Tampere University

SUSANNA NIEMELÄINEN

Colon Cancer Surgery in Aged Patients

Surgical and Functional Outcomes

Tampere University Dissertations 583

Tampere University Dissertations 583

SUSANNA NIEMELÄINEN

Colon Cancer Surgery in Aged Patients

Surgical and Functional Outcomes

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine and Health Technology
of Tampere University,
for public discussion in the Finn-Medi 5 auditorium
of the Finn-Medi 5, Biokatu 12, Tampere,
on 10 June 2022, at 12 o’clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Tampere University Hospital
Finland

Responsible supervisor	Docent Marja Hyöty Tampere University Finland	
Supervisors	Professor Esa Jämsen University of Helsinki Finland	Docent Jyrki Kössi University of Turku Finland
Pre-examiners	Docent Monika Carpelan-Holmström University of Helsinki Finland	Professor Jouko Laurila University of Oulu Finland
Opponent	Professor Juha Saarnio University of Oulu Finland	
Custos	Professor Johanna Laukkarinen Tampere University Finland	

Cover design: Roihu Inc.

ISBN 978-952-03-2359-2 (print)
ISBN 978-952-03-2360-8 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-2360-8

PunaMusta Oy – Yliopistopaino
Joensuu 2022

To my Mother and Father

ABSTRACT

Colon cancer is the fourth most diagnosed cancer of all age groups and the third most common in individuals aged 80 or over in Finland. Curative surgery is the primary treatment choice for colon cancer. However, physical and mental functioning of older people varies considerably from very fit to frail individuals with short life expectancy. Increasing numbers of recommendations and guidelines have recently been published regarding preoperative care planning and prognosis assessment in older patients. However, studies on the impact of surgery on postoperative outcomes and functional recovery are lacking.

This thesis aimed to analyse operative and functional outcomes of elective and curatively aimed colon cancer among patients aged 80 years and over. A further aim was to examine preoperative factors influencing postoperative outcomes in the short- and long-term.

The material in Studies I and II consisted of patients operated on in four Finnish secondary and tertiary hospitals between 2005 and 2016. The data, which included 387 patients, were collected from the colorectal databases of the hospitals concerned.

Study I evaluated preoperative risk factors affecting postoperative outcomes and survival in the short- and long-term. Severe complications were more common in patients living in assisted living accommodations and in patients with a history of hospitalisation six months before surgery. The 30-day and one-year mortality rates were significantly higher in patients with serious postoperative complications than in patients overall (30 % vs. 6.0% and 45% vs. 15%).

Study II focused on long-term overall survival after surgery comparing patients who survived over three months to patients who died within three months after surgery. Cardiovascular (13/29, 45 %) and surgical reasons (7/29, 24 %) were the most common causes of death within three months after surgery. However, advanced age, living in assisted living accommodation, multiple underlying diseases, and tumour stage according to TNM-classification were independently associated with shorter survival in patients who survived at least three months after surgery. The study showed that patients who were in good health before surgery, even with severe postoperative complications, had long-term outcomes and survival rates comparable to those of their unselected younger counterparts.

Prospective observational Studies III and IV were conducted in nine Finnish hospitals between April 2019 and August 2020. Study III, which included 161 patients, examined surgical outcomes within 30 postoperative days. Study IV, which included 167 patients, analysed changes in support for activities of daily living and mobility one-year after surgery.

Study III demonstrated that surgical outcomes among the fittest patients were comparable to those of younger patients. Surgeons should therefore not hesitate to perform invasive surgery based on age or comorbidities alone. The Clinical Frailty Scale (CFS), used as a frailty screening tool, predicted early postoperative complications well. Patients who were vulnerable or frail with CFS ≥3 had significantly more complications than patients in good health with CFS 1-2 (48 % vs 16%). The study concluded that CFS may be a user-friendly and quick screening implement for surgeons when assessing and identifying preoperative risks for postoperative complications.

Study IV showed that functionally independent and fit patients retained their independence in daily activities and mobility well during the first postoperative year. Preoperative optimisation of haemoglobin and preoperatively planned early rehabilitation and discharge are recommended for all patients. Patients needing more support with activities of daily living, having restricted mobility, or a history of cognitive impairment may require careful preoperative risk assessment, treatment planning and specific prehabilitation and postoperative rehabilitation planned jointly with a geriatrist before invasive cancer treatment.

In conclusion, this thesis showed that aged patients 80 years or over who are preoperatively appropriately selected and optimised, coped equally successfully with invasive cancer surgery with convergent short-and long-term outcome results as did their younger unselected counterparts. Careful assessment of the risks of surgical treatment, optimisation of patients´s physical performance and comprehensive treatment planning with the patient and relatives to avoid under-or overtreatment may be beneficial for aged colon cancer patients.

TIIVISTELMÄ

Paksusuolisyöpä on Suomen neljänneksi yleisin ja yli 80-vuotiailla kolmanneksi yleisin syöpäsairaus. Sairastumisen riski lisääntyy iän myötä. Kasvavan vanhusväestömäärän ja pidentyneen elinaikaodotteen seurauksena myös syöpäpotilasmäärät lisääntyvät. Kuratiivinen leikkaus on paksusuolisyövän ensisijainen hoitomuoto. Ikääntyneiden ihmisten fyysinen ja psyykkinen toimintakyky vaihtelee erittäin hyväkuntoisista hyvin hauraisiin yksilöihin. Viime aikoina on julkaistu kansainvälisiä hoitosuosituksia ikääntyneiden ihmisten leikkausta edeltävästä hoidon suunnittelusta ja ennusteen arvioimisesta. Sen sijaan on hyvin vähän tutkimustuloksia leikkauksen aiheuttamista lyhyt- ja pitkäaikaisvaikutuksista yli 80-vuotiaan paksusuolisyöpäpotilaan fyysiseen ja psyykkiseen toimintakykyyn sekä mahdolliseen avuntarpeeseen.

Tämän väitöskirjan tavoitteena oli selvittää 80-vuotiaiden ja sitä vanhempien paksusuolisyöpäpotilaiden leikkaushoidon komplikaatioita, kuolleisuutta ja siihen liittyviä riskitekijöitä. Lisäksi pyrittiin löytämään tekijöitä, joilla kyetään mittaamaan potilaan fyysistä ja kognitiivista toimintakykyä ennen mahdollisia syöpähoitoja. Näiden tekijöiden vaikutusta arvioitiin potilaan leikkauksen jälkeiseen toimintakykyyn ja avuntarpeeseen.

Kaksi ensimmäistä osatyötä koostuivat 387:sta levinneisyysasteen I-III paksusuolisyöpäpotilaasta, jotka leikattiin suunnitellusti neljässä suomalaisessa sairaalassa vuosina 2005–2016. Tiedot kerättiin takautuvasti sairaaloiden sähköisistä suolistosyöpärekistereistä.

Osatyö I kartoitti leikkauskomplikaatioiden riskitekijöitä ja vaikutuksia potilaiden leikkauksen jälkeiseen ennusteeseen. Vakavia komplikaatioita esiintyi erityisesti potilailla, jotka asuivat ympärivuorokautisessa palveluasumisessa ja potilailla, joilla oli leikkausta edeltäviä sairaalahoitojaksoja. Ensimmäisen kuukauden ja vuoden kuolleisuus oli merkitsevästi suurempi vakavia leikkauskomplikaatioita saaneilla potilailla (6% vs. 30% ja 15% vs. 45%).

Osatyö II tarkasteli paksusuolisyöpäleikkauksen pitkäaikaisennustetta ja vertasi potilaita, jotka selvisivät yli ja alle kolme kuukautta leikkauksesta. Sydän- ja verisuonisairaudet (13/29, 45%) ja kirurgiset syyt (7/29, 24%) olivat yleisimmät kuolinsyyt potilailla, jotka eivät selvinneet yli kolme kuukautta leikkauksesta. Korkea

ikä, ympärivuorokautinen palveluasuminen, useat perussairaudet ja kasvaimen leviämisaste heikensivät yli kolme kuukautta leikkauksesta selvinneiden potilaiden kokonaisennustetta. Tutkimus osoitti, että potilaat, jotka olivat ennen leikkausta fyysisesti hyväkuntoisia, toipuivat leikkauksesta erinomaisesti jopa vaikeiden komplikaatioiden jälkeen. Heidän pitkäaikaistuloksensa olivat vertailukelpoisia nuorempien paksusuolisyöpäleikkauspotilaiden kanssa.

Osatyöt III ja IV toteutettiin yhdeksässä suomalaisessa sairaalassa huhtikuun 2019 ja elokuun 2020 välisenä aikana. Osatyö III, johon rekrytoitiin 161 potilasta, selvitti prospektiivisesti leikkauskomplikaatioita ja niitä ennustavia riskitekijöitä 30 vuorokauden kuluessa toimenpiteestä. Osatyöhön IV rekrytoitiin 167 potilasta. Heidän avuntarpeensa ja liikkumisensa muutoksia analysoitiin vuoden kuluttua leikkauksesta.

Osatyö III osoitti, että toimintakyvyltään hyväkuntoiset ikäihmiset toipuvat erinomaisesti syöpäleikkauksesta, joten korkeasta iästä tai perussairauksista huolimatta heille voi suositella invasiivista kirurgista hoitoa. Tutkimuksessa gerastenian seulontatyökaluna käytetty kliininen gerastenia-asteikko (CFS) ennusti leikkauksen varhaiskomplikaatioita hyvin. Potilailla, joilla oli gerastenia tai sen esiaste (CFS $\geq$3) esiintyi merkitsevästi enemmän komplikaatioita kuin hyväkuntoisilla potilailla (48% vs. 16%). Tutkimuksen perusteella kliinistä gerastenia-asteikkoa (CFS) voidaan suositella kirurgeille helppokäyttöiseksi ja nopeaksi seulontatyökaluksi iäkkään potilaan leikkauskomplikaatioriskien arvioinnissa.

Osatyö IV osoitti, että toimintakyvyltään hyväkuntoiset yli 80-vuotiaat syöpäpotilaat säilyttivät leikkauksen jälkeisen vuoden seurannassa toimintakykynsä ilman merkitsevästi lisääntynyttä ulkopuolista avuntarvetta. Kaikki potilaat hyötyisivät leikkausta edeltävästä anemian korjaamisesta ja etukäteen suunnitellusta leikkauksen jälkeisestä varhaiskuntoutuksesta ja kotiutussuunnitelmasta. Potilaat, jotka ennen leikkausta tarvitsevat ulkopuolista apua jokapäiväisessä elämässä, joiden liikuntakyky on huonontunut tai joilla on muistivaikeuksia, mahdollisesti hyötyisivät huolellisesta kokonaisvaltaisesta hoidon suunnittelusta yhdessä geriatrin kanssa.

Tämän väitöskirjan johtopäätöksenä todetaan, että huolellisesti ja asianmukaisesti leikkaushoitoon valitut yli 80-vuotiaat paksusuolisyöpäpotilaat saavuttavat vertailukelpoiset lyhyt- ja pitkäaikaistulokset nuorempiin potilaisiin verrattuna. Huolellinen leikkaushoidon riskien arviointi, potilaan fyysisen kunnon optimointi ja kokonaisvaltainen, moniammatillisesti yhdessä potilaan ja hänen läheistensä kanssa suunniteltu hoito voi oleellisesti hyödyttää iäkästä paksusuolisyöpäpotilasta.

ORIGINAL PUBLICATIONS

The thesis is based on the following original publications, referred to in the text by Roman numerals (I-IV):

I Niemeläinen S, Huhtala H, Ehrlich A, Kössi J, Jämsen E, Hyöty M. Risk factors of short-term survival in the aged in elective colon cancer surgery: a population-based study. Int J Colorectal Dis. 2020 Feb; 35(2):305-15.

II Niemeläinen S, Huhtala H, Ehrlich A, Kössi J, Jämsen E, Hyöty M. Long-term survival following elective colon cancer surgery in the aged. A population-based cohort study. Colorectal Dis. 2020 Nov; 22(11):1585-96.

III Niemeläinen S, Huhtala H, Andersen J, Ehrlich A, Haukijärvi E, Koikkalainen S, Koskensalo S, Kössi J, Mattila A, Pinta T, Uotila-Nieminen M, Vihervaara H, Hyöty M, Jämsen E. Clinical Frailty Scale is a useful tool for predicting postoperative complications following elective colon cancer surgery in the age of 80 years and older: A prospective, multicentre observational study. Colorectal Dis. 2021 Jul; 23(7):1824–36.

IV Niemeläinen S, Huhtala H, Jämsen E, Kössi J, Andersen J, Ehrlich A, Haukijärvi E, Koikkalainen S, Koskensalo S, Mattila A, Pinta T, Uotila-Nieminen M, Vihervaara H, Hyöty M. One-year outcomes for colon cancer surgery in octogenarians: A prospective, multicenter observational study. (Submitted).

AUTHOR'S CONTRIBUTIONS

The author did the study design for Studies I-IV with the help of the supervisors and the statistician. For Studies I and II, the author did the data collection from the medical records and death certificates with the help of the co-authors. For Studies III and IV, the author was responsible for recruiting, operating on, arranging follow-up for consenting patients and collecting the data jointly with the co-authors. The author analysed the data of all the studies with the help of the supervisors and the statistician. The author wrote first drafts and was the first author in all the studies supported by the other co-authors. Finally, the author submitted the papers to the journals and provided the final versions of the papers.

ABBREVIATIONS

AA-CCI	Age-adjusted Charlson comorbidity index
ADL	Basic activities of daily living
AL	Anastomotic leakage
ARDS	Acute respiratory distress syndrome
ASA	American Society of Anesthesiologists
BMI	Body mass index
BRAF	B-Raf protein
CA 19-9	Carbohydrate antigen 19-9
CAPOX	Capecitabine plus oxaliplatin
CCI	Charlson comorbidity index
CD	Clavien-Dindo
CEA	Carcinoembryonic antigen
CFS	Clinical frailty scale
CGA	Comprehensive geriatric assessment
CIN	Chromosomal instability
CIMP	CpG island methylator phenotype
CSS	Cancer specific survival
CVL	Central vein ligation
CME	Complete mesocolic excision
COPD	Chronic obstructive pulmonary disease
CRC	Colorectal cancer
CT	Computed tomography
CTC	Computed tomographic colonography
CU	Ulcerative colitis
DFS	Disease-free survival
DNA	Deoxyribonucleic acid
ERAS	Enhanced recovery after surgery
ESPEN	European Society of clinical nutrition and metabolism
EURECCA	European Registration of cancer care

FAP	Familial adenomatous polyposis
FIT	Faecal immunochemical test
FOLFOX	Leucovorin plus fluorouracil plus oxaliplatin
FR	Functional recovery
GBD	Global burden of disease
HR	Hazard ratio
IADL	Instrumental activities in daily living
ICG	Indocyanine green
IMA	Inferior mesenteric artery
KRAS	K-Ras protein
LOI	Loss of independence
MBP	Mechanical bowel preparation
MDT	Multidisciplinary team
MMR	Mismatch repair
MMSE	Mini-mental state examination
MNA	Mini nutritional assessment
MNA-SF	Mini nutritional assessment short form
MOABP	Mechanical and oral antibiotic bowel preparation
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSI-H	Microsatellite instability high
OR	Odds ratio
OS	Overall survival
POCD	Postoperative cognitive disorder
POD	Postoperative delirium
POF	Postoperative fatigue
REDCAP	Research electronic data capture
SSI	Surgical site infections
TME	Total mesorectal excision
TNM	Tumour-node-metastasis
UICC	Union for International Cancer Control
UTI	Urinary tract infection
VTE	Venous thromboembolism

TABLE OF CONTENTS

List of Figures

List of Tables

1 INTRODUCTION

The number of older people is rapidly growing due to increased life expectancy. As most malignancies are increasingly related to older ages, the number of patients contracting colon cancer is expected to increase and thus become a significant treatment challenge to colorectal surgical units (Arnold et al. 2017; Perera et al. 2021). Among aged Finnish individuals 80 years or over, colon cancer was the third most commonly diagnosed malignancy in 2020. In all age groups, the overall reported number of new cases was 2216 and 30% of patients were 80 years or older. (Finnish Cancer Registry 2022).

The primary purpose of colon cancer treatment is to cure the disease while simultaneously minimising the surgical complications and maintaining the individual's functional status (Argiles et al. 2020). Older individuals constitute a heterogeneous group of patients ranging from very fit persons to frail ones with short life expectancy (Papamichael et al. 2015). Decision-making regarding surgery may thus be challenging. The high burden of comorbidities, impaired nutritional status, frailty, functional limitations, and history of cognitive disorder are risk factors for complications of cancer treatment and thus for reduced short- and long-term survival (Weerink et al. 2018; Ghignone et al. 2020). Consequently, chronological age as such is a poor predictor of treatment outcomes and life expectancy (Souwer et al. 2020). Concerns related to age should therefore not result in undertreatment of fit patients or overtreatment of frail patients.

Comprehensive progress in surgical and anaesthesiological procedures has improved perioperative care and thereby making colon cancer surgery more feasible even for very old patients. On the other hand, older individuals may prefer to retain their functional independence by choosing less effective non-invasive treatment options (Fried et al 2002; Rostoft et al. 2020). There has been an increase in the numbers of clinical guidelines and recommendations on the preoperative assessment and treatment of older colorectal cancer patients with multiple comorbidities, frailty or impaired functional or cognitive status.

However, reported data on real-life surgical and functional outcomes of colon cancer patients aged 80 years or older are lacking.

The purpose of this thesis was to analyse the postoperative surgical outcomes, functional recovery and overall survival in elective colon cancer surgery among patients 80 years and older. Further aim was to determine preoperative functional, nutritional and medical factors likely to affect postoperative outcomes.

2 REVIEW OF THE LITERATURE

2.1 Epidemiology and pathogenesis of colon cancer

2.1.1 Incidence of colon cancer

Colon cancer is globally the fifth most diagnosed malignant disease and the fifth leading cause of cancer deaths. In 2020, there were an estimated 1.1 million new colon cancer cases and 577,000 deaths worldwide (Sung et al. 2021). Many high-income countries with the historically highest colon cancer burden have stabilised or declining age-standardised incidence rates. This improvement is likely attributable to healthier lifestyle options, adoption of early diagnostic efforts such as faecal blood testing with intensive colonoscopy screening and removal of precursor lesions (Arnold et al. 2015; Sung et al. 2021). Nevertheless, globally the rates are gradually rising due to the proliferation of western lifestyle with ongoing harmful societal and economic developments, population growth and increased life expectancy (Arnold et al. 2017). In Finland, the age-standardised incidence rate for colon cancer was 37.7 per 100,000 person-years in 2020. Altogether 2,216 new colon cancer cases were diagnosed, which accounts for 6.7% of all cancer cases that year. (Finnish Cancer Registry, 2022).

In 2020 life expectancy for female and male Finnish individuals over 80 years was 10.1 and 8.4 years respectively. Statistics Finland estimates, that the number of individuals aged 80 years or older in Finland is expected to double from 330,000 in 2020 to 645,000 by 2050 (Statistics Finland 2022).

The number of diagnosed colon cancers has more than doubled over a period of 30 years and an 80-year-old individual has over a fivefold greater probability of being diagnosed with colon cancer than an individual of 60 years. Colon cancer is the fourth most diagnosed cancer overall and the third most diagnosed among patients over the age of 80 years. Recently, 30% of newly diagnosed colon cancer patients were aged 80 years or older (Finnish Cancer Registry, 2022).

Men have a slightly higher incidence of colon cancer than women (Sung et al. 2021). However, among individuals of aged 80 or older, the proportion of cancers in females is higher, mainly due to the longer life expectancy of women (Finnish Cancer Registry 2022). Approximately 40% of colon cancers occur in the proximal or transverse colon (Siegel et al. 2020). Right-side colon cancer is a more age- and sex-related disease, as increased numbers of proximal colon cancer cases are diagnosed among older patients and females (Lee et al. 2015; Reif de Paula et al. 2021).

Concurrently, mortality rates from colon cancer have steadily decreased in most high-income countries in North America and Western Europe, which is possibly due to easier access to initial diagnostic services, improved awareness and cancer screening as well as enhanced comprehensive treatment and patient care (Welch et al. 2016; Sung et al 2021). In 2019, 885 colon cancer deaths were diagnosed, which accounts for 6.8% of all deaths from cancer in Finland that year (Finnish Cancer Registry, 2022). In addition, colon cancer is predicted to have a mortality rate increase of 8.0% by 2035 due to the growing number of aged patients and increase in life expectancy (Araghi et al. 2019).

2.1.2 Risk factors of colon cancer

More than two-thirds of colon cancer cases and roughly 60% of deaths occur in Western countries with highly developed social structures (Arnold et al. 2017; Sung et al. 2021). This higher probability of contracting colon cancer is due to age, lifestyle, and history of chronic diseases. The western lifestyle, including dietary components with increased alcohol consumption, red and processed meat, and low dietary fibre, smoking and obesity, have been stated to be risk factors for colon cancer (van de Velde et al. 2014).

Sporadic cancers comprise 65-70% of all colon cancers. An estimated 30-35% of colon cancers may be attributable to heritable factors, mainly with a family history of a first-degree or second-degree relative with colorectal cancer (Marmol et al. 2017). Transparent genetic backgrounds, such as Lynch syndrome (LS), familial adenomatous polyposis (FAP) and other polyposis syndromes comprise only 3–5% of all colon cancer cases (Lynch et al. 2003; Balmana 2013). Over 40 genetic locations associated with weak effects on sporadic colorectal cancer have been discovered by recent genome-wide association studies. A profound understanding of the genetic map can lead to more focused and individualised surveillance and treatment alternatives (Peters et al. 2015).

Patients with inflammatory bowel diseases (Crohn's disease and ulcerative colitis) have an increased risk of colorectal cancer. Patients whose disease is diagnosed at a young age, have longer disease duration or extensive disease or more severe inflammation, have a 1.4- to 7.2-fold increased risk of colorectal cancer (Ola Olen et al .2020).

2.1.3 Pathogenesis of colon cancer

A widely agreed hypothesis regarding colorectal cancer development is the adenoma-carcinoma sequence (Jass 2007). The development pathway from adenoma to colorectal cancer is a subsequent accumulation of genetic mutation series targeting oncogenes, tumour suppressor genes and genes related to DNA repair mechanisms. Colorectal carcinomas can be classified as sporadic (65-70%), familial (25-30%) and inherited (3-5%) according to their original mutation (Marmol et al. 2017).

Three molecular pathways cause the formation of colorectal cancer. The most common is chromosomal instability (CIN), due to changes in the structures of chromosomes and mutations in specific tumour suppressor genes. Epigenetic instability is responsible for the CpG island methylator phenotype (CIMP) pathway, commonly associated with older age, female gender and proximal tumour location Microsatellite instability (MSI) is represented in 11-17% of cancer cases because of loss of DNA repair mechanisms (Galon et al. 2014; Marmol et al. 2017). Figure 1 illustrates the main pathogenesis routes of colorectal cancer.

The spectrum of colorectal cancer progress sequence expresses either conventional adenoma progress to carcinoma, sessile-serrated adenoma-carcinoma, or an MSI pathway. The traditional way appears to account for 70-75% of all cases. The serrated pathway, often initiated by a genetic mutation of BRAF or KRAS genes and progressing by the CIMP pathway, accounts for 20-30% of colorectal cancers. Tumours arising from the serrated pathway appear more on the right-side colon of aged patients predominantly in females. They express mucinous, MSI positive and BRAF-mutated histopathology (Galon et al. 2014; Lee et al. 2015). Lynch syndrome is the most common genetic propensity for hereditary colorectal cancer accounting for 1-3% of colorectal cancers. (Mecklin et al. 2007). Other known cancer-related gene mutated polyposis syndromes are familial adenomatous polyposis (FAP), juvenile polyposis and Peutz-Jeghers polyposis (Lynch et al. 2003; Balmana et al. 2013).

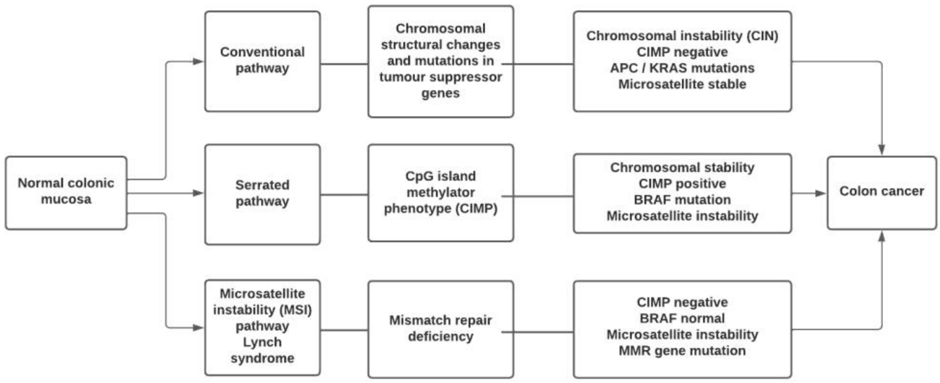

Figure 1. Main pathogenesis routes of colorectal cancer (Modifield from Galon et al 2014; Marmol et al 2017)

Microsatellite instable (MSI-H) cancers are located in the proximal colon, manifesting in patients younger than 50 years with hereditary Lynch syndrome or in aged patients, especially in females with sporadic conformation. They moreover have large local growth with mucinous appearance but are rarely accompanied by adjacent organ metastases. Microsatellite instability (MSI) appears to be a positive prognostic factor for a better survival rate with no need for postoperative adjuvant treatment (Seppälä et al. 2015; Argiles et al. 2020). KRAS mutation status plays a specific role in metastatic colorectal cancers and is associated with decreased overall survival. Patients whose tumours carry BRAF mutation have been shown to have a poorer prognosis in microsatellite stable colon carcinomas (Seppälä et al. 2015; Phipps et al. 2020).

2.2 Clinical presentation and diagnosis of colon cancer

2.2.1 Clinical examination and colonoscopy

Colon cancer arises from the bowel mucosa, growing into both the bowel lumen and wall and possibly spreading to adjacent organs. Symptoms are associated with relatively large tumours or advanced disease stages. Changes in bowel habits, iron deficiency and anaemia, especially with older patients, blood appears in the stool, general or localised abdominal pain, the presence of palpable abdominal mass and unexpected weight loss are the most common symptoms depending on the location and stage of the primary tumour (Argiles et al. 2020).

A total colonoscopy is the primary recommendation for diagnostic confirmation. The benefits comprise determining and marking the accurate tumour location with tattoo dye, a biopsy of the tumour and deleting synchronous lesions. When a complete colon examination is not successful before surgery due to tumour obstruction or other reasons, a total colonoscopy should be accomplished within 3–6 months postoperatively (Van de Velde et al. 2014; Argiles et al. 2020).

About 10-15% of colonoscopies are reported to be incomplete. Computed tomographic colonography (CTC) is considered the best radiological diagnostic examination option for large polyps with accuracy close to that of optical colonoscopy and high sensitivity for detecting proximally situated synchronous tumours. In colorectal tumours ≥10 mm, detection rates of over 90% have been reported but there is no option for biopsies or polypectomies (Tudyka et al. 2014; Spada et al. 2020).

2.2.2 Histopathology

Pathological examination of biopsies or postoperative specimens confirms the cancer diagnosis. Most tumours are adenocarcinomas (90%), other common histological types being mucinous, signet ring cell and medullary type (Galon et al. 2014). Structured pathological reporting is recommended for all cancer specimens (Sluijter et al. 2016, UICC 2017). The Union for International Cancer Control (UICC) Tumour-Node-Metastasis (TNM) system is used as a tool for planning surgical and oncological treatments, and it has been approved as the most valuable prognostic tool for predicting five-year survival in colon cancer. (Sluijter et al. 2016). Tables 1 and 2 illustrate the eighth edition of TNM classification and staging (UICC 2017).

Table 1. TNM classification of colon cancer (UICC 8th edition, 2017)

T	**PRIMARY TUMOUR**
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades subserosa or perirectal tissues
T4	Tumour directly invades other organs or structures and/or perforates visceral peritoneum
	T4a Tumour perforates visceral peritoneum
	T4b Tumour directly invades other organs or structure
N	**REGIONAL LYMPH NODES**
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
	N1a Metastasis in 1 regional lymph node
	N1b Metastasis in 2 to 3 regional lymph nodes
	N1c Tumour deposit(s), i.e., satellites, in the subserosa or perirectal soft tissue, without regional node metastasis
N2	Metastasis in 4 or more regional lymph nodes
	N2a Metastasis in 4-6 regional lymph nodes
	N2b Metastasis in 7 or more regional lymph nodes
M	**DISTANT METASTASIS**
M0	No distant metastasis
M1	Distant metastasis
	M1a Metastasis confined to one organ without peritoneal metastases
	M1b Metastasis in more than one organ
	M1c Metastasis to the peritoneum with or without other organ involvement

Table 2. TNM staging of colon cancer (UICC 8th edition, 2017)

STAGE	T	N	M
0	Tis	N0	M0
I	T1, T2	N0	M0
II	T3, T4	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
III	Any T	N1, N2	M0
IIIA	T1, T2	N1	M0
	T1	N2a	M0
IIIB	T1, T2	N2b	M0
	T2, T3	N2a	M0
	T3, T4a	N1	M0
IIIC	T3, T4a	N2b	M0
	T4a	N2a	M0
	T4b	N1, N2	M0
IV	Any T	Any N	M1
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b
IVC	Any T	Any N	M1c

Pathological staging of nodes expresses a strong association between the number of positive nodes and long-term survival but requires at least 12 harvested lymph nodes for prognostic feasibility (Scott et al. 1989). Other prognostic factors attached to pathological reporting as predictive morphological criteria are MSI status, tumour budding, lymph vascular and perineural invasion (Loughrey et al. 2018; Argilles et al. 2020).

2.2.3 Radiological imaging and laboratory tests

Synchronous metastases are diagnosed in 20% of newly diagnosed colon cancers. Liver is the most common organ (17%), accompanied by peritoneum (5%), lung (5%) and distant lymph nodes (3%) (Van der Geest et al. 2015; Argiles et al. 2020). Computed tomographic colonography (CT) of the thoracic and abdominal cavities is the primary radiological method for evaluating the presence of locoregional tumour extension and distant metastases. (Tudyka et al. 2014). Magnetic resonance imaging (MRI) is an option in patients with iodine-contrast allergies or chronic renal insufficiency (Hunter et al. 2016). The radiological reporting should be structured, including all mentioned evaluations (National Guidelines for Colorectal Cancer Treatment. 2022).

The serum level of carcinoembryonic antigen (CEA) is recommended to be measured before surgery for newly diagnosed cancers and monitored during postoperative surveillance to support the early detection of metastatic disease. However, CEA is insufficient for colon cancer diagnosis without a confirmatory tumour biopsy (Duffy et al. 2014; Konishi et al. 2018; Argiles et al. 2020). Another tumour marker, carbohydrate antigen (CA 19-9), is more seldom used. When preoperatively elevated, CA 19-9 has been shown to predict poorer survival (Carpelan-Holmström et al. 2004; Takakura et al. 2015). Although CA 19-9 shows some promise in postoperative surveillance, it is not currently recommended for clinical use (Argiles et al. 2020).

The implementation of screening programmes has been shown to cause short-term increases in colorectal cancer incidence because of increased detection of existing cases, thus impacting any long-term reduction in incidence and mortality from colorectal cancer (Lauby-Secretan et al. 2018). Recently in Finland, screening for colorectal cancer in people aged 56-74 years was adopted nationwide from the beginning of this year, 2022 (Finnish Ministry of Social Affairs and Health, 2022). However, with diminished life expectancy and burden of comorbidities, routine cancer screening is not recommended for patients aged 85 years and older. (DeSantis et al. 2019).

2.3 Treatment of colon cancer

Pre- and postoperative multidisciplinary team (MDT) assessment of colon cancer is recommended. The team should include a colon surgeon, an oncologist, a radiologist, a pathologist, and, if possible, a geriatrician. The MDT evaluates the patients' comorbidities, surgical approaches, treatment choices and aims for future treatment and care with consensus (National Guidelines for Colorectal Cancer Treatment 2022). The MDT may lead to significant changes in how cancer patients with colon cancer are assessed and managed. However, there is insufficient evidence of improvements in clinical outcomes resulting from MDT meetings (Pillay et al. 2016).

2.3.1 Surgical treatment

For early cancer stages (TisN0M0 or T1N0M0), endoscopic submucosal en-bloc resection could be performed if the morphological structure allows the management (NICE guidelines 2020; Argiles et al. 2020; National Guidelines for Colorectal Cancer Treatment 2022). Endoscopic resection is performed on aged patients with complete resection rates of 81-96% but is associated with risk of perforation (1.8-6.1%) and bleeding (3-3.7%) (Itatani et al. 2018).

Radical surgery is primarily recommended for invasive colon cancer, aiming at extensive resection of the bowel segment involved and its lymphatic drainage (Van de Velde et al. 2014; Argiles et al. 2020; NICE guidelines 2020; National Guidelines for Colorectal Cancer Treatment 2022). Jamieson described the principles of proper colon cancer surgery already more than 100 years ago (Jamieson et al. 1909). Depending on the location of the tumour, the surgical options are right hemicolectomy, extended right or left hemicolectomy, left hemicolectomy or sigmoid resection. The width extent of the colon resection is determined by the blood supply and distribution of regional lymph nodes. The recommendation is to remove a colon segment of at least 5-10 cm on both sides of the tumour. Still, more extensive margins frequently consist of the necessary ligation of the arterial blood supply. Adequate lymphadenectomy for clear pathological margins is mandatory to avoid locoregional recurrences and tumour cell spreading (Hohenberger et al. 2009; Bertelsen et al. 2016; Argiles et al. 2020).

The permanent stoma formation is exceedingly rare in elective colon cancer surgery, as most operations are performed with resection and bowel-to-bowel anastomosis. Stomas, on the contrary, can be specially performed in surgery with high-risk patients as temporary protection of the anastomosis with a delayed closure two to three months after primary cancer operation (Guenaga et al. 2007; Argiles et al. 2020).

Total Mesorectal Excision (TME), introduced by Heald (Heald et al. 1982), is the current gold standard for rectal cancer. It has significantly reduced local recurrence rates and improved oncological outcomes. A similar surgical principle called Complete Mesocolic Excision (CME) is increasingly used in colon cancer surgery. The technique includes sharp dissection of the embryological mesocolic plane combined with central vascular ligation (CVL) simultaneously with maximal removal of lymphatic vessels and nodes (Hohenberger et al. 2003; Hohenberger et al. 2009; West et al. 2010). Studies of CME at highly specialised centres have shown improvements in the quality of surgery with decreased local recurrence rates and improved disease-free (DFS) and long-term overall survival (OS) numbers compared to conventional colon cancer operations (Bertelsen et al. 2015; Merkel et al. 2016).

The technically challenging nature of the procedure, early results of marginally higher intra-operative complications and postoperative morbidity has limited the widespread use of CME technique (Kontovounisios et al. 2015; Kong et al. 2021). However, recent systematic reviews and meta-analyses, especially with right-sided tumours, have shown parallel short-term results, improved long-term survival rates and reduced risks of recurrences compared to conventional colon cancer surgery (Croner et al. 2018; Bertelsen et al. 2019; Mazzarella et al. 2021; Ow et al. 2021). Furthermore, despite the incomplete consensus on preferred operative technique, centralisation to larger units and standardisation of the surgical treatment of colon cancer with clearly structured dissection sequences with radical lymphadenectomy and high vascular ligation has improved the overall surgical and oncological outcomes (Bertelsen et al. 2011; Bernhoff et al. 2015; Merkel et al. 2016; National Guidelines for Colorectal Cancer Treatment 2022).

Historically, open surgery has been the cornerstone of cancer surgery. However, since the introduction of laparoscopic surgery for colon cancer in 1991 (Jacobs et al. 1991), the minimally invasive approach has increased worldwide. Laparoscopic resection of colon carcinoma is associated with similar short- and long-term outcomes regarding overall and cancer-related survival as well as recurrence rates compared with open colon resection (Theophilus et al. 2014; Stormark et al. 2016; Deijen et al. 2017). Laparoscopic surgery, in general, is associated with less perioperative blood loss, surgical stress response and faster postoperative functional recovery with shorter hospital stay (Veldkamp et al. 2005; Lorenzon et al. 2014). Besides, laparoscopy shows comparable long-term health-related quality of life outcomes with open surgery (Thong et al. 2020). Laparoscopic CME technique results in good long-term oncologic outcomes and offers comparable quality of the resected specimen to the open approach but more studies are needed for it to be considered a standard technique (Ehrlich et al. 2016; Negoi et al. 2017). Altogether, laparoscopic colon resection for cancer can be considered as a primary surgical technique compared to open surgery (Argiles et al. 2020; National Guidelines for Colorectal Cancer Treatment 2022).

Robotic-assisted surgery may benefit perioperative and short-term outcomes, but the operations have a longer duration and higher surgery costs. Thus, further robust evidence of a robotic approach for colon cancer surgery is required (Cuk et al. 2021).

Advanced age was initially considered a relative contraindication for laparoscopic surgery. Declining pulmonary compliance, increased systemic vascular resistance, acid-base disturbances and reduced splanchnic and renal perfusion caused by pneumoperitoneum may harm an aged patient with limited cardiopulmonary reserve (Bates et al. 2015). Despite these undesirable effects, laparoscopy, in general, has not resulted in increased perioperative complications in aged patients, with similar advantages compared to those in their younger counterparts (Kolarsick et al. 2020). Laparoscopic colorectal surgery leads to less immune response by reducing surgical stress, thereby improving postoperative recovery (Seishima et al. 2015; Chung et al. 2021). Thus, the laparoscopic approach may be considered the first choice for aged patients' cancer treatment unless specifically contraindicated (Kolarsick et al. 2020).

The enhanced recovery after surgery (ERAS) programme covers the entire perioperative period formulating it into a standardised protocol. It includes preoperative patient counselling, a multimodal approach to anaesthetic analgesics, minimally invasive surgical techniques and intraoperative balanced fluid therapy. Postoperatively, early enteral nutrition, avoidance of nasogastric tube and urinary catheter with early mobilisation and rehabilitation are encouraged (Fearon et al. 2005; Gustafsson et al. 2019). The ERAS strategy significantly accelerates functional recovery by reducing perioperative surgical stress response, sustaining postoperative physiological function, and expediting mobilisation after surgery. The ERAS program with a multidisciplinary approach has been repeatedly demonstrated to significantly reduce postoperative morbidity and mortality, shorten the length of hospital stay, decrease readmission rates and improve recovery from surgery thus optimising the utilisation of health care resources (Kehlet et al. 2008; Ehrlich et al. 2014; Greco et al. 2014; Ljunqvist et al. 2017).

The ERAS programme mainly focuses on peri- and postoperative factors to improve a patient recovery. Preoperative counselling predominantly targets on postoperative recovery time and does not include preoperative exercise or prehabilitation interventions (Orange et al. 2018). However, the preoperative period may offer more opportunities to optimise patients for invasive surgical treatment. Thus, an ERAS programme with additional prehabilitation interventions, which includes preoperative functional and exercise therapy with nutritional supplementation and treatment of iron-deficient anaemia, may have a better comprehensive impact on functional outcomes (Luther et al. 2018).

Recent studies show that ERAS protocols with aged colorectal cancer patients provide advantages with fewer disadvantages and shorter hospital stay with a reduction in postoperative mortality. Thus, ERAS programmes can be utilised safely with older cancer patients showing similar advantages as with younger counterparts. (Bagnall et al. 2014; Millan et al. 2020).

2.3.2 Adjuvant therapy

The pathological examination of the resected specimen should assess the risk of recurrence after colon cancer surgery, also including MMR/MSI status and at least 12 lymph nodes examined in the pathological sample. Patients with stage III disease have a 1.7- 4-fold higher risk of recurrence after surgery (Roth et al. 2012). Thus, after curative resection for all patients with stage III cancer, adjuvant chemotherapy is recommended. In addition, high-risk stage II patients with stage T4 tumours and a number of lymph nodes under 12 may benefit from adjuvant chemotherapy (van de Velde et al. 2014; Argiles et al. 2020).

The current guidelines for adjuvant treatment in stage III colon cancer recommend a combination of capecitabine and oxaliplatin (CAPOX) or leucovorin, fluorouracil and oxaliplatin (FOLFOX) (ESMO guidelines 2019; Argiles et al. 2020). The risks of recurrence and mortality have been shown to decreased by 40-41% and 20-30% respectively with stage III patients receiving adjuvant therapy compared to patients undergoing surgery alone (Laurie et al. 1989). The recommendation for low-risk stage III cancer is single CAPOX adjuvant therapy for three months or FOLFOX therapy for three to six months. Correspondingly, the recommendation for high-risk stage III cancer is three to-six-month adjuvant treatments with CAPOX or six-month adjuvant treatment with FOLFOX. With high-risk stage II cancer, corresponding treatment for that for stage III cancer is advisable. (ESMO guidelines 2019; Argiles et al. 2020; National Guidelines for Colorectal Cancer Treatment 2022).

Comparison of the treatment benefits and a possible risk of recurrences must consider patient´s biological age, comorbidities, functional status and life expectancy. Chemotherapy is considered toxic with cardiovascular, renal and liver complications. In addition, it causes neurotoxicity consisting mainly of peripheral neuropathy. Older patients with excess comorbidities, malnutrition and vulnerable physiological functional status are more susceptible to toxic influences (Itatani et al. 2018). The European Colon Cancer Group Study (EURECCA) showed substantial variation with adjuvant treatment for patients aged 80 years or older (Vermeer et al. 2018). However, the benefit of single capecitabine and toxicity as adjuvant chemotherapy appears similar in older and younger patients, therefore it can be recommended for older individuals without other contraindications (Abraham et al. 2013; Mayer et al. 2015; Itatani et al. 2018).

2.3.3 Non-surgical treatment

The majority of aged colon cancer patients referred for surgery will benefit from curative surgery (Argiles et al. 2020). Nevertless, some patients with multimorbidity, frailty, and decreased functional capacity are at elevated risk of postoperative morbidity and mortality outweighing surgical and oncological benefits. Consequently, a proportion of aged patients are treated conservatively, but the data on non-surgically treated patients´ clinical outcomes and survival are limited. A study from England showed that non-surgically treated patients with local colorectal cancer with poor fitness or comorbidity status had a two-year mortality rate of 76% with a median survival of 11 months (Abdem-Halim et al. 2019). Altogether, there are no data available comparing the outcomes of radical surgery vs palliative treatment for very old and vulnerable patients.

2.4 Postoperative complications of colon cancer surgery

Major abdominal surgery, even without complications, causes reduction in physiological and functional capacity (Lawrence et al. 2004). This reduced reservoir, called postoperative fatigue (POF), increases the level of physical and psychological tiredness for months after hospital discharge with a prolonged inability to regain preoperative baseline functional capacity (Zargar-Shoshtari et al. 2009). Surgery causes inflammation and tissue damage by releasing stress hormones and cell signal proteins called cytokines. This systemic inflammatory response syndrome causes changes in various metabolic functions, which lead to protein, glycogen and fat catabolism, insulin resistance, immunosuppression, impaired pulmonary function and hypoxia. In addition to the changes mentioned above, cancer patients may suffer from chronic low-grade inflammation, which inhibits adequate immune response (Weimann et al. 2017). The pathogenesis of postoperative complications is believed to involve the above-mentioned physiological changes (Wilmore 2002; Kehlet et al. 2008). The use of ERAS protocol may alleviate postoperative complications by 30% to 50% by reducing surgical stress and tissue trauma (Ljungqvist et al. 2017).

In general, 15-25% of patients undergoing elective colon surgery are reported to develop postoperative complications depending on the definition of these adverse events. (Kannan et al. 2015 ; Papageorge et al. 2016 ; Arnarson et al. 2019 ; GlobalSurg 2021). Postoperative complications after colon cancer surgery increase length of hospital stay, readmission rates and short-term mortality. Surgical complications partly increase the rate of reoperations, with reported rates of 1-11%, mainly more common in left-side colon operations (Li et al. 2020; Quintana et al. 2020). Moreover, these adverse events are associated with an excess one-year mortality rate of 15-30%, loss of independence, and poorer long-term survival (Gooiker et al. 2012; Artinyan et al. 2015; Arnarson et al. 2019; Gearhart et al. 2020). Apart from the prolonged dependency on health care services and personal suffering, complications after colon cancer surgery are associated with substantial healthcare costs (Govaert et al. 2015). Table 3 summarises studies on colon cancer surgery and complications for patients aged 80 years or older.

Table 3. Studies on elective colon cancer surgery and complications for patients aged 80 years or older. (Retro: retrospective study. Prosp: prospective study. Lap: laparoscopic. Pat: patients. Elect: elective. Compl: overall complications. Spec compl: specified complications. Mort: 30-day mortality. In-hosp: In hospital mortality).

