Morris EJ, Rotimi O, Cairns A, Finan PJ, Quirke P. Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. Lancet Oncol. 2008;9(9):857-65.

195. Siani LM, Pulica C. Stage I-IIIC right colonic cancer treated with complete mesocolic excision and central vascular ligation: quality of surgical specimen and long term oncologic outcome according to the plane of surgery. Minerva Chir. 2014;69(4):199-208.