Author	Country	Setting	Age range	Assigned groups Lap vs. open Age, Gender	Pat n	Elect %	Compl %	Spec compl %	Mort %
Leeuwen et al. 2008	Sweden	Retro	>80	<65, 65-80, >80 Female vs male	2851	68	25–35	Cardiovascular 12–20	7–11
Issa et al. 2011	Israel	Retro	80–87	Lap	46	100	30	Surgical 11 Pulmonary and urinary 13	2.1 (in-hosp)
			80–86	Open	47	100	35	Surgical 20 Pulmonary and urinary 20	6.5 (in-hosp)
Vallribera Valls et al. 2014	Spain	Retro	≥ 85	Lap <75, 75-84, ≥ 85	45	100	36	Surgical 18 Non-surgical 16	6.7
			≥ 85	Open <75, 75-84, ≥ 85	45	100	36	Surgical 29 Non-surgical 18	11
Hinoi et al. 2015	Japan	Retro	81–85	Lap	402	99	26	Surgical 15 Non-surgical 6.8	0 (in-hosp)
			81–86	Open	402	99	36	Surgical 18 Non-surgical 15	0.7 (in-hosp)
Duraes et al. 2016	USA	Retro	≥80	65, 65-79, ≥80	326	100	40	Surgical 14 Non-surgical 26	10
Roscio et al. 2016	Italy	Prosp	81–86	60-69, > 80	96	100	48	Surgical 24 Non-surgical 23 Severe 5.0	1.0 (in-hosp)
Denet et al. 2017	France	Retro	≥ 85	<64, 65-74, 75-84, ≥85	37	100	35	Surgical 24 Non-surgical 13 Severe 5.4	0.0 (in-hosp)
Arnarson et al. 2019	Sweden	Retro	> 80	<65, 65-80, >80	1647	85	27	Non-severe 17 Severe 9.5	-
Bare et al. 2020	Spain	Prosp	≥80	<50, 50-59, 60-69, 70-79, 80-85, >85	350	93	31–32	Surgical 16 Non-surgical 22–27	11–14 (in-hosp)
Barina et al. 2020	Italy	Retro	≥ 85	65-74, 75-84, ≥85	2671	79	34	Surgical 29 Non-surgical 28	2.8 (in-hosp)
Hirano et al. 2020	Japan	Retro	≥ 80	Lap <80, ≥80	87	100	18	Surgical 5.7 Non-surgical 13	1.0 (in-hosp)
Chung KC et al. 2021	Taiwan	Retro	≥80	Lap 80-84, 85-89, ≥ 90	9932	56	34	Surgical 24 Non-surgical 24	2.1 (in-hosp)
			≥80	Open 80-84, 85-89, ≥ 90	30519	54	44	Surgical 32 Non-surgical 30	6.1 (in-hosp)

Clavien–Dindo classification (CD), as illustrated in Table 4 is one of the most widely used methods of classifying complications and their severity. The classification grades the severity of complications according to the medical or surgical intervention required to manage the complication. CD classification defines the severity in a single patient according to the most serious complication, but the grade alone does not accurately reflect multiple complications. The CD classification has five grades; minor adverse events are classified from one to two, whereas major complications are graded from three to four. Five is graded as patient´s death (Dindo et al. 2004).

Table 4. Clavien-Dindo Classification of Surgical Complications (according to Dindo et al. 2004)

Grade		Definition
Grade I		Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are drugs as antiemetics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside Examples: wound infection, postoperative ileus, urinary retention
Grade II		Requiring pharmacological treatment with drugs other than those allowed for grade I complications Blood transfusions and total parenteral nutrition are also included Example: Pneumonia with iv antibiotics
Grade III		Requiring surgical, endoscopic or radiological intervention
	IIIa	Intervention not under general anaesthesia Example: intra-abdominal abscess needed radiological drainage
	IIIb	Intervention under general anaesthesia Example: anastomotic leakage
Grace IV		Life-threatening complication (including CNS complications, delirium) * requiring IC / ICU management Example: respiratory failure
	IVa	Single organ dysfunction (including dialysis)
	IVb	Multiorgan dysfunction
Grade V		Death of patient

*Brain haemorrhage, ischaemic stroke, subarachnoid bleeding but excluding transient ischaemic attacks. CNS: central nervous system, IC: intermediate care, ICU: intensive care unit

2.4.1 Risk factors for postoperative complications

Male gender and older age are risk factors for postoperative complications (Leeuwen et al. 2008; Allardyce et al. 2010; Aquina et al. 2017; Arnarson et al. 2019; Chung et al. 2021). However, the risk of postoperative complications cannot exclusively evaluate by chronological age due to differences in the physical and cognitive status of aged individuals (Papamichael et al. 2015; Watt et al. 2018). Mounting evidence has been presented that patients´ overall health, decline in functional status, excess comorbidities and frailty are strongly associated with postoperative complications in aged patients (Kirchhoff et al. 2010; Fagard et al. 2016; Watt et al. 2018).

Overweight (BMI 25-29.9 kg/m2) and obese (BMI ≥ 30 kg/m2) patients undergoing gastrointestinal cancer surgery are at increased risk of major postoperative complications compared to patients of normal weight (STARSurg Collaborative 2016). In a recent review article, overweight and obese patients had 20% and 50% greater risk than normal weight patients of surgical site infections with increased risk of reoperations, severe adverse events, hospital stay and additional costs of treatment (Gurunathan et al. 2017). In addition, active smokers have a higher risk for complications with a significantly increased risk for infectious surgical complications, including wound complications and anastomotic leakages, as well as non-surgical complications such as pulmonary and neurological complications. (Grönkjär et al. 2014).

Malnutrition, specified as a condition of nutritional deficiency or imbalance of energy, protein and other nutrients, causes measurable adverse consequences to an individual's body composition and functional ability (Cederholm et al. 2015; Cereda et al. 2016). Anorexia with poor food intake and body weight loss occurs in cancer-related malnutrition. Cachexia results from systemic inflammation and may also be present in cancer patients with malnutrition (Cederholm et al. 2017). The frequency of malnutrition among gastrointestinal cancer patients ranges from 20 to 80%. Malnutrition is strongly associated with cancer patients' adverse events such as postoperative complications, physical disability and mortality (Sorensen et al. 2008; Weimann et al. 2017)

Sarcopenia is a progressive and generalised skeletal muscle disorder, which causes accelerated loss of muscle mass and function. It is caused by ageing, malnutrition and immobilisation with reported rates of 15-71% among colorectal cancer patients (Malietzis et al. 2015). Sarcopenic obesity, defined as muscle loss with excess fat and extracellular water, is common in older patients (Cederholm et al. 2017). Sarcopenia and the presence of sarcopenic obesity are predictors of postoperative complications, physical disability, and mortality with poorer overall long-term survival (Cruz-Jentoft et al. 2019; Su et al. 2019; Aro et al. 2020).

Comorbidities, including renal failure, diabetes mellitus and chronic obstructive pulmonary disease (COPD), prolonged use of certain medications like corticosteroids and immunosuppressive drugs, are associated with increased postoperative adverse outcomes with excess major complications (Kirchhoff et al. 2010; Sogaard et al. 2013; Aquina et al. 2017; De Hert et al. 2018). Medical complications are common in colon cancer surgery due to an increased proportion of aged patients having multiple comorbidities and impaired functional status (Lemmens et al. 2007; Henneman et al. 2014; van der Sijp et al. 2016).

Mechanical bowel preparation (MBP) by mechanical irrigation and flushing of the colon has not been shown to reduce surgical site infections (Guenaga et al. 2011). Moreover, especially in aged patients, MBP is associated with electrolyte disturbances, dehydration, and cardiac complications (Guenaga et al. 2011). On the other hand, MBP may decrese the risk of cancer recurrence and mortality (Collin et al. 2014). Koller et al. and Koskenvuo et al. showed that combined mechanical and oral antibiotic bowel preparation (MOABP) has no notable advantage as regards surgical site infections. (Koller et al. 2018; Koskenvuo et al. 2019). However, another recent meta-analysis reported significantly lower rates of SSI using a combination of oral antibiotics and MBP (McSorley et al. 2018), also recommended by the American Perioperative Quality Group (Holubar et al. 2017).

2.4.2 Surgical complications

The most frequent postoperative surgical complications after colorectal resections are surgical site infections (SSI), including superficial wound infections intra-abdominal abscess or anastomotic leakage. The concept includes infections, which develop within 30 days of the primary operation. The incidence of surgical site infection in colorectal surgery varies from 3-20% and is more associated with male sex, obesity, smoking, diabetes mellitus, higher ASA score, immunosuppression, prolonged operating time, intraoperative complications and blood transfusion (Kirchhoff et al. 2010; Xu et al. 2020). In addition, SSI results in prolonged hospital stay, delayed rehabilitation with long-term disability, delayed oncological treatments and increased health care costs (Xu et al. 2020). After bowel obstruction, SSI is the second most common surgical cause of hospital readmission, accounting for 16% of readmitted patients (Li et al. 2013).

Anastomotic leakage (AL) is the most serious complication specific to intestinal surgery. It is associated with increased short-term morbidity, hospital stay and mortality with impaired long-term oncological outcomes and thus with an excess cost to health care (Govaert et al. 2015; Stormark et al. 2020). Its prevalence in colon cancer surgery varies 1-12% depending on patient-related factors, location of the tumour and anastomotic blood supply, the timing of surgery, perioperative anaesthetic and surgical technical factors. Thus, the aetiology of anastomotic leakage is multifactorial. Ileocolic and colorectal anastomosis cause lower incidences of leakages than the more distal colorectal anastomosis with reported rates of 1-5% (McDermott et al. 2015). Most frequently reported preoperative risk factors include male gender, age, obesity, smoking, preoperative malnutrition and hypoalbuminemia, comorbidities (diabetes mellitus, vascular and renal diseases), higher ASA class and immunosuppressive and corticosteroid medications (Bakker et al. 2014; McDermott et al. 2015; Sciuto et al. 2018; Chiarello et al. 2022).

Anastomotic leakages substantially increase 30-day mortality with reported rates from 2.6-4.3% to 16-29% with excess mortality rates of up to one year after surgery. In addition, secondary complications cause excessive morbidity and prolonged hospital stay (Kube et al. 2010; Gessler et al. 2017, Chiarello et al. 2022). Anastomotic leakage has been shown to be associated with impaired overall survival, with a 51-60% overall five-year survival rate among patients with anastomotic leakages compared to 73-75% with patients not experiencing this adverse event. Further, disease-free survival and cancer-specific survival improved 10-20% in patients without anastomotic leakage (Kube et al. 2010; Arnarson 2019; Bashir Mohamed et al. 2020).

High ligation of the inferior mesenteric artery (IMA) is mandatory with left colon cancer surgery. Consequently, the blood supply of the colonic segment proximal to the anastomosis may be significantly inhibited after high ligation of the IMA, resulting in bowel ischaemia potentially leading to anastomotic leakage (Salusjärvi et al. 2018; Chiarello et al. 2022). Increased risk for developing potentially lethal proximal colon ischemia is significantly associated with older patients having hypertension, cerebrovascular or atherosclerotic disease. Lower ligation of the inferior mesenteric artery preserving the left colic artery could prevent the occurrence of this specific type of ischaemia (Tsujinaka et al. 2012). The use of intraoperative angiography with indocyanine-green (ICG) fluorescent dye can assess the vascularisation of the colonic stump and anastomosis and thus reduce the incidence of anastomotic leakage (Blanco-Colino et al. 2018)

Complications related to abdominal wall closure are common in colorectal surgery and emerge as superficial infections, haematomas and seromas with reported incidence rates of 3-26%. Most of these complications manifest as mild discomfort requiring local wound care and antibiotics (Kirchhoff et al. 2010; Sutton et al. 2017). However, not infrequently, they necessitate reoperations and lead to increased postoperative mortality. In addition, the excess risk for wound complications increases in obese patients, male gender, and patients with diabetes mellitus, higher ASA score, smoking history, open surgery and perioperative blood transfusion (Sutton et al. 2017; Xu et al. 2020).

Wound dehiscence is a less frequent complication with high morbidity and severe additional complications. It is specified as the separation of the sutured edges of the abdominal fascia after surgery. It is mainly subclinical and later results in an incisional hernia. The excess risk for dehiscence rises among older and obese patients, in male gender and patients with smoking history and history of chronic pulmonary disease (Söderbäck et al. 2019). Clinically evident wound dehiscence manifests mainly as secretion from the wound but seldom with abdominal content protrusion through the fascia. The incidence of wound dehiscence in elective laparotomy is 0.4-1.2%, leading to increased postoperative morbidity and prolonged hospital stay with associated mortality rates between 15-35%. The increased incidence is mainly attributed to the fact that operations are performed on aged patients with more comorbidities, who are malnourished and have hypoalbuminemia and thus decreased ability to recover from reoperations (Söderbäck et al. 2019). A laparoscopic approach may dimmish the incidence of wound dehiscence (Colon Cancer Study Group. 2009).

Excess postoperative bleeding is a rare complication, depending on the type of surgery and operative approach, a patient's underlying diseases requiring anticoagulant medication and an individual patient's inadequate clotting system (Kirchhoff et al. 2010; Matar et al. 2019). Blood loss during laparoscopic surgery is significantly less than that during open surgery (Colon Cancer Study Group. 2009).

Postoperative ileus signifies a temporary interruption of gastrointestinal motility in the presence of abdominal distension, inability to tolerate oral diet, vomiting and delayed passage of flatus and stool. It is frequently diagnosed in gastrointestinal surgery, affecting approximately 7-18 % of patients (Wolthuis et al. 2016). The pathophysiology of postoperative ileus involves multiple factors, including the over-activation of adrenergic and non-adrenergic pathways by exaggerating inhibitory reflexes, the inflammatory phase, and surgical trauma (Chapman et al. 2018). Risk factors for prolonged postoperative ileus include male gender, older age, cardiac comorbidities, previous abdominal surgery and open surgical approach, longer duration of surgery and abundant postoperative use of opioids (Quiroga-Centeno et al. 2020). It delays hospital discharge, increases morbidity with potential hospital-obtained cross-infections and thromboembolism and increases hospital costs. Minimally invasive surgery, early oral feeding and the structural use of ERAS protocols with early recognition of postoperative complications may prevent postoperative ileus (Bragg et al. 2015; Chapman et al. 2018).

2.4.3 Non-surgical complications

Postoperative pulmonary complications after colorectal surgery are frequent, with reported rates ranging 2-11% (Schiphorst et al. 2015; Miskovic et al. 2017). Higher risk of pulmonary complications is associated with male gender, older age, smoking and poor preoperative functional status. Patients with excess comorbidities, recently diagnosed congestive heart failure and higher ASA class have more pulmonary complications. History of severe chronic obstructive pulmonary disease is associated with higher rates of in-hospital complications, intensive care unit admissions, readmission, and mortality after colorectal cancer surgery (Abd El Aziz et al. 2020).

Pulmonary complications include atelectasis (collapse of the pulmonary alveoli), pneumonia, pleural effusion, acute respiratory failure and respiratory distress syndrome (ARDS) with multifactorial aetiology ranging from mild to severe. Most of the events are considered mild with little impact on recovery or overall survival (Schiphorst et al. 2015). However, severe pulmonary events lead to higher morbidity and mortality rates. Of patients with pulmonary complications, 14-30% will die within 30 days, compared to 0.2–3% who do not develop complications (Miskovic et al. 2017).

Cardiac complications are frequent after major surgical operations, overall incidence ranging 2-20%, with increased incidence rates in aged patients. They are the leading causes of morbidity and mortality in the first 30 days after noncardiac surgery and account for over 33% of perioperative deaths. Preoperative acute cardiac conditions such as aneurysm rupture, replacement of coronary artery stent, high-risk coronary artery disease and recent stroke increase the risk of cardiac complications (Devereaux et al. 2015). The most common cardiac causes of postoperative mortality are myocardial infarction, cardiac arrest and congestive heart failure (Schiphorst et al. 2015; Devereaux et al. 2015; Liu et al. 2020).

Cardiac complications during and after non-cardiac surgery are overrepresented in patients with pre-existing cardio- and renovascular comorbidities and diabetes mellitus (Devereaux et al. 2015). The invasive treatment elicits a surgical stress response leading to haemodynamic derangements and so to myocardial ischaemia and heart failure. Postoperative cardiac failure still has a 30-day mortality rate of 8% regardless of its aetiology. Thus, outcomes can be improved for high-risk patients by identifying relevant risk factors and optimising their physical condition (Devereaux et al. 2015; Sellers et al. 2018).

Urinary tract related complications, including infection and retention, are common amongst cancer surgery patients, and the former is one of the most frequently diagnosed hospital-acquired infections. Urinary tract infections (UTI) develop in 2-6% of colorectal surgery patients. The risk of these events occurring is more common with females, aged patients, and patients with poor functional status, high ASA class, open surgery and prolonged catheterisation duration. Urinary tract infections lengthen hospital stay (Kang et al. 2012). Additionally, patients with urinary tract infections have a greater risk of developing sepsis than those without UTI, thereby causing extended postoperative mortality (Sheka et al. 2016).

Urinary retention is common after anaesthesia, and surgery with an incidence of 4-22%, mostly commonly in lower abdominal operations. It may be due to dissection of structures adjacent to pelvic parasympathetic nerves leading to neuropraxia and temporary urinary dysfunction. Guidelines recommend urinary catheter removal within 24 hours postoperatively in colon surgery. Early removal may increase the risk of urinary retention, while late removal may increase the risk of urinary infection. Thus, the optimal removal of the urinary catheter must be balanced with patients' preoperative urinary function, intraoperative fluid administration and postoperative urinary retention risk (Kang et al. 2012; Lee et al. 2019; Hollis et al. 2020)

Postoperative acute renal failure occurs in 3-7% of patients and is associated with extended hospital stay, risk of developing chronic kidney disease and higher mortality. Male gender, older age, preoperative kidney insufficiency, diabetes and congestive heart failure increases the risk of postoperative kidney failure (Romagnoli et al. 2018; Hollis et al. 2020). In addition, the risk may increase with ERAS protocol, as it uses more standardised intravenous fluid delivery. Thus, careful intra- and postoperative intravenous fluid rate and medication optimising are essential in older patients and those with diabetes mellitus and cardiac risk (Hollis et al. 2020).

Venous thromboembolism (VTE), consisting of deep venous thrombosis and pulmonary embolism, is associated with significantly higher inpatient mortality and greater disability among hospitalised colon cancer patients. Incidence rates reported at the time of cancer diagnosis vary 3-9%. Postoperatively the corresponding reported numbers range 1-3%, with high risk persisting one month after surgery (Aquina et al. 2017; Lewis-Lloyd et al. 2021). Older age, obesity, malnutrition, excess comorbidities, anaemia and preoperative steroid use constitute a greater risk of VTE. Additionally, open and emergency surgery, reoperation and postoperative complications are associated with VTE (Emoto et al. 2019).

Postoperative delirium (POD), which frequently emerges 24 to 96 hours after surgery, is defined as an acute and fluctuating disturbance of consciousness characterised by acute impairment of attention and awareness (Aldecoa et al. 2017; Jin et al. 2020). POD is particulary common among aged patients and those with existing neurocognitive disorders (Jin et al. 2020). The incidence of POD in colorectal surgery ranges from 8% to 54%, with an associated 30-day mortality rate of 7-10% (Scholz et al. 2016; Aldecoa et al. 2017; Jin et al. 2020; Lee et al. 2020). Colorectal cancer patients over 80 years old have an over five-fold greater POD risk than patients under 70 years (van der Sluis et al. 2017). Furthermore, with age, excess comorbidity burden, polypharmacy, poor nutrition, preoperative functional and cognitive impairment, frailty, excessive alcohol intake, emergency surgery and perioperative metabolic disturbances are strongly associated with postoperative delirium (Needham et al. 2017; Jin, et al. 2020; Lee et al. 2020).

POD is associated with major postoperative complications, longer postoperative hospital stay, higher rate of admission to long-term care with permanent institutionalisation and increased health-care costs, long-term functional and cognitive decline with limitations in activities of daily living, and increased mortality (Aldecoa et al. 2017; De Hert et al. 2018; Jin et al. 2020). In addition, postoperative delirium is associated with prolonged postoperative cognitive decline for up to one year and considerably increased risk of dementia (Aldecoa et al. 2017).

Postoperative cognitive dysfunctions (POCD) are characterised as problems in thinking and perception between seven days and one year after surgery (Needham et al. 2017). Approximately 12% of patients with no previous cognitive impairment undergoing anaesthesia will develop symptoms of cognitive dysfunction after their procedure. POCD is more prevalent with increasing age, pre-existing cognitive impairment, history of cerebrovascular disease, poor functional status and postoperative respiratory and infectious complications (Needham et al. 2017; Jin et al. 2020). Of POCD patients, 10% show long-term declining cognitive trajectory converting to dementia one year after surgery (Needham et al. 2017).

Along with old age, preoperative cognitive impairment is the most important risk factor for postoperative delirium and other perioperative outcomes, higher hospital mortality and long-term cognitive dysfunction (Needham et al. 2017; Watt et al. 2018; Kapoor et al. 2021). Patients with preoperative cognitive impairment may experience 22-60% decline in cognitive impairment during the first six months after surgery (Needham et al. 2017).

2.4.4 Mortality

The most common causes of short-term postoperative mortality are cardiovascular, such as cardiac infarction and arrhythmias, respiratory, such as pulmonary embolism and respiratory failure and infection most commonly caused by postoperative complications (De Hert et al. 2018). Excess cardiovascular and respiratory comorbidities, increasing age and postoperative complications are risk factors for 30-day mortality. Besides, both increasing age and complications are also significantly associated with higher 90-day and one-year overall mortality. Reported mortality rates for patients with stage I-III colon cancer and aged over 75 years are as follows: 30-days 3-14%, 90-days 4-18% and one-year 8-27% (Bos et al. 2019; Claassen et al. 2019; Taylor et al. 2021). A primary mortality risk factor is age: the risk for 30-day and one-year mortality is six-fold higher in patients aged over 80 years compared to patients under 60 years (Bos et al. 2019; Taylor et al 2021). Postoperative one-year mortality is as high as 52% in institutional care residents aged over 80 years (Finlayson et al. 2012).

Recent quality and safety trajectories in colon cancer treatment including developments in anaesthesia and increased use of minimally invasive methods have shown better short- and long-term outcomes for all colon cancer patients. The difference between older and younger patients' mortality rates in elective colon cancer surgery has decreased in recent years. Reported 30-day mortality has declined from 10-14% to 4-6 % in aged patients over 75 years compared to younger patients rate, which has declined from 2% to 1%. However, 30-day mortality after surgery is not a definite surgical risk measure for aged individuals. A notable proportion of patients die after this period with excess mortality persisting for up to one year after surgery. Reported mortality rates one year after surgery among aged patients over 75 years are 12-21% compared to those in younger patients at 4-10% (Breugom et al 2018; Brouwer et al. 2019).

2.5 Prognosis in colon cancer

Prognosis in colon cancer has improved steadily in recent decades. Among curatively treated colon cancer patients (stage I-III), reports on five-year overall survival rates range 65-80% and cancer-specific survival 81-95% (Buunen et al. 2009; Bokey et al. 2016; Ehrlich et al. 2016; Merkel et al. 2016). Among the oldest patients the overall survival rates continue to be poorer than among younger patients with reported 5-year survival rates of 36-56% in patients aged 75 years or over (Holleczek et al. 2015; Mäkelä et al. 2017; Oh et al. 2018; Weerink et al. 2018). Increased mortality rate in older patients has been found throughout the first year following surgery. However, patients who survive the first year after surgery, then achieve cancer-related survival rates similar to those among younger patients (Dekker et al. 2011; Sheridan et al. 2014; Mothes et al. 2017; Oh et al. 2018). Table 5 lists selected studies on five-year survival rates for patients aged over 80 years or older undergoing colon cancer surgery.

Table 5. Colon cancer surgery in patients aged 80 years or older: Five-year overall (OS) and cancer-specific survival (CSS) rates

Study	Country	Cancer	Patients (n)	Five-year OS	Five-year CSS
Leeuwen et al 2008	Sweden	colon			
stage I			309		79
stage II			1137		66
stage III			749		38
Tan et al. 2012	Singapore	colorectal			
stage I				75	
stage II				65	
stage III				40	
Kotake et al. 2014	Japan	colorectal			
stage I			586	85	94
stage II			1524	66	86
stage III			1060	50	65
Goldvaser et al. 2017	Israel	colorectal	136	39	63
Mothes et al. 2017	Germany	colorectal	161	30	78
Mäkelä et al. 2017	Finland	colorectal			
stage I			17	40	
stage II			97	34	
stage III			54	26	
Rinaldi et al. 2017	France	colorectal	123	61	
Oh et al. 2018	South Korea	colorectal	134	70	80
Rossi et al. 2020	UK	colorectal	292	48	
Ueda et al. 2020	Japan	colorectal	110	52–64	72–82
Sueda et al. 2021	Japan	colorectal	114	71	81
Utsumi et al. 2021	Japan	colorectal	113		79

In Finnish colon cancer patients registered in 2019, corresponding five-year cancer-related survival numbers were 62% for aged patients over 75 years old compared to 68-76% for patients under 75 years. The timeline change has improved remarkably, the overall five-year survival in all ages has increased from 47% to 66% in the past three decades (Finnish Cancer Registry 2021).

In overall survival, TNM stage is a recognised standard estimate of patient prognosis and a guide to management after resection for non-metastatic colon cancer (NICE guidelines, 2020). CME specialised centres have reported cancer-related survival rates of 95% in stages I-II and 81% in stage III, respectively (Hohenberger et al. 2003; Hohenberger et al. 2009, Bertelsen et al. 2011; Ehrlich et al. 2016; Merkel et al. 2016). A population-based study from Finland reported that MSI-H tumours were associated with better five-year disease-free survival and disease-specific survival than MSS tumours, 86% vs 75% and 83% vs 71% respectively. These findings reflect different biochemical tumour subtypes with molecular classification and colon cancer heterogeneity (Seppälä et al. 2015).

Postoperative complications result in a significant increase in mortality, which understandably tends to exceed the first postoperative month (Gooiker et al. 2012, Duraes et al. 2016). Severe complications, reportedly occurring in up to 25% of electively operated aged patients, significantly decrease short- and long-term survival (McSorley et al. 2016; Weerink et al. 2018). Complications after colon cancer resection are associated with weakened three-year disease-free and five-year overall survival in all aged patients. Decreased long-term survival associated with severe postoperative complications is mainly due to mechanisms other than cancer recurrence (McSorley et al. 2016; Arnarson et al. 2019).

2.6 Aged patients and colon cancer surgery

2.6.1 The older surgical patient

Ageing is a progressive deprivation of physiological reserves resulting in susceptibility to adverse events, functional decline and eventually death (Lopez-Otin et al., 2013). Normal physiological age-related alterations appear in the major organs such as cardiovascular, pulmonary and renal systems. The cardiovascular system is connected to the changes in the autonomic nervous system, which result in diminished cardiac responsiveness to stress. Lung function decreases due to oxygen diffusion capacity and lung and chest wall compliance loss. Renal function may decline related to the nephrotoxic effects of comorbidities and drugs ingested. Thus, together with stress response caused by acute disease, anaesthesia or the surgical procedure, these alterations frequently lead to adverse events (Griffiths et al. 2014; De Hert et al. 2018).

However, chronological age alone does not explain the physiological heterogeneity identified in the aged population. Consequently, patient-related factors such as comorbidities, differences in physiological and cognitive functional status and frailty are strongly and independently associated with adverse postoperative outcomes (Partridge et al. 2012; Papamichael et al. 2015; Fagard et al. 2016; De Hert et al. 2018).

Chronic diseases appear in more than 50% of patients over 70 years (Beard et al. 2016). Comorbidities are frequent in older colon cancer patients with estimated prevalence rates of 30-60%, with at least one chronic condition besides cancer (Lemmens et al. 2007; Fowler et al. 2020). Comorbidity potentially affects the timing of cancer diagnosis either by earlier detection or, on the contrary, by delayed diagnosis because of treatment geared to the specific comorbidity. Curative surgical treatment and adjuvant chemotherapy are less likely to be offered and administered to cancer patients with comorbidities (Sarfati et al. 2016).

The most common comorbidities among older colon cancer patients are hypertension, congestive heart failure, chronic obstructive pulmonary disease (COPD), diabetes mellitus and renal dysfunction. (Neuman et al. 2013; Jafari et al. 2014; Aquina et al. 2017). Venous thromboembolism is a well-known manifestation in colon cancer patients with a risk two-fold greater than in patients without cancer (Stein et al. 2006).

Polypharmacy, defined as five or more medications concurrently for treating one or more coexisting diseases, is related to comorbidities and is thus common in aged cancer patients. Polypharmacy increases the risk of drug-drug interactions and harmful effects of medications, which can be deleterious to cancer patients when combined with adjuvant therapy (Sharma et al. 2016; De Hert et al. 2018). The prevalence rate of polypharmacy in aged cancer patients ranges from 13% to 92%, with a growing risk of adverse events such as drug reactions associated with chemotoxicity, geriatric syndromes such as functional decline and cognitive impairment, and thus increased healthcare utilisation (Sharma et al. 2016; Aldecoa et al. 2017). Altogether, polypharmacy in geriatric oncology needs geriatric assessment before adjuvant therapy to evaluate the benefits and drawbacks of drug-drug interactions (Sharma et al. 2016).

Physiological and cognitive functional capacity, defined as physical and cognitive ability to perform activities of daily living, declines with advancing age (Gill et al. 2010; Griffiths et al. 2014). According to the Finnish Institute for Health and Welfare, 27% of individuals aged 75 years or older needed some form of assistance in daily living in 2020 (Finnish Institute for Health and Welfare 2021). Functional status influences the degree of old patients' autonomy with different changes in active motion, cognition and sensory functions. Functional impairment leads to disability, which is defined as an impairment in a patient's ability to perform daily activities. Physical disability frequently occurs in older individuals and is associated with predictably increased hospitalisation, need for long-term care and mortality and thus decreased life expectancy (Fried et al.; 2004; Keeler et al. 2010; De Hert et al. 2018).

Physiological functional reserve capacity is critically depleted in frailty. When exposed to stressors, this clinical state is defined as an individual´s increased predisposition to develop vulnerability to increment dependency and mortality (Morley et al. 2013). Frailty phenotype classification includes three or more of the following five physical components: unexpected self-reported weight loss ≥5% in the last year, muscle weakness seen in low grip strength, self-reported exhaustion, slowness while walking with slow gait, and low physical activity (Fried et al. 2001). Individuals with frailty are more prone to disability, unexpected care needs, falls and fractures, hospitalisations, impaired quality of life and early mortality (Clegg et al. 2013; Handforth et al. 2015).

Frailty is not an inevitable consequence of ageing; most aged patients are not frail. Among patients aged 65 years or older, the prevalence of frailty is 10-20%, which doubles in individuals aged 80 years or older (Hoogendijk et al. 2019). The frequency of pre-frailty is considerably higher, with a reported rate of 44% in aged individuals (Partridge et al. 2012; Clegg et al. 2013). Frailty is two-fold higher amongst women than men. When diagnosed with colorectal cancer, 28-45% of aged patients over 70 years are considered to be pre-frail or frail (Handforth et al. 2015). Patients aged 65 or over undergoing elective surgery demonstrate prevalence rates of 31-46% for pre-frailty and 10-37% for frailty with a two-fold rate with increasing age (Partridge et al. 2012; Clegg et al. 2013; Hewitt et al. 2018; Richards et al. 2018).

Cognitive impairment ranges from minimal decrements in cognition to mild cognitive impairment with no impact on functioning in daily living, and dementia which results in impairment in daily functioning (Wasef et al. 2021). Prevalence rates of 7-8% for diagnosed dementia have been reported in colon cancer patients aged over 67 years (Gupta et al. 2004; Neuman et al. 2013). By contrast, in preoperative testing with surgical patients aged 70 years or over, signs of possible cognitive diseases as high as 21% have been documented, suggesting a more frequent prevalence of cognitive impairment among aged surgical patients (Montroni et al. 2020). In a recently published review article, the prevalence of undiagnosed cognitive impairment in non-cardiac surgery patients over 75 years was 37% (Kapoor et al. 2021). In addition, the prevalence of diagnosed dementia among American nursing-home residents undergoing colon cancer surgery was 50% (Finlayson et al. 2012).

Ageing is associated with an increased risk of malnutrition (Cederholm et al. 2015; Cereda et al. 2016). Preoperative malnutrition is common in older colorectal cancer patients, with 22-46% exhibiting severe or moderate signs of low nutritional status (Looijaard et al. 2018). The nutritional risk is increased in cancer patients with geriatric syndromes, advanced disease, and impaired performance status (Paillaud et al. 2014; Huisman et al. 2016). With reported preoperative rates of 16-71%, sarcopenia is commonly diagnosed in aged colon cancer patients. (Looijaard et al. 2018; Aro et al. 2020). In-hospital immobilisation rapidly causes significant metabolic changes causing a decline in anabolic resistance to protein nutrition and muscle strength, reduced insulin sensitivity and physical performance (Lobo et al. 2020) and may thus expose to postoperative adverse events. These changes are commonly observed in older patients with sarcopenia and frailty with increased risks of falls, declining physical and cognitive status, postoperative morbidity and mortality (Aaldriks et al. 2013). Figure 2 summarises the overlapping of the main geriatric characteristics of the older patient.

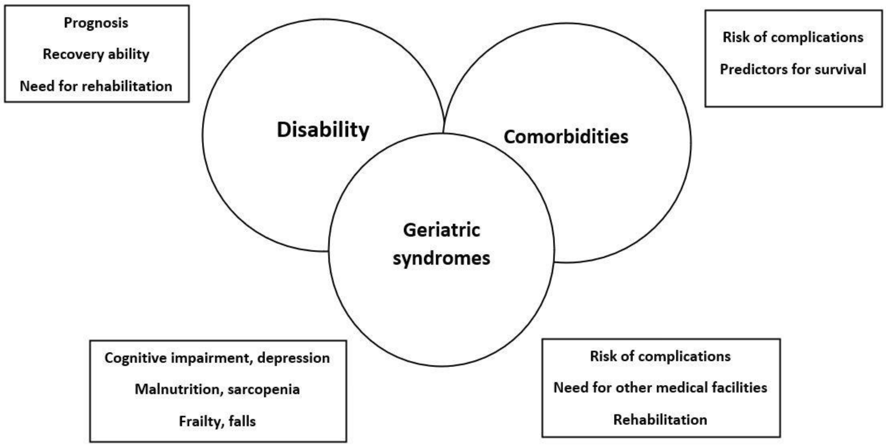

Figure 2. Overlapping of three main elements of geriatric patient and their influence on adverse events (Jämsen E, permission granted).

2.6.2 Effect of physical and cognitive status on postoperative outcomes

Surgery activates a systemic inflammatory response leading to a reduction in postoperative physiological and functional reserves (Lawrence et al. 2004). The risk of postoperative adverse events is increased with concomitant age-related physiological and cognitive decline, multimorbidity, frailty, and poor nutritional status (Lawrence et al. 2004; Partridge et al. 2012; De Hert et al. 2018). Thus, compared to their younger counterparts, aged surgical patients generally have higher rates of postoperative adverse events, including complications, prolonged hospital stay, higher readmission rates and unplanned discharge to other medical facilities. (Hamel et al. 2005; Griffiths et al. 2014).

Aged patients with comorbidities exhibit two-fold higher incidence of medical complications characteristic of patients with cardiovascular and pulmonary comorbidities (Lemmens et al. 2007; Griffiths et al. 2014; Biondi et al. 2016; De Hert et al. 2018). These comprise organ-specific aberrations like acute kidney failure, pulmonary complications such as hospital-acquired pneumonia and respiratory failure, cardiovascular events such as coronary ischaemia or arrhythmias, delirium and minor complications such as urinary tract infection and electrolyte imbalance (Biondi et al. 2016; Aquina et al. 2017). Colon cancer patients with comorbidities, especially with cardiovascular diseases, COPD, diabetes and history of venous thromboembolism have a two to a three-fold higher risk of 30-day postoperative morbidity and decreased overall survival compared to patients without comorbidities (Lemmens et al. 2007; Sogaard et al. 2013; Sarfati et al. 2016; Boakye et al. 2018; Watt et al. 2018).

Frailty is strongly associated with postoperative adverse events. Aged frail cancer patients have a significant four- to five-fold higher risk of developing major complications and three- to-four-fold increased risk of separate surgical and medical complications. In addition, frailty is associated with prolonged disability and functional recovery with a three- to-six-fold higher risk of short- and long-term mortality (Partridge et al. 2012; Handforth et al. 2015; Fagaard et al. 2016; Lin et al. 2016; Sandini et al. 2017; Boakye et al. 2018). Likewise, sarcopenia is associated with increased total and severe postoperative complication rates, prolonged hospital stays and discharge to assisted living accomodation with decreased functional recovery and overall survival (Trejo-Avila et al. 2021).

Preoperative cognitive impairment is an important risk factor for postoperative delirium and other perioperative outcomes, higher hospital mortality and long-term cognitive dysfunction (Needham et al. 2017; Watt et al. 2018; Kapoor et al. 2022). The incidence of preoperative cognitive impairment in aged patients varies 18-37% depending on the accuracy of diagnostic recognition and on the patient population selected for surgery (Kapoor et al. 2022). With aged patients, higher ASA status, history of dementia and delirium, frailty, functional and cognitive impairment are strongly associated with postoperative delirium (Jin et al. 2020; Lee et al. 2020).

2.6.3 Preoperative assessment and optimisation

Aged patients' preoperative assessment includes evaluating comorbidities, polypharmacy, nutritional and functional status, frailty, cognitive and sensorial impairments, level of independence and socio-economic status. (De Hert et al. 2018; Montroni et al. 2018). The preoperative evaluation aims to identify an individual's risks in anaesthesia, surgery and for postoperative complications. (Griffiths et al. 2014; De Hert 2018). Consequently, identifying and minimising the risk factors for adverse events improves the likelihood of successful surgical treatment (Griffiths et al. 2014).

The assessment includes an estimate of the benefits and the risks related to cancer surgery or non-surgical treatment, of which patients and their relatives or carers should be informed and which should be discussed (Griffiths et al. 2014; Papamichael et al. 2015; Rostoft et al. 2020). Thus, knowing patients´ preferences regarding treatment and postoperative outcomes is essential. In addition, an evaluation of life expectancy without cancer including comorbidities, frailty, functional status and patient's decision-making capacity is recommended (Rostoft et al. 2020). Consequently, the goal is to avoid under- and overtreatment by identifying fit, vulnerable and frail patients. (Korc-Grodzicki et al. 2014 ; Mohanty et al. 2016 ; De Hert et al 2018 ; Montroni et al. 2020). Figure 3 illustrates basic principles for the preoperative assessment of aged patients.

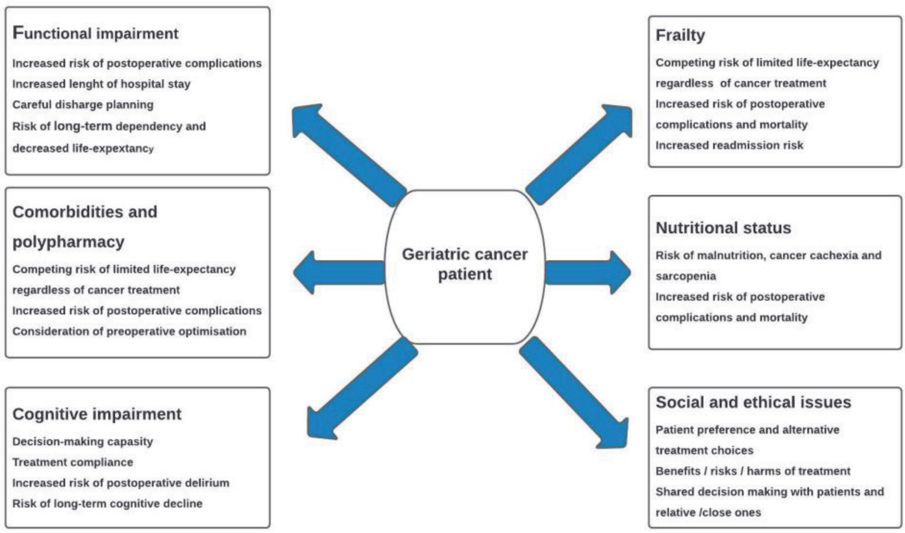

Figure 3. Principles of preoperative evaluation for geriatric colon cancer patients (according to Papamichael et al 2014)

Preoperative risk evaluation and screening is primarily performed by the surgeon in close consultation with an anaesthesiologist and is based on consultation and information on the patient's health status from his or her general practitioner. The assessment includes evaluating patients' comorbidities, basic functional, nutritional and cognitive status and identifying frailty utilising appropriate screening tools (Korc-Grodzicki et al. 2014; Decoster et al. 2015: Partridge et al. 2017; Ketelaers et al. 2020; Montroni et al. 2020; Souwer et al. 2020). In addition, information on the perioperative pathway, evaluation of the risks of complications, preferably enhanced recovery programmes, and a mini-invasive surgical approach is included (Griffith et al. 2014; De Hert et al. 2018). In addition, the aim of the assessment is to identify patients for whom preoperative optimisation and further evaluation by means of geriatric assessment might be beneficial (Mohanty et al. 2016).

Comprehensive functional performance and frailty status assessment need geriatric expertise. Comprehensive geriatric assessment (CGA) involves a systematic assessment and evaluation of the older patient's physical and mental comorbidities, prevention of POD, medications, geriatric syndromes, frailty status, functional impairments and social factors, including patients previously undiagnosed for the impairments mentioned above (Welsh et al. 2014; Partridge et al. 2017; Rostoft et al. 2020). Thus, the preoperative CGA assessment informs the clinicians´ shared decision-making regarding the potential benefits and risks of surgery, consultation on the patient's optimisation before surgery and possible alternative treatments (Montroni et al. 2020; Rostoft et al. 2020). CGA may have a positive impact on postoperative outcomes by reducing rates of medical complications, length of hospital stay and discharge to an increased level of care for rehabilitation (Partridge et al. 2017; Eamer et al. 2018).

Preoperative optimisation of patient's health status entails striking a balance between the risks of delaying surgery and successful surgical treatment (Griffith et al. 2014). It should reduce the risks of anaesthesia, surgery and postoperative complications (Griffith et al. 2014; Partridge et al. 2017; De Hert et al. 2018). A recently published review showed that in over 72% of cancer patients geriatric assessment was recommended for preoperative health status optimisation (Hamaker et al. 2018). The focus should primarily target the management of important comorbidities such as cardiopulmonary problems, renal problems, diabetes, anaemia and reduce the likelihood of cardiac complications, cerebral ischaemia and postoperative delirium (Griffith et al. 2014; De Hert et al. 2018). Polypharmacy and the patients at risk of POD may require consultation either with an internist or geriatrician to optimise or initiate preventive medication (Griffith et al. 2014; Aldecoa et al. 2017). According to the ESPEN guidelines, preoperatively malnourished patients or those at nutritional risk may benefit from short-term nutritional conditioning to avoid possible major adverse events (Weimann et al. 2017). In addition, preoperative consideration with the patient and relatives regarding potential discharge alternatives is essential to avoid prolonged length of hospital or rehabilitation stay (Partridge et al. 2017; Rostoft et al. 2020).

2.6.4 Preoperative screening tools

Risk evaluation screening tools for functional status and frailty are recommended to be used preoperatively and conveniently in daily clinical practice. These should have high predictive ability in screening frailty and identify patients likely to benefit from a comprehensive geriatric assessment. (Korc-Grodzicki et al. 2014, Ketelaers et al. 2020 ; Montroni et al. 2020).

General risk assessment tools for predicting risk in anaesthesia and perioperative mortality include the American Society of Anaesthesiologists classification of physical status (ASA) and the Charlson Comorbidity Index (CCI) (Owens et al. 1978; Charlson et al. 1987). ASA score reflects the preoperative general physical condition and the anaesthesiologic risk for perioperative mortality. The scoring ranges from one to five (American Society of Anaesthesiologists 2021). The Charlson Comorbidity Index (CCI), which includes 22 comorbidity conditions, evaluates the cumulative burden of comorbidities with an ability to identify patients at greater risk of postoperative mortality (Charlson et al. 1987). The age-adjusted-CCI (AA-CCI) score, which gives four points to all patients 80 years or older, helps to identify aged patients at greater risk of 90-day mortality after cancer surgery and to assess comorbidities and multiple morbidities (Chang et al. 2016; De Hert et al. 2018).

A higher ASA score (≥3) is significantly associated with increased postoperative morbidity, with reported mortality rates of 5-50% (Sheridan et al. 2014; Quintana et al. 2018). ASA and CCI scores have a moderate mutual correlation (Sankar et al. 2014). Higher ASA and CCI scores are strongly associated with increased postoperative complications and short-term mortality with mutual correlation in clinical practice (Dekker et al. 2012; Sankar et al. 2014; Souwer et al. 2020; Aitken et al. 2021). However, it is essential to evaluate the impact and relationship of specific comorbidity to the risk of anaesthesia and postoperative recovery (Griffith et al. 2014; De Hert et al. 2018).

Numerous nutritional status-screening tools are used in clinical practice. Tools used for aged patients should consider weight history, food intake, nutrition impact symptoms and physical performance. For older individuals, the European Society of Clinical Nutrition and Metabolism (ESPEN) recommends the use of the Mini Nutritional Assessment (MNA) or its short form (MNA-SF) (Cederholm et al. 2017). The Mini Nutritional Assessment-Short Form includes six parameters, namely mobility, appetite, weight loss, physical stress, neuropsychological problems and BMI prior to surgery. Patients with normal nutrition are scored over 11, patients at risk of malnutrition are scored between 8 and 11, and those who are malnourished are scored between 0 and 7 (Rubenstein et al. 2001). Poor nutritional status is associated with impaired physical and cognitive performance status and predicts postoperative adverse events (Huisman et al. 2016; De Hert et al. 2018).

Functional status and level of independence can be measured in numerous ways. The most frequently used tools are the Katz Index of Activities of Daily Living (ADL) and Lawton's Instrumental Activities of Daily Living (IADL). Reported functional impairments in onco-geriatric patients aged 60 years or older range from 7.5-38% with ADL and 12-77% with IADL (Huisman et al. 2017). In addition, functional status can be assessed with performance-based tests measuring muscle strength and mobility. The most common tests are the handgrip test and the timed Up-and-Go test (Huisman et al. 2017; Ghignone et al. 2020).

Basic cognitive assessments, such as the Mini-Cog or MMSE, are recommended for screening for preoperative cognitive decline, as 30-40% of cases of postoperative delirium are preventable. The degree of difficulty with diagnosed cognitive impairment must be assessed by a geriatrician (Mohanty et al. 2016; Aldecoa et al 2017; Needham et al. 2017; De Hert et al 2018; Montroni et al. 2020).

The G8 screening tool is specially devised for oncology, and it identifies vulnerable aged cancer patients for whom CGA would be beneficial. It strongly identifies old cancer patients at risk for adverse event and mortality in oncological treatments (Soubeyran et al. 2014). G8 is a modification of eight items including age, number of medications, MNA-SF and self-rated health status. The score ranges from 0 to 17. Geriatric evaluation is recommended for patients whose score is ≤ 14 (Bellera et al. 2012).

A wide range of frailty instruments is used in clinical settings before surgery. Most frailty assessment tools such as the Fried Phenotype, Edmonton Frail Scale, Frailty Index and Clinical Frailty Scale have a predictive accuracy of frailty with reported association with increased adverse events (De Hert et al. 2018; Aucoin et al. 2020). However, preoperatively used risk evaluation screening tools for frailty should be easy to use in daily clinical practice with the ability to screen for frailty and distinguish patients likely to benefit from CGA (Korc-Grodzicki et al. 2014; Ketelaers et al. 2020; Montroni et al. 2020).

The Clinical Frailty Scale (CFS) is a validated assessment tool for distinguishing between frail patients and fit patients. It is based on clinical judgement. The scoring ranges from one (very fit) to nine (terminally ill). Each point corresponds to a written description of frailty. A patient scoring five or higher is considered frail (Rockwood et al. 2005). It is associated with a high prediction rate of adverse outcomes such as complications, institutional discharge and mortality in hospitalised aged patients undergoing invasive operative treatments. It is easily adapted and has been shown to have reliable scores in identifying frailty when used by relatively inexperienced users (Aucoin et al. 2020).

2.6.5 Postoperative functional recovery and survival

Cancer-specific survival among older colon cancer patients without postoperative complications is comparable to that in younger patients, which speaks in favour of intended curative cancer surgery for aged patients (Sheridan et al. 2014; Holleczek et al. 2015; Mothes et al. 2017; Oh et al. 2018; Weerink et al. 2018; Bos et al. 2019). However, the traditional survival statistics for older patients with excess comorbidities, impaired postoperative cognitive impairment and functional independence, may not accurately relect complete postoperative recovery outcomes (Ronning et al. 2014).

One-year excess mortality is reported to be 9-27% among aged patients even without complications (Gooiker et al. 2012; Duraes et al. 2016; Bos et al. 2019; Claassen et al. 2019). Overall, older patients have five-year and ten-year overall survival rates of 36-60% and 24-40% while the corresponding figures for younger patients are 85% and 75-80% (Sheridan et al. 2014; Holleczek et al. 2015; Mothes et al. 2017; Mäkelä et al. 2017; Oh et al. 2018).

Functional recovery (FR) is a multidimensional, prolonged postoperative recovery process that includes functional independence and health-related quality of life (Lee et al. 2014). Prolonged decline in functional performances is reported in 5-62% of colorectal cancer patients three months after surgery. The corresponding numbers for six months after surgery are 6-49% and 5-33% for one year, with higher numbers among aged patients with complications (Lawrence et al. 2004; Hamaker et al. 2015, Giannotti et al. 2019, de Roo et al. 2020). Van Zutphen et al showed that 54% of colorectal cancer patients had not regained preoperative physical functional status six months after surgery (van Zutphen et al. 2017). In addition, even one year after surgery, half of survivors among American nursing home residents aged 80 years or older were unable to perform activities of daily living (Finlayson et al. 2012).

Postoperative loss of independence (LOI) is described as decline in ability to perform activities of daily living, impaired mobility and possibly requiring a new walking aid, increased need for support, such as the need for new home-care services or discharge to other medical facilities (Zhang et al. 2020). Among older patients undergoing colorectal cancer surgery, up to 20% experience LOI upon discharge from hospital. Patients with preoperative decline in functional status, severe postoperative complications and delirium experience 24-43% postoperative loss of independence (Gearhart et al. 2020; Zhang et al 2020). The risk of LOI after discharge increases significantly with age, with a reported share of 50% among patients under 75 years compared to 84% of patients over 84 years (Berian et al. 2016). Loss of independence is associated with a 70% increased risk of readmission into hospital. After discharge from a surgical unit, patients with LOI have a 6.7-fold increased mortality risk compared to patients without LOI (Berian et al. 2016; Zhang et al. 2020).

Significant prolonged functional impairment is observed for up to 16-28 months after colorectal surgery (Ronning et al. 2014). However, recovery rates of 65-100% of basic functional parameters such as ADL and IADL are feasible within six months after abdominal surgery even for patients considered frail preoperatively (Hamaker et al. 2015; van Zutphen et al. 2017; Sikder et al. 2019). Prolonged cognitive impairment three months after a surgery has been reported in up to 10% of aged patients preoperatively considered cognitively intact (Needham et al. 2017).

According to several studies, aged patients frequently value preserved physical and cognitive functions over overall survival and desire reliable information on the various treatment options and the impact on functional performance (Fried et al. 2002; Berian et al. 2016; Ghignone et al. 2020). Therefore, it is also important to consider palliative care options instead surgery. Moreover, a tailor-made approach should compare the oncological benefits of surgery with the risks of invasive treatment, including loss of functional dependence, poor functional recovery, risk of postoperative institutionalization, and thus impaired quality of life and life expectancy (Ghinone et al. 2020; Ketelaers et al. 2020; Santhirapala et al. 2020).

3 AIMS OF THE STUDY

The aims of this study were to analyse the postoperative outcomes, functional recovery and overall survival of elective colon cancer surgery in patients 80 years and older.

The specific aims were as follows:

1. To identify preoperative baseline measures and risk factors affecting postoperative outcomes and their impact on 30-day and one-year survival (I).
2. To analyse long-term overall survival and causes of death after surgery with focus on patients surviving for more than three months after surgery (II).
3. To identify pre- and perioperative factors and screening tools which may have an impact on postoperative outcomes (III).
4. To identify factors predicting need for increased support in activities of daily living and impaired mobility during the first postoperative year (IV).

4 PATIENTS AND METHODS

4.1 Study populations

The study populations comprised surgically treated stage I-III colon cancer patients aged 80 years or older at the time of the surgery (Studies I and II) or recruitment (Studies III and IV). Patients with metastatic disease, perioperatively diagnosed benign disease, palliative or emergency surgery and non-surgically treated were excluded. The studies, considered as population-based, were conducted in several Finnish public hospitals, which are mainly responsible for the treatment of malignant diseases.

Registry-based Studies I-II consisted of all patients referred to surgical units with non-metastatic cancer who had undergone elective curatively aimed cancer surgery. The operations were conducted between 2005 and 2016 in four hospitals (Central Hospital of Central Finland, Päijät-Häme Central Hospital, Hatanpää City Hospital and Valkeakoski Hospital), which were mainly responsible for elective colon cancer surgery in their catchment areas (total 750,000 inhabitants, range 4.0-5.2% aged 80 years or over).

For Study III, the patient population was recruited between April 2019 and July 2020. For Study IV, recruitment continued until August 2020. A multicentre observational cohort study was conducted in nine Finnish hospitals (total catchment area population of 3.88 million people amounting to 70% of the population of Finland, 5.7% aged 80 years or over). All patients with stage I-III colon cancer were invited to participate in the study if they fulfilled the inclusion criteria. Detailed information regarding the study was given by the recruiting surgeons and written consent was provided by the patients. In case of severe cognitive impairment, the consent form was signed by a legally authorised representative. Table 6 presents the study arrangements for Studies I-IV. The study protocol for Studies III and IV is described in detail in Appendix 1.

Table 6. Study arrangements for patients undergoing colon cancer surgery (Studies I-IV)

	Study I	Study II	Study III	Study IV
Study design	Retrospective Registry-based	Retrospective Registry-based	Prospective Multicentre Observational	Prospective Multicentre Observational
Hospital types	Tertiary referral centre hospital (2) Secondary care hospital (2)	Tertiary referral centre hospital (2) Secondary care hospital (2)	University hospitals (3) Tertiary referral hospital (6)	University hospitals (3) Tertiary referral hospital (6)
Catchment area / inhabitants	750,000	750,000	3,880,000	3,880,000
Number of patients	386	386 / 357	161	167
Follow-up time, med (range) months	75.6 (0.04–144)	75.6 (0.04–144)	1.0	18 (0.6–27.6)
Primary outcomes	Postoperative complication and mortality 30 days and 1 year after surgery	Overall survival for all patients and for those who survived over 3 months after surgery	Postoperative complications and mortality 30 days after surgery	Changes in support for activities in daily life and mobility one year after surgery

4.2 Methods

4.2.1 Preoperative evaluation and surgery

All patients considered candidates for radical colon cancer treatment were referred for consultation to the surgical units (Studies I-IV). Patients had histologically confirmed primary adenocarcinoma of the colon diagnosed preoperatively by colonoscopy. Computed tomography was used to detect the presence of distant metastases and locoregional tumour spreading. In Studies III and IV, preoperative evaluation in multidisciplinary team (MDT) meetings was conducted in most participating hospitals.

Patients underwent radical colon cancer surgery for the primary tumour. The tumour location determined the type of procedure, and the individual surgeon responsible for the operation decided on the surgical approach. Detailed technical aspects were not described, but recommended nationwide, standardised protocols included sufficient resected bowel segment length and lymph node harvest. Recorded operative procedure data included type of colon resection and surgical approach, duration of operation, perioperative blood loss, length of hospital stay, discharge destination and readmission rate (Studies I-IV).

Tumour staging was conducted according to the UICC system. TNM classification and staging and number of lymph nodes were registered (Studies I-IV). The number of positive lymph nodes (LNs) and the total number of LNs were recorded in Studies III and IV.

4.2.2 Preoperatively collected data

In every study the clinical data collected from patients included baseline characteristics such as age, gender, body mass index (BMI), living arrangements, hospitalisations six months before surgery, comorbidities, American Society of Anaesthesiologists (ASA) physical status classification, modified age-adjusted Charlson Comorbidity Index (AA-CCI) score, other malignancies and symptoms of cancer. For Studies III and IV, several medications, haemoglobin, creatine and albumin values, onco-geriatric screening tool (G8), the Mini Nutritional Assessment-Short Form (MNA-SF) and the Clinical Frailty Scale (CFS), were included.

Age (Studies II-IV) and BMI (Studies (I-IV) were divided into three categories. For Studies III and IV consumption of alcohol and history of smoking was elicited. Alcohol consumption response options were none, once a month, once a week or several times a week modifield from Audit-C (Bradley et al. 2007). In addition, CFS was assessed at the preoperative outpatient clinic by the surgeon responsible for the surgical treatment. Patients were also asked if they had a living will. Table 7 shows the tools used for preoperative risk assessment.

Table 7. Risk-assessment tools for predicting postoperative complications and functional outcomes

Test	Abbreviation	Range of possible scores	Classification for statistical analyses	Purpose
Age			80-84, 85-89, ≥90	Age
American Society of Anaesthesiology score	ASA	1–5	2,3,4	Preoperative evaluation of general physical condition and anaesthesiologic risk
Age-adjusted Charlson Comorbidity Index	AA-CCI	4–37	4,5,6,7-15 (Study I) ≤6, >6 (Studies II-IV)	Evaluation of cumulative burden of comorbidities
Medication			<5, ≥5 (Studies III-IV)	Polypharmacy
Body Mass Index (kg / m^2)	BMI		<25, 25-29.9, ≥30 (Studies I-II) <24, 24-29, >29 (Studies III-IV)	Cut-off based on histogram (I-II) Finnish nutritional guidelines for aged patients (III-IV) *
Haemoglobin (g/l)	Hb		≤120 (anaemia) >120 (normal Hb)	Haemoglobin level, estimation of anaemia Cut-off for clinical utility
Albumin (g/l)	Alb		≤30 (hypoalbuminemia) 31–34 (mild hypoalbuminemia) >34 (normal)	Albumin level, estimation of malnutrition Cut-off for clinical relevance
Glomerular Filtration Rate (ml/min)	GFR		<45 (moderately to severely decreased renal function) 45-60 (mildly to moderately decreased renal function) >60 (normal to mildly decreased renal function)	Estimated glomerular filtration rate Calculated using CKD-EPI equation**
Clinical Frailty Scale	CFS	1–9	1-2 (very fit or fit) 3-4 (independent, but not regularly active in daily-life or vulnerable) 5-9 (frail, with severe limitations in daily-life activities)	Evaluation of frailty status and distinquishing frail patients from fit patients
Onco-geriatric screening tool (G8)	G8	0–17	<12 12–14 >14 (normal)	Detection of onco-geriatric patients who may benefit from comprehensive geriatric assessment (CGA)
Mini Nutritional Assessment-Short Form	MNA-SF	0–14	0-7 (malnourished) 8-11 (risk of malnutrition) ≥12 (nutritional status as normal	Evaluation of nutritional status taking into account appetite, weight loss, mobility, neuropsychological problems, physical stress, BMI

*Finnish nutritional guidelines for aged patients (Suominen et al. 2014)

** Kidney Disease: Improving Global Outcomes (KDIGO) Work Group, 2013

4.2.3 Patient questionnaires

The pre-and postoperative questionnaires were specially developed for Studies III and IV. All forms used were identical and printed in large font size (Calibri 16) so as to facilitate responding. They were written in Finnish or Swedish according to patient preference. The patient questionnaires elicited living arrangements, mobility, use of mobile aid, support for activities in daily life outdoors and indoors, nutritional and cognitive status. These variables were used to formulate validated G8 and MNA-SF values (Niemeläinen et al. 2021, Appendix 2). These values were collected personally before surgery at the outpatient clinic and by mail or personally after surgery (one, three, six and twelve months).

In Studies III and IV, pre-and postoperative patient questionnaires contained similar questions one, three, six and twelve months after surgery to elicit alterations in patients physical and cognitive status. They also included pre-and postoperatively reported self-related health status compared with individuals of the same age and self-reported perceptions of how their condition had changed since surgery. Missing data from patients questionnaires were excluded from the final analysis. (Patient questionnaires in Finnish, Appendix 2 and 3).

4.2.4 Postoperative outcomes

In all four studies, postoperative morbidity was documented during the hospital stay and at 30 days after surgical treatment. Postoperative morbidity (surgical and non-surgical) was defined according to the CD classification. Multiple complications in the same patients were assessed independently with the highest CD value used in the final analyses. Postoperative mortality was recorded at 30 days (Study III) and at three, six and twelve months (Studies I, II and IV). Causes and dates of death were acquired from the Death Certificate Register of Statistics Finland (Studies I and II) and the hospital medical records (Studies III-IV).

Postoperative morbidity and mortality 30 days (Studies I and III) and one year after surgery (Studies I and IV) were the primary outcome measures. In Study II, the primary outcomes were overall survival in all patients and in those who survived three months postoperatively. In Study IV, the primary outcomes were changes in need for support in activities of daily living and mobility one year after surgery.

4.2.5 Data collection

Prospectively maintained colorectal databases in the study hospitals were used to collect the study population for Studies I and II. Medical records was reviewed by the surgeon in charge of data collection. ICD codes C18-19 (colon and recto sigmoid cancer) were used to identify patients from the database. Data content was combined, processed and analysed by the main investigator at Tampere University Hospital and Tampere University.

For the Studies III and IV, the data was gathered online to a secure web plat form electronic database (Research Electronic Data Capture, REDCAP). The version was specially designed for these studies by the main investigators. Surgeons in the participating hospitals received a personal username and password for the electronic database in order to enter the data confidentially. The main investigators at Tampere University Hospital and Tampere University had exclusively access to the database.

A study number was assigned to each patient. The identification key was kept separate from the database with a secure username and password at each study hospital. The data from patient questionnaires was transferred manually to an electronic database Relevant protocol deviations such as metastatic disease, reported benign tissue pathology or withdrawal from the study were documented.

The patient questionnaires were completed at the time of inclusion and one, three, six and twelve months after surgery. If the patient was unable to complete the questionnaire, a family member, legally authorised representative or the nurse responsible for the patient completed the form. The principal investigators or research nurses in the participating hospitals ensured that the patient questionnaires were completed.

Patients were able to withdraw from the study at any time during the study period. In those cases, data collected before withdrawal was allowed to be used in the analyses.

4.2.6 Statistical methods

In all studies, percentages were used to describe demographic data and the proportion of observed complications. Median and range were calculated for age, preoperative laboratory values, body mass index (BMI), duration of surgery and perioperative blood loss. The chi-square test or Fisher´s exact test was used to test associations between categorical variables, when appropriate, and continuous variables with Student's t-test.

In Study II, the Kaplan-Meier method was used to calculate survival and recurrence rates from primary surgery and was compared using the log-rank test. In all studies, when appropriate, associations between the categorical variables were tested with the chi-square test or Fisher's exact test for univariate analysis. Binary logistic regression was used for uni- and multivariable analysis of the factors influencing morbidity, 30-day and one-year mortality, need for support in activities of daily living and mobility at one-year as well as overall survival. All variables clinically or statistically significant in the univariate model ($p<0.05$) were included in the multivariable model. SPSS version 27 (IBM, Armonk, NY, USA) was used to perform the statistical analyses.

4.3 Ethical aspects

All four studies adhered to the principles of the Declaration of Helsinki on medical research protocols and ethics. For Studies I and II, the Ethics Committee of Pirkanmaa Hospital District (R18188) approved the research protocol of the prospectively gathered, registry-based study. The other two participating hospitals provided statements granting permission to use patients data for the study. For Studies III and IV, the study protocol was approved by the Expert Responsibility Area of Tampere University Hospital (reference approval number R19028) and subsequently approved by the institutional review boards of each participating hospital.

5 RESULTS

5.1 Baseline characteristics and surgical treatment

For Studies I and II, 386 patients, undergoing elective colon cancer surgery were identified. For Study II, data on patients surviving for at least three months after surgery were likewise analysed, for which a total of 356 patients were identified. The baseline and clinical, demographic characteristics of those patients were not significantly different from those of the study population as a whole.

For Study III, 180 out of 241 patients (75%) consented to participate. Non-surgical treatment was offered to 11 patients because of diminished functional performance status, excess comorbidities or personal refusal. Eight patients were excluded because of perioperatively diagnosed metastatic or benign disease. Consequently, 161 patients were treated surgically for their cancer and included in the study. Preoperatively, almost all patients scored G8 ≤14 (92%) and 77% were considered vulnerable or frail (CFS ≥ 3). Most of the patients (91%) were at risk of malnutrition (MNA-SF= 8-11) or were malnourished (MNA-SF = 0-7). Study IV analysed 167 eligible patients with similar G8, CFS and MNA-SF distribution. In addition, most patients performed preoperatively daily activities independently (54%), were mobile without a mobility aid (60%) and mobile inside and outside the home (73%).

The surgery was performed mostly by right-sided hemicolectomy (65-68%) and laparoscopy (65-66%) in all studies. In Studies I, III and IV discharge to other hospital wards or medical facilities instead of their original place of residence was implemented for 50%, 56% and 54% of patients respectively. In Study I, readmission occurred in 25 patients (6.5%) and in study III in 13 patients (6.5%) within 30 days of discharge. Table 8 summarises the demographic data of Studies I-IV.

Table 8. Demographic data on patients undergoing colon cancer surgery (Studies I-IV)

	Study I n=386 n (%)	Study II n=357 n (%)	Study III n=161 n (%)	Study IV n=167 n / med
Gender				
Female	217 (56.2)	205 (57.4)	97 (60.2)	99 (59.3)
Male	169 (43.8)	152 (42.6)	64 (39.8)	68 (40.7)
Age				
80–84	247 (64.0)	233 (65.3)	91 (56.5)	93 (55.7)
85–89	109 (28.2)	96 (26.9)	48 (29.8)	51 (30.5)
≥90	30 (7.8)	28 (7.8)	22 (13.7)	23 (13.8)
BMI (kg/m2)				
<24	134 (41.9)	123 (41.4)	55 (34.2)	59 (35.3)
24–29	129 (40.3)	118 (39.7)	68 (42.2)	70 (41.9)
≥29	57 (17.8)	56 (18.9)	38 (23.6)	38 (22.8)
Living arrangements				
Own home	336 (90.1)	313 (91.0)	158 (98.1)	164 (98.2)
Assisted living accommodation	37 (9.9)	31 (9.0)	3 (1.9)	3 (1.8)
Hospital admissions <6 months				
None	279 (73.4)	266 (75.8)	81 (50.9)	85 (51.5)
One or more	101 (26.6)	85 (24.2)	78 (49.1)	80 (48.5)
ASA*				
2	36 (9.5)	34 (9.5)	40 (25.5)	43 (26.1)
3	263 (69.0)	248 (69.5)	105 (66.9)	110 (66.7)
4	82 (21.5)	70 (19.6)	12 (7.6)	12 (7.8)
AA-CCI**				
4–6	322 (83.4)	302 (84.6)	99 (61.5)	99 (59.3)
7–12	64 (16.6)	55 (15.4)	62 (38.5)	68 (40.7)
Type of surgery				
Open	169 (43.8)	153 (42.8)	54 (33.5)	55 (32.9)
Laparoscopy	217 (56.2)	204 (57.1)	107 (66.5)	112 (67.1)
Conversion	35 (13.9)	33 (13.9)	15 (12.3)	15 (11.8)
Postoperative complications				
None	232 (60.1)	229 (64.1)	95 (59.0)	97 (58.1)
CD I-II	85 (22.0)	83 (23.2)	42 (26.1)	49 (29.3)
CD III-V	69 (17.9)	45 (12.6)	24 (14.9)	21 (12.6)
Surgical complications				
No	294 (76.2)	276 (77.3)	122 (75.8)	129 (77.2)
Yes	92 (23.8)	81 (22.7)	39 (24.2)	38 (22.8)
Non-surgical complications				
No	317 (82.1)	303 (84.9)	125 (77.6)	129 (77.2)
Yes	69 (17.9)	54 (15.1)	36 (22.4)	38 (22.8)
Length of hospital stay	7 (1–58)	7 (2–58)	5 (2–36)	5 (2–56)
Discharge destination				
Own home	172 (45.6)	170 (48.9)	90 (55.9)	91 (54.5)
Other hospital for rehabilitation	187 (49.6)	178 (51.1)	70 (43.5)	75 (44.9)
Died during hospital stay	18 (4.8)	-	1 (0.6)	1 (0.6)
Reoperations	39 (10.1)	32 (9.0)	16 (9.9)	16 (9.6)
Readmission	25 (6.5)	23 (6.4)	13 (8.1)	14 (8.4)
TNM stage				
1	41 (12.7)	46 (12.8)	29 (18.1)	30 (18.3)
2	191 (49.5)	176 (49.2)	86 (53.4)	88 (53.7)
3	146 (37.8)	135 (38.0)	45 (28.0)	46 (28.0)
Mortality				
30-days	23 (6.0)	-	3 (1.9)	3 (1.8)
90-days	29 (7.5)	-	-	
One-year	59 (15.3)	30 (8.4)	-	11 (6.6)

* American Society of Anesthesiologists physical status classification system

** Age-adjusted Charlson Comorbidity Index

Postoperative adjuvant chemotherapy was administered to 80 patients (21%). According to TNM-stage, 67 (46%) stage III patients received postoperative adjuvant therapy (Studies I and II). The corresponding numbers in Studies III and IV were 31% (14/45) and 28% (13/47).

5.2 Postoperative complications

In Studies I and II, 154 patients (40%) had postoperative complications. Severe complications, graded III-V according to the Clavien-Dindo classification, were recorded in 69 patients (18%). Surgical complications were reported in 92 (24%) patients. Ileus (7.0%), anastomotic or intra-abdominal bleeding (6.2%) and anastomotic leakage (5.7%) were the most common causes of complications. Cardiovascular (6.0%) and pulmonary (4.7%) reasons were the most commonly diagnosed non-surgical complications. Reoperation was performed in 39 patients (10%) due to surgical complications such as anastomotic leakages and wound ruptures.

Study III showed a total postoperative morbidity of 41% with 24% of patients having surgical complications. The most frequent surgical complications were ileus (12%), anastomotic leakage (5%), superficial surgical site infection (3.6%) and wound dehiscence (2.5%). In four patients an iatrogenic bowel perforation was diagnosed, and one patient developed a postoperative colon necrosis. Sixteen patients (10%) were reoperated on due to surgical complication. Non-surgical complications were mainly cardiovascular (6%) and pulmonary (8%). Venous thromboembolism was diagnosed in two patients (1.2%). One patient had a massive cerebral stroke, which caused permanent disability. Nine patients had both surgical and non-surgical complications mainly associated with postoperative ileus (78%). According to the CD classification, 15% of patients had severe complications (CD III-V). Most of those were surgical complications as only three patients suffered purely non-surgical complications (1.8%) requiring admission to the intensive care unit.

5.3 Predictors for postoperative complications

Study I showed that postoperative complications were significantly more common with patient-related factors such as male gender (46% vs. 35%, p=0.027), coronary artery disease (52% vs. 36%, p=0.003), diabetes mellitus (51% vs. 37%, p=0.023) and rheumatic disease (67% vs. 39%, p=0.032). Patients living preoperatively in assisted living accomodation (30% vs. 17%, p= 0.05), had hospital admissions during the six months prior to surgery (31% vs. 15%, p=0.018) or experienced excess intraoperative blood loss (100 ml vs median 50 ml, p=0.006), suffered more severe complications according to CD classification.

In Study III, postoperative complications were decidedly more frequent in patients with a history of cerebral stroke (64% vs. 37%, p = 0.02), albumin level 31–34 g/l (57% vs. 32% with albumin >34 g/l, p = 0.007) and ASA >3 (77% vs. 28%, p = 0.006). In addition, overall complication rate in patients with CFS 3–9 was higher (48% vs. 16% in CFS 1–2, p<0.001) Patients with CFS 3–9 suffered more non-surgical complications (27% vs. 8%, p=0.018) and surgical complications (28% vs. 11%, p=0.030) than patients with CFS 1–2.

In Study III, major complications (CD III–V) were significantly more common in patients with renal failure (25% vs. 12%, p = 0.021), chronic obstructive pulmonary disease (43% vs. 13%, p = 0.047), CCI score >6 (23% vs. 10%, p = 0.034) and albumin level 31–34 g/l (26% vs. 8% in patients with albumin >34 g/l, p = 0.014).

Table 9 summarises the statistically significant predictors for increased risks of postoperative complications in Studies I and III.

Table 9. Statistcally significant predictors of 30-day postoperative complications (p<0.05)

	Univariate analysis			Multivariable analysis		
	OR	95 % CI	p-value	OR	95 % CI	p-value
Study 1						
Gender (male)	1.59	1.05–2.40	0.027	1.42	0.88–2.30	0.154
Higher BMI	1.06	1.00–1.11	0.037	1.06	1.00–1.12	0.053
Diabetes Mellitus	1.75	1.08–2.85	0.023	1.76	1.00–3.10	0.049
Coronary disease	1.94	1.25–3.02	0.003	1.69	1.01–2.83	0.046
Rheumatic diseases	3.14	1.05–9.36	0.032	4.28	1.27–14.4	0.019
Severe complications						
Patients living in assisted living accommodation	2.12	0.99–4.53	0.050			
Hospital admissions < 6 months	1.96	1.12–3.40	0.018			
Study III						
History of cerebral stroke	3.05	1.20–7.76	0.020	2.53	0.85–7.52	0.096
CFS 3-4	4.92	1.85–13.1	0.001	6.06	1.88–19.5	0.003
CFS 5-9	4.49	1.56–13.0	0.005	3.54	0.95–13.2	0.060
ASA score 4	7.91	1.80–34.7	0.006	3.08	0.57–16.8	0.193
Albumin 31–34 g/l	2.88	1.34–6.16	0.007	3.88	1.61–9.38	0.003
Severe complications						
COPD	4.91	1.02–23.6	0.047	0.60	0.04–8.21	0.701
Renal insufficiency	3.01	1.18–7.98	0.021	1.47	0.40–5.48	0.563
CFS 3-4	3.40	0.73–15.9	0.121	8.16	0.89–75.0	0.064
CFS 5-9	4.63	0.93–23.0	0.061	7.69	0.70–85.1	0.096
CCI ≥6	2.60	1.07–6.28	0.034	1.96	0.48–7.95	0.346
Albumin 31–34 g/l	3.77	1.30–10.9	0.014	4.39	1.31–14.7	0.017

5.4 Short-term survival

In Studies I and II, the respective overall 30-day and 90-day mortality rates were 6% and 7.5%. The causes of death within three months after surgical treatment were mainly of cardiopulmonary origin (16/29, 55%) or surgical complications

(7/29, 24%). The corresponding numbers for three months after surgery were 46% and 1% (Study II).

In Study III, total 30-day mortality rate was 1.9%, but rosed to 8.3% in those with CD grade III–IV complications. Out of three deaths, one patient with wound dehiscence died on the twenty-third postoperative day after protracted ileus and two reoperations. One patient died on the twenty-fifth postoperative day after relaparotomy for anastomotic leakage. The third patient died on the eighteenth postoperative day of complications due to ischaemic heart disease.

In Studies I and II, the overall one-year mortality rate was 15%. A mortality rate of 23% was noted in patients aged 90 years or over in comparison to 13% in patients aged 80-84 years. The mortality rates for patients operated on with an open versus laparoscopy technique were higher, 21% and 12% respectively. Less than half (45%) of the patients suffering major surgery-related complications survived more than one year after surgery. Patients without postoperative complications had a survival rate of 91%, which is comparable to that among patients with Clavien Dindo I-II complications.

In Study IV, the overall one-year mortality rate was 6.6%. The main causes for death at one year were cardiopulmonary (36%), colon cancer (27%) and surgery-related (18%) reasons. The one-year mortality rate for preoperatively independent patients, partly dependent patients, or those dependent on supportive care were 5.6%, 4.3% and 9.7% respectively. The one-year mortality rates for preoperatively independently mobile patients without walking aids, independently mobile patients with walking aids and dependent patients were 4.3%, 8.9% and 33% respectively.

5.5 Long-term survival

In Study II, with a median follow-up duration of 6.3 years (ranging from 10 days to 13.9 years or until death), 232 patients died during this follow-up period. The one-year, three- and five-year survival rates were 85%, 66% and 55% and the corresponding numbers for patients surviving for three months after surgery were 92%, 71% and 59% respectively. The main causes of death were cardiovascular (32%), colon cancer (30%) and pulmonary diseases (15%). Figure 4 presents the causes of death within and after three months of surgery (Studies II and IV).

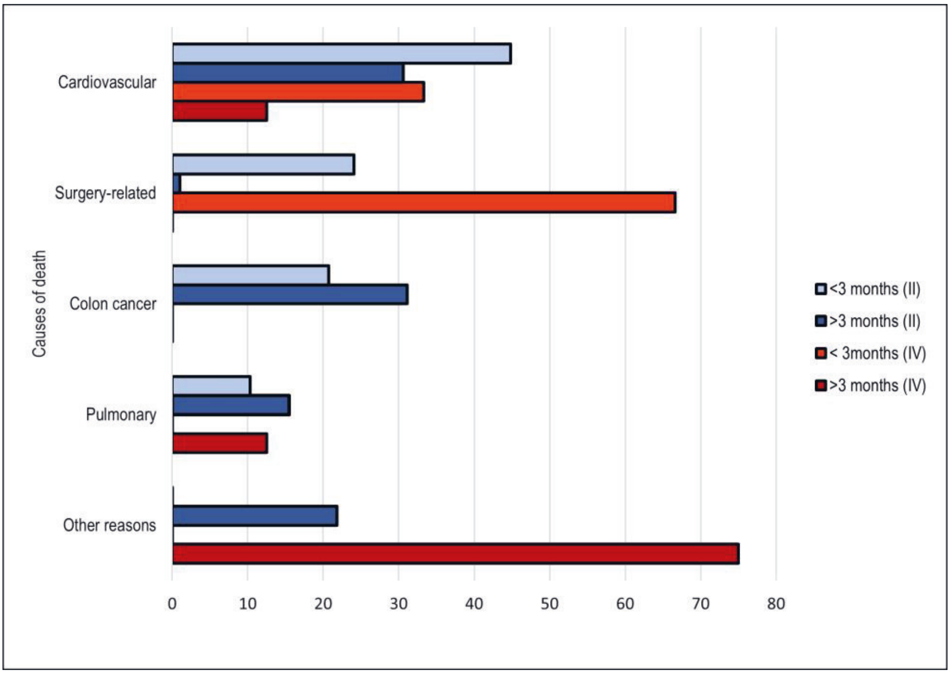

Figure 4. Causes of death (%) within three months and after three months of surgery (n=29 and n= 193 (Study II), n=5 and n=11 (Study IV)).

Patients who preoperatively lived in assisted living accomodations had a median survival time of 2.9 years (95% CI 1.80-4.00) the corresponding time for those living in their own homes being of 5.5 years (4.77-6.20). The median survival time for all patients with no complications was 5.9 years (5.30–6.50) and for those with major complications 1.8 years (0.18–3.34). However, the corresponding number for patients who survived more than three months after surgery was 5.9 years (5.28–6.59) and for patients with major complications 6.1 years (2.30-9.91).

Most of the cancer recurrences appeared within three years after surgery (84%). The overall recurrence rate for all patients was 18%. For tumour stages, I, II and III the respective median overall survival times were 5.9, 6.5, and 3.5 years. Stage III disease patients with postoperative adjuvant chemotherapy had a median survival time of 5.4 years, compared to 2.3 years and 3.3 years for those who did not receive postoperative chemotherapy and survived over three months after surgery. Figure 5 shows the Kaplan-Meier analysis of overall survival with and without complications (CD 0-V) and tumour stages (I-III).

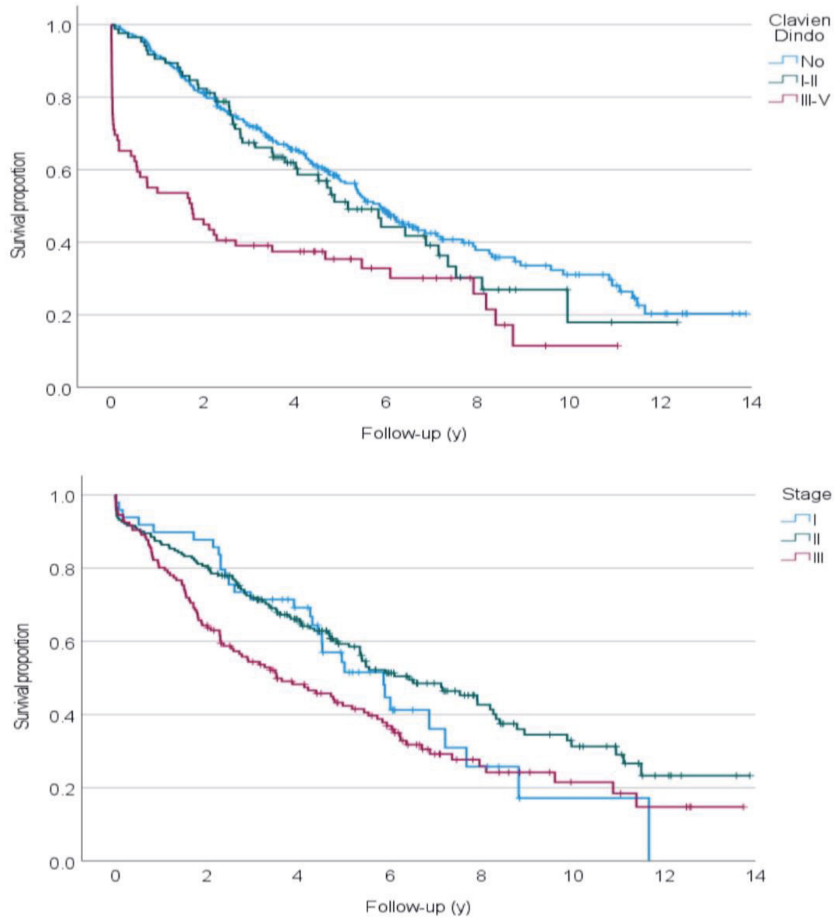

Figure 5. Kaplan-Meier analysis of overall survival (n=386) with and without complications graded with Clavien-Dindo classification (above, p<0.001, log-rank) and according to tumour stages I-III (below, p<0.001, log-rank).

5.6 Predictors of short- and long-term survival

Study I showed that increased 30-day mortality was associated with living in assisted living accomodation (16% vs 5%, p=0.012), hospital admissions six months before surgery (13% vs 4%, p=0.002) and CCI score ≥ 6 (10% vs 3%, p=0.012). In addition, longer duration of surgery (p=0.038), greater intraoperative blood loss (p=0.005) and severe postoperative complications

(30% vs 0.6%, p<0.001) increased the risk of 30-day mortality. Hospital admissions six months before surgery (OR 3.05, 95% CI 1.25-7.43, p=0.014) and severe postoperative complications (85.61, 10.68-686.1, p<0.001) were the only variables in multivariate analysis significantly affecting 30-day mortality.

In Study I, greater one-year mortality after surgery was associated with age over 89 years (23% vs 13% with years 80-84, p=0.004), hospital admissions six months before surgery (22% vs 13%, p=0.035), open compared to laparoscopic technique (21% vs 12%, p=0.027), longer duration of surgery, greater intraoperative blood loss, severe postoperative complications (45% vs 9% with no complications, p<0.001). Severe postoperative complications were the only significant patient-related variable affecting one-year mortality.

In Study IV, increased one-year mortality was associated with BMI< 24kg/m^2 (14% vs 3%, p=0.039), non-surgical complications (16% vs 4%, p=0,017) and severe complications (19% vs 5%, p=0.023). In the multivariate logistic regression analysis non-surgical and severe postoperative complications were the only significant patient-related variables affecting one-year mortality. Table 10 summarises the statistically significant predictors for increased mortality rate.

Table 10. Predictors of 30-day and one-year mortality in elective colon cancer surgery in the aged (univariate analysis)

	30-day mortality			1-year mortality		
	OR	95 % CI	*P*-value	OR	95 % CI	*P*-value
Study I						
Age	1.11	0.99–1.24	0.079	1.12	1.04–1.21	0.004
Living in assisted living accommodation	3.63	1.34–9.88	0.012	1.93	0.86–4.34	0.112
Hospital admissions ≤ 6 months	3.97	1.68–9.38	0.002	1.88	1.04–3.38	0.035
CCI score ≥7	7.64	1.57–37.2	0.012	2.08	0.93–4.65	0.075
Open surgery	1.79	0.67–4.17	0.178	1.88	1.08–3.30	0.027
Surgical complication	25.05	3.13–200.7	0.002	2.76	1.40–5.46	0.004
Non-surgical complication	61.29	7.83–479.5	<0.001	5.05	2.50–10.2	<0.001
Severe complications (CD III-V)	101.06	13.3–769.5	<0.001	8.65	4.47–16.7	<0.001
Study IV						
BMI < 24 kg/m^2				5.33	1.09 -26.2	0.039
Non-surgical complication	-	-	-	4.56	1.31–16.0	0.017
Severe complications (CD III-V)	-	-	-	4.67	1.24–17.6	0.023

In Study II, decreased overall survival in the whole study population was independently associated with higher age (HR 1.08, 95% CI 1.04–1.13, p< 0.001), living in assisted living accommodation (1.54, 1.03–2.30, p= 0.034), age-adjusted CCI score ≥ 6 (1.47, 1.07–2.01, p= 0.018) and ASA score ≥ 4 (2.62, 1.32–5.21, p= 0.006). In addition, open surgery compared to laparoscopic approach (1.41, 1.05–1.88, p= 0.020), postoperative major complications (2.11, 1.49–2.99, p < 0.001) and stage III tumour (1.88, 1.40–2.52, p< 0.001) were shown to substantially diminish overall survival.

5.7 Functional outcomes

Of all eligible population in Study IV, information on support for activities of daily living within one year was available on 165 patients (99%). Increased postoperative need for support one-year after surgery was observed in 22% (n=35/159) at three months, 25% (n=35/153) at six months, and 30% (n=50/165) at one year. Patients requiring more support for activities of daily living had a history of preoperative cognitive impairment (44% vs 24%, p=0.010) and were dependent on support when outside the home (65% vs 31%, p<0.001).

In multivariate logistic regression analysis, preoparative need for support for activities of daily living outside the home (OR 3.23, 95% CI 1.06-9.80, p=0.039) was independently associated with increased need for supportive care.

Of all eligible population in Study IV, information on mobility was available on 157 patients (94%). Decreased postoperative mobility was reported in 17% (n=27/159) at three months, in 15% (n=25/163) at six months, and in 22% (n=35/157) of patients at one year. Patients with impaired mobility were preoperatively independently mobile compared with patients with walking aids (26% vs 14%, p=0.030) and had haemoglobin level <120 g/l (29% vs 11%, P=0.013). These patients were also more often treated with open surgery (31% vs 18%, p=0.010), were diagnosed with surgical or non-surgical complications (34% vs 19%, p=0.046 and 42% vs 17%, p=0.002) and were postoperatively more frequently discharged to other hospitals for rehabilitation (34% vs 12%, p<0.001).

In multivariate logistic regression analysis, history of cognitive impairment (OR 3.15, 95% CI 1.06-9.34, p=0.038), preoperative haemoglobin level <120 g/l (7.48, 1.97-28.4, p=0.003) and discharge postoperatively to other medical facilities (4.72, 1.39-16.0, p=0.013) were independently associated with impaired mobility. Conversely, patients who were independently mobile with walking aids (0.17, 0.05-0.64, p=0.009) significantly maintained or improved their mobility. Figures 6 and 7 show changes in support for daily life and mobility one year after surgery.

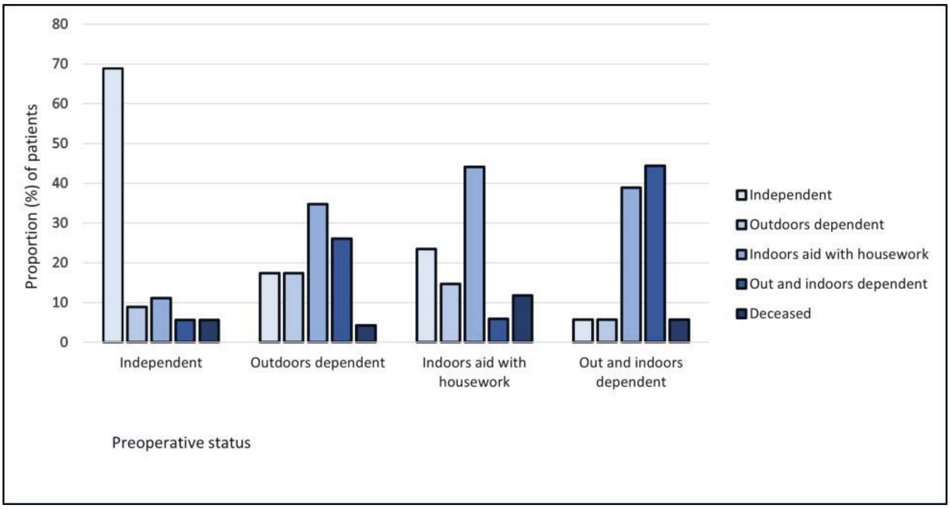

Figure 6. Changes in support for activities of daily living one year after surgery.

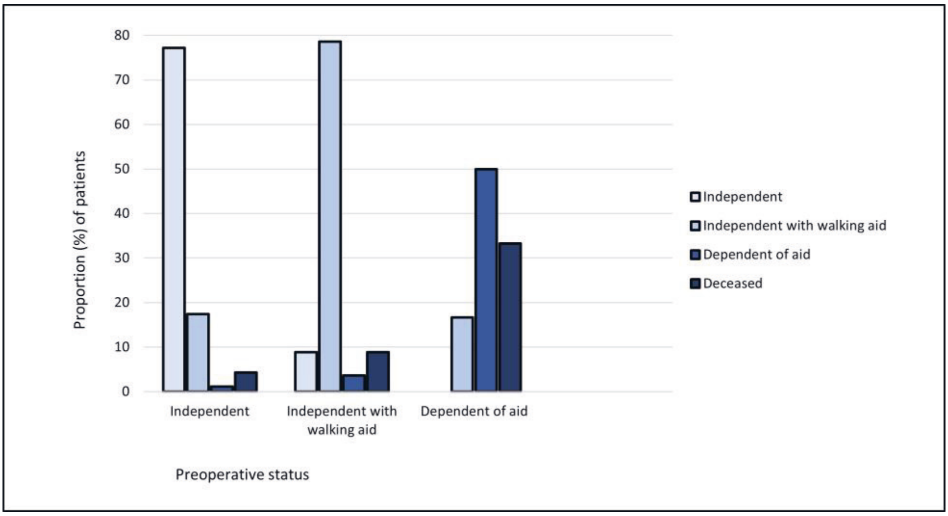

Figure 7. Changes in mobility one year after surgery

6 DISCUSSION

The number of aged people is rising, which is mainly due to increased life expectancy. As colon cancer has the highest incidence rates around the age of 80 years, the number of those individuals experiencing colon cancer is expected to increase and thus become a significant treatment challenge to health care systems, especially for colorectal surgical units. (Finnish Cancer Registry, 2022).

The primary treatment goal of colon cancer is radical surgery intended to minimise adverse events and maintain individuals functional status. Aged individuals constitute a heterogeneous group of patients, ranging from fit to frail with short life expectancy. Consequently, chronological age alone should not mean refusal of curative treatment before a comprehensive preoperative risk assessment (Millan et al. 2015; Montroni et al. 2018). Consensus guidelines regarding preoperative assessment, optimisation and geriatric evaluation for those over 70 years of age possibly with multiple comorbidities, frailty or impaired functional status have recently been published (Papamichael et al. 2015; Montroni et al. 2018; Rostoft et al. 2020; Sauer et al. 2020). However, data on functional recovery and outcomes as reported by colon cancer patients aged 80 years or older are lacking. It is thus essential to have real-life data on those age groups´ functional outcomes for comprehensive preoperative shared decision-making involving surgeons and patients.

6.1 Complications and short-term mortality

Study I retrospectively analysed colorectal databases without fully assessing the severity of comorbidities, disability and functional status. In Study III, patients were prospectively recruited with specific knowledge of their medical and functional status. Nevertheless, both studies reported high rates for total and severe complications being respectively 40-41% and 15-18%. These figures are comparable to those of previously published studies. Furthermore, they emphasised that even with the development and wider use of modern comprehensive surgical and anaesthesiological options, complication rates remained high and consequently require diagnostic tools to detect those who are on greater risk for adverse postoperative events.

The surgical complication rate of 24% in both studies appeared similar to those of other studies focused on complications of colon cancer surgery among older patients (Roscio et al. 2016; Denet et al. 2017; Barina et al. 2020). Study III reported a notably higher proportion of postoperative ileus than Study I (12% vs 7%) but probably a more realistic incidence rate. Anastomotic leakage rates of 5-5.7% were in line with acceptable morbidity numbers. In Study III, iatrogenic bowel perforations and colon necrosis were associated with laparoscopic procedures with a reported rate of 3%. With the increasing use of the laparoscopic approach in the study hospitals (56%) as a primary recommended surgical approach, careful technical performance and analysis of bowel circulation status may help to prevent these adverse events (Chiarello et al. 2022). In the present study, surgical complications were the most important causes of short-term mortality. Systematic standardised surgical techniques and ERAS protocol may also be beneficial to reduce the rate of surgical complications.

Non-surgical complication rates were 18% and 22%, respectively. These figures concur with a recently published review article reporting non-surgical complication rates of 2-44% after colorectal surgery for all ages (Schiphorst et al. 2015). The most common non-surgical complications were cardiological and pulmonary in nature (11-12%); these are generally common comorbidities in aged individuals. These findings emphasise the importance of optimising a patient’s cardiopulmonary status. Remarkably, the proportion of postoperative delirium in both studies was extremely low (1.3-1.8%) as other studies focusing on postoperative delirium have reported incidence rates of 13-50%. These figures may reflect possibly underrated and thus underdiagnosed symptoms of delirium favouring particular preoperative caution regarding cognitive status and postoperative awareness of delirium symptoms.

Studies I and II presented 30-day and one-year mortality rates of 6% and 15%, respectively. Those figures were in line with earlier published data of 6–16% in 30-day and 14–37% one-year mortality (Gooiker et al. 2012; Weerink et al. 2018). Patients with severe complications had comparable mortality rates of 30% and 45% respectively. On the contrary, improved survival comparable to that of younger patients was reported in Studies III and IV with 30-day and one-year mortality rates of 1.9% and 6.6% and with severe complications in 8.3% and 18% respectively. This progression is also shown in a recently published registry-based study from the Netherlands, reporting a marked decrease in mortality between 2005 and 2016 in patients aged over 75 years. The 30-day and one-year mortality rates declined from 10% to 4.0% and 15.2% to 5.4% respectively (Brouwer et al. 2019).

Altogether, from 2005 to 2016 in Study I and later confirmed in Study III, short-term mortality rates progressively decreased. This favourable development trend is mostly explained by comprehensive preoperative risk assessment, awareness of frailty, improved perioperative anaesthesia care and surgical advances (laparoscopy, technical standardisation) and standardised multimodal approach using ERAS protocol. Thus, the increasing utilisation of systematic, multimodal and possibly multiprofessional treatment pathways appears to be beneficial for aged colon cancer patients.

6.2 Predictors of complications and short-term mortality

In Study I, male gender, diabetes mellitus and coronary and rheumatic diseases were significantly associated with postoperative complications, in line with published data. However, in Study III, no specific comorbidities despite a history of cerebral stroke were associated with an increased number of complications. These findings possibly emphasise improved knowledge in precise preoperative assessment and optimising patients' comorbidity status and improved perioperative care (Ketelaers et al. 2020). Conversely, patients with COPD and renal failure suffered significantly from severe complications necessitating special caution regarding preoperative pulmonary and renal status.

Preoperatively diagnosed mildly reduced albumin level was associated with increased complication rate. In recently published studies, hypoalbuminemia has been associated with postoperative complications (Haskins 2017, Hu 2019). This result may reflect the lack of a fully standardised nutritional protocol in the study hospitals, as only patients with significant malnutrition are likely to be treated preoperatively. The risk of preoperative malnutrition is elevated in aged individuals, and although a low albumin level is insufficient to determine nutritional status, it could be used as a screening tool (Hu et al. 2019). These results suggest that serum albumin measurement could be used more frequently before surgery as a valuable tool enabling surgeons to select patients for more detailed nutritional evaluation. In addition, the use of MNA-SF or a similar nutrition screening tool may be advisable for all aged patients before cancer surgery.

Both studies showed that preoperative functional status and frailty were significantly associated with increased adverse events. In Study III, according to CFS, almost 50% of patients, even those with mildly impaired functional status (CFS ≥3), suffered complications. All severe complications were three- to four-fold more common than among functionally fit patients (CFS 1-2). In Study I, no precise functional or frailty status was concluded because of the retrospective nature of the study. Patients living in assisted living accommodation or with a relatively large number of hospital admissions before surgery suffered significantly more severe complications. These patients presumably were particularly vulnerable due to their impaired functional status. Assisted living is usually an option for older individuals who can no longer cope at home even with multiple daily visits by home carers. In addition, most of them probably had some degree of cognitive impairment. Altogether, the results confirm the published consensus recommendations and thus underline the importance and specific need for attention to aged patients´ preoperative functional and frailty status assessment in order to prevent any adverse events. According to our study, CFS has been shown to be a valuable screening tool for frailty and thus for more precise geriatric evaluation.

Severe postoperative complications were strongly associated with 30-day mortality. Patients who lived in assisted living accommodation, had multiple hospital admissions during the six months preceding surgery and a high comorbidity burden (CCI score ≥ 6) had a higher mortality rate as they suffered more severe adverse events. Corresponding patient-related factors and open surgical approach were associated with increased one-year mortality after surgery. The studies summarised here concluded that severe postoperative complications were the most important patient-related factor affecting mortality within the first postoperative year. These findings demonstrate the need for intensive pre- and perioperative strategies for identifying risk factors for complications and timely treatment of these adverse events.

Compared to open surgical technique, laparoscopy served to reduce 30-day complications (Study III) and one-year mortality rates (Study I). Although those patients undergoing open surgery may have presented with more challenging surgical circumstances, laparoscopy could be a preferable primary surgical approach for aged patients.

6.3 Long-term survival

Study II analysed postoperative mortality three months before and after surgery. Cardiopulmonary (55%) and surgery-related factors (24%) accounted for 79% of all mortalities occuring within three months of surgery. In addition, severe complications significantly reduced median and overall survival compared to the rates among patients without complications (3.7 months vs 2.9 years and 1.8 years vs 5.9 years, respectively). However, the data for patients who survived for three months after surgery, even after suffering severe complications were comparable to those among other patients.

The present study reported comparable survival rates with those of aged individuals in general. The respective survival rates for patients alive three months postoperatively at one, three and five years were 92%, 71% and 59%. Aged patients generally have chronic conditions and multiple comorbidities, which increase mortality. Consequently, the burden of comorbidities, higher age and locally metastatic disease (stage III) were associated with reduced overall survival. In addition, laparoscopic surgery was found to be safe and achieved better long-term survival than the open approach (5.8 years vs. 4.4 years). Patients receiving postoperative adjuvant chemotherapy had a median survival of 5.4 years, compared to 3.3 years for patients not given postoperative treatment.

Altogether, these results confirm that preoperatively physically and functionally fit patients can achieve acceptable long-term survival rates. Hence, curatively aimed laparoscopic approach, and if possible additional adjuvant chemotherapy are primarily recommended for this patient group.

6.4 Functional outcomes

In Study IV, patients with preoperative support in activities outside the home created increased demand for additional aid. However, the baseline functional status of those patients might have already been declined, and consequently, invasive surgery resulted in further depletion of their physiological and functional capacity. A comprehensive evaluation of possible preoperative geriatric syndromes, malnutrition and cognitive impairment might thus be beneficial. In addition, those patients might benefit from a structured geriatric assessment. Otherwise, patients preoperatively independent in activities of daily living retained their independence with minor decline over the first postoperative year. This finding supports the use of radical surgery in the treatment of cancer in these patients despite chronological age.

Long-term mobility level at one year declined by 24% among independently mobile patients and by 14% in patients with walking aids compared to 60% of patients who were dependent on personal assistance. Our study showed a slight decline in mobility among functionally independent patients during the first three postoperative months but thereafter a steady notable recovery within the first postoperative year. Additionally, patients who postoperatively were not discharged home experienced significant long-term impaired mobility. This may be a long-term consequence of patients´ preoperative mobility status with incomplete early mobilisation and rehabilitation at the operating hospital. Furthermore, patients´ impaired performance status with complications and open surgery may delay the start of postoperative rehabilitation. Immobilisation increases the risk of sarcopenia, thus causing a further delay in rehabilitation. Consequently, maintaining mobility during and after surgical treatment and even introducing a new walking aid may be essential for patient-related satisfactory long-term recovery from major surgery. Altogether, these findings emphasise the essential significance of pre- and postoperative mobility with active and personally designed early rehabilitation for a successful postoperative functional result. Therefore, systematic programmes that maintain and improve pre- and postoperative functional performance could be incorporated throughout the surgical pathway in colon cancer.

6.5 Strengths and limitations of the studies

The patient materials in Studies I and II were retrospective data from a prospectively collected hospital database. They represented a large population of aged patients 80 years or older with an understanding of their real-life colon cancer surgery and its outcomes. The strengths of Studies III and IV included large and nationally representative cohorts derived from real-life circumstances. The data populations were homogenous and comprehensive as the study hospitals followed nationally uniform and standardised protocols for colon cancer surgery. The proportion of patients consenting to participate in the studies was high (75%). Consequently, the studies corresponded to standard everyday surgical practice and covered virtually all colon cancer patients referred to surgical units from large catchment areas.

The results in Study IV are of considerable significance for an individual aged patient regarding functional recovery. Study IV, with one-year follow-up, provided a comprehensive patient-related view of the impact of surgery on aged patients. Follow-up was adequate as data of 2 (1.2%) with support in daily living and 10 (6.0%) with mobility was missing.

In all studies, the initial patient material included those, referred to surgical units and thus the study population did not totally represent the colon cancer population aged 80 years or over. The data for Studies I and II were retrospectively collected. Therefore, detailed information on daily physical and cognitive functional status and the severity of the comorbidities were not included. However, invasive surgical treatment was likely offered to most patients but possibly witheld from those with decidedly poor health status. Due to the variety of diagnostic symptoms, intensity and fluctuation, accurate delirium diagnoses were not feasible in this study. As this is known to be one of the major complications among very old surgical patients with high incidence and prevalence, this is a clear limitation. Invasive postoperative investigations of possible cancer recurrences may not have been accomplished for patients who were physically and cognitively unfit as routine long-term postoperative follow-ups were lacking. Consequently, precise long-term data on cancer recurrences and thus causes of death were not complete.

6.6 Future prospects and implications

In the future, more cautious and comprehensive multidisciplinary treatment planning together with surgeons, anaesthesiologists and geriatricians is recommended to be established as a routine in the hospitals involved in this study. Preoperative nutritional and frailty evaluation with systematic implementation in every-day practice is advisable. The influence of early rehabilitation, prevention of sarcopenia and postoperative delirium on long-term cognitive performance should be analysed. After two or more years postoperatively, functional outcomes and recovery from prospectively collected data are to be analysed. In addition, the outcome and survival data from patients not undergoing surgery and who were recruited for the prospective study are to be analysed.

7 CONCLUSION

The main conclusions of the present thesis are:

1. Curatively aimed, elective colon cancer surgery for patients aged 80 years or older showed high postoperative complication rate. Increased 30 day and one-year postoperative mortality rates were significantly more common in patients with severe complications, thus favouring preoperative identification of patients at risk.

2. Patients who were physically and cognitively fit to survive three months after colon cancer surgery, even though suffering severe complications, had long-term survival rates comparable to those of younger patients.

3. The Clinical Frailty Scale (CFS) predicted early postoperative complications well. Preoperative CFS may be a useful screening implement to identify patients at risk of excess postoperative complications and thus to select patients for possible geriatric assessment.

4. Preoperatively increased need for support, cognitive impairment, anaemia, poor nutritional status and discharge to other medical facilities predict an increased need for support or impaired mobility one year after surgery. Preoperative assessment and optimisation should focus especially on mobility and nutritional status.

8 ACKNOWLEDGEMENTS

This study was carried out at the Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital and at the Faculty of Medicine and Health Technology, Tampere University. It was financially supported by the Competitive State Research Financing of the Expert Responsibility Area of the University Hospital, the Cancer Foundation Finland, the Mary and Georg Ehrnrooth Foundation and the Finnish Cultural Foundation.

I warmly thank the Head of Alimentary Tract Surgery, Professor Johanna Laukkarinen for encouraging, enabling and supporting the clinical and scientific work in the Department of Gastroenterology and Alimentary Tract Surgery.

I owe my most profound gratitude to my supervisors Docent Marja Hyöty and co-supervisors Professor Esa Jämsen and Docent Jyrki Kössi for their guidance and support. Sincere thanks are also due to Marja for her unfailing support and mentoring in both clinical and scientific work and for sharing my interest in the well-being of older patient. I want to thank Esa for introducing me to the field geriatric medicine and for sharing his vast clinical and science experience in this speciality previously unknown to me. I want to thank Jyrki for his continuous positive feedback and profoundly wise responses when revising my manuscripts.

I would like to express my deepest gratitude to Heini Huhtala, MSc for her amazing statistical expertise, tireless support and patience in analysing the data, and for sharing with me those long hours with statistical problems.

I am very grateful to the official reviewers, Professor Jouko Laurila and Docent Monika Carpelan-Holmström for their work in providing me with insightful criticism and valuable comments to improve the manuscript in its final stage. I wish to express my warmest gratitude to Professor Juha Saarnio of the University of Oulu for kindly agreeing to act as the opponent at the public defence of this dissertation.

I wish to thank my co-workers: Anu Ehrlich, MD, PhD, Mirjami Uotila-Nieminen, MD, Hanna Vihervaara, MD, PhD, Tarja Pinta, MD, PhD, Selja Koskensalo, MD, PhD, Anne Mattila, MD, PhD, Eija Haukijärvi, MD Jan

Andersen, MD and Suvi Koikkalainen, MD for their valuable contribution to the success of the multicentre study. I am thankful to Research Nurse Mrs. Sanna-Mari Hartikainen for her help in collecting the patients-questionnaires. I thank Mrs. Virginia Mattila, MA for her expertise in revising the English of the manuscripts. I warmly thank Kirk Langley, MD for his help in editing the English language of the articles.

I am privileged indeed to have worked with colleagues and co-workers in Iisalmi, North Carelia, Valkeakoski, Hatanpää and Tampere University Hospitals. I specially want to express my gratitude to my clinical "mentors", Heikki Ahtola, MD and Ritva Laitakari, MD for introducing me to gastrosurgery with a holistic approach.

Many of my friends and relatives have supported me during this process. I am grateful to "Vaeltajat" for all the unforgettable moments since medical school. I am grateful to Heltsi for special friendship and valuable help and comments on this thesis. My warmest thanks go to Hansu and my lifelong "Soulsisters" Ellu, Kaarina, Maiju, Marika, and Seija for their invaluable friendship, endless encouragement and background support for this project and life outside the medical world.

I am very fortunate to have Saara, Hanna and Sampsa as part of our family. I warmly thank you all for your interest and support throughout this work and the joy you bring to me and the family. I thank my mother-in-law Pirjo for her support and proving that age is not just numbers.

I warmly thank my sister Kata and brother Pekka and their families for a precious, lifelong friendship and background support throughout this thesis. You have always been there to share and support me in the ups and downs of my life. The lifelong support, encouragement and love I have received from my parents Marjut and Kauko is priceless. With your everyday example to everyone around, I dedicate this book to you, you are my greatest idols.

Finally, my deepest gratitude goes to my husband Arto for always being my tower of strength to lean on in all areas of life and for bringing happiness and love to me every day. I deeply thank our children Matias, Saara and Markus for their endless interest on my "daily colon news" and for their unconditional love. You and our newborn granddaughter Bea are my dearest treasures. I thank you for the love and joy you bring me every day.

Tampere, March 2022

Susanna Niemeläinen

9 REFERENCES

Aaldriks, A. A., van der Geest, L. G., Giltay, E. J., le Cessie, S., Portielje, J. E., et al. Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy. (2013). J Geriatr Oncol, 4(3):218-26. doi: 10.1016/j.jgo.2013.04.001.

Abd El Aziz, M A, Perry, W. R., Grass, F., Mathis, K. L., Larson, D. W., Mandrekar, J., et al. (2020). Predicting primary postoperative pulmonary complications in patients undergoing minimally invasive surgery for colorectal cancer. Updates in Surgery, 72(4), 977-983.

Abdel-Halim, M., Wu, H., Poustie, M., Beveridge, A., Scott, N., & Mitchell, P. J. (2019). Survival after non-resection of colorectal cancer: The argument for including non-operatives in consultant outcome reporting in the UK. The Annals of the Royal College of Surgeons of England, 101(2), 126-132.

Abraham, A., Habermann, E. B., Rothenberger, D. A., Kwaan, M., Weinberg, A. D., Parsons, H. M., et al. (2013). Adjuvant chemotherapy for stage III colon cancer in the oldest old: Results beyond clinical guidelines. Cancer, 119(2), 395-403.

Aitken, R., Harun, N. S., & Maier, A. B. (2021). Which preoperative screening tool should be applied to older patients undergoing elective surgery to predict short-term postoperative outcomes? Lessons from systematic reviews, meta-analyses and guidelines. Internal and Emergency Medicine, 16(1), 37-48.

Aldecoa, C., Bettelli, G., Bilotta, F., Sanders, R. D., Audisio, R., Borozdina, A., et al. (2017). European society of anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. European Journal of Anaesthesiology, 34(4), 192-214.

Allardyce, R. A., Bagshaw, P. F., Frampton, C. M., Frizelle, F. A., Hewett, P. J., Rieger, N. A., et al. (2010). Australasian laparoscopic colon cancer study shows that elderly patients may benefit from lower postoperative complication rates following laparoscopic versus open resection. The British Journal of Surgery, 97(1), 86-91.

American Society of Anaesthesiologists. http://www.asahq.org/Home/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System/. Accessed 15 dec 2021.

Aquina, C. T., Mohile, S. G., Tejani, M. A., Becerra, A. Z., Xu, Z., Hensley, B. J., et al. (2017). The impact of age on complications, survival, and cause of death following colon cancer surgery. British Journal of Cancer, 116(3), 389-397.

Argiles, G., Tabernero, J., Labianca, R., Hochhauser, D., Salazar, R., Iveson, T., et al. (2020). Localised colon cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology: Official Journal of the European Society for Medical Oncology, 31(10), 1291-1305.

Arnarson, O., Butt-Tuna, S., & Syk, I. (2019). Postoperative complications following colonic resection for cancer are associated with impaired long-term survival. Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland, 21(7), 805-815.

Arnold, M., Karim-Kos, H. E., Coebergh, J. W., Byrnes, G., Antilla, A., Ferlay, J., et al. (2015). Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European cancer observatory. European Journal of Cancer, 51(9), 1164-1187.

Arnold, M., Sierra, M. S., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2017). Global patterns and trends in colorectal cancer incidence and mortality. Gut, 66(4), 683–691. doi:10.1136/gutjnl-2015–310912

Aro, R., Makarainen-Uhlback, E., Ammala, N., Rautio, T., Ohtonen, P., Saarnio, J., et al. (2020). The impact of sarcopenia and myosteatosis on postoperative outcomes and 5-year survival in curatively operated colorectal cancer patients - A retrospective register study. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 46(9), 1656-1662. doi: S0748-7983(20)30353-X

Artinyan, A., Orcutt, S. T., Anaya, D. A., Richardson, P., Chen, G. J., & Berger, D. H. (2015). Infectious postoperative complications decrease long-term survival in patients undergoing curative surgery for colorectal cancer: A study of 12,075 patients. Annals of Surgery, 261(3), 497-505. doi:10.1097/SLA. 0000000000000854

Aucoin, S. D., Hao, M., Sohi, R., Shaw, J., Bentov, I., Walker, D., et al. (2020). Accuracy and feasibility of clinically applied frailty instruments before surgery: A systematic review and meta-analysis. Anesthesiology, 133(1), 78-95. doi:10.1097/ ALN.0000000000003257

Bagnall, N. M., Malietzis, G., Kennedy, R. H., Athanasiou, T., Faiz, O., & Darzi, A. (2014). A systematic review of enhanced recovery care after colorectal surgery in elderly patients. Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland, 16(12), 947-956. doi: 10.1111/codi.12718

Bakker, I. S., Grossmann, I., Henneman, D., Havenga, K., & Wiggers, T. (2014). Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit. The British Journal of Surgery, 101(4), 424-32; discussion 432. doi:10.1002/bjs.9395

Balmana, J., Balaguer, F., Cervantes, A., Arnold, D., & ESMO Guidelines Working Group. (2013). Familial risk-colorectal cancer: ESMO clinical practice guidelines. Annals of Oncology: Official Journal of the European Society for Medical Oncology, 24 Suppl 6, vi73-80. doi:10.1093/annonc/mdt209

Baré, M., Mora, L., Pera, M., Collera, P., Redondo, M., et al. (2020). Type and Consequences of Short-Term Complications in Colon Cancer Surgery, Focusing on the Oldest Old. Clin Colorectal Cancer, 19(1): e18-e25. doi: 10.1016/j.clcc.2019.11.003.

Barina, A., Nardelli, M., Gennaro, N., Corti, M. C., Marchegiani, F., et al (2020). Impact of laparoscopic approach on the short-term outcomes of elderly patients with colorectal cancer: a nationwide Italian experience. Surg Endosc, 34(10):4305-4314. doi: 10.1007/s00464-019-07197-9.

Bashir Mohamed, K., Hansen, C. H., Krarup, P. M., Fransgard, T., Madsen, M. T., & Gogenur, I. (2020). The impact of anastomotic leakage on recurrence and long-term survival in patients with colonic cancer: A systematic review and meta-analysis. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 46(3), 439-447. doi: S0748-7983(19)30918-7

Bates, A. T., & Divino, C. (2015). Laparoscopic surgery in the elderly: A review of the literature. Aging and Disease, 6(2), 149-155. doi:10.14336/AD.2014.0429

Beard, J. R., Officer, A., de Carvalho, I. A., Sadana, R., Pot, A. M., Michel, J. P., et al. (2016). The world report on ageing and health: A policy framework for healthy ageing. Lancet (London, England), 387(10033), 2145-2154. doi: S0140-6736(15)00516-4

Bellera, C. A., Rainfray, M., Mathoulin-Pelissier, S., Mertens, C., Delva, F., Fonck, M., et al. (2012). Screening older cancer patients: First evaluation of the G-8 geriatric screening tool. Annals of Oncology: Official Journal of the European Society for Medical Oncology, 23(8), 2166-2172. doi: S0923-7534(19)38102-5

Berian, J. R., Mohanty, S., Ko, C. Y., Rosenthal, R. A., & Robinson, T. N. (2016). Association of loss of independence with readmission and death after discharge in older patients after surgical procedures. JAMA Surgery, 151(9), e161689. doi:10.1001/jamasurg.2016.1689

Bernhoff, R., Martling, A., Sjovall, A., Granath, F., Hohenberger, W., & Holm, T. (2015). Improved survival after an educational project on colon cancer management in the county of Stockholm--a population-based cohort study. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 41(11), 1479-1484. doi: 10.1016/j.ejso.2015.07.019

Bertelsen, C. A., Bols, B., Ingeholm, P., Jansen, J. E., Neuenschwander, A. U., & Vilandt, J. (2011). Can the quality of colonic surgery be improved by standardization of surgical technique with complete mesocolic excision? Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland, 13(10), 1123-1129. doi:10.1111/j.1463-1318.2010. 02474.x

Bertelsen, C. A., Neuenschwander, A. U., Jansen, J. E., Wilhelmsen, M., Kirkegaard-Klitbo, A., Tenma, J. R., et al. (2015). Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: A retrospective, population-based study. The Lancet. Oncology, 16(2), 161-168. doi:10.1016/S1470-2045(14)71168-4

Bertelsen, C. A., Kirkegaard-Klitbo, A., Nielsen, M., Leotta, S. M., Daisuke, F., & Gogenur, I. (2016). Pattern of colon cancer lymph node metastases in patients undergoing central mesocolic lymph node excision: A systematic review. Diseases of the Colon and Rectum, 59(12), 1209-1221. doi:10.1097/ DCR.0000000000000658

Bertelsen, C. A., Neuenschwander, A. U., Jansen, J. E., Tenma, J. R., Wilhelmsen, M., Kirkegaard-Klitbo, A., et al. (2019). 5-year outcome after complete mesocolic excision for right-sided colon cancer: A population-based cohort study. The Lancet Oncology, 20(11), 1556-1565. doi: S1470-2045(19)30485-1

Biondi, A., Vacante, M., Ambrosino, I., Cristaldi, E., Pietrapertosa, G., & Basile, F. (2016). Role of surgery for colorectal cancer in the elderly. World Journal of Gastrointestinal Surgery, 8(9), 606-613. doi:10.4240/wjgs. v8.i9.606

Blanco-Colino, R., & Espin-Basany, E. (2018). Intraoperative use of ICG fluorescence imaging to reduce the risk of anastomotic leakage in colorectal surgery: A systematic review and meta-analysis. Techniques in Coloproctology, 22(1), 15-23. doi:10.1007/s10151-017-1731-8

Boakye, D., Rillmann, B., Walter, V., Jansen, L., Hoffmeister, M., & Brenner, H. (2018). Impact of comorbidity and frailty on prognosis in colorectal cancer patients: A systematic review and meta-analysis. Cancer Treatment Reviews, 64, 30-39. doi: S0305-7372(18)30013-6

Bokey, L., Chapuis, P. H., Chan, C., Stewart, P., Rickard, M. J., Keshava, A., et al. (2016). Long-term results following an anatomically based surgical technique for resection of colon cancer: A comparison with results from complete mesocolic excision. Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland, 18(7), 676-683. doi:10.1111/codi.13159

Bos, A C R K, Kortbeek, D., van Erning, F. N., Zimmerman, D. D. E., Lemmens, V E P P, Dekker, J. W. T., et al. (2019). Postoperative mortality in elderly patients with colorectal cancer: The impact of age, time-trends and competing risks of dying. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 45(9), 1575-1583. doi: S0748-7983(19)30412-3

Bradley, K. A., DeBenedetti, A. F., Volk, R. J., Williams, E. C., Frank, D., Kivlihan, D. R. (2007). AUDIT-C as a Brief Screen for Alcohol Misuse in Primary Care. Alcohol Clin Exp Res, 31 (7): 1308–1217.

Bragg, D., El-Sharkawy, A. M., Psaltis, E., Maxwell-Armstrong, C. A., & Lobo, D. N. (2015). Postoperative ileus: Recent developments in pathophysiology and management. Clinical Nutrition (Edinburgh, Scotland), 34(3), 367-376. doi: 10.1016/j.clnu.2015.01.016

Breugom, A. J., Bastiaannet, E., Dekker, J. W. T., Wouters, M W J M, van de Velde, C J H, & Liefers, G. J. (2018). Decrease in 30-day and one-year mortality over time in patients aged >/=75 years with stage I-III colon cancer: A population-based study. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 44(12), 1889-1893. doi: S0748-7983(18)31284-8

Brouwer, N. P. M., Heil, T. C., Olde Rikkert, M G M, Lemmens, V E P P, Rutten, H. J. T., de Wilt, J H W, et al. (2019). The gap in postoperative outcome between older and younger patients with stage I-III colorectal cancer has been bridged: results from the Netherlands cancer registry. European Journal of Cancer, 116, 1-9. doi: S0959-8049(19)30295-3

Carpelan-Holmstrom, M., Louhimo, J., Stenman, U. H., Alfthan, H., Jarvinen, H., & Haglund, C. (2004). CEA, CA 242, CA 19-9, CA 72-4 and hCGbeta in the diagnosis of recurrent colorectal cancer. Tumour Biology, 25(5-6), 228-234. doi:81385

Cederholm, T., Bosaeus, I., Barazzoni, R., Bauer, J., Van Gossum, A., Klek, S., et al. (2015). Diagnostic criteria for malnutrition-a ESPEN consensus statement. Clinical Nutrition (Edinburgh, Scotland), 34(3), 335-340. doi: 10.1016/j.clnu.2015.03.001

Cederholm, T., Barazzoni, R., Austin, P., Ballmer, P., Biolo, G., Bischoff, S. C., et al. (2017). ESPEN guidelines on definitions and terminology of clinical nutrition. Clinical Nutrition (Edinburgh, Scotland), 36(1), 49-64. doi: S0261-5614(16)31242-0 [pii]

Cereda, E., Pedrolli, C., Klersy, C., Bonardi, C., Quarleri, L., Cappello, S., et al. (2016). Nutritional status in older persons according to healthcare setting: A systematic review and meta-analysis of prevalence data using MNA((R)). Clinical Nutrition (Edinburgh, Scotland), 35(6), 1282-1290. doi: S0261-5614(16)00099-6

Chang, C., Yin, W., Wei, C., Wu, C., Su, Y., Yu, C., et al. (2016). Adjusted age-adjusted Charlson comorbidity index score as a risk measure of perioperative mortality before cancer surgery. PloS One, 11(2), e0148076.

Chapman, S. J., Pericleous, A., Downey, C., & Jayne, D. G. (2018). Postoperative ileus following major colorectal surgery. The British Journal of Surgery, 105(7), 797-810. doi:10.1002/bjs.10781

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases, 40(5), 373-383. doi:10.1016/0021-9681(87)90171-8

Chiarello, M., M., Fransvea, P., Cariati, M., Adams, N., J., et al. (2022). Anastomotic leakage in colorectal cancer surgery. Surg Oncol, 40;101708. doi: 10.1016/j.suronc.2022.101708. Epub 2022 Jan 24.

Chung, K. C., Lee, K. C., Chen, H. H., Cheng, K. C., Wu, K. L., & Song, L. C. (2021). Differential short-term outcomes of laparoscopic resection in colon and rectal cancer patients aged 80 and older: An analysis of nationwide inpatient sample. Surgical Endoscopy, 35(2), 872-883. doi:10.1007/s00464-020-07459-x

Claassen, Y., Bastiaannet, E., van Eycken, E., Van Damme, N., Martling, A., Johansson, R., et al. (2019). Time trends of short-term mortality for octogenarians undergoing a colorectal resection in north Europe. European Journal of Surgical Oncology, 45(8), 1396-1402.

Clegg, A., Young, J., Iliffe, S., Rikkert, M. O., & Rockwood, K. (2013). Frailty in elderly people. Lancet (London, England), 381(9868), 752-762. doi:10.1016/S0140-6736(12)62167-9

Collin, Å., Jung, B., Nilsson, E., Påhlman, L., Folkesson, J. (2014). Impact of mechanical bowel preparation on survival after colonic cancer resection. Br J Surg, 101. 1594-1600.

Colon Cancer Laparoscopic or Open Resection Study Group, Buunen, M., Veldkamp, R., Hop, W. C., Kuhry, E., Jeekel, J., et al. (2009). Survival after laparoscopic surgery versus open surgery for colon cancer: Long-term outcome of a randomised clinical trial. The Lancet Oncology, 10(1), 44-52. doi:10.1016/S1470-2045(08)70310-3

Croner, R.S., Ptok; H, Merkel., S., Hohenberger., W. (2018). Implementing complete mesocolic excision for colon cancer- mission completed? Innov Surg Sci, 3(1), 17-29. doi: 10.1515/iss-2017-0042

Cruz-Jentoft, A. J., Bahat, G., Bauer, J., Boirie, Y., Bruyere, O., Cederholm, T., et al. (2019). Sarcopenia: Revised European consensus on definition and diagnosis. Age and Ageing, 48(1), 16-31. doi:10.1093/ageing/afy169

Cuk, P., Kjaer, M. D., Mogensen, C. B., Nielsen, M. F., Pedersen, A. K., & Ellebaek, M. B. (2022). Short-term outcomes in robot-assisted compared to laparoscopic colon cancer resections: A systematic review and meta-analysis. Surgical Endoscopy, 36(1), 32-46. doi:10.1007/s00464-021-08782-7

De Hert, S., Staender, S., Fritsch, G., Hinkelbein, J., Afshari, A., Bettelli, G., et al. (2018). Pre-operative evaluation of adults undergoing elective noncardiac surgery:

Updated guideline from the European society of anaesthesiology. European Journal of Anaesthesiology, 35(6), 407-465. doi:10.1097/EJA. 0000000000000817

De Roo, A. C., Li, Y., Abrahamse, P. H., Regenbogen, S. E., & Suwanabol, P. A. (2020). Long-term functional decline after high-risk elective colorectal surgery in older adults. Diseases of the Colon and Rectum, 63(1), 75-83. doi: 10.1097/DCR.0000000000001541

Decoster, L., Van Puyvelde, K., Mohile, S., Wedding, U., Basso, U., Colloca, G., et al. (2015). Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: An update on SIOG recommendationsdagger. Annals of Oncology: Official Journal of the European Society for Medical Oncology, 26(2), 288-300. doi:10.1093/annonc/mdu210

Deijen, C.L, Vasmel, J.E., de Lange-de Klerk, E.S.M., Cuesta, M.A., Coene, P.L.O., et al. (2017). Ten-year outcomes of randomised trial of laparoscopic versus open surgery for colon cancer. Surg Endosc, 31(6), 2607-2615. doi: 10.1007/s00464-016-5270-6.

Dekker, J. W. T., van den Broek, Colette BM, Bastiaannet, E., van de Geest, Lydia GM, Tollenaar, R. A., & Liefers, G. (2011). Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. Annals of Surgical Oncology, 18(6), 1533-1539.

Dekker, J. W., Gooiker, G. A., van der Geest, L G, Kolfschoten, N. E., Struikmans, H., Putter, H., et al. (2012). Use of different comorbidity scores for risk-adjustment in the evaluation of quality of colorectal cancer surgery: Does it matter? European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 38(11), 1071-1078. doi: 10.1016/j.ejso.2012.04.017

Denet, C., Fuks, D., Cocco, F., Chopinet, S., Abbas, M., et al. (2017). Effects of age after laparoscopic right colectomy for cancer: Are there any specific outcomes? Dig Liver Dis, 49(5):562-567. doi: 10.1016/j.dld.2016.12.014.

DeSantis, C. E., Miller, K. D., Dale, W., Mohile, S. G., Cohen, H. J., Leach, C. R., et al. (2019). Cancer statistics for adults aged 85 years and older, 2019. CA: A Cancer Journal for Clinicians, 69(6), 452-467. doi:10.3322/caac.21577

Devereaux, P. J., & Sessler, D. I. (2015). Cardiac complications in patients undergoing major noncardiac surgery. The New England Journal of Medicine, 373(23), 2258-2269. doi:10.1056/NEJMra1502824

Dindo, D., Demartines, N., & Clavien, P. (2004). Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of Surgery, 240(2), 205.

Duffy, M. J., Lamerz, R., Haglund, C., Nicolini, A., Kalousova, M., Holubec, L., et al. (2014). Tumor markers in colorectal cancer, gastric cancer and gastrointestinal stromal cancers: European group on tumor markers 2014 guidelines update. International Journal of Cancer, 134(11), 2513-2522. doi:10.1002/ijc.28384

Duraes, L. C., Stocchi, L., Dietz, D., Kalady, M. F., Kessler, H., Schroeder, D., et al. (2016). The disproportionate effect of perioperative complications on mortality within 1 year after colorectal cancer resection in octogenarians. Annals of Surgical Oncology, 23(13), 4293-4301.

Eamer, G, Taheri, A., Chen, S. S., Daviduck, Q., Chambers, T., Shi, X., & Khadaroo, R. G. (2018). Comprehensive geriatric assessment for older people admitted to a surgical service. Cochrane Database of Systematic Reviews, 1, CD012485. doi: 10.1002/14651858.CD012485.pub2

Ehrlich, A., Wagner, B., Kairaluoma, M., Mecklin, J. P., Kautiainen, H., & Kellokumpu, I. (2014). Evaluation of a fast-track protocol for patients undergoing colorectal surgery. Scandinavian Journal of Surgery: SJS: Official Organ for the Finnish Surgical Society and the Scandinavian Surgical Society, 103(3), 182-188. doi:1457496913516295

Ehrlich, A., Kairaluoma, M., Bohm, J., Vasala, K., Kautiainen, H., & Kellokumpu, I. (2016). Laparoscopic wide mesocolic excision and central vascular ligation for carcinoma of the colon. Scandinavian Journal of Surgery: SJS: Official Organ for the Finnish Surgical Society and the Scandinavian Surgical Society, 105(4), 228-234. doi:10.1177/1457496915613646

Emoto, S., Nozawa, H., Kawai, K., Hata, K., Tanaka, T., et al. (2019). Venous thromboembolism in colorectal surgery: Incidence, risk factors, and prophylaxis. Asian Journal of Surgery, 42(9), 863-873. doi: S1015-9584(18)30805-4

ESMO Guidelines Committee. (2019). eUpdate-Early Colon Cancer Treatment Recommendations.https://www.esmo.org/guidelines/gastrointestinal-cancers/localised-colon-cancer/eupdate-early-colon-cancer-treatment-recommendations. Accessed 25 Feb 2022.

Fagard, K., Leonard, S., Deschodt, M., Devriendt, E., Wolthuis, A., Prenen, H., et al. (2016). The impact of frailty on postoperative outcomes in individuals aged 65 and over undergoing elective surgery for colorectal cancer: A systematic review. Journal of Geriatric Oncology, 7(6), 479-491. doi: S1879-4068(16)30058-3

Fearon, K. C., Ljungqvist, O., Von Meyenfeldt, M., Revhaug, A., Dejong, C. H., Lassen, K., et al. (2005). Enhanced recovery after surgery: A consensus review of clinical care for patients undergoing colonic resection. Clinical Nutrition (Edinburgh, Scotland), 24(3), 466-477. doi: S0261-5614(05)00023-3

Finlayson, E., Zhao, S., Boscardin, W. J., Fries, B. E., Landefeld, C. S., & Dudley, R. A. (2012). Functional status after colon cancer surgery in elderly nursing home residents. Journal of the American Geriatrics Society, 60(5), 967-973. doi:10.1111/j.1532-5415.2012. 03915.x

Finnish Cancer Registry. https://cancerregistry.fi /statistics/cancer-statistics. Accessed 25 Feb 2022.

Finnish Institute for Health and Welfare. https://thl.fi/en/web/thlfi-en/statistics-and-data. Accessed 25 Feb 2022.

Finnish Ministry of Social Affairs and Health. https://valtioneuvosto.fi/ paatokset/paatos? decision. Id=0900908f8074049d. Accessed 25 Feb 2022.

Fowler, H., Belot, A., Ellis, L., Maringe, C., Luque-Fernandez, M. A., Njagi, E. N., et al. (2020). Comorbidity prevalence among cancer patients: A population-based cohort study of four cancers. BMC Cancer, 20(1), 2-9. doi:10.1186/s12885-019-6472-9

Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. The Journal of Gerontology. Series A, Biological Sciences and Medical Sciences, 59(3), 255-263. doi:10.1093/gerona/59.3.m255

Fried, T. R., Bradley, E. H., Towle, V. R., & Allore, H. (2002). Understanding the treatment preferences of seriously ill patients. The New England Journal of Medicine, 346(14), 1061-1066. doi:10.1056/NEJMsa012528

Galon, J., Mlecnik, B., Bindea, G., Angell, H. K., Berger, A., Lagorce, C., et al. (2014). Towards the introduction of the 'immunoscore' in the classification of malignant tumours. The Journal of Pathology, 232(2), 199-209. doi:10.1002/path.4287

Gearhart, S. L., Do, E. M., Owodunni, O., Gabre-Kidan, A. A., & Magnuson, T. (2020). Loss of independence in older patients after operation for colorectal cancer. Journal of the American College of Surgeons, 230(4), 573-582. doi: S1072-7515(20)30106-X

Gessler, B., Eriksson, O., & Angenete, E. (2017). Diagnosis, treatment, and consequences of anastomotic leakage in colorectal surgery. International Journal of Colorectal Disease, 32(4), 549-556. doi:10.1007/s00384-016-2744-x

Ghignone, F., Hernandez, P., Mahmoud, N. N., & Ugolini, G. (2020). Functional recovery in senior adults undergoing surgery for colorectal cancer: Assessment tools and strategies to preserve functional status. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 46(3), 387-393. doi: S0748-7983(20)30003-2

Giannotti, C., Sambuceti, S., Signori, A., Ballestrero, A., Murialdo, R., Romairone, E., et al. (2019). Frailty assessment in elective gastrointestinal oncogeriatric surgery: Predictors of one-year mortality and functional status. Journal of Geriatric Oncology, 10(5), 716-723. doi: S1879-4068(18)30344-8

Gill, T. M., Gahbauer, E. A., Han, L., & Allore, H. G. (2010). Trajectories of disability in the last year of life. The New England Journal of Medicine, 362(13), 1173-1180. doi:10.1056/NEJMoa0909087

GlobalSurg & The NIHR Global Health Research Unit on Global Surgery. https://globalsurg.org. Accessed 15 Dec 2021.

Gooiker, G. A., Dekker, J. W. T., Bastiaannet, E., van der Geest, Lydia GM, Merkus, J. W., van de Velde, Cornelis JH, et al. (2012). Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. Annals of Surgical Oncology, 19(8), 2428-2434.

Goldvaser, H., Katz Shroitman, N., Ben-Aharon, I., Purim, O., Kundel, Y., et al. (2017). Octogenarian patients with colorectal cancer. Characterizing an emerging clinical entity. World J Gastroenterol, 28;23(8):1387-1396. doi: 10.3748/wjg. v23.i8.1387.

Govaert, J. A., Fiocco, M., van Dijk, W. A., Scheffer, A. C., de Graaf, E. J., Tollenaar, R. A., et al. (2015). Costs of complications after colorectal cancer surgery in the Netherlands: Building the business case for hospitals. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 41(8), 1059-1067. doi: 10.1016/j.ejso.2015.03.236

Greco, M., Capretti, G., Beretta, L., Gemma, M., Pecorelli, N., & Braga, M. (2014). Enhanced recovery program in colorectal surgery: A meta-analysis of randomized controlled trials. World Journal of Surgery, 38(6), 1531-1541. doi: 10.1007/s00268-013-2416-8

Griffiths, R., Beech, F., Brown, A., Dhesi, J., Foo, I., Goodall, J., et al. (2014). Peri-operative care of the elderly 2014: Association of Anaesthetists of Great Britain and Ireland. Anaesthesia, 69 Suppl 1, 81-98. doi:10.1111/anae.12524

Gronkjär, M., Eliasen, M., Skov-Ettrup, L. S., Tolstrup, J. S., Christiansen, A. H., Mikkelsen, S. S., et al. (2014). Preoperative smoking status and postoperative complications: A systematic review and meta-analysis. Annals of Surgery, 259(1), 52-71. doi:10.1097/SLA.0b013e3182911913

Guenaga, K. F., Lustosa, S. A., Saad, S. S., Saconato, H., & Matos, D. (2007). Ileostomy or colostomy for temporary decompression of colorectal anastomosis. The Cochrane Database of Systematic Reviews, (1): CD004647. doi(1), CD004647. doi: 10.1002/14651858.CD004647.pub2

Guenaga, K. F., Matos D., & Wille-Jorgensen P. (2011). Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev. (9): CD001544. doi: 10.1002/14651858.CD001544.pub4.

Gupta, S. K., & Lamont, E. B. (2004). Patterns of presentation, diagnosis, and treatment in older patients with colon cancer and comorbid dementia. Journal of the American Geriatrics Society, 52(10), 1681-1687. doi:10.1111/j.1532-5415.2004.52461.x

Gurunathan, U., Ramsay, S., Mitric, G., Way, M., Wockner, L., & Myles, P. (2017). Association between obesity and wound infection following colorectal surgery: Systematic review and meta-analysis. Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract, 21(10), 1700-1712. doi:10.1007/s11605-017-3494-y

Gustafsson, U. O., Scott, M. J., Hubner, M., Nygren, J., Demartines, N., Francis, N., et al. (2019). Guidelines for perioperative care in elective colorectal surgery: Enhanced recovery after surgery (ERAS ((R))) society recommendations: 2018. World Journal of Surgery, 43(3), 659-695. doi:10.1007/s00268-018-4844-y

Hamaker, M. E., Prins, M. C., Schiphorst, A. H., van Tuyl, S. A., Pronk, A., & van den Bos, F. (2015). Long-term changes in physical capacity after colorectal cancer treatment. Journal of Geriatric Oncology, 6(2), 153-164. doi: 10.1016/j.jgo.2014.10.001

Hamaker, M. E., Te Molder, M., Thielen, N., van Munster, B. C., Schiphorst, A. H., van Huis, L.H. (2018). The effect of a geriatric evaluation on treatment decisions and outcome for older cancer patients - A systematic review. J Geriatr Oncol, 9(5):430-440. doi: 10.1016/j.jgo.2018.03.014.

Hamel, M. B., Henderson, W. G., Khuri, S. F., & Daley, J. (2005). Surgical outcomes for patients aged 80 and older: Morbidity and mortality from major noncardiac surgery. Journal of the American Geriatrics Society, 53(3), 424-429. doi: JGS53159

Handforth, C., Clegg, A., Young, C., Simpkins, S., Seymour, M. T., Selby, P. J., et al. (2015). The prevalence and outcomes of frailty in older cancer patients: A systematic review. Annals of Oncology: Official Journal of the European Society for Medical Oncology, 26(6), 1091-1101. doi: S0923-7534(19)31789-2

Haskins, I. N., Baginsky, M., Amdur, R. L., & Agarwal, S. (2017). Preoperative hypoalbuminemia is associated with worse outcomes in colon cancer patients. Clinical Nutrition (Edinburgh, Scotland), 36(5), 1333-1338. doi: S0261-5614(16)30222-9

Heald, R. J., Husband, E. M., & Ryall, R. D. (1982). The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? The British Journal of Surgery, 69(10), 613-616. doi:10.1002/bjs.1800691019

Henneman, D., Ten Berge, M. G., Snijders, H. S., van Leersum, N. J., Fiocco, M., Wiggers, T., et al. (2014). Safety of elective colorectal cancer surgery: Non-surgical complications and colectomies are targets for quality improvement. Journal of Surgical Oncology, 109(6), 567-573. doi:10.1002/jso.23532

Hewitt, J., Long, S., Carter, B., Bach, S., McCarthy, K., & Clegg, A. (2018). The prevalence of frailty and its association with clinical outcomes in general surgery: A systematic review and meta-analysis. Age and Ageing, 47(6), 793-800. doi:10.1093/ageing/afy110

Hinoi, T., Kawaguchi, Y., Hattori, M., Okajima, M., Ohdan, H., et al. (2015). Laparoscopic versus open surgery for colorectal cancer in elderly patients: a multicenter matched case-control study. Ann Surg Oncol, 22(6):2040-50. doi: 10.1245/s10434-014-4172-x.

Hirano, Y., Hiranuma, C., Hattori, M., Douden, K., Yamaguchi, S. (2020). Single-port laparoscopic colectomy in elderly patients with colon cancer: A propensity score-matched comparison with younger patients. Asian J Endosc Surg, 13(2):175-179. doi: 10.1111/ases.12719.

Hohenberger W., Reingruber B., Merkel S. (2003). Surgery for colon cancer. Scand J Surg, 92, 45-52.

Hohenberger, W., Weber, K., Matzel, K., Papadopoulos, T., & Merkel, S. (2009). Standardized surgery for colonic cancer: Complete mesocolic excision and central ligation--technical notes and outcome. Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland, 11(4), 354-5. doi:10.1111/j.1463-1318.2008. 01735.x

Holleczek, B., Rossi, S., Domenic, A., Innos, K., Minicozzi, P., Francisci, S., et al. (2015). On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999–2007–results from the EUROCARE-5 study. European Journal of Cancer, 51(15), 2158-2168.

Hollis, R. H., & Kennedy, G. D. (2020). Postoperative complications after colorectal surgery: Where are we in the era of enhanced recovery? Current Gastroenterology Reports, 22(6), 26-5. doi:10.1007/s11894-020-00763-5

Holubar, S. D., Hedrick, T., Gupta, R., Kellum, J., Hamilton, M., Gan, T. J., et al. (2017). American society for enhanced recovery (ASER) and perioperative quality initiative (POQI) joint consensus statement on prevention of postoperative infection within an enhanced recovery pathway for elective colorectal surgery. Perioperative Medicine (London, England), 6, 4-2. eCollection 2017. doi:10.1186/s13741-017-0059-2

Hoogendijk, E O, Afilalo, J., Ensrud, K. E., Kowal, P., Onder, G., & Fried, L. P. (2019). Frailty: implications for clinical practice and public health. The Lancet (British Edition), 394(10206), 1365-1375. doi:10.1016/s0140-6736(19)31786-6

Holte K., Nielsen K.G., Madsen J.L., et al. (2004). Physiologic effects of bowel preparation. Dis Colon Rectum, 47:1397-402.

Hu, W. H., Eisenstein, S., Parry, L., & Ramamoorthy, S. (2019). Preoperative malnutrition with mild hypoalbuminemia associated with postoperative mortality

and morbidity of colorectal cancer: A propensity score matching study. Nutrition Journal, 18(1), 33-y. doi :10.1186/s12937-019-0458-y
Huisman, M. G., Veronese, G., Audisio, R. A., Ugolini, G., Montroni, I., de Bock, G. H., et al. (2016). Poor nutritional status is associated with other geriatric domain impairments and adverse postoperative outcomes in onco-geriatric surgical patients - A multicentre cohort study. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 42(7), 1009-1017. doi: 10.1016/ j. ejso.2016.03.005
Huisman, M. G., Kok, M., de Bock, G. H., & van Leeuwen, B. L. (2017). Delivering tailored surgery to older cancer patients: Preoperative geriatric assessment domains and screening tools - A systematic review of systematic reviews. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 43(1), 1-14. doi: S0748-7983(16)30197-4
Hunter, C., Blake, H., Jeyadevan, N., Abulafi, M., Swift, I., Toomey, P., et al. (2016). Local staging and assessment of colon cancer with 1.5-T magnetic resonance imaging. The British Journal of Radiology, 89(1064), 20160257. doi:10.1259/ bjr.20160257
Issa, N., Grassi, C., Melki, Y., Powsner, E., Dreznik, Z. (2011). Laparoscopic colectomy for carcinoma of the colon in octogenarians. J Gastrointest Surg, 15(11):2011-5. doi: 10.1007/s11605-011-1671-y.
Itatani, Y., Kawada, K., & Sakai, Y. (2018). Treatment of elderly patients with colorectal cancer. BioMed Research International, 2018, 2176056. doi:10.1155/2018/ 2176056
Jacobs, M., Verdeja, J. C., & Goldstein, H. S. (1991). Minimally invasive colon resection (laparoscopic colectomy). Surgical Laparoscopy & Endoscopy, 1(3), 144-150.
Jafari, M. D., Jafari, F., Halabi, W. J., Nguyen, V. Q., Pigazzi, A., Carmichael, J. C., et al. (2014). Colorectal cancer resections in the aging US population: A trend toward decreasing rates and improved outcomes. JAMA Surgery, 149(6), 557-564.
Jamieson, J. K., & Dobson, J. F. (1909). VII. Lymphatics of the colon: With special reference to the operative treatment of cancer of the colon. Annals of Surgery, 50(6), 1077-1090. doi:10.1097/00000658-190912000-00007
Jass, J. R. (2007). Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. Histopathology, 50(1), 113-130. doi: HIS2549
Jin, Z., Hu, J., & Ma, D. (2020). Postoperative delirium: Perioperative assessment, risk reduction, and management. British Journal of Anaesthesia, 125(4), 492-504. doi: S0007-0912(20)30566-3
Kang, C. Y., Chaudhry, O. O., Halabi, W. J., Nguyen, V., Carmichael, J. C., Mills, S., et al. (2012). Risk factors for postoperative urinary tract infection and urinary retention in patients undergoing surgery for colorectal cancer. The American Surgeon, 78(10), 1100-1104.
Kannan, U., Reddy, V. S., Mukerji, A. N., Parithivel, V. S., Shah, A. K., Gilchrist, B. F., et al. (2015). Laparoscopic vs open partial colectomy in elderly patients: Insights from the American College of Surgeons - national surgical quality improvement program database. World Journal of Gastroenterology, 21(45), 12843-12850. doi:10.3748/wjg. v21.i45.12843

Kapoor, P., Chen, L., Saripella, A., Waseem, R., Nagappa, M., et al. (2022). Prevalence of preoperative cognitive impairment in older surgical patients. A systematic review and meta-analysis. J Clin Anesth, 76:110574. doi: 10.1016/ j.jclinane. 2021.110574.

Keeler, E., Guralnik, J. M., Tian, H., Wallace, R. B., & Reuben, D. B. (2010). The impact of functional status on life expectancy in older persons. The Journal of Gerontology. Series A, Biological Sciences and Medical Sciences, 65(7), 727-733. doi:10.1093/gerona/glq029

Kehlet, H., & Wilmore, D. W. (2008). Evidence-based surgical care and the evolution of fast-track surgery. Annals of Surgery, 248(2), 189-198. doi: 10.1097/ SLA.0b013e31817f2c1a

Ketelaers, S. H. J., Fahim, M., Rutten, H. J. T., Smits, A. B., & Orsini, R. G. (2020). When and how should surgery be performed in senior colorectal cancer patients? European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 46(3), 326-332. doi: S0748-7983(20)30007-X

Ketelaers, S. H. J., Orsini, R. G., Burger, J. W. A., Nieuwenhuijzen, G. A. P., & Rutten, H. J. T. (2019). Significant improvement in postoperative and 1-year mortality after colorectal cancer surgery in recent years. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 45(11), 2052-2058. doi: S0748-7983(19)30511-6

Kirchhoff, P., Clavien, P. A., & Hahnloser, D. (2010). Complications in colorectal surgery: Risk factors and preventive strategies. Patient Safety in Surgery, 4(1), 5-5. doi:10.1186/1754-9493-4-5

Kolarsick, P. A., Sacchi, M., Spinelli, A., & Wexner, S. D. (2020). Minimizing the impact of colorectal surgery in the older patient: The role of minimally invasive surgery in the geriatric population. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 46(3), 333-337. doi: S0748-7983(19)31513-6

Koller, S. E., Bauer, K. W., Egleston, B. L., Smith, R., Philp, M. M., Ross, H. M., et al. (2018). Comparative effectiveness and risks of bowel preparation before elective colorectal surgery. Annals of Surgery, 267(4), 734-742. doi:10.1097/SLA.0000000000002159

Kong, J. C., Prabhakaran, S., Choy, K. T., Larach, J. T., Heriot, A., & Warrier, S. K. (2021). Oncological reasons for performing a complete mesocolic excision: A systematic review and meta-analysis. ANZ Journal of Surgery, doi:10.1111/ans.16518

Konishi, T., Shimada, Y., Hsu, M., Tufts, L., Jimenez-Rodriguez, R., Cercek, A., et al. (2018). Association of preoperative and postoperative serum carcinoembryonic antigen and colon cancer outcome. JAMA Oncology, 4(3), 309-315. doi:10.1001/jamaoncol.2017.4420

Kontovounisios, C., Kinross, J., Tan, E., Brown, G., Rasheed, S., & Tekkis, P. (2015). Complete mesocolic excision in colorectal cancer: A systematic review. Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland, 17(1), 7-16. doi:10.1111/codi.12793

Korc-Grodzicki, B., Downey, R. J., Shahrokni, A., Kingham, T. P., Patel, S. G., & Audisio, R. A. (2014). Surgical considerations in older adults with cancer. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 32(24), 2647-2653. doi:10.1200/JCO.2014.55.0962

Koskenvuo, L., Lehtonen, T., Koskensalo, S., Rasilainen, S., Klintrup, K., Ehrlich, A., et al. (2019). Mechanical and oral antibiotic bowel preparation versus no bowel preparation for elective colectomy (MOBILE): A multicentre, randomised, parallel, single-blinded trial. Lancet (London, England), 394(10201), 840-848. doi: S0140-6736(19)31269-3

Kube, R., Mroczkowski, P., Granowski, D., Benedix, F., Sahm, M., Schmidt, U., et al. (2010). Anastomotic leakage after colon cancer surgery: A predictor of significant morbidity and hospital mortality, and diminished tumour-free survival. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 36(2), 120-124. doi: 10.1016/j.ejso.2009.08.011

Laurie, J. A., Moertel, C. G., Fleming, T. R., Wieand, H. S., Rubin, J., et al. (1989). Surgical adjuvant therapy of large-bowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil. The North Central Cancer Treatment Group and the Mayo Clinic. J Clin Oncol, 7(10), 1447–1456.

Lauby-Secretan, B., Vilahur, N., Bianchini, F., Guha, N., Straif, K., & International Agency for Research on Cancer Handbook Working Group. (2018). The IARC perspective on colorectal cancer screening. The New England Journal of Medicine, 378(18), 1734-1740. doi:10.1056/NEJMsr1714643

Lawrence, V. A., Hazuda, H. P., Cornell, J. E., Pederson, T., Bradshaw, P. T., Mulrow, C. D., et al. (2004). Functional independence after major abdominal surgery in the elderly. Journal of the American College of Surgeons, 199(5), 762-772. doi: S1072-7515(04)00922-6

Lee, G. H., Malietzis, G., Askari, A., Bernardo, D., Al-Hassi, H. O., & Clark, S. K. (2015). Is right-sided colon cancer different to left-sided colorectal cancer? - a systematic review. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 41(3), 300-308. doi: 10.1016/j.ejso.2014.11.001

Lee, L., Trang, T., Mayo, N., E., Carli, F., Feldman, L., S. (2014). What does it really mean to "recover" from an operation? Surgery, 155 (2), 211-216.

Lee, S. H., & Lim, S. W. (2020). Risk factors for postoperative delirium after colorectal surgery: A systematic review and meta-analysis. International Journal of Colorectal Disease, 35(3), 433-444. doi:10.1007/s00384-019-03498-6

Lee, Y., McKechnie, T., Springer, J. E., Doumouras, A. G., Hong, D., & Eskicioglu, C. (2019). Optimal timing of urinary catheter removal following pelvic colorectal surgery: A systematic review and meta-analysis. International Journal of Colorectal Disease, 34(12), 2011-2021. doi:10.1007/s00384-019-03404-0

Leeuwen, BL.; Påhlman, L., Gunnarson, U., Sjövall, A., Martling, A. (2008). 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, 67(3):229-36. doi: 10.1016/j.critrevonc.2008.03.005.

Lemmens, V. E., Janssen-Heijnen, M. L., Houterman, S., Verheij, K. D., Martijn, H., van de Poll-Franse, L., et al. (2007). Which comorbid conditions predict complications after surgery for colorectal cancer? World Journal of Surgery, 31(1), 192-199. doi:10.1007/s00268-005-0711-8

Lewis-Lloyd, C. A., Pettitt, E. M., Adiamah, A., Crooks, C. J., & Humes, D. J. (2021). Risk of postoperative venous thromboembolism after surgery for colorectal malignancy: A systematic review and meta-analysis. Diseases of the Colon and Rectum, 64(4), 484-496. doi:10.1097/DCR.0000000000001946

Li, L. T., Mills, W. L., White, D. L., Li, A., Gutierrez, A. M., Berger, D. H., et al. (2013). Causes and prevalence of unplanned readmissions after colorectal surgery: A systematic review and meta-analysis. Journal of the American Geriatrics Society, 61(7), 1175-1181. doi:10.1111/jgs.12307

Li, Y. S., Meng, F.C., Lin. J. K. (2020). Procedural and post-operative complications associated with laparoscopic versus open abdominal surgery for right-sided colonic cancer resection: A systematic review and meta-analysis. Medicine (Baltimore), 2; 99(40): e22431. doi: 10.1097/MD.0000000000022431.

Lin, H. S., Watts, J. N., Peel, N. M., & Hubbard, R. E. (2016). Frailty and post-operative outcomes in older surgical patients: A systematic review. BMC Geriatrics, 16(1), 157-8. doi:10.1186/s12877-016-0329-8

Liu, Z., Xu, G., Xu, L., Zhang, Y., & Huang, Y. (2020). Perioperative cardiac complications in patients over 80 years of age with coronary artery disease undergoing noncardiac surgery: The incidence and risk factors. Clinical Interventions in Aging, 15, 1181-1191. doi:10.2147/CIA.S252160

Ljungqvist, O., Scott, M., & Fearon, K. C. (2017). Enhanced recovery after surgery: A review. JAMA Surgery, 152(3), 292-298. doi:10.1001/jamasurg.2016.4952

Lobo, D. N., Gianotti, L., Adiamah, A., Barazzoni, R., Deutz, N. E. P., et al. (2020). Perioperative nutrition: Recommendations from the ESPEN expert group. Clin Nutr, 39(11):3211-3227. doi: 10.1016/j.clnu.2020.03.038.

Looijaard, S M L M, Slee-Valentijn, M. S., Otten, R. H. J., & Maier, A. B. (2018). Physical and nutritional prehabilitation in older patients with colorectal carcinoma: A systematic review. Journal of Geriatric Physical Therapy, 41(4), 236-244. doi:10.1519/JPT.0000000000000125

Lopez-Otin, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2013). The hallmarks of aging. Cell, 153(6), 1194-1217. doi: 10.1016/j.cell.2013.05.039

Lorenzon, L., La Torre, M., Ziparo, V., Montebelli, F., Mercantini, P., Balducci, G., et al. (2014). Evidence based medicine and surgical approaches for colon cancer: Evidence, benefits and limitations of the laparoscopic vs open resection. World Journal of Gastroenterology, 20(13), 3680-3692. doi:10.3748/wjg. v20.i13.3680

Loughrey, M. B., Quirke, P., & Shepherd, N. A. (2018). Standards and datasets for reporting cancers: Dataset for histopathological reporting of colorectal cancer. The Royal College of Pathologists Website. https://www.Rcpath.Org/Profession/Publications/Cancer-Datasets. Accessed 15 Dec 2021.

Luther, A., Gabriel, J., Watson, R. P., & Francis, N. K. (2018). The impact of total body prehabilitation on post-operative outcomes after major abdominal surgery: A systematic review. World Journal of Surgery, 42(9), 2781-2791. doi:10.1007/s00268-018-4569-y

Lynch, H. T., & de la Chapelle, A. (2003). Hereditary colorectal cancer. The New England Journal of Medicine, 348(10), 919-932. doi:10.1056/NEJMra012242 [doi]

Malietzis, G., Aziz, O., Bagnall, N.M., Johns, N., Fearon, K.C. (2015). The role of body composition evaluation by computerized tomography in determining colorectal cancer treatment outcomes: A systematic review. Eur J Surg Oncol, 41(2):186-96. doi: 10.1016/j.ejso.2014.10.056.

Marmol, I., Sanchez-de-Diego, C., Pradilla Dieste, A., Cerrada, E., & Rodriguez Yoldi, M. J. (2017). Colorectal carcinoma: A general overview and future perspectives in colorectal cancer. International Journal of Molecular Sciences, 18(1), 10.3390/ijms18010197. doi: E197

Matar, C. F., Kahale, L. A., Hakoum, M. B., Tsolakian, I. G., Etxeandia-Ikobaltzeta, I., Yosuico, V. E., et al. (2018). Anticoagulation for perioperative thromboprophylaxis in people with cancer. The Cochrane Database of Systematic Reviews, 7, CD009447. doi: 10.1002/14651858. CD009447.pub3

Mayer, B., Sander, S., Paschke, S., Henne-Bruns, D., Link, K. H., Kornmann, M., et al. (2015). Stratified survival analysis after adjuvant chemotherapy of colon cancer reveals a benefit for older patients. Anticancer Research, 35(10), 5587-5593. doi:35/10/5587

Mazzarella, G., Muttillo, E. M., Picardi, B., Rossi, S., & Muttillo, I. A. (2021). Complete mesocolic excision and D3 lymphadenectomy with central vascular ligation in right-sided colon cancer: A systematic review of postoperative outcomes, tumour recurrence and overall survival. Surgical Endoscopy, doi: 10.1007/s00464-021-08529-4

McDermott, F. D., Heeney, A., Kelly, M. E., Steele, R. J., Carlson, G. L., & Winter, D. C. (2015). Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. The British Journal of Surgery, 102(5), 462-479. doi:10.1002/bjs.9697

McSorley, S. T., Horgan, P. G., & McMillan, D. C. (2016). The impact of the type and severity of postoperative complications on long-term outcomes following surgery for colorectal cancer: A systematic review and meta-analysis. Critical Reviews in Oncology/Hematology, 97, 168-177. doi: 10.1016/j.critrevonc.2015.08.013

McSorley, S.T., Steele, C.W., McMahon, A.J. (2018). Meta-analysis of oral antibiotics, in combination with preoperative intravenous antibiotics and mechanical bowel preparation the day before surgery, compared with intravenous antibiotics and mechanical bowel preparation alone to reduce surgical-site infections in elective colorectal surgery. BJS Open, 10;2(4):185–194. doi: 10.1002/bjs5.68.

Mecklin, J. P., Aarnio, M., Laara, E., Kairaluoma, M. V., Pylvanainen, K., Peltomaki, P., et al. (2007). Development of colorectal tumors in colonoscopic surveillance in lynch syndrome. Gastroenterology, 133(4), 1093-1098. doi: S0016-5085(07)01476-X

Merkel, S., Weber, K., Matzel, K. E., Agaimy, A., Göhl, J., & Hohenberger, W. (2016). Prognosis of patients with colonic carcinoma before, during and after implementation of complete mesocolic excision. British Journal of Surgery, 103(9), 1220-1229.

Millan, M., & Renau-Escrig, A. I. (2020). Minimizing the impact of colorectal surgery in the older patient: The role of enhanced recovery programs in older patients. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 46(3), 338-343. doi: S0748-7983(19)31511-2

Miskovic, A., & Lumb, A. B. (2017). Postoperative pulmonary complications. British Journal of Anaesthesia, 118(3), 317-334. doi:10.1093/bja/aex002

Mohanty, S., Rosenthal, R. A., Russell, M. M., Neuman, M. D., Ko, C. Y., & Esnaola, N. F. (2016). Optimal perioperative management of the geriatric patient: A best practices guideline from the American College of Surgeons NSQIP and the American Geriatrics Society. Journal of the American College of Surgeons, 222(5), 930-947. doi: 10.1016/j.jamcollsurg.2015.12.026

Montroni, I., Rostoft, S., Spinelli, A., Van Leeuwen, B. L., Ercolani, G., Saur, N. M., et al. (2020). GOSAFE - geriatric oncology surgical assessment and functional rEcovery after surgery: Early analysis on 977 patients. Journal of Geriatric Oncology, 11(2), 244-255. doi: S1879-4068(19)30168-7

Morley, J, Vellas, B., van Kan, G., Anker, S., Bauer, J., Bernabei, R., Walston, J. (2013). Frailty consensus: a call to action. Journal of the American Medical Directors Association, 14(6), 392-397. doi://dx.doi.org/10.1016/j.jamda.2013.03.022

Mothes, H., Bauschke, A., Schuele, S., Eigendorff, E., Altendorf-Hofmann, A., & Settmacher, U. (2017). Surgery for colorectal cancer in elderly patients: How can we improve outcome? Journal of Cancer Research and Clinical Oncology, 143(9), 1879-1889.

Mäkelä, J. T., Klintrup, K. H., & Rautio, T. T. (2017). Mortality and survival after surgical treatment of colorectal cancer in patients aged over 80 years. Gastrointestinal Tumours, 4(1-2), 36-44.

National Guidelines for Colorectal Cancer Treatment in Finland. https://www.terveysportti.fi/apps/ltk/article/hsu00007. Accessed 2 Mar 2022.

Needham, M. J., Webb, C. E., & Bryden, D. C. (2017). Postoperative cognitive dysfunction and dementia: What we need to know and do. British Journal of Anaesthesia, 119(suppl_1), i115-i125. doi:10.1093/bja/aex354

Negoi, I., Hostiuc, S., Negoi, R. I., & Beuran, M. (2017). Laparoscopic vs open complete mesocolic excision with central vascular ligation for colon cancer: A systematic review and meta-analysis. World Journal of Gastrointestinal Oncology, 9(12), 475-491. doi:10.4251/wjgo. v9.i12.475

Neuman, H. B., O'Connor, E. S., Weiss, J., Loconte, N. K., Greenblatt, D. Y., Greenberg, C. C., et al. (2013). Surgical treatment of colon cancer in patients aged 80 years and older: Analysis of 31,574 patients in the SEER-medicare database. Cancer, 119(3), 639-647. doi:10.1002/cncr.27765

NICE guidelines for colon cancer. (2020). https://pathways.nice.org.uk/pathways/colorectal-cancer. Accessed 15 Dec 2021.

Oh, B. Y., Huh, J. W., Kim, H. C., Park, Y. A., Cho, Y. B., Yun, S. H., et al. (2018). Oncologic outcome of colorectal cancer patients over age 80: A propensity score-matched analysis. International Journal of Colorectal Disease, 33(8), 1011-1018.

Olen, O., Erichsen, R., Sachs, M. C., Pedersen, L., Halfvarson, J., Askling, J., et al. (2020). Colorectal cancer in ulcerative colitis: A Scandinavian population-based cohort study. Lancet (London, England), 395(10218), 123-131. doi: S0140-6736(19)32545-0

Orange, S. T., Northgraves, M. J., Marshall, P., Madden, L. A., & Vince, R. V. (2018). Exercise prehabilitation in elective intra-cavity surgery: A role within the ERAS pathway? A narrative review. International Journal of Surgery (London, England), 56, 328-333. doi: S1743-9191(18)30741-6

Ow, Z. G. W., Sim, W., Nistala, K. R. Y., Ng, C. H., Koh, F. H., Wong, N. W., et al. (2020). Comparing complete mesocolic excision versus conventional colectomy for colon cancer: A systematic review and meta-analysis. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, doi: S0748-7983(20)30778-2

Owens, W.D., Felts J.A., Spitznagel E.L. Jr. (1978) ASA Physical Status Classifications: A Study of Consistency of Ratings. Anesthesiology, 49:239-43.

Paillaud, E., Liuu, E., Laurent, M., Le Thuaut, A., Vincent, H., Raynaud-Simon, A., et al. (2014). Geriatric syndromes increased the nutritional risk in elderly cancer patients independently from tumour site and metastatic status. The ELCAPA-05 cohort study. Clinical Nutrition (Edinburgh, Scotland), 33(2), 330-335. doi: 10.1016/j.clnu.2013.05.014

Papageorge, C. M., Zhao, Q., Foley, E. F., Harms, B. A., Heise, C. P., Carchman, E. H., et al. (2016). Short-term outcomes of minimally invasive versus open colectomy for colon cancer. The Journal of Surgical Research, 204(1), 83-93. doi: 10.1016/j.jss.2016.04.020

Papamichael, D., Audisio, R. A., Glimelius, B., de Gramont, A., Glynne-Jones, R., Haller, D., et al. (2015). Treatment of colorectal cancer in older patients: International society of geriatric oncology (SIOG) consensus recommendations 2013. Annals of Oncology: Official Journal of the European Society for Medical Oncology, 26(3), 463-476. doi:10.1093/annonc/mdu253

Paredes S, Cortinez L, Contreras V, Silbert B. (2016). Post-operative cognitive dysfunction at 3 months in adults after non-cardiac surgery: a qualitative systematic review. Acta Anaesthesiol Scand, 60(8):1043–58. doi: 10 1111/aas.12 724.

Partridge, J. S., Harari, D., & Dhesi, J. K. (2012). Frailty in the older surgical patient: A review. Age and Ageing, 41(2), 142-147. doi:10.1093/ageing/afr182 [doi]

Partridge, J. S., Harari, D., Martin, F. C., Peacock, J. L., Bell, R., Mohammed, A., et al. (2017). Randomized clinical trial of comprehensive geriatric assessment and optimization in vascular surgery. The British Journal of Surgery, 104(6), 679-687. doi:10.1002/bjs.10459

Peters, U., Bien, S., & Zubair, N. (2015). Genetic architecture of colorectal cancer. Gut, 64(10), 1623-1636. doi:10.1136/gutjnl-2013-306705

Phipps, A. I., Alwers, E., Harrison, T., Banbury, B., Brenner, H., Campbell, P. T., et al. (2020). Association between molecular subtypes of colorectal tumours and patient survival, based on pooled analysis of 7 international studies. Gastroenterology, 158(8), 2158-2168.e4. doi: S0016-5085(20)30240-7

Pillay, B., Wootten, A. C., Crowe, H., Corcoran, N., Tran, B., Bowden, P., et al. (2016). The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings: A systematic review of the literature. Cancer Treatment Reviews, 42, 56-72. doi: 10.1016/j.ctrv.2015.11.007

Quintana, J. M., Anton-Ladislao, A., Gonzalez, N., Lazaro, S., Bare, M., Fernandez-de-Larrea, N., et al. (2018). Predictors of one- and two-years' mortality in patients with colon cancer: A prospective cohort study. PloS One, 13(6), e0199894. doi: 10.1371/journal.pone.0199894

Quintana, J. M., Anton-Ladislao, A., Lázaro, S., Gonzalez, N., Bare, M., et al. (2020). Predictors of readmission and reoperation in patients with colorectal cancer. Support Care Cancer, 28(5):2339-2350. doi: 10.1007/s00520-019-05050-2.

Quiroga-Centeno, A. C., Jerez-Torra, K. A., Martin-Mojica, P. A., Castaneda-Alfonso, S. A., Castillo-Sanchez, M. E., Calvo-Corredor, O. F., et al. (2020). Risk factors for prolonged postoperative ileus in colorectal surgery: A systematic review and meta-analysis. World Journal of Surgery, 44(5), 1612-1626. doi:10.1007/s00268-019-05366-4

Reif de Paula, T., Simon, H. L., Profeta da Luz, M M, & Keller, D. S. (2021). Right sided colorectal cancer increases with age and screening should be tailored to reflect this: A national cancer database study. Techniques in Coloproctology, 25(1), 81-89. doi:10.1007/s10151-020-02329-z

Richards, S. J. G., Frizelle, F. A., Geddes, J. A., Eglinton, T. W., Hampton, M. B. (2018). Frailty in surgical patients. Int J Colorectal Dis, 33(12):1657-1666. doi: 10.1007/s00384-018-3163-y.

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D. B., McDowell, I., et al. (2005). A global clinical measure of fitness and frailty in elderly people. Canadian Medical Association Journal, 173(5), 489-495. doi :173/5/489

Romagnoli, S., Ricci, Z., & Ronco, C. (2018). Perioperative acute kidney injury: Prevention, early recognition, and supportive measures. Nephron, 140(2), 105-110. doi:10.1159/000490500

Ronning, B., Wyller, T. B., Jordhoy, M. S., Nesbakken, A., Bakka, A., Seljeflot, I., et al. (2014). Frailty indicators and functional status in older patients after colorectal cancer surgery. Journal of Geriatric Oncology, 5(1), 26-32. doi: 10.1016/j.jgo.2013.08.001

Roscio, F., Boni, L., Clerici, F., Frattini, P., Cassinotti, E., Scandroglio, I. (2016). Is laparoscopic surgery really effective for the treatment of colon and rectal cancer in very elderly over 80 years old? A prospective multicentric case-control assessment. Surg Endosc, 30(10):4372-82. doi: 10.1007/s00464-016-4755-7.

Rossi, B. W. P., Labib, P., Ewers, E., Leong, S., Coleman, M., Smolarek, S. (2020). Long-term results after elective laparoscopic surgery for colorectal cancer in octogenarians. Surg Endosc, 34(1):170-176. doi: 10.1007/s00464-019-06747-5.

Rostoft, S., van den Bos, F., Pedersen, R., & Hamaker, M. E. (2020). Shared decision-making in older patients with cancer - what does the patient want? Journal of Geriatric Oncology, doi: S1879-4068(20)30400-8

Roth, A. D., Delorenzi, M., Tejpar, S., Yan, P., Klingbiel, D., et al. (2012). Integrated analysis of molecular and clinical prognostic factors in stage II/III colon cancer. J Natl Cancer Inst, 104(21):1635-46. doi: 10.1093/jnci/djs427.

Rubenstein, L. Z., Harker, J. O., Salva, A., Guigoz, Y., & Vellas, B. (2001). Screening for undernutrition in geriatric practice: Developing the short-form mini-nutritional assessment (MNA-SF). The Journals of Gerontology.Series A, Biological Sciences and Medical Sciences, 56(6), 366. doi:10.1093/gerona/56.6.m366

Salusjarvi, J. M., Carpelan-Holmstrom, M. A., Louhimo, J. M., Kruuna, O., & Scheinin, T. M. (2018). Intraoperative colonic pulse oximetry in left-sided colorectal surgery: Can it predict anastomotic leak? International Journal of Colorectal Disease, 33(3), 333-336. doi:10.1007/s00384-018-2963-4

Sandini, M., Pinotti, E., Persico, I., Picone, D., Bellelli, G., & Gianotti, L. (2017). Systematic review and meta-analysis of frailty as a predictor of morbidity and mortality after major abdominal surgery. BJS Open, 1(5), 128-137. doi:10.1002/bjs5.22 [doi]

Sankar, A., Johnson, S. R., Beattie, W. S., Tait, G., & Wijeysundera, D. N. (2014). Reliability of the American society of anaesthesiologists physical status scale in clinical practice. British Journal of Anaesthesia, 113(3), 424-432. doi:10.1093/bja/aeu100

Sarfati, D., Koczwara, B., & Jackson, C. (2016). The impact of comorbidity on cancer and its treatment. CA: A Cancer Journal for Clinicians, 66(4), 337-350. doi:10.3322/caac.21342

Saur, N. M., Montroni, I., Shahrokni, A., Kunitake, H., Potenti, F. M., Goodacre, R. C., et al. (2020). Care of the geriatric colorectal surgical patient and framework for creating a geriatric program: A compendium from the 2019 American society of colon and rectal surgeons' annual meeting. Diseases of the Colon and Rectum, 63(11), 1489-1495. doi:10.1097/DCR.0000000000001793

Schiphorst, A. H., Verweij, N. M., Pronk, A., Borel Rinkes, I. H., & Hamaker, M. E. (2015). Non-surgical complications after laparoscopic and open surgery for colorectal cancer - A systematic review of randomised controlled trials. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 41(9), 1118-1127. doi: 10.1016/j.ejso.2015.04.007

Scholtz, A.F.M., Oldroyd, C., McCarthy, K., Quinn, T. J., Hewitt, J. (2016). Systematic review and meta-analysis of risk factors for postoperative delirium among older patients undergoing gastrointestinal surgery. Br J Surg, 103(2), e21-8.doi: 10.1002/bjs.10062.

Sciuto, A., Merola, G., De Palma, G. D., Sodo, M., Pirozzi, F., Bracale, U. M., et al. (2018). Predictive factors for anastomotic leakage after laparoscopic colorectal surgery. World Journal of Gastroenterology, 24(21), 2247-2260. doi:10.3748/wjg. v24.i21.2247

Scott, K.W., Grace, R. H. (1989). Detection of lymph node metastases in colorectal carcinoma before and after fat clearance. Br J Surg, 76(11), 1165-1167.

Seishima, R., Okabayashi, K., Hasegawa, H., Tsuruta, M., Shigeta, K., Matsui, S., et al. (2015). Is laparoscopic colorectal surgery beneficial for elderly patients? A systematic review and meta-analysis. Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract, 19(4), 756-765. doi:10.1007/s11605-015-2748-9

Sellers, D., Srinivas, C., & Djaiani, G. (2018). Cardiovascular complications after non-cardiac surgery. Anaesthesia, 73 Suppl 1, 34–42. doi:10.1111/anae.14138

Seppala, T. T., Bohm, J. P., Friman, M., Lahtinen, L., Vayrynen, V. M., Liipo, T. K., et al. (2015). Combination of microsatellite instability and BRAF mutation status for subtyping colorectal cancer. British Journal of Cancer, 112(12), 1966-1975. doi:10.1038/bjc.2015.160 Ar

Sharma, M., Loh, K. P., Nightingale, G., Mohile, S. G., Holmes, H. M. (2016). Polypharmacy and potentially inappropriate medication use in geriatric oncology. J Geriatr Oncol, 7(5):346-53. doi: 10.1016/j.jgo.2016.07.010.

Sheka, A. C., Tevis, S., & Kennedy, G. D. (2016). Urinary tract infection after surgery for colorectal malignancy: Risk factors and complications. American Journal of Surgery, 211(1), 31-39. doi: 10.1016/j.amjsurg.2015.06.006

Sheridan, J., Walsh, P., Kevans, D., Cooney, T., O'Hanlon, S., Nolan, B., et al. (2014). Determinants of short-and long-term survival from colorectal cancer in very elderly patients. Journal of Geriatric Oncology, 5(4), 376-383.

Siegel, R. L., Miller, K. D., Goding Sauer, A., Fedewa, S. A., Butterly, L. F., Anderson, J. C., et al. (2020). Colorectal cancer statistics, 2020. CA: A Cancer Journal for Clinicians, 70(3), 145-164. doi:10.3322/caac.21601

Sikder, T., Sourial, N., Maimon, G., Tahiri, M., Teasdale, D., et al. (2019). Postoperative Recovery in Frail, Pre-frail, and Non-frail Elderly Patients Following Abdominal Surgery. World J Surg, 43(2):415-424. doi: 10.1007/s00268-018-4801-9.

Sluijter, C. E., van Lonkhuijzen, L. R., van Slooten, H. J., Nagtegaal, I. D., & Overbeek, L. I. (2016). The effects of implementing synoptic pathology reporting in cancer diagnosis: A systematic review. Virchows Archiv: An International Journal of Pathology, 468(6), 639-649. doi:10.1007/s00428-016-1935-8

Sobin, L. H., Gospodarowicz, M. K., & Wittekind, C. (2009). TNM classification of malignant tumours John Wiley & Sons.

Sogaard, M., Thomsen, R. W., Bossen, K. S., Sorensen, H. T., & Norgaard, M. (2013). The impact of comorbidity on cancer survival: A review. Clinical Epidemiology, 5 (Suppl 1), 3-29. doi:10.2147/CLEP.S47150

Soubeyran, P., Bellera, C., Goyard, J., Heitz, D., Curé, H., et al. (2014). Screening for vulnerability in older cancer patients: the ONCODAGE Prospective Multicenter Cohort Study. PLoS One, 9(12): e115060. doi: 10.1371/journal.pone.0115060.

Sorensen, J., Kondrup, J., Prokopowicz, J., Schiesser, M., Krahenbuhl, L., Meier, R., et al. (2008). EuroOOPS: An international, multicentre study to implement nutritional risk screening and evaluate clinical outcome. Clinical Nutrition (Edinburgh, Scotland), 27(3), 340-349. doi: 10.1016/j.clnu.2008.03.012

Souwer, E. T. D., Bastiaannet, E., Steyerberg, E. W., Dekker, J. T., van den Bos, F., & Portielje, J. E. A. (2020). Risk prediction models for postoperative outcomes of colorectal cancer surgery in the older population - a systematic review. Journal of Geriatric Oncology, 11(8), 1217-1228. doi: S1879-4068(19)30412-6

Spada, C., Hassan, C., Bellini, D., Burling, D., Cappello, G., Carretero, C., et al. (2020). Imaging alternatives to colonoscopy: CT colonography and colon capsule. European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) guideline - update 2020. European Radiology, doi: 10.1007/s00330-020-07413-4

STARSurg Collaborative. (2016). Multicentre prospective cohort study of body mass index and postoperative complications following gastrointestinal surgery. The British Journal of Surgery, 103(9), 1157-1172. doi:10.1002/bjs.10203

Statistics Finland. https://www.stat.fi. Accessed 25 Feb 2022.

Stein, P. D., Beemath, A., Meyers, F. A., Skaf, E., Sanchez, J., & Olson, R. E. (2006). Incidence of venous thromboembolism in patients hospitalized with cancer. The American Journal of Medicine, 119(1), 60-68. doi: S0002-9343(05)00564-4

Stormark, K., Soreide, K., Soreide, J. A., Kvaloy, J. T., Pfeffer, F., Eriksen, M. T., et al. (2016). Nationwide implementation of laparoscopic surgery for colon cancer: Short-term outcomes and long-term survival in a population-based cohort. Surgical Endoscopy, 30(11), 4853-4864. doi:10.1007/s00464-016-4819-8

Stormark, K., Krarup, P.M., Sjövall, A., Søreide, K., Kvaløy, J.T., et al. (2020). Anastomotic leak after surgery for colon cancer and effect on long-term survival. Colorectal Dis, 22(9), 1108-1118. doi: 10.1111/codi.14999.

Su, H., Ruan, J., Chen, T., Lin, E., & Shi, L. (2019). CT-assessed sarcopenia is a predictive factor for both long-term and short-term outcomes in gastrointestinal oncology patients: A systematic review and meta-analysis. Cancer Imaging: The Official

Publication of the International Cancer Imaging Society, 19(1), 82-0. doi:10.1186/s40644-019-0270-0

Sueda, T., Tei, M., Nishida, K., Yoshikawa, Y., Matsumura, T., et al. (2021). Evaluation of short- and long-term outcomes following laparoscopic surgery for colorectal cancer in elderly patients over 80 years old: a propensity score-matched analysis. Int J Colorectal Dis, 36(2):365-375. doi: 10.1007/s00384-020-03770-0.

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, doi:10.3322/caac.21660

Sutton, E., Miyagaki, H., Bellini, G., Shantha Kumara, H. M., Yan, X., Howe, B., et al. (2017). Risk factors for superficial surgical site infection after elective rectal cancer resection: A multivariate analysis of 8880 patients from the American College of Surgeons national surgical quality improvement program database. The Journal of Surgical Research, 207, 205-214. doi: S0022-4804(16)30356-0

Söderback, H., Gunnarsson, U., Martling, A., Hellman, P., & Sandblom, G. (2019). Incidence of wound dehiscence after colorectal cancer surgery: Results from a national population-based register for colorectal cancer. International Journal of Colorectal Disease, 34(10), 1757-1762. doi:10.1007/s00384-019-03390-3

Takakura, Y., Ikeda, S., Imaoka, Y., Urushihara, T., & Itamoto, T. (2015). An elevated preoperative serum carbohydrate antigen 19-9 level is a significant predictor for peritoneal dissemination and poor survival in colorectal cancer. Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland, 17(5), 417-425. doi:10.1111/codi.12865

Tan, K. K., Koh, F. H., Tan, Y. Y., Liu, J. Z., Sim, R. (2012). Long-term outcome following surgery for colorectal cancers in octogenarians: a single institution's experience of 204 patients. J Gastrointest Surg, 16(5):1029-36. doi: 10.1007/s11605-011-1818-x.

Taylor, J. C., Iversen, L. H., Burke, D., Finan, P. J., Howell, S., Pedersen, L., et al. (2021). Influence of age on surgical treatment and postoperative outcomes of patients with colorectal cancer in Denmark and Yorkshire, England. Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland, doi:10.1111/codi.15910

Theophilus, M., Platell, C., & Spilsbury, K. (2014). Long-term survival following laparoscopic and open colectomy for colon cancer: A meta-analysis of randomized controlled trials. Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland, 16(3), 75. doi:10.1111/codi.12483

Thong, M. S. Y., Jansen, L., Chang-Claude, J., Hoffmeister, M., Brenner, H., & Arndt, V. (2020). Association of laparoscopic colectomy versus open colectomy on the long-term health-related quality of life of colon cancer survivors. Surgical Endoscopy, 34(12), 5593-5603. doi:10.1007/s00464-019-07360-2

Trejo-Avila, M., Bozada-Gutierrez, K., Valenzuela-Salazar, C., Herrera-Esquivel, J., & Moreno-Portillo, M. (2021). Sarcopenia predicts worse postoperative outcomes and decreased survival rates in patients with colorectal cancer: A systematic review and meta-analysis. International Journal of Colorectal Disease, 36(6), 1077-1096. doi: 10.1007/s00384-021-03839-4

Tsujinaka, S., Kawamura, Y. J., Tan, K. Y., Mizokami, K., Sasaki, J., Maeda, T., et al. (2012). Proximal bowel necrosis after high ligation of the inferior mesenteric artery in colorectal surgery. Scandinavian Journal of Surgery: SJS: Official Organ for the Finnish Surgical Society and the Scandinavian Surgical Society, 101(1), 21-25. doi:10.1177/145749691210100105

Tudyka, V., Blomqvist, L., Beets-Tan, R. G., Boelens, P. G., Valentini, V., van de Velde, C J, et al. (2014). EURECCA consensus conference highlights about colon & rectal cancer multidisciplinary management: The radiology experts review. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 40(4), 469-475. doi: 10.1016/j.ejso.2013.10.029

Ueda, Y., Shiraishi, N., Kawasaki, T., Akagi, T., Ninomiya, S., et al. (2020). Short- and long-term outcomes of laparoscopic surgery for colorectal surgery in elderly aged over 80 years versus non-elderly: a retrospective cohort study. BMC Geriatr, 20(1):445. doi: 10.1186/s12877-020-01779-2.

Utsumi, M., Matsuda, T., Yamashita, K., Hasegawa, H., Agawa, K., et al. (2021) Short- and long-term outcomes after laparoscopic surgery for elderly patients with colorectal cancer aged over 80 years: a propensity score matching analysis. Int J Colorectal Dis, 36(11):2519-2528. doi: 10.1007/s00384-021-03973-z.

UICC (2017). TNM classification of malignant tumour, 8th edition. John Wiley & Sons Ltd, UK.

Vallribera Valls, F., Landi, F., Espín Basany, E., Sánchez García, J. L., Jiménez Gómez, L. M., Martí Gallostra, M. (2014). Laparoscopy-assisted versus open colectomy for treatment of colon cancer in the elderly: morbidity and mortality outcomes in 545 patients. Surg Endosc, 28(12):3373-8. doi: 10.1007/s00464-014-3597-4.

van de Velde, C J, Boelens, P. G., Borras, J. M., Coebergh, J. W., Cervantes, A., Blomqvist, L., et al. (2014). EURECCA colorectal: Multidisciplinary management: European consensus conference colon & rectum. European Journal of Cancer (Oxford, England: 1990), 50(1), 1.e1-1. e34. doi: 10.1016/j.ejca.2013.06.048

van der Geest, L G, Lam-Boer, J., Koopman, M., Verhoef, C., Elferink, M. A., & de Wilt, J. H. (2015). Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. Clinical & Experimental Metastasis, 32(5), 457-465. doi:10.1007/s10585-015-9719-0

van der Sijp, M P, Bastiaannet, E., Mesker, W. E., van der Geest, L G, Breugom, A. J., Steup, W. H., et al. (2016). Differences between colon and rectal cancer in complications, short-term survival and recurrences. International Journal of Colorectal Disease, 31(10), 1683-1691. doi:10.1007/s00384-016-2633-3

van der Sluis, F. J., Buisman, P. L., Meerdink, M., Aan de Stegge, W. B., van Etten, B., et al. (2017). Risk factors for postoperative delirium after colorectal operation. Surgery, 161(3):704-711. doi: 10.1016/j.surg.2016.09.010.

van Zutphen, M., Winkels, R. M., van Duijnhoven, F. J., van Harten-Gerritsen, S. A., Kok., D. E., van Duijvendijk, P., et al. (2017). An increase in physical activity after colorectal cancer surgery is associated with improved recovery of physical functioning: A prospective cohort study. BMC Cancer, 17(1), 74-2. doi:10.1186/s12885-017-3066-2

Vermeer, N. C. A., Claassen, Y. H. M., Derks, M. G. M., Iversen, L. H., van Eycken, E., Guren, M. G., et al. (2018). Treatment and survival of patients with colon cancer aged 80 years and older: A EURECCA international comparison. The Oncologist, 23(8), 982-990. doi: 10.1634 / theoncologist.2017-0551

Wasef, S., Laksono, I., Kapoor, P., Tang-Wei, D., Gold, D., et al. (2021). Screening for subjective cognitive decline in the elderly via subjective cognitive complaints and informant-reported questionnaires: a systematic review. BMC Anesthesiol, 21(1):277. doi: 10.1186/s12871-021-01493-5.

Watt, J., Tricco, A. C., Talbot-Hamon, C., Pham, B., Rios, P., Grudniewicz, A., et al. (2018). Identifying older adults at risk of harm following elective surgery: A systematic review and meta-analysis. BMC Medicine, 16(1), 2-2. doi:10.1186/s12916-017-0986-2

Weerink, L. B., Gant, C. M., van Leeuwen, B. L., de Bock, G. H., Kouwenhoven, E. A., & Faneyte, I. F. (2018). Long-term survival in octogenarians after surgical treatment for colorectal cancer: Prevention of postoperative complications is key. Annals of Surgical Oncology, 25(13), 3874-3882.

Weimann, A., Braga, M., Carli, F., Higashiguchi, T., Hubner, M., Klek, S., et al. (2017). ESPEN guideline: Clinical nutrition in surgery. Clinical Nutrition (Edinburgh, Scotland), 36(3), 623-650. doi: S0261-5614(17)30063-8

Welch, H. G., & Robertson, D. J. (2016). Colorectal cancer on the decline--why screening can't explain it all. The New England Journal of Medicine, 374(17), 1605-1607. doi:10.1056/NEJMp1600448

Welsh, T. J., Gordon, A. L., & Gladman, J. R. (2014). Comprehensive geriatric assessment--a guide for the non-specialist. International Journal of Clinical Practice, 68(3), 290-293. doi:10.1111/ijcp.12313

West, N. P., Hohenberger, W., Weber, K., Perrakis, A., Finan, P. J., & Quirke, P. (2010). Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 28(2), 272-278. doi:10.1200/JCO.2009.24.1448

Wilmore, D. W. (2002). From Cuthbertson to fast-track surgery: 70 years of progress in reducing stress in surgical patients. Annals of Surgery, 236(5), 643-648. doi:10.1097/00000658-200211000-00015

Wolthuis, A. M., Bislenghi, G., Fieuws, S., de Buck van Overstraeten, A, Boeckxstaens, G., & D'Hoore, A. (2016). Incidence of prolonged postoperative ileus after colorectal surgery: A systematic review and meta-analysis. Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland, 18(1), 1. doi:10.1111/codi.13210

Xu, Z., Qu, H., Kanani, G., Guo, Z., Ren, Y., & Chen, X. (2020). Update on risk factors of surgical site infection in colorectal cancer: A systematic review and meta-analysis. International Journal of Colorectal Disease, 35(12), 2147-2156. doi:10.1007/s00384-020-03706-8

Zargar-Shoshtari, K., & Hill, A. G. (2009). Postoperative fatigue: A review. World Journal of Surgery, 33(4), 738-745. doi:10.1007/s00268-008-9906-0

Zhang, L. M., Hornor, M. A., Robinson, T., Rosenthal, R. A., Ko, C. Y., & Russell, M. M. (2020). Evaluation of postoperative functional health status decline among older adults. JAMA Surgery, 155(10), 950-958. doi:10.1001/jamasurg.2020.2853

APPENDICES

APPENDIX 1.

STUDY PROTOCOL

Surgical and functional outcomes and survival following colon cancer surgery in the aged: a study protocol for a prospective, observational multicentre study

Susanna Niemeläinen, Heini Huhtala, Anu Ehrlich, Jyrki Kössi, Esa Jämsen, Marja Hyöty

BMC Cancer. 2021 Jun 14; 21(1):698. doi: 10.1186/s12885-021-08454-8.

Niemeläinen et al. BMC Cancer (2021) 21:698
https://doi.org/10.1186/s12885-021-08454-8

BMC Cancer

STUDY PROTOCOL Open Access

Surgical and functional outcomes and survival following Colon Cancer surgery in the aged: a study protocol for a prospective, observational multicentre study

Susanna Niemeläinen[1*], Heini Huhtala[2], Anu Ehrlich[3], Jyrki Kössi[4], Esa Jämsen[5,6,7] and Marja Hyöty[1]

Abstract

Background: The number of colorectal cancer patients increases with age. The decision to go through major surgery can be challenging for the aged patient and the surgeon because of the heterogeneity within the older population. Differences in preoperative physical and cognitive status can affect postoperative outcomes and functional recovery, and impact on patients' quality of life.

Methods / design: A prospective, observational, multicentre study including nine hospitals to analyse the impact of colon cancer surgery on functional ability, short-term outcomes (complications and mortality), and their predictors in patients aged ≥80 years. The catchment area of the study hospitals is 3.88 million people, representing 70% of the population of Finland. The data will be gathered from patient baseline characteristics, surgical interventional data, and pre- and postoperative patient-questionnaires, to an electronic database (REDCap) especially dedicated to the study.

Discussion: This multicentre study provides information about colon cancer surgery's operative and functional outcomes on older patients. A further aim is to find prognostic factors which could help to predict adverse outcomes of surgery.

Trial registration: ClinicalTrials.gov (NCT03904121). Registered on 1 April 2019.

Keywords: Colon cancer, Surgery, Aged patients, Functional ability, short-term outcome

* Correspondence: susanna.niemelainen@pshp.fi
[1]Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tays Hatanpää, P.O. Box 2000, 33521 Tampere, Finland
Full list of author information is available at the end of the article

Introduction

Background and rationale

The proportion of older people is increasing rapidly in western countries. In Finland, the estimated portion of the population aged over 70 will increase from the current 15.8 to 20% in 2030 and 25% in 2070 [1]. As the incidence of colon cancer increases with age [1, 2], the number of colon cancer patients can also be expected to increase, although the incidence has not dramatically changed over the decades [2].

The primary recommended treatment for colon cancer is surgery [3], but the decision to go through a major operation can be challenging for both the aged patient and the surgeon. Therefore, age-related concerns may lead to undertreatment of older patients, who compose a heterogeneous group with vastly different physiological and cognitive performance status [4]. Many older patients may have significant comorbidities, poor nutritional, and functional status [5, 6], which have been associated with severe postoperative complications associated with reduced 30-day and 1-year survival after colon cancer surgery [7]. Careful assessment is therefore required to make individual treatment decisions [8].

Modern medical and operative developments, including perioperative anaesthesia care, surgical performance (laparoscopy, technical standardisation), enhanced recovery program (ERAS) and oncological treatments, have improved outcomes for aged colorectal cancer patients [9, 10]. The difference in short-term postoperative mortality between older and younger colorectal patients has reduced during the last decade [11]. Conversely, frailty, a state of diminished physiological reserve capacity [12], has been identified as a significant predictor of postoperative complications leading to a prolonged hospital stay, discharge to nursing homes or long-term care facilities, and higher mortality rates than for fit patients [13, 14]. Preoperative screening tests for evaluating malnutrition, functional performance status, anaesthesiologist risks, and the cumulative burden of comorbidities can help identify factors that increase the risks of postoperative adverse events. However, comprehensive geriatric evaluations are often time-consuming and demand resources, highlighting the need for easily implemented screening tools, which produce crucial and objective results [15].

Older patients commonly prioritise functional outcomes before survival after cancer surgery [16]. Recent studies from the Netherlands and Norway reported positive impacts on quality of life after surgery for aged patients with colorectal cancer [17, 18]. There is growing evidence that physical and mental prehabilitation strategies, together with innovative surgical and postoperative treatments, can enhance long-term outcomes, functional recovery, and quality of life after surgery [19, 20]. A recently published international multicentre prospective study, Geriatric Oncology Surgical Assessment and Functional rEcovery after Surgery (GOSAFE), showed that 68.4% of patients over 70 years experiencing cancer surgery are frail. Thus, frailty evaluation has an essential role in predicting postoperative morbidity and mortality correlating with quality of life and physical and cognitive functional recovery [21].

There is little prospectively collected published data about the influence of colorectal surgery on postoperative outcomes and functional recovery for very old patients. The consensus recommendations and studies are mainly made for patients over 70 years [4, 8, 21]. Patients over 80 years are seldom included in prospective clinical trials, so the optimal treatment of these patients remains unclear [22]. In Finland, the incidence of colon cancer patients over 80 years has increased from 183 to 216 per 100,000 in the past 20 years, and 28% of patients were aged 80 years or more in 2018 [23]. Thus, it is significant to have adequate and trustworthy information about colon cancer surgery and its effect on postoperative morbidity, functional recovery, and survival. Recognition of frailty is essential to reduce adverse outcomes. Preoperative real-life clinical data can provide objective and helpful measures to the surgeons planning interventions for aged patients [24]. These instruments should accurately predict surgery's adverse outcomes and be easy to implement, and thus able to guide comprehensive decision-making [25].

Objectives

This multicentre study aims to analyse the impact of colon cancer surgery on patients over 80 years, their functional ability, the occurrence of complications, and mortality during the first postoperative year and highlight predictors of these adverse outcomes. We also aim to investigate non-operatively treated patients' progress and subsequent functional ability and survival [26].

Methods

Study design and setting

The study is an observational, prospective, cohort, multicentre study of patients aged 80 years or older diagnosed with stage I-III colon cancer. The patients are treated either non-operatively or with curative resection or a palliative procedure. The participating hospitals are Helsinki University Hospital, Tampere University Hospital, Turku University Hospital, Central Finland Central Hospital, North Karelia Central Hospital, Päijät-Häme Central Hospital, Satakunta Central Hospital, South Ostrobothnia Central Hospital and Vaasa Central Hospital. The catchment area of the study hospitals is 3.88 million people (of whom 219,900 are aged 80 years or over), representing 70.4% of Finland's population [1].

The public health care system almost exclusively performs the treatment of malignant diseases in Finland. All citizens have equal access to health care independent of social or insurance status. These study hospitals represent majority of Finnish hospitals operating colon cancer patients. Hence, the study provides a nationwide spectrum of operative management of colon cancer on the aged population. The study is independent of any industrial sponsorships.

Participants

Patients aged 80 years or over with recently diagnosed stage I-III colon cancer will be assessed for suitability for inclusion. General practitioners or endoscopic units make most consultations of colon cancer patients, so the data includes only the patients referred to surgical units for operative treatment.

Eligibility criteria (Fig. 1)

Inclusion criteria

- Stage I-III colon cancer
- Age 80 years or older at the time of recruitment
- The study's information is approved and signed by the patient, or a legally authorised representative or family member if the patient's cognitive status has declined.

Exclusion criteria

- Metastatic cancer of any type at the time of diagnosis with no possibility of curative surgery
- Patient undergoing emergency operation for colon cancer
- The patient has an expected life expectancy of less than 6 months due to colon cancer or other reasons.

Primary intervention

All the patients have a preoperative colonoscopy, computed tomography, and presentation at a multidisciplinary team (MDT) meeting. They will undergo either radical surgery or a palliative procedure for the primary tumour, or nonoperative treatment according to hospital-standardised protocols for treatment and follow-up based on national EBM guidelines [27, 28]. The decision for definitive treatment choice is made collectively with the patient or, when needed, with a family member or legally authorised representative.

Outcomes

The study's primary outcomes are morbidity (surgical and non-surgical complications) and mortality, and their effect on functional recovery within 1 year after the primary surgical procedure, or after the date the decision for non-operative treatment is made. Postoperative

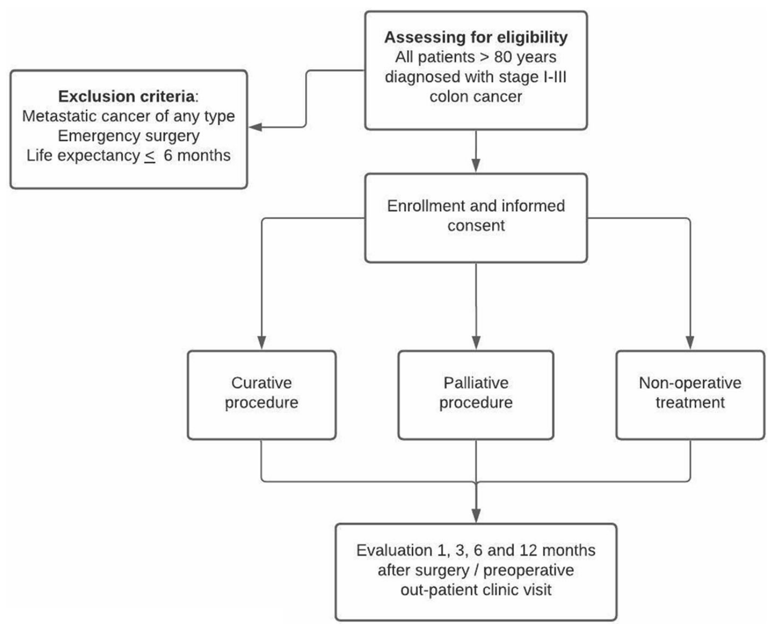

Fig. 1 Eligibility criteria

morbidity will be recorded during the hospital stay, and at 30 days and 90 days after surgery, recorded at the outpatient clinic. Postoperative morbidity (surgical and non-surgical) will be assessed according to the Clavien-Dindo (CD) classification [29]. Mild complications are graded as CD I-II and severe complications as CD III-V. It will be recorded if patients with non-operative treatment require readmission to the study hospital. Mortality will be recorded at 30 days, 90 days and 1 year after surgery, or after the date that the decision for non-operative treatment is made.

Secondary outcomes are reoperations, length of hospital stay, discharge destination, readmission rate, and recruited patient (nursing home admission, mobility, and self-related health status [30]).

Long-term outcomes concerning functional recovery and mortality will be collected analogously 3 and 5 years after the cancer treatment decision.

Tools for preoperative risk assessment

G-8: Onco-geriatric screening tool includes eight items modified from MNA-SF, age, number of medications and self-rated health status [31]. The G-8 score ranges from 0 to 17. Geriatric evaluation is recommended for patients whose score is ≤14 [32].

MNA-SF: Mini Nutritional Assessment-Short Form describes nutritional status as the normal, risk of malnutrition or malnourished. The score ranges from 0 to 14 and with cancer patients from 0 to 12. The risk of malnutrition is scored between 8 and 11 and malnourished patients between 0 and 7 [33].

CFS: Canadian Study on Health and Aging Clinical Frailty Scale, as assessed by the surgeon. The scale ranges from 1 to 9. Patients are described as frail with score ≥ 4 [34].

ASA: American Society of Anaesthesiologists physical status classification, which evaluates preoperative anaesthesiologist risk. The score ranges from 1 to 5. Categories are divided as 1 (a normal healthy patient), 2 (a patient with mild systemic disease, age > 65 years), 3 (a patient with severe systemic disease that is not incapacitating), 4 (a patient with an incapacitating systemic disease that is a constant threat to life), 5 (a dying patient who is not expected to survive for 24 h with or without operation) [35].

AA-CCI: Age-adjusted Charlson comorbidity index, which identifies cancer patients with increased risk of perioperative mortality. The scale ranges from 4 to 15; solid tumour excluded with two points, all patients 80 years or older contribute four points [36].

Other information

Table 1 shows the information that is collected in addition to the risk assessment tools. The study surgeons record each patient's baseline and data related to the surgery, perioperative hospitalisation, postoperative complications, and mortality. Patient-related questionnaires (Additional file 1) are collected before surgery, one, three, six and twelve months after surgery or the date non-operative treatment decision was made. The questionnaires will be collected either during the outpatient clinic visit, by telephone interview or by mail. All the information from the data mentioned above is recorded to the electronic database (REDCap) by the study surgeons. The dates and causes of death are obtained from the Death Certificate Register of Statistics Finland, which registers all deaths in Finland [37].

Recruitment

All patients aged 80 years or older who have been diagnosed with stage I-III colon carcinoma and are referred to participating hospitals to consider surgery are eligible for the study. Surgeons responsible for the treatment will inform the patients about the possible advantages and disadvantages of the intervention and the study protocol of patient-questionnaires during their visit to the outpatient clinic before the definitive treatment. The information and consent forms are specially designed for the study and include the surgeons responsible for recruitment at each study site. After properly informed consent is obtained, the patient is recruited to the study.

Non-operative treatment is chosen if the patient is deemed unfit to survive the operation due to anaesthesiologic, physiological or cognitive status. If necessary, an anaesthesiologist, cardiologist, the pulmonary or geriatric specialist is consulted in decision-making. Patients may also refuse surgery after receiving information about possible advantages and disadvantages of the procedure. The ultimate decision will be made collectively with the patient and, if possible, with relations.

Both non-operatively and operatively treated patients are included, and they are not randomised in any way.

Allocation

The study is an observational, prospective study without randomisation. All patients who voluntarily sign the consent form are included in the study. According to standardised protocols for treatment and follow-up, they will be treated at the study hospitals based on national EBM guidelines [27, 28]. The excluded patients are not followed up.

Questionnaires used in the study

The pre-and postoperative questionnaires are specially designed for the study and are all convergent. The questions survey living status, use of implements, outside personal aid, functional and cognitive ability, and nutrition utilising G-8, MNA-SF and CFS [31, 33, 34]. They

Table 1 Collected information

	Preoperative	Surgery	Hospital stay	1 month	3 months	6 months	12 months
PRE-AND POST-INTERVENTION DATA							
Age	x						
Sex	x						
Height and weight, BMI	x						
Medication	x			x	x	x	x
ASA classification	x						
Clinical Frailty Scale-index (CFS)	x						
Comorbidities (include diseases subsumed in modifield Charlson Comorbidity Index)	x						
Haemoglobin, creatine, estimated GFR, albumin	x						
History of smoking and alcohol-consumption	x			x	x	x	x
Other reported cancers excluding colon cancer	x						
Diagnostic procedures (colonoscopy, CT scan)	x						
Onco-geriatric screening tool (G-8)	x			x	x	x	x
Mini Nutritional Assessment- Short Form (MNA-SF)	x			x	x	x	x
Status of living	x			x	x	x	x
Mobility	x			x	x	x	x
Neuropsychological status	x			x	x	x	x
Weight loss and food intake	x			x	x	x	x
Self-related health status	x			x	x	x	x
Patient information and approval	x						
INTERVENTION DATA							
Date of operation		x					
Used surgical technique (laparoscopy, open, conversion)		x					
Curative or palliative operation		x					
Demand for stoma		x					
Operative time and blood lose		x					
POSTOPERATIVE DATA							
Surgical complications (anastomotic leakage, bleeding, ileus, wound dehiscence or infection, other) Clavien-Dindo classification		x	x	x	x		
Non-surgical complications (cardiovascular, pulmonary, urinary, delirium, other) Clavien-Dindo classification		x	x	x	x		
Reoperations			x	x	x		
Length of stay			x	x			
Place of discharge			x	x			
Readmissions			x	x	x		
Pathological report (TNM-status)				x			
Postoperative adjuvant treatment				x	x	x	
Recurrences (local and distant)				x	x	x	x
Date of death							

are collected before surgery and one, three, six and twelve months after surgery. The use of large font size (Calibri 16) aims to help these older people to answer the questions. The questionnaires are writing in Finnish or Swedish thus patients can use their native language.

The questionnaires (Additional file 1) are composed of following questions:

– status of living (home, nursing home, health centre wards)
– mobility (with or without implements, outside help)
– neuropsychological problems
– nutrition (food intake, weight-loss)
– self-rated health status in comparison with other people of the same age
– number of medications
– number of hospital admissions 6 months before the index surgery
– smoking habits and alcohol consumption
– living will (yes or no)

Participant timeline

Recruitment started in April 2019 at Tampere University Hospital. The data collected from the participants and follow-up timeline is presented in Table 1. Short-term outcomes, including discharge history and complications, will be monitored at discharge, 1 and 3 months after primary operation by the surgeon responsible for recruitment.

Sample size

The primary endpoints are the surgical and non-surgical postoperative complications and mortality. Previously published Finnish registry-based cohort studies on patients over 80 years with colorectal cancer reported complications rates 30–40% and severe complications 18–21%, respectively [7, 38]. In a large population-based cohort study with very old colorectal cancer patients, one-year mortality rates after surgery were 15–24% [39]. Frail patients had 2–3 times higher risk than non-frail patients of developing moderate to severe complications [14], leading to a disproportionately high risk of short-term mortality. A recently published study showed five times higher one-year mortality rate for patients with severe complications (8.6 vs 45%) [7].

Based on expected incidences of complications of 30% (fit patients) and 55% (frail patients), a sample size of 140 is needed to give 80% power to detect a significant difference between CFS 1–3 vs ≥ 4 groups, with two-sided type 1 error of 5%. Each group would comprise 70 patients. Additionally, with an estimated rate of one-year mortality of 10% (fit patients) and 25% (frail patients), we will need to study 113 frail subjects and 113 fit control subjects to be able to reject the null hypothesis that the failure rates for frail and fit subjects are equal with probability (power) 0.8. The type I error probability associated with this test of this null hypothesis is 0.05. We will use a continuity-corrected chi-squared statistic or Fisher's exact test to evaluate this null hypothesis.

The first patient was included in the study 17th of April 2019 and operated on 29th April 2019. The preliminary estimate is that the final data will be collected by the end of April 2021.

Data collection methods

Data management

An electronic database REDCap (https://www.project-redcap.org/) is used to gather the study data. REDCap is a secure web platform for building and managing online databases and surveys with online and offline data support. The main investigators have designed a dedicated version for this prospectively collected study data. All the surgeons responsible for the study at their hospital site receive a personal username and password for the electronic database to handle the data with confidentiality. Access to the whole database is limited to the main investigators in Tampere University Hospital and Tampere University.

All patients receive a study number, and the identification key is kept separately from the database on a username and password secured server at each study site. Data will be entered manually from paper case report forms (CRFs) into an electronic database (REDCap) protected by an automatic backup of server data and firewalls against external violation. All electronic case report forms (eCRFs) are handled with a particular study ID.

The occurrence of relevant protocol deviations such as metastatic disease, report of benign pathological tissue, or refusal to continue in the study will be determined and documented. Data verification and validation will be performed, and the results are analysed with code numbers not to identify the patient. When patient data and questionnaires have been coded, validated, and locked, a clean file will be declared.

Data collection

The principal investigator at each study site is responsible for the data collection and is reviewed by the main investigator. Each patient is asked to fill out patient-questionnaires at the time of inclusion, and at one, three, six and twelve months after surgery. If the patient cannot complete the questionnaire, a family member, legally authorised representative, or nurse in charge of the patient will complete the form. The principal investigators or research nurses of each study site are charged with ensuring that the patient questionnaires are completed.

Patients can resign from the study at any time during the study period, in this event data collected before resignation can be used in the analyses, following the last observation carried forward to practice.

Data monitoring

Instructions for data collection and storage have been provided to the surgeons responsible for recruitment at the study sites. The main investigator in Tampere University Hospital, who has full access to the full study register, will continuously monitor data. The other surgeons only have access to the patient register at their study site hospital. Technical and statistical monitoring, and advanced conduct with full access to the register, is given to the statistics expert from Tampere University.

Statistical methods

Percentages will be used to describe demographic data and the proportion of observed complications. The mean and standard deviation will be reported for age and the median and range for preoperative laboratory values and body mass index (BMI). Associations between the categorical variables are tested with the Chi-Square-test or the Fisher exact test, when appropriate. A uni- and multivariable analysis of the factors influencing morbidity and mortality will be carried out using binary logistic regression. All variables that were statistically significant in the univariate model are included in the multivariable model. Statistical analyses are performed using SPSS version 27.

Ethics and dissemination

Research ethic approval

The study adheres to the Declaration of Helsinki on medical research protocols and ethics. Each participating hospital applies for study permission from the institutional review boards at their unit. The Regional Ethics Committee has approved the study protocol of the Expert Responsibility area of Tampere University Hospital (reference approval number R19028).

Protocol amendments

Significant protocol modifications are communicated with the Regional Ethics Committee of the Expert Responsibility area of Tampere University Hospital by amendments. All changes are also registered at ClinicalTrials.gov (NCT03904121).

Confidentiality

Patient confidentiality will be strictly maintained. Patients will be assigned a study ID, and all data will be handled without a name or personal social security number. Access to patient records is limited to the study group and the investigator-delegated study coordinator.

Dissemination policy

According to an agreement with the internationally accepted guidelines for authorship (International Committee of Medical Journal Editors), the study group members who are actively planning, recruiting, analysing, or writing will be part of the writing committee. Results will be published in peer-reviewed scientific journals. Results will also be communicated through professional meetings and the media.

Discussion

With the increased life expectancy with the world population, the risk of developing colon cancer grows [2]. The decision to progress with invasive treatment can be challenging, as it should consider differences in preoperative physical and cognitive status that affect postoperative outcomes and functional recovery among the older population [19, 40]. Because of these differences, decision-making should not be based only on age. Instead, surgeons should evaluate the severity of comorbidities, functional and cognitive performance status to optimise a patient's preoperative condition. Preoperative risk assessments of postoperative outcomes, recognition of frailty, and identification of patients at greater risk of unfavourable treatment consequences, should be easy to implement.

This prospective, multicentre study will analyse colon cancer surgery's impact on patients over 80 years, a patient group that will increase markedly in the coming years [1, 23]. The main objectives are short-term outcomes during the first postoperative year and their influences on functional ability and survival. These short-term outcomes are relevant as older colon cancer patients' prognosis seems to be quite good (60% surviving at 5 years) if they avoid postoperative complications and survive the first postoperative year [41, 42].

Recent data from the GOSAFE study showed that 68.4% of patients were considered frail according to the G-8 score (≤14), and 36% had a cumulative burden of comorbidities (AA-CCI ≥7). In that study, 36.8% of patients were aged ≥80 years [21]. The present study will focus only on patients 80 years or older with potentially curable colon cancer. The very old express significant heterogeneity in physical and cognitive status, so we can expect frail patients with functional and cognitive impairment. In Finland, the life expectancy of an 80-year-old person is 8.3 years (male) and 10.2 years (female) [1], so it is essential to identify and evaluate prognostic factors, both favourable and adverse, which may predict how these patients recover from radical operative treatment. The collected data include readily available patient-related information about preoperative functional performance, preoperative examinations, the surgery, and the early postoperative course. Thereby, it allows analysis of patient- and surgery-related factors as predictors of early postoperative complications. Another advantage is that, unlike most previous studies, the study will also include non-operatively treated patients from the same hospitals, allowing evaluation of patient-selection and possible side-effects of non-operative treatment.

Although an observational study cannot answer whether the surgery is beneficial or not, performing a randomised trial in this patient group is not realistic. Instead, it is clinically more relevant to study outcomes in an observational setting with less selection bias and more relevance to real-life. This study's strengths include examining a representative cohort, independent of social or insurance status, treated at several secondary and tertiary care hospitals instead of single-centre analysis. The multicentre nature of this study also allows for the timely collection of the data. It is acknowledged that the tests used (e.g. G-8, Clinical Frailty Scale, MNA-SF, CCI) represent screening tests, and more thorough geriatric evaluation would be needed for precise diagnoses. However, geriatric services are not widely available in surgical units at present. Evaluation of comprehensive geriatric assessment and preoperative optimisation protocols [43] in older colon cancer patients remains a question for later studies. The present results could, however, provide the basis for patient-selection in such later intervention studies.

This is the first prospective, observational, multicentre study of aged Finnish patients with non-metastatic colon cancer focusing on their treatment and its effects on postoperative outcomes and functional recovery. Finland follows uniform and standardised protocols for colon cancer treatment so that this study will provide realistic and novel information on aged patients postoperative functional recovery.

Trial status

The trial recruitment started on 17 April 2019, and it is estimated to be complete by the end April 2021.

Abbreviations

AA-CCI: Age-adjusted Charlson comorbidity index; ASA: American Society of Anaesthesiologists physical status classification; BMI: Body mass index; CFS: Clinical Frailty Scale; CRF: Case report forms; eCRF: Electronic case report form; EBM: Evidence-Based Medicine; ERAS: Enhanced recovery after surgery; G-8: Onco-geriatric screening tool; GOSAFE: Geriatric Oncology Surgical Assessment and Functional rEcovery after Surgery; ID: Identity documentation; MDT: Multidisciplinary team; MNA-SF: Mini Nutritional Assessment-Short Form; REDCap: Secure web application for electronic database

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-021-08454-8.

Additional file 1.

Acknowledgements

The authors warmly thank M. D Kirk Langley Fremantle Hospital, WA Australia for his help in editing the English language.

Authors' contributions

The study was designed by SN, HH, AE, JK, EJ and MH. The principal investigator of the study is SN. SN was a major contributor in writing the manuscript. HH designed the statistical methods of the study. All authors participated in writing and revising the manuscript. All authors read and approved the final manuscript.

Funding

This study is financially partly supported by the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital. Cancer Foundation Finland obtained external funding by awarding a grant, but they did not have any role in designing of the study, collection, analysis, interpretation of the data or writing the manuscript.

Availability of data and materials

The datasets generated or analysed during the current study are not publicly available due to Finnish laws on privacy protection.

Declarations

Ethics approval and consent to participate

Regional Ethics Committee of the Expert Responsibility area of Tampere University Hospital has approved the study and its consent to participate (number R19028). Informed consent will be obtained from all study participants with their native language (Finnish or Swedish).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tays Hatanpää, P.O. Box 2000, 33521 Tampere, Finland. [2]Faculty of Social Sciences, Tampere University, Tampere, Finland. [3]Jorvi Hospital, Helsinki University Hospital, Helsinki, Finland. [4]Päijät-Häme Central Hospital, Lahti, Finland. [5]Tampere University Hospital, Centre of Geriatrics, Tampere, Finland. [6]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland. [7]Gerontology Research Center (GEREC), Tampere, Finland.

Received: 6 January 2021 Accepted: 7 June 2021
Published online: 14 June 2021

References

1. Statistics Finland. www.stat.fi/tup/statfin/index.html. Accessed 30 Oct 2020.
2. Jafari MD, Jafari F, Halabi WJ, Nguyen VQ, Pigazzi A, Carmichael JC, et al. Colorectal cancer resections in the aging US population: a trend toward decreasing rates and improved outcomes. JAMA Surg. 2014;149(6):557–64. https://doi.org/10.1001/jamasurg.2013.4930.
3. Van de Velde CJ, Boelens PG, Borras JM, Coebergh JW, Cervantes A, Blomqvist L, et al. EURECCA colorectal: Multidisciplinary management: European consensus conference colon & rectum. Eur J Cancer. 2014;50(1):1. e 1–1. e 34.
4. Papamichael D, Audisio RA, Glimelius B, de Gramont A, Glynne-Jones R, Haller D, et al. Treatment of colorectal Cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations. Ann Oncol. 2015;26(3):463–76. https://doi.org/10.1093/annonc/mdu253.
5. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012;380(9836):37–43. https://doi.org/10.1016/S0140-6736(12)60240-2.
6. Huisman MG, Veronese G, Audisio RA, Ugolini G, Montroni I, de Bock GH, et al. Poor nutritional status is associated with other geriatric domain impairments and adverse postoperative outcomes in Onco-geriatric surgical patients - a multi-Centre cohort study. Eur J Surg Oncol. 2016;42(7):1009–17. https://doi.org/10.1016/j.ejso.2016.03.005.
7. Niemeläinen S, Huhtala H, Ehrlich A, Kössi J, Jämsen E, Hyöty M. Risk factors of short-term survival in the aged in elective colon cancer surgery: a

population-based study. Int J Color Dis. 2020;35(2):307–15. https://doi.org/10.1007/s00384-019-03488-8.
8. Montroni I, Ugolini G, Saur NM, Spinelli A, Rostoft S, Millan M, et al. Personalized management of elderly patients with rectal cancer: expert recommendations of the European Society of Surgical Oncology, European Society of Coloproctology, International Society of Geriatric Oncology, and American College of Surgeons Commission on Cancer. Eur J Surg Oncol. 2018;44(11):1685–702. https://doi.org/10.1016/j.ejso.2018.08.003.
9. Seishima R, Okabayashi K, Hasegawa H, Tsuruta M, Shigeta K, Matsui S, et al. Is laparoscopic colorectal surgery beneficial for elderly patients? A systematic review and meta-analysis. J Gastrointest Surg. 2015;19(4):756–65. https://doi.org/10.1007/s11605-015-2748-9.
10. Bagnall NM, Malietzis G, Kennedy RH, Athanasiou T, Faiz O, Darzi A. A systematic review of enhanced recovery care after colorectal surgery in elderly patients. Color Dis. 2014;16(12):947–56. https://doi.org/10.1111/codi.12718.
11. Brouwer NPM, Heil TC, Olde Rikkert MGM, Lemmens VEPP, Rutten HJT, de Wilt JHW, et al. The gap in postoperative outcome between older and younger patients with stage I-III colorectal cancer has been bridged: results from the Netherlands cancer registry. Eur J Cancer. 2019;116:1–9. https://doi.org/10.1016/j.ejca.2019.04.036.
12. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call for action. J Am Med Dir Assoc. 2013;14(6):392–7. https://doi.org/10.1016/j.jamda.2013.03.022.
13. Okabe H, Ohsaki T, Ogawa K, Ozaki N, Hayashi H, Akahoshi S, et al. Frailty predicts severe postoperative complications after elective colorectal surgery. Am J Surg. 2019;217(4):677–81. https://doi.org/10.1016/j.amjsurg.2018.07.009.
14. Fagard K, Leonard S, Deschodt M, Devriendt E, Wolthuis A, Prenen H, et al. The impact of frailty on postoperative outcomes in individuals aged 65 and over undergoing elective surgery for colorectal Cancer: a systematic review. J Geriatr Oncol. 2016;7(6):479–91. https://doi.org/10.1016/j.jgo.2016.06.001.
15. Huisman MG, Kok M, de Bock GH, van Leeuwen BL. Delivering tailored surgery to older Cancer patients: preoperative geriatric assessment domains and screening tools - a systematic review of systematic reviews. Eur J Surg Oncol. 2017;43(1):1–14. https://doi.org/10.1016/j.ejso.2016.06.003.
16. Akishita M, Ishii S, Kojima T, Kozaki K, Kuzuya M, Arai H, et al. Priorities of health care outcomes for the elderly. J Am Med Dir Assoc. 2013;14(7):479–84. https://doi.org/10.1016/j.jamda.2013.01.009.
17. Souwer ETD, Oerlemans S, van de Poll-Franse LV, van Erning FN, van den Bos F, Schuijtemaker JS, et al. The impact of colorectal surgery on health-related quality of life in older functionally dependent patients with Cancer - a longitudinal follow-up study. J Geriatr Oncol. 2019;10(5):724–32. https://doi.org/10.1016/j.jgo.2019.04.013.
18. Rønning B, Wyller TB, Nesbakken A, Skovlund E, Jordhøy MS, Bakka A, et al. Quality of life in older and frail patients after surgery for colorectal cancer—a follow-up study. J Geriatr Oncol. 2016;7(3):195–200. https://doi.org/10.1016/j.jgo.2016.03.002.
19. Ghignone F, Hernandez P, Mahmoud NN, Ugolini G. Functional recovery in senior adults undergoing surgery for colorectal cancer: assessment tools and strategies to preserve functional status. Eur J Surg Oncol. 2020;46(3):387–93. https://doi.org/10.1016/j.ejso.2020.01.003.
20. Karlsson E, Egenvall M, Farahnak P, Bergenmar M, Nygren-Bonnier M, Franzén E, et al. Better preoperative physical performance reduces the odds of complication severity and discharge to care facility after abdominal Cancer resection in people over the age of 70 - a prospective cohort study. Eur J Surg Oncol. 2018;44(11):1760–7. https://doi.org/10.1016/j.ejso.2018.08.011.
21. Montroni I, Rostoft S, Spinelli A, Van Leeuwen BL, Ercolani G, Saur NM, et al. GOSAFE - geriatric oncology surgical assessment and functional rEcovery after surgery: early analysis on 977 patients. J Geriatr Oncol. 2020;11(2):244–55. https://doi.org/10.1016/j.jgo.2019.06.017.
22. Vermeer NCA, Claassen YHM, Derks MGM, Iversen LH, van Eycken E, Guren MG, et al. Treatment and survival of patients with Colon Cancer aged 80 years and older: a EURECCA international comparison. Oncologist. 2018;23(8):982–90. https://doi.org/10.1634/theoncologist.2017-0551.
23. Finnish Cancer Registry. www.cancerregistry.fi. Accessed 30 Oct 2020.
24. Amrock LG, Neuman MD, Lin HM, Deiner S. Can routine preoperative data predict adverse outcomes in the elderly? Development and validation of a simple risk model incorporating a chart-derived frailty score. J Am Coll Surg. 2014;219(4):684–94. https://doi.org/10.1016/j.jamcollsurg.2014.04.018.
25. Huisman MG, Ghignone F, Ugolini G, Sidorenkov G, Montroni I, Vigano A, et al. Long-term survival and risk of institutionalization in Onco-geriatric surgical patients: long-term results of the PREOP study. J Am Geriatr Soc. 2020;68(6):1235–41. https://doi.org/10.1111/jgs.16384.
26. Abdel-Halim M, Wu H, Poustie M, Beveridge A, Scott N, Mitchell PJ. Survival after non-resection of colorectal Cancer: the argument for including non-operatives in consultant outcome reporting in the UK. Ann R Coll Surg Engl. 2019;101(2):126–32. https://doi.org/10.1308/rcsann.2018.0180.
27. https://www.terveysportti.fi/dtk/ltk/koti?p_artikkeli=hsu00007. Accessed 30 Oct 2020.
28. https://www.terveysportti.fi/apps/ltk/article/ykt00397/search/palliatiivinen%20hoito. Accessed 30 Oct 2020.
29. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13. https://doi.org/10.1097/01.sla.0000133083.54934.ae.
30. Jylhä M. What is self-rated health and why does it predict mortality? Towards a unified conceptual model. Soc Sci Med. 2009;69(3):307–16. https://doi.org/10.1016/j.socscimed.2009.05.013.
31. Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, et al. Screening older Cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol. 2012;23(8):2166–72. https://doi.org/10.1093/annonc/mdr587.
32. Decoster L, Van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations. Ann Oncol. 2015;26(2):288–300. https://doi.org/10.1093/annonc/mdu210.
33. Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. Screening for Undernutrition in geriatric practice: developing the short-form mini nutritional assessment (MNA-SF). J Geront. 2001;56A:M366–77.
34. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489–95. https://doi.org/10.1503/cmaj.050051.
35. Owens WD, Felts JA, Spitznagel EL Jr. ASA physical status classifications: a study of consistency of ratings. Anesthesiology. 1978;49(4):239–43. https://doi.org/10.1097/00000542-197810000-00003.
36. Chang CM, Yin WY, Wei CK, Wu CC, Su YC, Yu CH, et al. Adjusted age-adjusted Charlson comorbidity index score as a risk measure of perioperative mortality before Cancer surgery. PLoS One. 2016;11(2):e0148076. https://doi.org/10.1371/journal.pone.0148076.
37. Lahti RA, Penttilä A. The validity of death certificates: routine validation of death certification and its effects on mortality statistics. Forensic Sci Int. 2001;115(1-2):15–32. https://doi.org/10.1016/S0379-0738(00)00300-5.
38. Mäkelä JT, Klintrup KH, Rautio TT. Mortality and survival after surgical treatment of colorectal cancer in patients aged over 80 years. Gastrointest Tumors. 2017;4(1–2):36–44. https://doi.org/10.1159/000477721.
39. Claassen YHM, Bastiaannet E, van Eycken E, Van Damme N, Martling A, Johansson R, et al. Time trends of short-term mortality for octogenarians undergoing a colorectal resection in North Europe. Eur J Surg Oncol. 2019;45(8):1396–402. https://doi.org/10.1016/j.ejso.2019.03.041.
40. Rostoft S, Hamaker ME. Basic geriatric principles for colorectal surgeons: how to optimize assessment and Care of Older Patients in the perioperative period. Eur J Surg Oncol. 2020;46(3):310–5. https://doi.org/10.1016/j.ejso.2019.07.027.
41. Niemeläinen S, Huhtala H, Ehrlich A, Kössi J, Jämsen E, Hyöty M. Long-term survival following elective colon cancer surgery in the aged. A population-based cohort study. Colorectal Dis. 2020;9. https://doi.org/10.1111/codi.15242.
42. Mothes H, Bauschke A, Schuele S, Eigendorff E, Altendorf-Hofmann A, Settmacher U. Surgery for colorectal cancer in elderly patients: how can we improve outcome? J Cancer Res Clin Oncol. 2017;43:1879–89.
43. Partridge JLS, Harari D, Martin FC, Dhesi JK. The impact of pre-operative comprehensive geriatric assessment on postoperative outcomes in older patients undergoing scheduled surgery: a systematic review. Anaesthesia. 2014;69(Suppl 1):8–16. https://doi.org/10.1111/anae.12494.

Publisher's Note

APPENDIX 2.

IÄKKÄÄN PAKSUSUOLISYÖPÄPOTILAAN LEIKKAUSHOITO- TUTKIMUS

ESITIETOLOMAKE päivämäärä

Nimi:
Syntymäaika:
Sukupuoli: □ Nainen □ Mies
Pituus (cm): Paino (kg):
Missä asutte? □ Kotona □ Palvelutalossa □ Tehostetun palveluasumisen yksikössä
Kenen kanssa asutte? □ Yksin □ Puolison tai läheisen kanssa □ Jonkun muun kanssa
Tarvitsetteko toisen ihmisen apua? □ En □ Kyllä, kodin ulkopuolella □ Kyllä, kotitöissä □ Kyllä, itsestäni huolehtimisessa
Miten liikutte? □ Täysin itsenäisesti □ Apuvälinettä käyttäen itsenäisesti □ Vain avustettuna
Miten liikutte kodin ulkopuolella? □ Yksin □ Kyllä, saattajan kanssa □ En liiku ulkona
Liikkumisenne apuvälineet: □ Pyörätuoli □ Rollaattori □ Keppi tai kyynärsauvat □ En käytä apuvälineitä

Millainen on terveytenne verrattuna muihin samanikäisiin? □ Parempi □ Yhtä hyvä □ Huonompi □ En osaa sanoa
Onko teillä muistivaikeutta tai masennusta? □ Ei □ Kyllä, muistini on heikentynyt ja/ tai minulla on lievä masennus □ Kyllä, minulla on todettu muistisairaus /dementia ja /tai masennus
Onko ravinnonsaantinne huonontunut viimeisen kolmen kuukauden aikana? □ Kyllä, huomattavasti □ Kyllä, hieman □ Ei □ En osaa sanoa
Onko painonne laskenut viimeisen kolmen kuukauden aikana? □ Kyllä, laskenut yli 3 kg □ Kyllä, laskenut 1–3 kg □ Ei, painoni on ennallaan tai noussut □ En osaa sanoa
Oletteko ollut sairaalahoidossa (terveyskeskus tai sairaala) viimeisen kuuden kuukauden aikana? □ En □ Kyllä, yhden kerran □ Kyllä, useita kertoja
Kuinka monta lääkettä teillä on säännöllisessä käytössä? Lukumäärä?
Käytättekö alkoholia? □ En □ Kyllä, kerran kuukaudessa tai harvemmin □ Kyllä, kerran viikossa □ Kyllä, useita kertoja viikossa
Tupakoitteko? □ En □ Kyllä
On teillä hoitotahto? □ Ei □ Kyllä
Kuka täytti lomakkeen? □ Potilas □ Omainen □ Hoitaja □ Joku muu

APPENDIX 3.

IÄKKÄÄN PAKSUSUOLISYÖPÄPOTILAAN LEIKKAUSHOITOTUTKIMUS

SEURANTALOMAKE päivämäärä

Nimi:
Syntymäaika:
Sukupuoli: □ Nainen □ Mies
Paino (kg)
Missä asutte? □ Kotona □ Palvelutalossa □ Tehostetun palveluasumisen yksikössä
Kenen kanssa asutte? □ Yksin □ Puolison tai läheisen kanssa □ Jonkun muun kanssa
Tarvitsetteko toisen ihmisen apua? □ En □ Kyllä, kodin ulkopuolella □ Kyllä, kotitöissä □ Kyllä, itsestäni huolehtimisessa
Miten liikutte? □ Täysin itsenäisesti □ Apuvälinettä käyttäen itsenäisesti □ Vain avustettuna
Miten liikutte kodin ulkopuolella? □ Yksin □ Kyllä, saattajan kanssa □ En liiku ulkona
Liikkumisenne apuvälineet: □ Pyörätuoli □ Rollaattori □ Keppi tai kyynärsauvat □ En käytä apuvälineitä
Millainen on terveytenne verrattuna muihin samanikäisiin? □ Parempi □ Yhtä hyvä □ Huonompi □ En osaa sanoa

Onko teillä muistivaikeutta tai masennusta? □ Ei □ Kyllä, muistini on heikentynyt ja/ tai minulla on lievä masennus □ Kyllä, minulla on todettu muistisairaus /dementia ja /tai masennus
Onko ravinnonsaantinne huonontunut viimeisen kolmen kuukauden aikana? □ Kyllä, huomattavasti □ Kyllä, hieman □ Ei □ En osaa sanoa
Onko painonne laskenut viimeisen kolmen kuukauden aikana? □ Kyllä, laskenut yli 3 kg □ Kyllä, laskenut 1–3 kg □ Ei, painoni on ennallaan tai noussut □ En osaa sanoa
Kuinka monta lääkettä teillä on säännöllisessä käytössä? Lukumäärä?
Miten leikkaus on vaikuttanut terveydentilaanne? □ Parantanut □ Pysynyt ennallaan □ Huonontanut □ En osaa sanoa
Kuka täytti lomakkeen? □ Potilas □ Omainen □ Hoitaja □ Joku muu

ORIGINAL PUBLICATIONS

PUBLICATION
I

Risk factors of short-term survival in the aged in elective colon cancer surgery: a population-based study.

Susanna Niemeläinen, Heini Huhtala, Anu Ehrlich, Jyrki Kössi, Esa Jämsen, Marja Hyöty

Int J Colorectal Dis. 2020 Feb; 35(2):305-15. doi: 10.1007/s00384-019-03488-8.

International Journal of Colorectal Disease (2020) 35:307–315
https://doi.org/10.1007/s00384-019-03488-8

ORIGINAL ARTICLE

Risk factors of short-term survival in the aged in elective colon cancer surgery: a population-based study

Susanna Niemeläinen [1,2] · Heini Huhtala [3] · Anu Ehrlich [4] · Jyrki Kössi [5] · Esa Jämsen [6,7,8] · Marja Hyöty [1]

Accepted: 4 December 2019 / Published online: 18 December 2019

Abstract

Purpose Patients aged ≥ 80 years represent an increasing proportion of colon cancer diagnoses. Selecting patients for elective surgery is challenging because of possibly compromised health status and functional decline. The aim of this retrospective, population-based study was to identify risk factors and health measures that predict short-term mortality after elective colon cancer surgery in the aged.

Methods All patients ≥ 80 years operated electively for stages I–III colon cancer from 2005 to 2016 in four Finnish hospitals were included. The prospectively collected data included comorbidities, functional status, postoperative surgical and medical outcomes as well as mortality data.

Results A total of 386 patients (mean 84.0 years, range 80–96, 56% female) were included. Male gender (46% vs 35%, $p = 0.03$), higher BMI (51% vs 37%, $p = 0.02$), diabetes mellitus (51% vs 37%, $p = 0.02$), coronary artery disease (52% vs 36%, $p = 0.003$) and rheumatic diseases (67% vs 39%, $p = 0.03$) were related to higher risk of complications. The severe complications were more common in patients with increased preoperative hospitalizations (31% vs 15%, $p = 0.05$) and who lived in nursing homes (30% vs 17%, $p = 0.05$). The 30-day and 1-year mortality rates were 6.0% and 15% for all the patients compared with 30% and 45% in patients with severe postoperative complications ($p < 0.001$). Severe postoperative complications were the only significant patient-related variable affecting 1-year mortality (OR 9.60, 95% CI 2.33–39.55, $p = 0.002$).

Conclusions The ability to identify preoperatively patients at high risk of decreased survival and thus prevent severe postoperative complications could improve overall outcome of aged colon cancer patients.

Keywords Colon cancer · Surgery · Aged patients · Risk factors · Short-term mortality

✉ Susanna Niemeläinen
susanna.niemelainen@pshp.fi

1 Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere, Finland

2 Department of Surgery, Tays Hatanpää, P.O. Box 2000, 33521 Tampere, Finland

3 Faculty of Social Sciences, Tampere University, Tampere, Finland

4 Central Hospital of Central Finland, Jyväskylä, Finland

5 Päijät-Häme Central Hospital, Lahti, Finland

6 Centre of Geriatrics, Tampere University Hospital, Tampere, Finland

7 Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

8 Gerontology Research Center (GEREC), Tampere, Finland

Introduction

The incidence of colorectal cancer has tripled during the past five decades, and the risk of having colorectal cancer increases with age [1]. According to the Finnish Cancer Registry data from 2016, 27% of all colorectal patients were aged 80 years or more [1]. The number of aged people diagnosed with colorectal cancer will increase as the population ages [2].

If possible, colon cancer is managed by radical surgical resection [3, 4]. Previous studies show comparable disease-specific survival rates for all age groups, which advocates tumour resection with curative purpose [5, 6]. In the EUROCARE-5 study, 5-year overall survival rate was 49% for colon cancer patients of 75 years or older while overall survival rate for all ages was 57% in Europe [7]. Corresponding numbers from 2016 in Finland were 60% for patients of 75 years and 66% for all ages [1]. In the oldest patients, however, the survival benefit of operative treatment (compared with other treatments) is only apparent after the first two postoperative years due to the risks of surgery [8–10].

Increased age, physical and cognitive disabilities, and previous hospitalizations may predispose to postoperative morbidity and mortality [11]. Colorectal cancer surgery is considered high risk, with reported postoperative major complication and 30-day mortality rates of 16–24% and 1–6%, respectively [12, 13]. Operative treatment of colorectal cancer in the aged is associated with higher morbidity (35–45%) and mortality rates both in the immediate postoperative period and during the first year after surgery (6–16% in 30 days, 14–37% at 1 year) [12–17]. Compared with younger people, the 30-day mortality in the group of aged patients underestimates 1-year mortality due to prolonged impact of the perioperative period [8, 18]. However, a recent Dutch study shows better postoperative outcome with almost equal 1-year survival rates for older and younger colorectal patients, supporting tailor-made decisions on surgical treatments for older patients [19].

It is important to have relevant and reliable data concerning older aged colorectal cancer patient's surgery and postoperative morbidity and survival numbers. Surgeons and oncologists treating patients with colon cancer should become aware of that 43% of their patients are > 75 years and that many of these older patients are frail with comorbidities which demand careful patient assessment [20]. Proper patient selection and careful consideration of appropriate surgical candidates including preoperative optimization of medical comorbidities, nutritional status and physical performance enables colorectal cancer surgery to be performed with reduced morbidity and mortality rates with improved survival [21, 22].

The aim of this study was to identify preoperative risk factors and measures of overall health status affecting postoperative morbidity and mortality and their impact on 30-day and 1-year survival in colon cancer patients aged 80 years and older. In addition, the aim was to investigate time-trends in postoperative short-term mortality and possible factors affecting the outcome.

Material and methods

All patients aged 80 years and over who underwent an elective resection for colon cancer during the period of 2005 and 2016 in four Finnish hospitals were retrospectively analyzed. The catchment area of these hospitals ranged from 100,000 to 250,000 inhabitants (in total, approximately 750,000 inhabitants). Exclusion criteria were metastatic or recurrent disease and palliative or emergency surgery. Treatment of malignant diseases is almost exclusively performed by public health care system in Finland. We consider this study population-based because patients are referred to certain hospital based on their place of residence.

All the patients had histologically confirmed primary adenocarcinoma of the colon, and preoperatively had colonoscopy and computed tomography. They underwent radical surgery for the primary tumour. Patients were evaluated for their fitness for elective surgery with general anaesthesia but were not preselected any other way. Decision to proceed with surgery was based on patient's general condition and comorbidities. Prior geriatric evaluation was not routinely used.

For this study, cancer- and surgery-related data was collected from prospectively maintained, institutionally approved and password-protected electronic colorectal databases in the study hospitals and was supplemented by review of medical records. Patients with colorectal cancer were identified using ICD codes C18-C19 [23]. The collected clinical data included patients´ characteristics, living status, hospitalizations in the 6 months before surgery, comorbidities, modified age-adjusted Charlson Comorbidity Index [24] score (4–15; solid tumour excluded with two points, all patients ≥ 80 years which contributes four points for all patients), other malignancies, symptoms, operative procedures and postoperative recovery. Postoperative complications were defined and determined using the Clavien-Dindo classification [25], and severe complications were graded into classes III–V. Tumours were staged according to the Union for International Cancer Control (UICC) TNM classification [26] and graded according to the World Health Organization histological classification system [27]. The number of lymph nodes was recorded in every case. Patients with macroscopic or residual tumour were excluded.

Postoperative surveillance was performed in out-patient clinics according to the follow-up programs of the four hospitals. Local recurrences and distant metastasis were identified radiologically (ultrasound, computed tomography) or histologically. The information was collected from the hospital medical records and Statistics Finland for all patients with or without arranged follow-up program.

The primary outcome measures were postoperative morbidity (surgical and non-surgical complications) and mortality 30 days and 1 year after primary treatment. Mortality data including causes of death were obtained from the population-based statistics of Statistics Finland. Mortality was assessed at 30 days and 1 year following surgery. The follow-up duration data was calculated from the date of surgery to the date of death or date of active follow-up in the clinics (1 year after surgery).

The associations between categorical variables were tested with the chi-square test or the Fisher exact test, when appropriate, and continuous variables with the Student's t test. Survival rates were calculated from the time of primary surgery using the Kaplan-Meier method and were compared by the log-rank test. A uni- and multivariable analysis of the factors which influenced 30-day and 1-year mortality was carried out using binary logistic regression. All variables (Table 4) that were statistically significant in the univariate model were included in the multivariable model. Statistical analyses were performed using SPSS version 23.

The study was approved by the ethics committee of Pirkanmaa Hospital District, Tampere, Finland (R18188).

Results

A total of 386 patients were identified from the prospective records of the four hospitals. The mean age of the study population was 84.1 years (range 80–96 years). Most of the patients were female (56%), had an ASA III classification (69%) and CCI score 4–5 (62%). Most of the patients lived at home (90%), were not dependent on others for daily help (56%) and had no hospital admission in the previous 6 months (73%). Of the patients, 106 (28%) were operated in 2005–2008, 143 (37%) in 2009–2012 and 137 (35%) in 2013–2016. Table 1 shows the patients` baseline characteristics.

Most of the operative procedures were performed for right-sided colon cancer (68%). An intended laparoscopic resection was performed in 252 patients (65%) and in 35 cases (14%), the operation was converted to an open surgery due to anatomical or technical reasons. One hundred eighty-seven patients (50%) were discharged to other hospitals or wards of healthcare centres. Readmission within 30 days of discharge occurred for 6.5% of the patients. Postoperative adjuvant chemotherapy was given to 46% (67/146) of stage III patients. Table 2 shows surgical characteristics and outcomes.

Table 1 Patients' baseline characteristics ($n = 386$)

	n / med	% / (range)
Gender		
Female	217	56.2
Male	169	43.8
Age, years	83.0	(80–96)
BMI, kg/m^2	24.9	(15.4–40.6)
< 25	163	50.9
25–29.9	111	34.7
30-	46	14.4
Not available	66	
Type of living		
Home	336	90.1
Nursing home	37	9.9
Not known	13	
Aid at home		
No	152	55.9
Relatives	62	22.8
Other	58	21.3
Not known	114	
Hospital admissions < 6 months		
No	279	73.4
One	88	23.3
Two or more	13	3.3
ASA score		
2	36	9.5
3	263	69.0
4	82	21.5
Not known	5	
CCI score (4–15)		
4	109	28.2
5	131	33.9
6	82	21.3
7–15	64	16.6
Operation year		
2005–2008	106	27.5
2009–2012	143	37.0
2013–2016	137	35.5

Morbidity

Overall postoperative morbidity was 40% (154/386), with 24% (92/386) of patients having surgical complications. The most common surgical complications were ileus (7.0%), intra-abdominal or anastomotic bleeding (6.2%) and anastomotic leakage (5.7%). The most common non-surgical complications were cardiovascular (6.0%) and pulmonary (4.7%). Both surgical and non-surgical complications were recorded only for 1.8% (7/386) of the patients. According to the Clavien-Dindo classification, 18% (69/386) of patients had severe complications (grades III–V), accounting for 45% (69/154) of all complications. (Table 3).

Male gender (46% vs 35%, $p = 0.03$), diabetes mellitus (51% vs 37%, $p = 0.02$), coronary artery disease (52% vs 36%, $p = 0.003$) and rheumatic diseases (67% vs 39%, $p = 0.03$) were related to higher number of complications. Patients with complications had higher BMI (26 vs 25, $p = 0.04$). Operative approach (open or laparoscopic) and operating time were not associated with increased rate of complications.

More severe postoperative complications (Clavien-Dindo III–V) were experienced by patients living in a nursing home compared with those living in their own home (30% vs 17%, $p = 0.05$), and by those who had hospital admissions during the 6 months prior surgery compared with those who had none (31% vs 15%, $p = 0.05$). Patients with severe complications also had more intraoperative blood loss (median 50 ml vs 100 ml, $p = 0.006$).

Table 2 Surgical characteristics and outcomes

	n / med	% / (range)
Procedure		
Right hemicolectomy	261	67.6
Transversum resection	6	1.6
Left hemicolectomy	22	5.7
Sigmoid resection	83	21.5
Other colonic resection	14	3.6
Type of surgery		
Open	134	34.7
Laparoscopy	252	65.3
Conversion	35	13.9
Operation time (min)	130	33–445
Bleeding (ml)	50	5–1000
Postoperative length of hospital stay (days)	7	1–58
Discharge destination		
Home	172	45.6
Other hospital or health centre	187	49.6
Death during hospital stay	18	4.8
Reoperation	39	10.1
Readmission	25	6.5
TNM stage		
1	41	12.7
2	191	49.5
3	146	37.8
Number of lymph nodes	14.8	3–71

Table 3 Postoperative complications and mortality

	N	%
Surgical complications		
No	294	76.2
Yes	92	23.8
Ileus	27	7.0
Bleeding	24	6.2
Anastomotic leakage	22	5.7
Wound dehiscence	7	1.8
Wound infection	2	0.5
Others	10	2.6
Non-surgical complications		
No	317	82.1
Yes	69	17.9
Cardiovascular	23	6.0
Respiratory	18	4.7
Urinary	11	2.8
Delirium	5	1.3
Other	12	3.1
30-day mortality	23	6.0
90-day mortality	29	7.5
1-year mortality	59	15.3

Mortality

The overall 30-day mortality was 6.0% (23/386). Six patients died due to anastomotic leakage and three due to other surgical complications (ileus, intraoperative haemorrhage and small intestine perforation). Seven patients died due to cardiac complications, three due to pulmonary problems and three due to cerebral haemorrhage. One patient died of a ruptured abdominal aneurysm 6 days after surgery.

The overall 1-year mortality was 15% (59/386). The most important causes of death were cardiopulmonary (43%) and surgery-related postoperative complications (17%). Cancer-related mortality was 4.4%, accounting for 29% (17/59) of deaths within 1 year. Over half (55%, 17/31) of the patients who had severe, surgery-related complications (anastomotic leakage, intra-abdominal haemorrhage, ileus) died within 1 year after surgery whereas 1-year mortality was 8.6% (20/232) for the patients without postoperative complications. In patients with mild complications (Clavien-Dindo I–II), mortality was 9.4%. Patients with severe postoperative complications (Clavien-Dindo III–V) had mortality 45% (31/69). (Fig. 1).

Patients with stage III disease (n = 146) and treated with postoperative chemotherapy had lower 1-year mortality rate compared with patients not receiving adjuvant treatment (10.4% vs 27.8%, $p = 0.007$).

Univariate logistic regression analysis showed that living in a nursing home, hospital admissions 6 months before surgery, CCI score $\geq$ 6, longer operation time, greater intraoperative blood loss and severe postoperative complications were significant patient-related variables affecting 30-day mortality. Higher age, hospital admissions 6 months before surgery, open compared with laparoscopic operation, longer operative time, greater intraoperative blood loss and severe postoperative complications were associated with greater 1-year mortality after surgery (Table 4). In multivariate logistic regression analysis, hospital admissions 6 months before surgery and

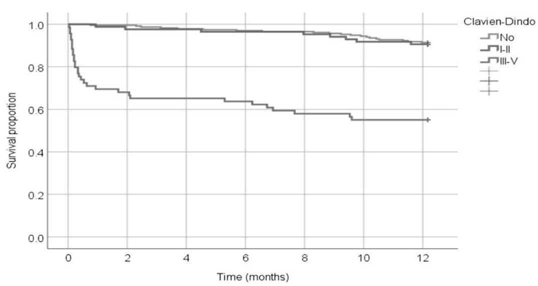

Fig. 1 Kaplan-Meier analysis of 1-year overall survival in electively operated colon cancer patients $\geq$ 80 years of age with and without complications according to Clavien-Dindo classification ($p < 0.001$, log-rank)

Table 4 Predictors of 30-day and 1-year mortality in elective colon cancer surgery in the aged (univariate analysis)

	30-day mortality			1-year mortality		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age	1.11	0.99–1.24	0.079	1.12	1.04–1.21	*0.004*
Gender						
Female	1			1		
Male	2.09	0.88–4.95	0.095	1.10	0.63–1.92	0.739
BMI (kg/m^2)	0.94			0.96		
< 25	1			1		
25–29.9	1.19	0.45–3.11	0.725	0.95	0.49–1.85	0.887
>=30	0.34	0.04–2.73	0.310	0.64	0.23–1.78	0.395
Type of living						
Home	1			1		
Nursing home	3.63	1.34–9.88	*0.012*	1.93	0.86–4.34	0.112
Hospital admissions $\leq$ 6 months						
No	1			1		
One or more	3.97	1.68–9.38	*0.002*	1.88	1.04–3.38	*0.035*
ASA						
2	1			1		
3	0.88	0.19–4.09	0.875	1.86	0.54–6.36	0.324
4	1.86	0.38–9.23	0.447	3.14	0.86–11.5	0.083
CCI score (4–15)						
4	1			1		
5	2.57	0.51–13.0	0.254	1.15	0.55–2.42	0.710
6	5.0	1.01–24.7	*0.049*	1.05	0,45–2.45	0.910
7–15	7.64	1.57–37.2	*0.012*	2.08	0.93–4.65	0.075
Stage						
1–2	1			1		
3	0.87	0.36–2.11	0.757	1.74	0.99–3.03	0.053
Type of surgery						
Laparoscopy/conversion	1			1		
Open	1.79	0.67–4.17	0.178	1.88	1.08–3.30	*0.027*
Operation time (min)	1.01	1.00–1.01	*0.038*	1.01	1.00–1.01	*0.010*
Blood loss (10 ml) n = 197	1.03	1.01–1.05	*0.005*	1.03	1.01–1.05	*0.001*
Clavien-Dindo classification						
No	1			1		
I–II	2.75	0.17–44.46	0.480	1.10	0.47–2.60	0.830
III–V	101.06	13.3–769.5	< *0.001*	8.65	4.47–16.73	< *0.001*
Complications						
No	1			1		
Surgical	25.05	3.13–200.7	*0.002*	2.76	1.40–5.46	*0.004*
Non-surgical	61.29	7.83–479.5	< *0.001*	5.05	2.50–10.20	< *0.001*
Operation year						
2005–2008	1			1		
2009–2012	0.73	0.26–2.00	0.536	0.62	0.32–1.21	0.161
2013–2016	0.66	0.23–1.88	0.436	0.54	0.27–1.08	0.082

Italic entries were statistically significant

severe postoperative complications were the only significant patient-related variables affecting 30-day mortality (OR 3.05, 95% CI 1.25–7.43, p = 0.014 and OR 85.61, 95% CI 10.68–686.1, p < 0.001). Severe postoperative complications were the only significant patient-related variable affecting 1-year mortality (OR 9.60, 95% CI 2.33–39.55, $p = 0.002$).

Mortality rates in 30 days seemed to decrease between operation years 2005–2008 (7.5%), 2009–2012 (5.6%) and 2013–2016 (5.1%). The corresponding numbers in 1 year were 21% (2005–2008), 14% (2009–2012) and 12% (2013–2016). For severe complications (CD III–V), the 30-day mortality rates were 2005–2008 (30.8%), 2009–2012 (35%) and 2013–2016 (26.1%). The corresponding numbers in 1 year were 50% (2005–2008), 45% (2009–2012) and 39% (2013–2016). There was no statistically significant difference between time-trends and mortality.

Table 4 shows predictors for 30-day and 1-year mortality in univariate analysis (binary logistic regression).

Discussion

For this retrospective population-based, cohort study, short-term morbidity and mortality differences were analyzed in the electively operative non-metastatic colon cancer patients aged 80 years and over in a large, regionally representable materials. To our knowledge, our material consisting of 386 patients is the largest dataset regarding elective colon cancer surgery with curative intent and focusing on both postoperative complications and short-term mortality in this age group. Most of the similar studies featured surgical patients with colorectal cancers [6, 8, 14, 28]. Patients undergoing resection for rectal cancer have more personalized, multimodal treatment options and a greater number of severe complications such as anastomotic leakage compared with colon cancer surgery [29]. Thus, the patient data in our study was more homogenous focusing only on colon surgery. Furthermore, in Finland, treatment of colorectal cancer is based on national EBM guidelines [30]. The study hospitals also had standardized protocols for colon cancer treatments, and the patients' baselines as well as operative outcomes and tumour characteristics were similar.

For non-metastatic colorectal cancer patients, surgical resection is the best option for curative treatment [3, 4]. A recent multinational study showed that patients over 80 years have 30-day and 1-year mortality rates of 5.5–11.4% and 17.1–23.6%, respectively [16]. In the present study, 1-year survival rate was 91.4% for the patients without postoperative complications, and the overall 1-year mortality was 15.3%. Most of the older patients do as well as younger patients after elective surgery and have acceptable survival numbers. For example, recent data from Netherlands showed similar 1-year overall survival rates for patients under and over 75 years [18]. However, 30-day mortality rate remains high among the oldest, and it continues to increase well beyond the initial postoperative month causing excess 1-year mortality. Previous studies show that major postoperative complications are related to higher mortality rates and are among the strongest risk factors for reduced survival in the aged [28, 31]. Our data showed similar postoperative morbidity and survival numbers reflecting the results of previous studies considering excess mortality beyond initial postoperative month [8, 13]. In our study, 1-year mortality rate of patients with major postoperative complications was 44.9%, this being the most important factor for diminished short-term survival after colon surgery.

Our study indicated high morbidity rates in early postoperative period. Almost 40% (153/386) of the patients developed postoperative complications, and 45% (69/153) of these were major complications. These figures are comparable with other studies of colorectal cancer surgery reporting total complication rates 35–45% and major complications 20–25%, respectively [14–17, 31]. Our data included all patients who were willing and fit enough for surgery according to ASA classification and other comorbidities. Risk factors for complications were male gender, diabetes, coronary artery and rheumatic diseases. Severe complications were more common in patients who had increased preoperative hospitalizations and who lived in nursing homes. These findings support recent studies from Norway and Japan [32, 33] emphasizing the importance of preoperative evaluation of patient's physical and cognitive performance, to prevent complications in colon cancer surgery. In Finland, aged people move to nursing homes when they cannot survive with maximal help at home and most of them have some degree of cognitive impairment. Therefore, residing in a nursing home is a kind of proxy for cognitive impairment and disability in activities of daily living. Unfortunately, the diagnoses for hospitalizations before surgery were not documented accurately in our study data, and the reasons for hospitalizations were heterogenous.

Postoperative complications are associated with a disproportionately high risk of 30-day and 1-year mortality in elderly patients [28, 31]. In our study, the overall 30-day mortality rate was 6.0% but increased to 30.4% in patients with severe postoperative complications. Other factors associated with increased 30-day mortality included living in a nursing home, hospital admissions 6 months before surgery, CCI score $\geq$ six, longer operation time, greater intraoperative blood loss and severe postoperative complications. Patients with diminished physical and mental resources had more severe postoperative complications leading to higher mortality rates indicating that limited performance state of patients plays an important role in postoperative outcome [33]. Cardiopulmonary problems and surgery-related issues were the most important factors contributing to 1-year mortality whereas cancer-related mortality was significantly low. This finding emphasizes the importance of preoperative evaluation on patient's physical and cognitive performance with specific focus on preoperative cardiopulmonary status and medical optimization. Non-surgical, symptomatic treatments are worth considering when individualized treatment decisions are made for patients with limited performance status. On the contrary, patients with stage III disease treated with postoperative chemotherapy had significantly lower 1-year mortality rate compared with those who were not giving postoperative adjuvant treatment. That underlines the importance of identify patients who can benefit from the radical cancer treatments.

30-day and 1-year mortality rates decreased progressively between operation years 2005–2008, 2009–2012 and 2013–2016, but this was not statistically significant. During the study period, there were no preoperative arrangements for nutrition and physical performance status assessment, or geriatric assessment. Conversely, all the participating hospitals in our study had high proportion (56%) of operations done by laparoscopy, and enhanced recovery after surgery (ERAS) program was gradually adopted to clinical work during the study period. A recent meta-analysis demonstrated that laparoscopic colorectal surgery has positive impact in terms of significant decrease in postoperative morbidity and mortality among the aged compared with open colorectal surgery [34]. ERAS is a multimodal approach that aims to optimize perioperative management [35]. Old patients adhered to and benefited from an ERAS program have similar postoperative outcome advantages to their younger counterparts [36]. These facts can partly explain the similar time-trends in morbidity and mortality between the study years, together with developments in perioperative anaesthesia care, surgical performance (laparoscopy, technical standardization) and oncological treatments.

Some limitations exist in our study. First, although we were able to categorize specific comorbidities, we found little relationship between multiple morbidities and overall survival. This may reflect the fact that there was no information available regarding the severity of the comorbidities. Additionally, we were unable to fully assess disability and functional as well as cognitive performance state of patients because of imprecise patient files. Information about daily physical and cognitive functional activity and general performance was not routinely recorded. It is likely that the conditions that lead to a patient being considered frail are only documented in those patients whose condition had significant negative impact on their overall well-being. The same applies to comorbidities. However, undervaluation of such conditions would lead to underrate of the risks and false negative results, and hence, the reported risks are rather underestimates than overestimates. In addition, and result of the previous reasons, healthier patients were likely selected for surgical treatment. However, our findings suggest that surgical treatment in aged patients diagnosed with colon cancer can lead to acceptable and similar results compared with younger patients.

Our data indicate that postoperative morbidity following elective colon cancer surgery is common in aged patients and results in a significant increase in mortality, which lasts beyond the first postoperative month. Age, comorbidities, disability and the occurrence of severe postoperative complications were factors most strongly associated with reduced 30-day and 1-year survival after surgery. Although we have demonstrated an increase in survival rates, the impact of surgical treatment on postoperative functional outcome is not clear. Regardless of the new achievements, there seems to be a tendency to offer fewer surgical resections to older compared with younger patients [37, 38]. Therefore, the information on present-day postoperative morbidity and mortality rates of older patients is important for shared decision-making regarding surgical treatment. If aged colon cancer patients survive the first year after surgery, they have a reasonably good long-term survival. Older patients often give higher priority to functional outcomes than to survival [39]. Further research should therefore focus not only on further increasing postoperative survival rates in older patients but also on quality of life and improvement of postoperative physical functioning. Prehabilitation programs could play a role in achieving this goal [40, 41].

In conclusion, mortality in the present study is related to postoperative complications. Identifying effective strategies for both prevention and tailor-made treatments of postoperative complications in colon cancer surgery in the aged could potentially improve patient overall outcomes.

Acknowledgments The authors thank warmly M.D. Ville Väyrynen Central Hospital of Central Finland and M.D. Anu Välikoski Tays Hatanpää Tampere University Hospital for their dedicated data collection.

Funding information This study was financially partly supported by the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital.

Compliance with ethical standards The study was approved by the ethics committee of Pirkanmaa Hospital District, Tampere, Finland (R18188).

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Finnish Cancer Registry. www.cancerregistry.fi. Accessed 6 Oct 2019

2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F (2017) Global patterns and trends in colorectal cancer incidence and mortality. Gut 66(4):683–691
3. Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K et al (2012) ESMO consensus guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Ann Oncol 23(10):2479–2516
4. Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S (2009) Standardized surgery for colonic cancer: complete mesocolic excision and central ligation–technical notes and outcome. Color Dis 11(4):354–364
5. Mothes H, Bauschke A, Schuele S, Eigendorff E, Altendorf-Hofmann A, Settmacher U (2017) Surgery for colorectal cancer in elderly patients: how can we improve outcome? J Cancer Res Clin Oncol 143(9):1879–1889
6. Mäkelä JT, Klintrup KH, Rautio TT (2017) Mortality and survival after surgical treatment of colorectal cancer in patients aged over 80 years. Gastrointest Tumors 4(1–2):36–44
7. Holleczek B, Rossi S, Domenic A, Innos K, Minicozzi P, Francisci S et al (2015) Ongoing improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007. Results from the EUROCARE-5 study. Eur J Cancer 51(15):2158–2168
8. Dekker JW, van den Broek CB, Bastiaannet E, van de Geest LG, Tollenaar RA, Liefers GJ (2011) Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. Ann Surg Oncol 18(6):1533–1539
9. Ng O, Watts E, Bull CA, Morris R, Acheson A, Banerjea A (2016) Colorectal cancer outcomes in patients aged over 85 years. Ann R Coll Surg Engl 98(3):216–221
10. Abdel-Halim M, Wu H, Poustie M, Beveridge A, Scott N, Mitchell PJ (2019) Survival after non-resection of colorectal cancer: the argument for including non-operatives in consultant outcome reporting in UK. Ann R Coll Surg Engl 101(2):126–132
11. Neuman HB, Weiss JM, Leverson G, O'Connor ES, Greenblatt DY, Loconte NK et al (2013) Predictors of short-term postoperative survival after elective colectomy in colon cancer patients ≥ 80 years of age. Ann Surg Oncol 20(5):1427–1435
12. Morris EJ, Taylor EF, Thomas JD, Quirke P, Finan PJ, Coleman MP, Rachet B, Forman D (2011) Thirty-day postoperative mortality after colorectal cancer surgery in England. Gut 60(6):806–813
13. Al-Refaie WB, Parsons HM, Habermann EB, Kwaan M, Spencer MP, Henderson WG, Rothenberger DA (2011) Operative outcomes beyond 30-day mortality: colorectal cancer surgery in oldest old. Ann Surg 253(5):947–952
14. Ihedioha U, Gravante G, Lloyd G, Sangal S, Sorge R, Singh B, Chaudhri S (2013) Curative colorectal resections in patients aged 80 years and older: clinical characteristics, morbidity, mortality and risk factors. Int J Color Dis 28(7):941–947
15. Aquina CT, Mohile SG, Tejani MA, Becerra AZ, Xu Z, Hensley BJ et al (2017) The impact of age on complications, survival, and cause of death following colon cancer surgery. Br J Cancer 116(3):389–397
16. Claassen YHM, Bastiaannet E, van Eycken E, Van Damme N, Martling A, Johansson R et al (2019) Time trends of short-term mortality for octogenarians undergoing a colorectal resection in North Europe. Eur J Surg Oncol 45(8):1396–1402
17. Duraes LC, Stocchi L, Dietz D, Kalady MF, Kessler H, Schroeder D, Remzi FH (2016) The disproportionate effect of perioperative complications on mortality within 1 year after colorectal cancer resection in octogenarians. Ann Surg Oncol 23(13):4293–4301
18. Bos ACRK, Kortbeek D, van Erning FN, Zimmerman DDE, Lemmens VEPP, Dekker JWT et al (2019) Postoperative mortality in elderly patients with colorectal cancer: the impact of age, time-trends and competing risks of dying. Eur J Surg Oncol 45(9):1575–1583
19. Brouwer NPM, Heil TC, Olde Rikkert MGM, Lemmens VEPP, Rutten HJT, de Wilt JHW, van Erning F (2019) The gap in postoperative outcome between older and younger patients with stage I-III colorectal cancer has been bridged; results from the Netherlands cancer registry. Eur J Cancer 116:1–9
20. Papamichael D, Audisio RA, Glimelius B, de Gramont A, Glynne-Jones R, Haller D et al (2013) Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. Ann Oncol 26(3):463–476
21. Örum M, Gregersen M, Jensen K, Meldgaard P, Damsgaard EMS (2018) Frailty status but not age predict complications in elderly cancer patients: a follow-up study. Acta Oncol 57(11):1458–1466
22. Kunitake H, Zingmond DS, Ryoo J, Ko CY (2010) Caring for octogenarian and nonagenarian patients with colorectal cancer: what should our standards and expectations be? Dis Colon Rectum 53(5):735–743
23. WHO (2010) International statistical classification of diseases and related health problems. 10th revision
24. Chang CM, Yin WY, Wei CK, Wu CC, Su YC, Yu CH, Lee CC (2016 Feb 5) Adjusted age-adjusted Charlson comorbidity index score as a risk measure of perioperative mortality before cancer surgery. PLoS One 11(2):e0148076. https://doi.org/10.1371/journal.pone.0148076
25. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240(2):205–213
26. Sobin LH, Gospodarowicz MK, Wittekind CH (2009) TNM classification of malignant tumours, 7th edn. Wiley-Blackwell, Hoboken
27. Loughrey MB, Quirke P, Shepherd NA (2017) Dataset for histopathological reporting of colorectal cancer, 4th edn. The Royal College of Pathologists, London
28. Weerink LBM, Gant CM, van Leeuwen BL, de Bock GH, Kouwenhoven EA, Faneyte IF (2018) Long-term survival in octogenarians after surgical treatment for colorectal cancer: prevention of postoperative complications is key. Ann Surg Oncol 25(13):3874–3882
29. Montroni I, Ugolini G, Saur NM, Spinelli A, Rostoft S, Millan M, Wolthuis A, Daniels IR, Hompes R, Penna M, Fürst A, Papamichael D, Desai AM, Cascinu S, Gèrard JP, Myint AS, Lemmens VEPP, Berho M, Lawler M, de Liguori Carino N, Potenti F, Nanni O, Altini M, Beets G, Rutten H, Winchester D, Wexner SD, Audisio RA (2018) Personalized management of elderly patients with rectal cancer: expert recommendations of the European Society of Surgical Oncology, European Society of Coloproctology, International Society of Geriatric Oncology, and American College of Surgeons Commission on Cancer. Eur J Surg Oncol 44(11):1685–1702
30. https://www.terveysportti.fi/dtk/ltk/koti?p_artikkeli=hsu00007. Accessed 6. Oct 2019
31. Gooiker GA, Dekker JW, Bastiaannet E, van der Geest LG, Merkus JW, van de Velde CJ, Tollenaar RA, Liefers GJ (2012) Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. Ann Surg Oncol 19(8):2428–2434
32. Furnes B, Storli KE, Forsmo HM, Karliczek A, Eide GE, Pfeffer F (2019) Risk factors for complications following introduction of radical surgery for colon cancer: a consecutive patient series. Scand J Surg 108(2):144–151
33. Okabe H, Ohsaki T, Ogawa K, Ozaki N, Hayashi H, Akahoshi S et al (2019) Frailty predicts severe postoperative complications after elective colorectal surgery. Am J Surg 217(4):677–681
34. Seishima R, Okabayashi K, Hasegawa H, Tsuruta M, Shigeta K, Matsui S, Yamada T, Kitagawa Y (2015) Is laparoscopic colorectal

surgery beneficial for elderly patients? A systematic review and meta-analysis. J Gastrointest Surg 19(4):756–765
35. Fearon K, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K et al (2005) Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clin Nutr 24(3):466–477
36. Forsmo HM, Erichsen C, Rasdal A, Körner H, Pfeffer F (2017) Enhanced recovery after colorectal surgery (ERAS) in elderly patients is feasible and achieves similar results as in younger patients. Geront Geriatr Med 3:2333721417706299
37. Egenvall M, Schubert Samuelsson K, Klarin I, Lökk J, Sjövall A, Martling A et al (2014) Management of colon cancer in the elderly: a population-based study. Color Dis 16(6):433–441
38. Doat S, Thiébaut A, Samson S, Ricordeau P, Guillemot D, Mitry E (2014) Elderly patients with colorectal cancer: treatment modalities and survival in France. National data from the ThInDiT cohort study. Eur J Cancer 50(7):1276–1283
39. Banks E, Byles JE, Gibson RE, Rodgers B, Latz IK, Robinson IA et al (2010) Is psychological distress in people living with cancer related to the fact of diagnosis, current treatment or level of disability? Findings from a large Australian study. Med J Aust 193(5 Suppl):S62–S67
40. Ommundsen N, Wyller TB, Nesbakken A, Bakka AO, Jordhøy MS, Skovlund E et al (2018) Preoperative geriatric assessment and tailored interventions in frail older patients with colorectal cancer: a randomized controlled trial. Color Dis 20(1):16–25
41. Van Rooijen S, Carli F, Dalton S, Thomas G, Bojesen R, Le Guen M et al (2019) Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation. BMC Cancer 19(1):98. https://doi.org/10.1186/s12885-018-5232-6

PUBLICATION
II

Long-term survival following elective colon cancer surgery in the aged. A population-based cohort study.

Susanna Niemeläinen, Heini Huhtala, Anu Ehrlich, Jyrki Kössi, Esa Jämsen, Marja Hyöty

Colorectal Dis. 2020 Nov; 22(11):1585-96. doi: 10.1111/codi.15242.

Original Article

doi:10.1111/codi.15242

Long-term survival following elective colon cancer surgery in the aged. A population-based cohort study

S. Niemeläinen*, H. Huhtala†, A. Ehrlich‡, J. Kössi§, E. Jämsen¶,,†† and M. Hyöty***

*Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere, Finland, †Faculty of Social Sciences, Tampere University, Tampere, Finland, ‡Central Hospital of Central Finland, Jyväskylä, Finland, §Päijät-Häme Central Hospital, Lahti, Finland, ¶Centre of Geriatrics, Tampere University Hospital, Tampere, Finland, **Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland, and ††Gerontology Research Center (GEREC), Tampere, Finland

Received 2 April 2020; accepted 18 June 2020; Accepted Article online 6 July 2020

Abstract

Aim The number of colorectal cancer patients increases with age. Long-term data support personalized management due to heterogeneity within the older population. This registry- and population-based study aimed to analyse long-term survival, and causes of death, after elective colon cancer surgery in the aged, focusing on patients who survived more than 3 months postoperatively.

Methods The data included patients ≥ 80 years who had elective surgery for Stage I–III colon cancer in four Finnish centres. The prospectively collected data included comorbidities, functional status, postoperative outcomes and long-term survival. Univariate and multivariate Cox regression analysis were conducted to determine factors associated with long-term survival.

Results A total of 386 surgical patients were included, of whom 357 survived over 3 months. Survival rates for all patients at 1, 3 and 5 years were 85%, 66% and 55%, compared to 92%, 71% and 59% for patients alive 3 months postoperatively, respectively. Higher age, American Society of Anesthesiologists (ASA) score ≥ 4, Charlson Comorbidity Index ≥ 6, tumour Stage III, open compared to laparoscopic surgery and severe postoperative complications were independently associated with reduced overall survival. Higher age (hazard ratio 1.97, 1.14–3.40), diabetes (1.56, 1.07–2.27), ASA score ≥ 4 (3.27, 1.53–6.99) and tumour Stage III (2.04, 1.48–2.81) were the patient-related variables affecting survival amongst those surviving more than 3 months postoperatively. Median survival time for patients given adjuvant chemotherapy was 5.4 years, compared to 3.3 years for patients not given postoperative treatment.

Conclusions Fit aged colon cancer patients can achieve good long-term outcomes and survival with radical, minimally invasive surgical treatment, even with additional chemotherapy.

Keywords Colon cancer, surgery, aged patients, long-term outcome

What does this paper add to the literature?
This register-based cohort study shows that aged colon cancer patients who are physically and functionally fit to survive surgery can achieve acceptable long-term outcomes and survival with radical surgical treatment and additional chemotherapy.

Introduction

Colorectal cancer is the second most diagnosed malignancy in Finland, and the third most diagnosed in the world [1,2]. The age-standardized incidence of colorectal cancer has globally increased 9.5%, and in Finland 17.3%, between the years 1990 and 2017. The global burden of colorectal cancer is expected to grow by 60% by 2030, to more than 2.2 million new cases and 1.1 million deaths [2]. As the population ages, older people are increasingly diagnosed with colorectal cancer [3]. Between 2013 and 2017, 26% of Finnish colorectal cancer patients were aged 80 years or older at the time of diagnosis [1].

Surgery is the cornerstone of treatment for colorectal cancer [4]. The increased number of older people results in more operations for colorectal cancer in this group [5]. Current studies show comparable disease-specific long-term survival rates for all age groups,

Correspondence to: Susanna Niemeläinen, Department of Surgery, Tays Hatanpää, PO Box 2000, 33521 Tampere, Finland.
E-mail: susanna.niemelainen@pshp.fi

which advocates for surgery with curative intent [5–7]. Conversely comorbidities, disability and the occurrence of severe postoperative complications are strongly associated with reduced short-term survival after surgery [8]. Thus, heterogeneity within the older population and differences in physical and cognitive condition make it impossible to base decision-making only on chronological age; some will survive just as younger adults, whereas others experience increased postoperative morbidity and reduced overall survival [9].

If patients survive the first year after surgery, they have reasonably good long-term survival [10]. Patients with more comorbidities have compromised postoperative outcomes [11,12]. Older patients value outcomes with good quality of life [13]. In a recent study from Italy, the authors call for studies focusing on long-term functional outcomes, to provide reliable information to patients on what to expect from cancer surgery [14]. This is important because informing older patients of the risk factors for postoperative morbidity, and diminished long-term outcomes, is essential for shared decision-making regarding surgical and non-surgical treatments [15].

The aim of this study was to analyse the long-term survival and causes of death in a consecutive population-based cohort of aged patients having colon cancer surgery. Because postoperative complications are a major risk factor of short-term mortality [8], the focus in this study was especially on the patients who survived at least 3 months after surgery.

Patients and Materials

Colon cancer patients aged 80 years and older at the time of surgery and operated in four Finnish public hospitals during 2005–2016 were included. Two of the hospitals were tertiary referral centre hospitals and two were small volume secondary care hospitals. These hospitals are responsible for colon cancer surgery in their catchment areas (100 000–250 000 inhabitants, total 750 000 inhabitants). As all colon cancer surgery in Finland is performed in public hospitals independent of social class or insurance status, the materials can be considered representative at population level.

Patients with metastatic or recurrent disease and palliative or emergency surgery were excluded. Data were extracted from prospective local colorectal databases and completed from hospital records. The dates and causes of death were obtained from the Death Certificate Register of Statistics Finland, which registers all deaths in Finland [16]. The duration of survival was calculated from the date of surgery to the date of death or to the closure of follow-up on 31 December 2018.

Recorded variables included age, living and functional status, comorbidities, modified Charlson Comorbidity Index (CCI) [17], surgical and postoperative outcomes, colon cancer recurrences or metastasis, overall survival and, for those who survived > 3 months after surgery, date and cause of death. Details of the patients' baseline characteristics and operative variables included in the study have been presented previously [8]. The diagnosis of colon cancer, operative treatment and postoperative surveillance were performed according to the standards of the study hospitals and national guidelines [18]. The postoperative complications were graded with Clavien–Dindo classification [19]. Clinical follow-up was continued for 5 years after surgery, or until death. Personal follow-up was arranged for patients considered too unfit or frail to attend a routine follow-up programme.

The data analysis focused on those patients who survived more than 3 months after the primary cancer operation, intended to exclude the effect of early postoperative mortality. The primary outcome measure was overall survival, reported separately for all patients and for those who survived over 3 months after the primary treatment.

Associations between the categorical variables were tested with the chi-squared test or the Fisher exact test, as appropriate. Survival and recurrence rates were calculated from the time of primary surgery using the Kaplan–Meier method. Log minus log plots were used to validate the proportional hazard assumption. Univariate and multivariate analyses of the factors influencing overall survival were carried out using binary logistic regression. All variables that were statistically significant in the univariate model were included in the multivariate model. Statistical analyses were performed using SPSS version 23 (IBM, Armonk, NY, USA).

The study was approved by the ethics committee of Pirkanmaa Hospital District, Tampere, Finland (R18188).

Results

A total of 386 patients fulfilled the inclusion criteria. Their median age was 83 years (range 80–96 years) and 56.2% were women. Most of the surgeries were right-sided hemicolectomy (n = 261, 67.6%), and two-thirds of the surgeries were laparoscopic (n = 252, 65.3%). 154 patients (40%) had postoperative complications with 92 (24%) patients having surgical and 62 (16%) non-surgical complications. According to the Clavien–Dindo classification, 69 (18%) patients had severe complications (Grades III–V). Reoperation was needed in 39 patients (10%), most commonly due to anastomotic leakage (n = 19). Three per cent of patients who lived at home before surgery were discharged to nursing homes. Postoperative adjuvant chemotherapy was given to 80 patients (21%), the majority of whom (n = 67, 84%) had Stage III disease. Of patients with Stage II tumour, 7.3% (13/176) received adjuvant treatment mainly due to a pT4 tumour. The detailed data of patients' baseline and clinical characteristics as well as complications and early postoperative outcomes have been described elsewhere [8]. Of the study population, 29 patients died within 3 months after surgery, mainly due to cardiovascular causes or surgical complications. The baseline and clinical characteristics of the 357 patients who survived over 3 months after surgery are shown in Table 1.

Follow-up and survival

Of the whole cohort, a total of 232 patients (60.1%) died during the follow-up period (median follow-up 6.3 years, ranging from 1 day to 14 years). Therefore, the overall survival rate was 39.9%. The 1-year survival rate was 85% (327/386), and the 3- and 5-year rates were 66% (255/386) and 55% (211/386), respectively. The median overall survival time was 5.4 years (95% CI 4.72–6.08). For patients who survived the first 3 months after surgery (n = 357), the 1-, 3- and 5-year survival rates were 92%, 71% and 59%, respectively. The median survival time for these patients was 5.9 years (95% CI 5.31–6.48). Age-related survival for patients who survived over 3 months after surgery is presented in Fig. 1. The overall median survival time for patients with no complications was 5.9 years (95% CL 5.30–6.50), with mild complications 5.2 years (3.87–6.49) and with severe complications 1.8 years (0.18–3.34). The survival analysis of complications in patients who survived over 3 months after operation is shown in Fig. 2, and the respective survival proportions at 1, 3 and 5 years are shown in Table 2.

Recurrences and adjuvant chemotherapy

The recurrence rate for the whole study population was 17.6% (68 patients). Distant recurrence rate was 15%, involving liver (27 patients), lung (12 patients), peritoneum (17 patients) and pelvis (two patients). Local recurrence rate was 2.6% (10 patients). According to the Union for International Cancer Control stages, recurrences developed in 8.2%, 8.4% and 32.9% of Stage I, Stage II and Stage III tumours, respectively. The recurrence rate was 8.5% (33 patients) at 1 year, 14.7% (57 patients) at 3 years and 16.1% (62 patients) at 5 years. The median survival times with tumour Stages I, II and III in the whole study cohort were 5.9 (95% CI 4.16–7.58), 6.5 (4.67–8.37) and 3.5 years (2.04–5.01), respectively. The comparable figures for patients who survived over 3 months postoperatively were 5.9 years (95% CI 4.65–7.15) for Stage I, 7.5 years (5.89–9.19) for Stage II and 4.4 years (3.03–5.75) for Stage III.

Patients with Stage III disease who received postoperative adjuvant chemotherapy had a median survival time of 5.4 years, compared to 2.3 years for those who did not receive postoperative chemotherapy (P = 0.001, log-rank). The respective figures for patients who survived over 3 months after surgery were 5.4 and 3.3 years (P = 0.025, log-rank). The survival analysis for patients who survived over 3 months with different tumour stages (I–III) is shown in Fig. 3.

Causes for death

The most frequent causes of death within 3 months after surgery (n = 29) were cardiopulmonary (55%) and surgery-related (24%) factors. Of the deaths that occurred after 3 months of surgery (n = 203), 30% were due to colon cancer, 44% due to cardiopulmonary reasons and 10% due to dementia. The causes of death within and after 3 months of surgery are shown in Fig. 4.

Factors influencing survival

Univariate Cox regression analysis showed that higher age, living in a nursing home, diabetes, coronary disease, congestive heart failure, chronic renal insufficiency, American Society of Anesthesiologists (ASA) score ≥ 3, CCI score ≥ 6, open compared to laparoscopic operation, tumour stage and severe postoperative complications were associated with poor survival after surgery. Multivariate Cox regression survival analysis showed that higher age [hazard ratio (HR) 1.08, 95% CI 1.04–1.13, P < 0.001], living in a nursing home (HR 1.54, 1.03–2.30, P = 0.034), ASA score ≥ 4 (HR 2.62, 1.32–5.21, P = 0.006), CCI score ≥ 6 (HR 1.47, 1.07–2.01, P = 0.018), tumour Stage III (HR 1.88, 1.40–2.52, P < 0.001), open compared to laparoscopic surgery (HR 1.41, 1.05–1.88, P = 0.020) and severe postoperative complications (HR 2.11, 1.49–2.99, P < 0.001) were independently associated with diminished overall survival in the whole cohort. For patients who survived over 3 months after surgery these same patient-related variables, except chronic renal insufficiency and type of surgery, were significant in univariate Cox regression analysis. In multivariate Cox regression analysis age ≥ 90 years, living in a nursing home, diabetes, ASA score ≥ 4 and tumour Stage III were independently associated with diminished survival. Detailed

Table 1 Baseline and clinical characteristics of patients who survived at least 3 months after surgery.

	n, median	% (range)
Gender ratio (female/male)	205/152	57/43
Age (years)	83.0	(80–96)
80–84	233	65
85–89	96	27
≥ 90	28	8
Type of living		
Home	313	87.7
Nursing home	31	8.7
Not known	13	3.6
Aid at home		
No	145	40.6
Yes	109	30.5
Not known	103	28.9
BMI (kg/m^2)	25.0	15.4–40.6
< 25	150	42.0
25–29.9	102	28.6
30–	45	12.6
Not available	60	16.8
ASA score		
2	34	9.5
3	248	69.5
4	70	19.6
Not known	5	1.4
CCI (modified)		
4–5	227	63.6
7–12	130	36.4
Procedure		
Right-sided colectomy	250	70.0
Left-sided colectomy	93	26.0
Other colonic resection	14	4.0
Type of surgery		
Open	120	33.6
Laparoscopy	204	57.1
Conversion	33	9.2
Postoperative complications		
None	229	64.1
Minor complications (CD I–II)	83	23.2
Major complications (CD III–V)	45	12.6
Length of hospitalization (days)	7	2–58
Reoperation	32	9.0
Readmission	23	6.4
TNM stage		
1	46	12.9
2	176	49.3
3	135	37.8
Number of lymph nodes	15	0–71
Postoperative adjuvant therapy	80	22.4
Stage III (*n* = 135)	67	43.3

ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson Comorbidity Index; CD, Clavien–Dindo classification.

analysis data of patients who survived over 3 months are shown in Table 3.

Discussion

Treatment decisions for colon cancer in the aged population have become extremely important as the number of these patients rises due to increased life expectancy. The results of this register- and population-based cohort study of 386 electively operated, non-metastatic colon cancer patients aged ≥ 80 years suggest that, for physically and cognitively fit patients, surgical treatment with curative intent can lead to similar long-term survival as for younger patients. This is especially true when the patients survive the critical first 3 months after surgery.

The study hospitals had standardized protocols for treatment and follow-up based on national evidence based medicine guidelines [18], and the nationwide registers ensured comprehensive death records. There were no statistical differences in patients' baseline characteristics, operative outcomes and tumour characteristics between the four operating hospitals. Considering the older population, it was valuable that we could identify preoperative morbidity and living arrangements, although functional ability could not be clarified in detail. Supporting earlier observations [20,21], postoperative complications were common (40%) and almost half of them (45%) were severe (Grade III–V according to the Clavien–Dindo classification). As complications are a major predictor of short-term mortality [8], we intended to analyse their continued effect among the patients who survived the early postoperative period, through longer-term follow-up. Among all patients with severe complications (Clavien–Dindo III–V), 1-year and overall survival were 45% and 27.5%. However, those who survived the first three postoperative months had survival rates comparable to those with no or mild complications. Thus, preventing complications through preoperative health evaluation is essential, especially for high-risk patients [8].

In 2018, the median life expectancy for Finns aged 80 years and over was 9.9 years for women and 8.2 years for men [22]. In our study (with an average age of 83 years), the overall median survival time was 5.4 years, increasing to 5.9 years when early postoperative deaths were excluded. The 5-year survival rates (54.7% in the whole cohort and 59.1% in patients who survived over 3 months after surgery) are comparable or slightly higher than the figures reported in the EUROCARE-5 study (49% for colon cancer patients aged 75 years or older and 57% for all ages) [23]. The large SEER database study from the USA shows similar

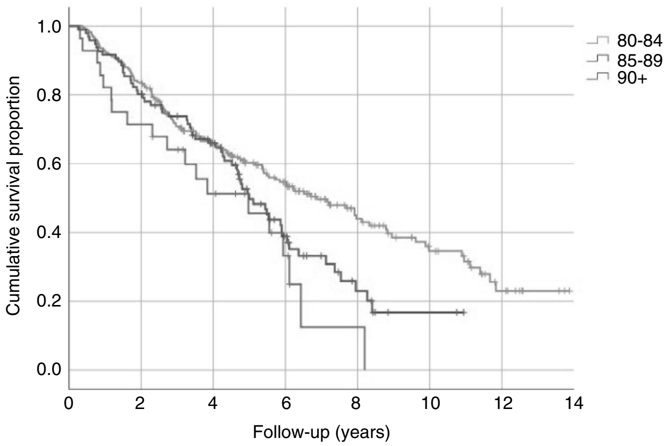

Figure 1 Kaplan–Meier analysis of age-related overall survival in patients who survived at least 3 months after surgery ($P = 0.005$, log-rank).

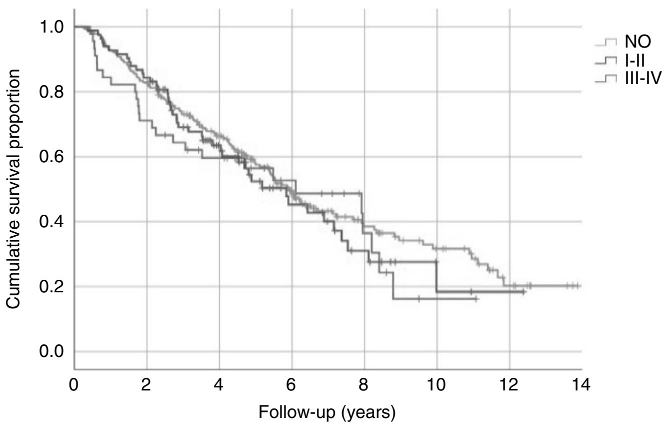

Figure 2 Kaplan–Meier analysis of overall survival in patients who survived at least 3 months after surgery with and without complications graded with Clavien–Dindo classification ($P = 0.575$, log-rank).

survival rates for Stage II rectal cancers for patients aged 80 years or over treated with resection and neoadjuvant therapy as for younger patients [24], and patients treated non-operatively had lower survival than those who underwent surgery. In an English study, which included non-operatively treated Stage I–III colorectal cancer patients over 80 years, the average life expectancy following diagnosis was 1.5 years, and only 20% of patients survived over 3 years [25]. The non-operative outcomes are as essential as surgical outcomes to patients. The authors thus suggested that cancer surgery is not beneficial for frail aged patients and has higher risks for postoperative morbidity and reduced survival than for physically and mentally fit patients. Conversely, in a recent case series study from the UK, elective surgical management of carefully selected nonagenarian (over 90 years) patients enabled the majority to return to the same functional level of care following discharge [26].

Altogether, our data and previous reports show that elderly patients who are fit enough to survive the early perioperative period have similar overall survival times to younger patients. On the other hand, severe ill-health, living in a nursing home and the occurrence of complications considerably impair long-term survival. Generally, chronic conditions and multiple morbidities increase mortality and prolonged hospitalizations in the

Table 2 Survival proportion at 1, 3 and 5 years of patients who survived at least 3 months after surgery.

	Survival proportion (%)							
	n	%	1 year	*P* value	3 years	*P* value	5 years	*P* value
Gender								
Male	152	42.6	93.4	0.337	69.7	0.556	59.2	1.000
Female	205	57.4	90.2		72.7		59.0	
Age								
80–84	233	65.3	92.7	0.163	71.2	0.605	62.2	0.238
85–89	96	26.9	91.7		74.0		54.2	
≥ 90	28	7.8	82.1		64.3		50.0	
BMI (kg/m^2)								
< 25	150	42.0	91.3	0.966	70.7	0.972	55.3	0.516
25–29.9	102	28.6	92.2		70.6		61.8	
≥ 30	45	12.6	91.1		68.9		62.2	
Type of living								
Home	313	87.7	92.0	0.729	72.2	0.098	60.1	0.051
Nursing home	31	8.7	90.3		58.1		41.9	
Aid at home								
None	145	40.6	93.8	0.751	84.1	< 0.001	73.1	< 0.001
Relatives	58	16.2	91.4		58.6		44.8	
Other	51	14.3	92.2		58.8		41.2	
Hospital admissions								
< 6 months								
No	266	74.5	91.4	0.643	70.3	0.499	58.6	0.977
One or more	85	23.8	92.9		74.1		58.8	
ASA score								
2	34	9.5	97.1	0.463	76.5	0.001	76.5	0.002
3	248	69.5	90.7		76.2		61.7	
4	70	19.6	91.4		54.3		42.9	
CCI (modified)								
4–6	302	84.6	92.1	0.434	73.8	0.023	61.9	0.016
7–12	55	15.4	89.1		58.2		43.6	
Type of operation								
Laparoscopy	204	57.2	94.1	0.140	74.5	0.312	61.8	0.282
Conversion	33	9.2	87.9		69.7		63.6	
Open	120	33.6	88.3		66.7		53.3	
Postoperative complications								
None	229	64.1	92.6	0.180	73.4	0.451	59.8	0.933
CD I–II	83	23.2	92.8		69.9		57.8	
CD III–V	45	12.6	84.4		64.4		57.8	
Tumour stage								
I	45	12.9	95.7	0.031	78.3	< 0.001	58.7	0.003
II	176	49.3	94.3		79.0		67.6	
III	135	37.8	86.7		59.3		48.1	
Postoperative adjuvant therapy (Stage III)								
No	68	50.4	83.8	0.449	51.5	0.080	39.7	0.059
Yes	67	49.6	89.6		67.2		56.7	

ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson Comorbidity Index; CD, Clavien–Dindo classification.

elderly [27], and severe complications are more common in patients who have preoperative hospitalizations and who live in nursing homes [28]. Complications and older age [29] are associated with lower health-related quality of life after cancer surgery. Thus, careful preoperative assessment of physical and cognitive fitness, and

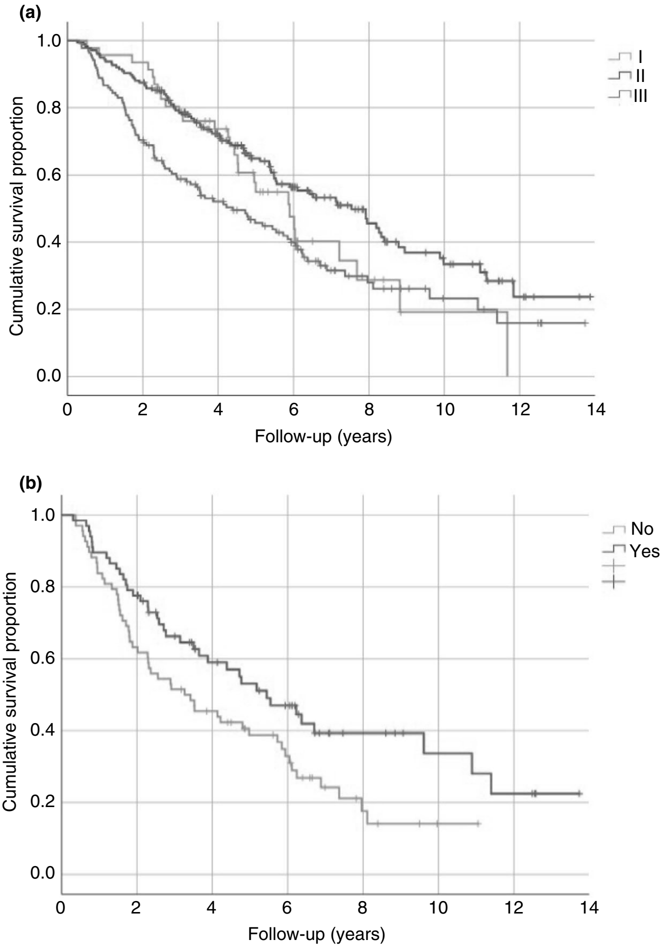

Figure 3 Kaplan–Meier analysis of overall survival in patients who survived at least 3 months after surgery, according to (a) tumour stage ($P = 0.002$, log-rank) and (b) adjuvant therapy ($P = 0.025$, log-rank).

the provision of accurate and clear information about treatment options, allows patients to participate in management decisions and contributes to good outcomes and long-term patient satisfaction and quality of life.

The leading causes of death in our cohort were cardiovascular (31%), colon cancer (28%), pulmonary (14%) and dementia (8.6%). Noticeably, colon cancer is not the most frequent cause of death in these older cancer patients. Diabetes, coronary artery disease and congestive heart failure were important predictors of mortality in very old age in a large Finnish follow-up study [27]. The same factors were significantly associated with reduced survival in our data. In the total study population, only 3.9% of patient deaths were directly related to surgery, although patients with severe surgical complications had greatly reduced median survival (3.7 months) compared to patients with cardiopulmonary causes (2.9 years) [8]. However, those patients with severe surgical complications who survived more than 3 months had similar long-term outcomes to those without or with minor complications. In contrast, a Dutch study reported that severe postoperative complications were most predictive of diminished long-term survival [30].

Studies from Spain and Italy show that laparoscopy is safe in the older population with increased comorbidity and leads to better short-term outcomes than open procedures and equivalent long-term oncological

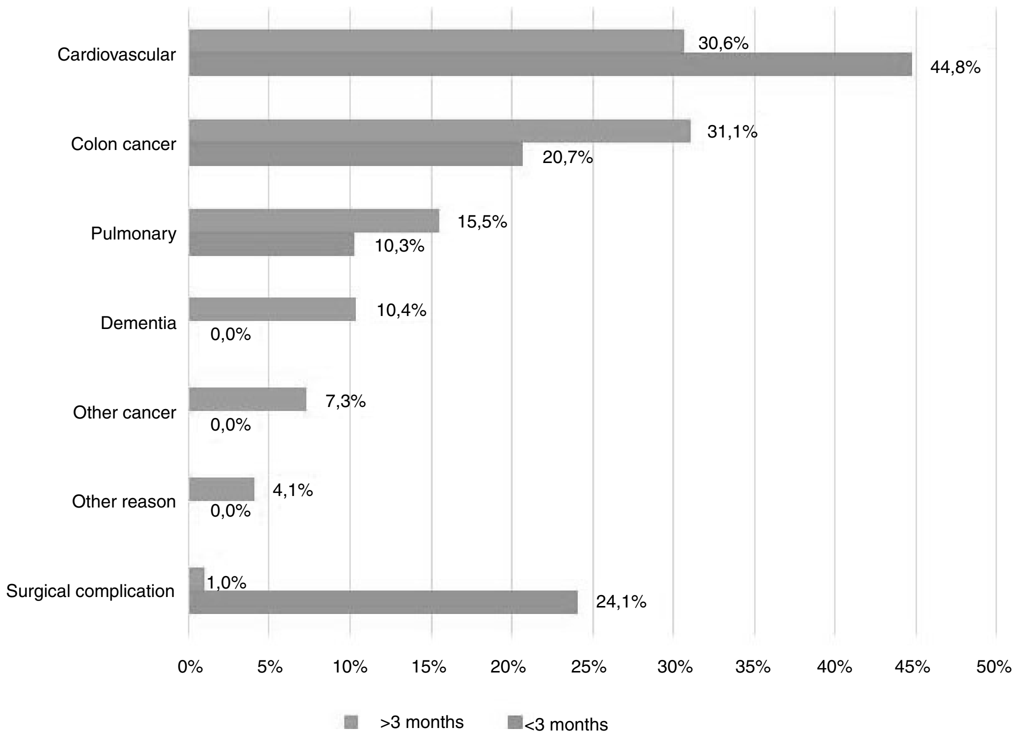

Figure 4 Causes of death within and after 3 months of surgery (n = 29 and n = 193).

outcomes [31,32]. A review article from the UK shows that age is not a risk factor or a limitation for laparoscopic colorectal surgery, and even very old patients may benefit from a minimally invasive approach [33]. In our study the overall median survival time for patients operated with a laparoscopic approach (5.8 years) was significantly better than survival after an open operation (4.4 years). The knowledge of the benefits of minimally invasive surgery has changed our study hospitals' practices, and laparoscopy is now considered the best approach for colon cancer surgery for aged patients.

Besides age, high comorbidity burden and complications, the only significant factor affecting survival was tumour stage. Long-term survival and recurrent disease depend on the stage of tumour [30]. Stage III disease is associated with diminished survival [4,30,34]. The recurrence rate was 17.6%, with Stage I 8.2%, Stage II 8.4% and Stage III 32.9%. The high proportion of Stage I recurrences may reflect the quality of individual pathology reports (lymph nodes counted 10–18 in four Stage I patients) or tumour biology. Otherwise the numbers correspond to recent studies from Sweden and Denmark [35,36]. However, the real rate of recurrences in our series may have been higher, as further investigations and treatment may have been stopped by an unwilling patient or by a physician who considered a patient too frail or unfit. Some of the patients may have died from non-cancer-related causes while having recurrences. In contrast, patients with Stage III disease receiving adjuvant chemotherapy had significantly better overall survival rate compared to patients not having postoperative therapy, comparable to recent studies [37,38]. That finding suggests that, for patients fit enough to survive radical surgery, adjuvant chemotherapy is advisable.

There are some limitations to our study. Due to its retrospective nature, detailed information on daily physical and cognitive functional activity as well as the severity of the comorbidities could not be documented. Thus, patients with better health status were likely to be selected for operative treatment. Exact long-term data of cancer recurrences was not complete, as invasive investigations may not have been performed for physically and cognitively unfit patients. However, our

Table 3 Factors influencing survival with patients who survived at least 3 months after surgery (Cox regression analysis).

	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (years)						
80–84	1					
85–89	1.45	1.06–1.99	0.020	1.29	0.91–1.83	0.148
> 90	1.96	1.20–3.20	0.007	1.97	1.14–3.40	0.015
Gender						
Female	1					
Male	1.12	0.84–1.48	0.450			
Type of living						
Home	1			1		
Nursing home	1.76	1.17–2.65	0.006	1.56	1.01–2.43	0.047
Hospital admissions ≤ 6 months						
No	1					
Yes	1.06	0.76–1.46	0.746			
BMI (kg/m^2)						
< 25	1					
25–29.9	0.89	0.63–1.25	0.506			
> 30	0.89	0.57–1.40	0.616			
Diabetes						
No	1			1		
Yes	1.45	1.05–2.01	0.026	1.56	1.07–2.27	0.022
Hypertension						
No	1					
Yes	1.06	0.80–1.41	0.672			
Coronary heart disease						
No	1			1		
Yes	1.50	1.11–2.01	0.008	0.98	0.69–1.38	0.890
Congestive heart failure						
No	1			1		
Yes	1.65	1.04–2.63	0.033	1.24	0.69–2.21	0.470
Arteriosclerosis obliterans (ASO)						
No	1					
Yes	0.710	0.22–2.27	0.563			
Renal failure						
No	1					
Yes	1.61	0.97–2.69	0.067			
Celebral stroke						
No	1					
Yes	1.49	0.99–2.26	0.057			
Atrial fibrillation						
No	1					
Yes	1.28	0.93–1.76	0.130			
Chronic pulmonary disease						
No	1					
Yes	1.38	0.61–3.11	0.442			
Rheumatic diseases						
No	1					
Yes	1.24	0.61–2.51	0.554			
Dementia						
No	1					
Yes	1.22	0.79–1.89	0.378			

Table 3 (Continued).

	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Other cancer						
No	1					
Prostate	1.35	0.77–2.39	0.297			
Breast	1.02	0.45–2.32	0.957			
Colorectal	1.35	0.66–2.76	0.404			
Urinary tract	0.68	0.17–2.73	0.583			
Gynaecology	0.77	0.25–2.41	0.652			
Other cancer	1.68	1.02–2.77	0.043	0.94	0.51–1.75	0.849
ASA score						
2	1			1		
3	2.22	1.23–4.02	0.008	1.93	0.99–3.75	0.053
4	3.92	2.05–7.48	< 0.001	3.27	1.53–6.99	0.002
CCI (modified)						
4–5	1			1		
6–12	1.68	1.26–2.22	< 0.001	1.52	0.99–2.34	0.055
Tumour stage						
1–2	1			1		
3	1.61	1.23–2.12	0.001	2.04	1.48–2.81	< 0.001
Type of operation						
Laparoscopy/conversion	1			1		
Open	1.35	1.02–1.78	0.038	1.37	1.00–1.88	0.051
Postoperative complications						
CD 0–II[b]	1					
CD III–V	1.17	0.78–1.77	0.450			
Surgical complication						
No	1					
Yes	1.23	0.88–1.71	0.228			
Non-surgical complication						
No	1					
Yes	1.04	0.71–1.54	0.836			

ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson Comorbidity Index; CD, Clavien–Dindo classification; HR, hazard ratio.

findings propose that surgery in aged patients diagnosed with colon cancer can lead to acceptable long-term outcomes, comparable with younger patients.

In conclusion, this study extends our earlier findings [8] and suggests that aged colon cancer patients who are physically and functionally fit to survive surgery can achieve acceptable long-term outcomes and survival with radical surgical treatment and additional chemotherapy. Further prospective studies are required to identify patients who are at risk of complications and able to recover from them as well as the effects of colon cancer surgery on the quality of life in long-term follow-up.

Acknowledgements

The authors warmly thank M.D. Ville Väyrynen, Central Hospital of Central Finland, and M.D. Anu Välikoski Tays Hatanpää, Tampere University Hospital, for their contribution to data collection, and M.D. Kirk Langley, Fremantle Hospital, WA, Australia, for his help in editing English language.

Funding

This study was financially partly supported by the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1 Finnish Cancer Registry. www.cancerregistry.fi (accessed March 2020).

2 GBD 2017 Colorectal Cancer Collaborators. The global, regional, and national burden of colorectal cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2019; **4:** 913–33.

3 Neuman HB, O'Connor ES, Weiss J *et al.* Surgical treatment of colon cancer in patients aged 80 years and older: analysis of 31,574 patients in the SEER-Medicare database. *Cancer* 2013; **119:** 639–47.

4 Merkel S, Weber K, Matzel KE, Agaimy A, Göhl J, Hohenberger W. Prognosis of patients with colonic carcinoma before, during and after implementation of complete mesocolic excision. *Br J Surg* 2016; **103:** 1220–9.

5 Jafari MD, Jafari F, Halabi WJ *et al.* Colorectal cancer resections in the aging US population: a trend toward decreasing rates and improved outcomes. *JAMA Surg* 2014; **149:** 557–64.

6 Mothes H, Bauschke A, Schuele S, Eigendorff E, Altendorf-Hofmann A, Settmacher U. Surgery for colorectal cancer in elderly patients: how can we improve outcome? *J Cancer Res Clin Oncol* 2017; **43:** 1879–89.

7 Oh BY, Huh JW, Kim HC *et al.* Oncologic outcome of colorectal cancer patients over age 80: a propensity score-matched analysis. *Int J Colorectal Dis* 2018; **33:** 1011–8.

8 Niemeläinen S, Huhtala H, Ehrlich A, Kössi J, Jämsen E, Hyöty M. Risk factors of short-term survival in the aged in elective colon cancer surgery: a population-based study. *Int J Colorectal Dis* 2020; **35:** 307–15.

9 Papamichael D, Audisio RA, Glimelius B *et al.* Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2015. *Ann Oncol* 2015; **26:** 463–76.

10 Bos ACRK, Kortbeek D, van Erning FNT *et al.* Postoperative mortality in elderly patients with colorectal cancer: the impact of age, time-trends and competing risks of dying. *Eur J Surg Oncol* 2019; **45:** 1575–83.

11 Sheridan J, Walsh P, Kevans D *et al.* Determinants of short- and long-term survival from colorectal cancer in very elderly patients. *J Geriatr Oncol* 2014; **5:** 376–83.

12 Tominaga T, Nonaka T, Takeshita H *et al.* The Charlson Comorbidity Index as an independent prognostic factor in older colorectal cancer patients. *Indian J Surg* 2018; **80:** 54–60.

13 Souwer ETD, Oerlemans S, van de Poll-Franse LV *et al.* The impact of colorectal surgery on health-related quality of life in older functionally dependent patients with cancer – a longitudinal follow-up study. *J Geriatr Oncol* 2019; **10:** 724–32.

14 Giannotti C, Sambuceti S, Signori A *et al.* Frailty assessment in elective gastrointestinal oncogeriatric surgery: predictors of one-year mortality and functional status. *J Geriatr Oncol* 2019; **10:** 716–23.

15 Samuelsson KS, Egenvall M, Klarin I, Lökk J, Gunnarsson U, Iwarzon M. The older patient's experience of the healthcare chain and information when undergoing colorectal cancer surgery according to the enhanced recovery after surgery concept. *J Clin Nurs* 2018; **27:** e1580–e88.

16 Lahti RA, Penttilä A. The validity of death certificates: routine validation of death certification and its effects on mortality statistics. *Forensic Sci Int* 2001; **115:** 15–32.

17 Chang CM, Yin WY, Wei CK *et al.* Age-adjusted Charlson Comorbidity Index score as a risk measure of perioperative mortality before cancer surgery. *PloS One* 2016; **11:** e0148076.

18 HUS FICAN working committee. Finnish National Guidelines for the treatment of colorectal cancer. 2019.

19 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240:** 205–13.

20 Fagard K, Casaer J, Wolthuis A *et al.* Postoperative complications in individuals aged 70 and over undergoing elective surgery for colorectal cancer. *Colorectal Dis* 2017; **19:** O329–38.

21 Aquina CT, Mohile SG, Tejani MA *et al.* The impact of age on complications, survival, and cause of death following colon cancer surgery. *Br J Cancer* 2017; **116:** 389–97.

22 Statistics Finland. www.tilastokeskus.fi (accessed March 2020).

23 Holleczek B, Rossi S, Domenic A *et al.* Ongoing improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999–2007. Results from the EUROCARE-5 study. *Eur J Cancer* 2015; **51:** 2158–68.

24 Bhangu A, Kiran RP, Audisio R *et al.* Survival outcome of operated and non-operated elderly patients with rectal cancer: a Surveillance, Epidemiology, and End Results analysis. *Eur J Surg Oncol* 2014; **40:** 1510–6.

25 Bethune R. What happens when we do not operate? Survival following conservative bowel cancer management. *Ann R Col Surg* 2016; **98:** 409–12.

26 Au S, Ventham NT, Yalamarthi S, Manimaran N. Colorectal cancer outcomes in nonagenarian patients: a case series. *Int J Surg* 2018; **55:** 139–44.

27 Halonen P, Raitanen J, Jämsen E, Enroth L, Jylhä M. Chronic conditions and multimorbidity in population aged 90 years and over: associations with mortality and long-term care admission. *Age Ageing* 2019; **48:** 564–70.

28 Okabe H, Ohsaki T, Ogawa K *et al.* Frailty predicts severe postoperative complications after elective colorectal surgery. *Am J Surg* 2019; **217:** 677–81.

29 Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. *Ann Surg* 2014; **259:** 916–23.

30 Weerink LBM, Gant CM, van Leeuwen BL, de Bock GH, Kouwenhoven EA, Faneyte IF. Long-term survival in octogenarians after surgical treatment for colorectal cancer:

prevention of postoperative complications is key. *Ann Surg Oncol* 2018; **25:** 3874–82.

31 Vallribera Valls F, Landi F, Espín Basany E *et al.* Laparoscopy-assisted versus open colectomy for treatment of colon cancer in the elderly: morbidity and mortality outcomes in 545 patients. *Surg Endosc* 2014; **28:** 3373–8.

32 Roscio F, Boni L, Clerici F, Frattini P, Cassinotti E, Scandroglio I. Is laparoscopic surgery really effective for the treatment of colon and rectal cancer in very elderly over 80 years old? A prospective multicentric case–control assessment. *Surg Endosc* 2016; **30:** 4372–82.

33 Devoto L, Celentano V, Cohen R, Khan J, Chand M. Colorectal cancer surgery in the very elderly patient: a systematic review of laparoscopic versus open colorectal resection. *Int J Colorectal Dis* 2017; **32:** 1237–42.

34 Tan KK, Koh FH, Tan YY, Liu JZ, Sim R. Long-term outcome following surgery for colorectal cancers in octogenarians: a single institution's experience of 204 patients. *J Gastrointest Surg* 2012; **16:** 1029–36.

35 Osterman E, Glimelius B. Recurrence risk after up-to-date colon cancer staging, surgery, and pathology: analysis of the entire Swedish population. *Dis Colon Rectum* 2018; **61:** 1016–25.

36 Bertelsen CA, Neuenschwander AU, Jansen JE *et al.* Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a retrospective, population-based study. *Lancet Oncol* 2015; **16:** 161–8.

37 Delgado MV, Serrano CS, de la Fuente EC *et al.* Efficacy of adjuvant chemotherapy for elderly patients with colon cancer. *Ann Oncol* 2018; **29(Suppl 5):** v65.

38 Kawamura H, Morishima T, Sato A, Honda M, Miyashiro I. Effect of adjuvant chemotherapy on survival benefit in stage III colon cancer patients stratified by age: a Japanese real-world cohort study. *BMC Cancer*. 2020; **20:** 19.

PUBLICATION III

The Clinical Frailty Scale is a useful tool for predicting postoperative complications following elective colon cancer surgery in the age of 80 years and older: A prospective, multicentre observational study.

Susanna Niemeläinen, Heini Huhtala, Jan Andersen, Anu Ehrlich, Eija Haukijärvi, Suvi Koikkalainen, Selja Koskensalo, Jyrki Kössi, Anne Mattila, Tarja Pinta, Mirjami Uotila-Nieminen, Hanna Vihervaara, Marja Hyöty, Esa Jämsen

.

Colorectal Dis. 2021 Jul;23(7):1824-36. doi: 10.1111/codi.15689.

Clinical Frailty Scale is a useful tool for predicting postoperative complications following elective colon cancer surgery in the age of 80 years and older: A prospective, multicentre observational study.

Susanna Niemeläinen[1], Heini Huhtala[2], Jan Andersen[3], Anu Ehrlich[4], Eija Haukijärvi[1], Suvi Koikkalainen[6], Selja Koskensalo[4,5], Jyrki Kössi[7], Anne Mattila[8], Tarja Pinta[9], Mirjami Uotila-Nieminen[10], Hanna Vihervaara[11,12], Marja Hyöty[1], Esa Jämsen[13,14,15]

Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere, Finland[1], Faculty of Social Sciences, Tampere University, Tampere, Finland[2], Department of Surgery, Vaasa Central Hospital, Vaasa, Finland[3], Department of Abdominal Surgery, Helsinki University Hospital, Finland[4], Faculty of Medicine, Helsinki University, Helsinki, Finland[5], Department of Surgery, Satakunta Central Hospital, Pori, Finland[6], Department of Surgery, Päijät-Häme Central Hospital, Lahti, Finland[7], Department of Surgery, Central Hospital of Central Finland, Jyväskylä, Finland[8], Department of Surgery, Seinäjoki Central Hospital, Seinäjoki, Finland[9], Department of Surgery, North Karelia Central Hospital, Joensuu, Finland[10], Division of Digestive Surgery and Urology, Turku University Hospital, Turku, Finland[11], Faculty of Medicine, Turku University, Turku[12], Finland, Centre of Geriatrics, Tampere University Hospital, Tampere, Finland[13], Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland[14], Gerontology Research Center (GEREC), Tampere, Finland[15].

Corresponding author: MD Susanna Niemeläinen, Department of Gastroenterology and Alimentary Tract Surgery, TAYS Hatanpää, Tampere University Hospital, Tampere, Finland. P.O. Box 2000, 33521 Tampere, Finland

Email address: susanna.niemelainen@pshp.fi). ORCID number 0000-0003-1910-2640.

What does this paper add to the literature? This study showed that aged patients have high morbidity rates after curative colon cancer surgery despite modern achievements in operative treatment. However, the fittest patients had acceptable and similar operative outcomes to younger patients. Clinical Frailty Scale appears like a beneficial screening tool for predicting these adverse events.

Abstract

Background Identifying risks of postoperative complications may be challenging in older patients with heterogeneous physical and cognitive status. The aim of this multicentre, observational study was to identify variables that affect colon cancer surgery outcomes and, especially to find tools to quantify the risks related to surgery.

Methods Patients aged ≥80 years with electively operated stage I-III colon cancer were recruited. The prospectively collected data included comorbidities, onco-geriatric screening tool (G-8), Clinical Frailty Scale (CFS), Charlson Comorbidity Index (CCI), Mini Nutritional Assessment-Short Form (MNA-SF), operative and postoperative outcomes.

Results A total of 161 patients (mean 84.5 years, range 80-97, 60% female) were included. History of cerebral stroke (64% vs 37%, p=0.02), albumin level 31-34 g/L compared to ≥35 g/L (57% vs 32%, p=0.007), CFS 3-4 and 5-9 compared to CFS 1-2 (49% and 47% vs 16%, respectively) and ASA >3 (77% vs 28%, p=0.006) were related to higher risk of complications. In multivariate logistic regression analysis CFS ≥3 (OR 6.06, 95% CI 1.88-19.5, p=0.003) and albumin level 31-34 g/L (OR 3.88, 1.61-9.38, p=0.003) were significantly associated with postoperative complications. Severe complications were more common in patients with COPD (43% vs 13%, p=0.047), renal failure (25% vs 12%, p=0.021), albumin level 31-34 g/L (26% vs 8%, p=0.014) and CCI >6 (23% vs 10%, p=0.034).

Conclusion Surgery on physically and cognitively fit aged colon cancer patients with CFS 1-2 can lead to excellent operative outcomes, like those of younger patients. CFS could be a useful screening tool for predicting postoperative complications.

Introduction

Colorectal cancer is the second leading cause of cancer death and the fourth most diagnosed malignancy in the world (1). The risk of developing colorectal cancer increases with age. Thus, as the world population ages, the number of patients experiencing colorectal cancer rises (2). Colorectal cancer surgery in the aged is considered high risk for postoperative complications and compromised functional recovery (3). The incidence of adverse events with colon cancer surgery ranges from 20% to 76% (4,5,6,7). It is more significant with advancing age and frailty, identified as a greater vulnerability in physical and cognitive status (7,8).

Old people are a heterogeneous group of patients, so the risk of postoperative complications cannot be judged only by chronological age (9). Preoperative risk estimation of postoperative complications, recognition of frailty, and identification of patients at greater risk of unfavourable treatment consequences are essential for optimising aged patients for surgery and thereby improving postoperative outcomes (10,11).

Tools used in the preoperative comprehensive geriatric assessment of onco-geriatric surgical patients are often time-consuming and require special training and knowledge of gerontology (12). Clinical Frailty Scale (CFS) has been developed for rapid frailty screening without the need for specific geriatric expertise or functional testing (13). The only prospective study concerning CFS and postoperative complications in older patients after elective colorectal cancer surgery concluded that frail patients (CFS ≥4) had more severe postoperative complications, leading to higher mortality rates (14). Otherwise, prospective studies in elective colon cancer surgery with aged patients focusing on preoperative frailty and postoperative complications are lacking.

This prospective observational multicentre study aimed to identify characteristics of aged colon cancer patients that affect postoperative morbidity and mortality. Special interest was focused on screening tools like CFS and their relationship to postoperative outcomes with patients 80 years and over.

Patients and methods

Study design

A multicentre, prospective observational cohort study of patients aged 80 years or older with stage I-III colon cancer was designed to analyse the impact of surgery on functional ability, complications, and mortality along with the predictors of these outcomes. Nine Finnish hospitals participated in the study. The total catchment area was 3.88 million people, representing 70.4% of Finland's population. Treatment of colon cancer in Finland is performed by public health care. Patients were treated at precise hospitals based on their place of residence, so the study provided a nationwide spectrum of operative management of colon cancer in the aged.

This study followed the STROBE guidelines (15) (Appendix 1). The Ethics Committee of Tampere University Hospital and the institutional review boards at each study site approved the study protocol (reference approval number R19028). The study was registered in ClinicalTrials.gov (NCT03904121) in April 2019.

Participants

Recruitment was initiated in April 2019 and, for this study, continued until July 2020. All patients aged 80 years or over with recently diagnosed stage I-III colon cancer referred to surgical units for consideration of operative treatment were eligible to participate in the study. Patients were informed of the study and gave written informed consent. If the patient was cognitively impaired, the consent was provided by a legally authorised representative or family member. Patients with metastatic disease, emergency operations, or an expected life expectancy of less than six months were excluded. Patients who consented to the study but were treated nonoperatively, had metastatic or benign disease at surgery were excluded from the present analysis.

Data collection

Data was collected prospectively to the electronic case record forms using RedCap (Research Electronic Data Capture) database (16). The primary investigator, who was the managing surgeon at each study site, was responsible for data collection. The primary investigator or research nurses of each study site were charged to ensure that the patient questionnaires (Appendix 1) were completed. Operative data and postoperative outcomes were gathered prospectively during hospital stay and at follow-up visits. Patient questionnaires were collected before and one month after surgery at outpatient clinics, and surgical follow-ups conducted either by telephone call or by mail.

The collected clinical data included patient physical and functional characteristics, G-8 (17), CFS (13), comorbidities, nutritional status and characteristics of surgical treatment (Appendix 2). Postoperative complications were defined and determined using the Clavien-Dindo classification (CD) graded from grade 0 to V (18). Classes III-V complications were considered severe. Tumours were staged according to the Union for International Cancer Control (UICC) TNM classification (19). The number of positive and total number of lymph nodes was recorded in every case. The lymph node ratio (LN) ratio (20) was calculated by defining the proportion of metastatic lymph nodes from the total number of LNs examined.

Definition of variables

Age was analysed in three groups of 80-84 years, 85-89 years, and ≥90 years. Body mass index (BMI) was categorised into three groups: <24 kg/m^2, 24-29 kg/m^2 and ≥30 kg/m^2 (21).

G-8 ranged from 0 to 17. Geriatric evaluation is recommended for patients whose score was ≤14 (17). For analyses, patients were divided into three groups: <12, 12-14 and >14 for the clinical facility.

CFS was subdivided and analysed in three groups: very fit or fit (1-2), independent but not regularly active in daily life or vulnerable (3-4) and frail with severe limitations in daily activities (5-9) (13).

American Society of Anaesthesiologists risk score ASA (22), and age-adjusted Charlson Comorbidity Index CCI (23) were used as measures of anaesthesiologist, comorbidity burden and mortality risk. Based on ASA, the patients were analysed in three groups: 2, 3 and 4 (the lowest score was 2, as all patients were 80 years or older). CCI scores ranged from 4–15 (solid tumour was ignored, all patients received four points for their age). Patients were analysed in two groups: ≤6 and >6.

Mini Nutritional Assessment–Short Form (MNA-SF) classifies nutritional status as normal (scores >11), risk of malnutrition (8-11) or malnourished (<8) (24).

Patients with haemoglobin ≤120 g/L (cut-off selected for clinical utility) were considered to have anaemia. Albumin was analysed in three groups: ≤30, 31-34 and >34 g/L for clinical relevance. Renal function was categorised in three groups based on estimated glomerular filtration rate (GFR), calculated using CKD-EPI equation (25): normal to mildly decreased (≥60 mL/min), mildly to moderately decreased (45-60 mL/min) or moderately to severely decreased (<45 mL/min) renal function.

The LN ratio was analysed in three groups: <10% (LN ratio 1), 10-25% (LN ratio 2) and >25% (LN ratio 3).

Outcomes

The primary outcome measures were postoperative morbidity and mortality 30 days after primary treatment. The complications were graded with CD classification (18). Outcome measures were assessed during the hospital stay and at one-month clinical follow-up visits. Multiple complications occurring in the same patient were independently rated, and the highest CD grade experienced was used in the analyses.

Sample size

The sample size calculation for postoperative complications was based on earlier studies (4,5,6,7) showing 21% incidence of complications in fit patients and 48% in frail patients. To identify 2-fold differences in complication rates with α value of 0.05 and 80% power, it was calculated that 96 patients needed to be recruited and analysed.

Statistical analysis

Percentages were used to describe demographic data and the occurrence of outcomes. The median and range were calculated for age, preoperative laboratory values, body mass index (BMI), operation time and perioperative blood loss. Associations between the categorical variables were tested with the Chi-Square-test or the Fisher's exact test, when appropriate. Uni- and multivariate analysis of the factors influencing morbidity and mortality were carried out using logistic regression. Results are shown as odds ratios (OR) with 95% confidence interval (95% CI). All variables that were statistically significant ($p<0.005$) in the univariate model were included in the multivariate model. Statistical analyses were performed by using SPSS version 26.

Results

Patients and clinical characteristics

Of the 241 eligible patients, 180 (75%) patients consented to participate. Eleven patients were treated non-operatively because of their age or personal refusal, declined functional status or risk of anaesthesia due to severe comorbidities. Most of the non-operatively treated patients were considered frail (CFS ≥5; 90%) and to have increased risk of postoperative complications and recovery (G-8 ≤14; 100%, ASA ≥3; 100%, CCI >6; 70%). Eight patients were excluded because of metastatic or benign findings in operation or pathological sample. Figure 1 shows patient flowchart.

Altogether 161 patients were included in the study. The median age was 84.5 years (range 80-97 years and 60% were female. Most patients had an ASA III classification (67%), and CCI score ≤6 (62%). Almost all patients scored ≤14 (92%) in G-8, and 77% were considered vulnerable or frail (CFS ≥3). Most of the patients (91%) were at risk of malnutrition or malnourished (MNA-SF<12). Table 1 shows patients` baseline characteristics.

TNM-stages were as follows: stage I 29 patients (18%), stage II 86 patients (54%) and stage III 45 patients (28%). Lymph node ratio was as follows: 84% ratio 1, 10% ratio 2 and 6% ratio 3. Postoperative adjuvant therapy was given to 27% (12/45) of stage III patients.

Most of the operative procedures were performed for right-sided colon cancer (65%). An intended laparoscopic resection was performed in 122 patients (76%), and 15 cases (9.3%) were converted to open surgery due to anatomical or technical reasons. Median operation time was 129 min (range 54-433 min) and blood loss 50 ml (range 0-2390 ml). The median length of stay in the operating hospital was five days (range 2-36 days). Ninety patients (56%) were discharged home and the rest of the patients to other hospitals or primary healthcare centre wards.

Morbidity and mortality

Overall postoperative morbidity was 41% (66/161) with 24% (39/161) of patients having surgical complications. The most common surgical complications were ileus (12%), anastomotic leakage (5%), superficial surgical site infections (3.6%) and wound dehiscence (2.5%). Four patients had iatrogenic bowel perforations, and one patient had postoperative colon necrosis. Sixteen patients (10%) were reoperated. The reasons for reoperations were anastomotic leakage (8/16), iatrogenic bowel perforation after the primary operation (4/16), wound dehiscence (2/16), colon necrosis after right hemicolectomy (1/16) and unclear abdominal infection (1/16). The most common non-surgical complications were cardiovascular 6% (9/161) and pulmonary 8% (12/161). One patient had a massive cerebral stroke, causing permanent disability. Nine patients had both surgical and non-surgical complications. According to the CD classification, 15% (24/161) of patients had severe complications. Table 2 shows postoperative complications and figure 2 incidence of complications compared to CFS.

Readmission within 30 days of discharge occurred for 13 patients (8.1%). Nine had surgical, and four had non-surgical reasons for readmission. One patient needed reoperation because of new anastomotic leakage after primary relaparotomy with re-resection. The third operation was finished with protective stoma formation.

The overall 30-day mortality rate was 1.9% (3/161), but 8.3% (2/24) for those with CD grade III-IV complications. One patient died on the 23rd postoperative day after prolonged ileus and two reoperations due to wound dehiscence. One patient died on the 25th postoperative day, after relaparotomy for anastomotic leakage and peritonitis. The third patient died on the 18th postoperative day from complications of ischemic heart disease.

Predictors of postoperative complications

Postoperative complications were significantly more common with patients with a history of cerebral stroke (64% vs 37%, p=0.02), albumin level 31-34 g/L (57% vs 32% in patients with albumin ≥35 g/L, p=0.007), CFS 3-4 and 5-9 (49% and 47% vs 16% in CFS 1-2, respectively) and ASA >3 (77% vs 28%, p=0.006). In patients with CFS 5-9, non-surgical complications were more common than surgical complications (34% vs 25%), whereas in patients with CFS 1-2, both complication types were equally common (8% vs 11%). Age, BMI, preoperative hospital admissions, polypharmacy, comorbidity burden, G-8, nutritional status, anaemia, type of operation, duration of operation or operative blood loss were not associated with increased rates of complications. In multivariate logistic regression analysis CFS ≥3 (OR=6.06, 95% CI 1.88-19.5, p=0.003) and albumin level 31-34 g/L (OR=3.88, 1.61-9.38, p=0.003) were significantly associated with postoperative complications. AUC for all complications was 0.747, (95% CI 0.67-0.83). Table 3 shows predictors of postoperative complications.

Severe complications (CD III-V) were significantly more frequent for patients with chronic obstructive pulmonary disease COPD (43% vs 13%, p=0.047), renal failure (25% vs 12%, p=0.021), albumin level 31-34 g/L (26% vs 8% in patients with albumin >34 g/L, p=0.014) and CCI-score >6 (23% vs 10%, p=0.034). Patients with CFS 3-4 and 5-9 seemed to have more severe complications (OR 3.40, 0.73-15.9, p=0.121 and OR 4.63, 0.93-23.0, p=0.061) compared to patients with CFS 1-2, but the differences were not statistically significant. In multivariate logistic regression analysis, albumin level 31-34 g/L (OR 4.39, 1.31-14.7, p=0.017) was the only Significant variable causing postoperative complications. AUC for severe complications was 0.756, (95% CI 0.65-0.86). Table 4 shows predictors of severe postoperative complications. Figure 3 shows distributions of all and severe postoperative complications, according to CFS.

Discussion

This prospective study demonstrated that CFS (13) predicts early postoperative complications following elective curatively aimed colon cancer surgery with aged patients. Patients, who are vulnerable or frail with CFS scores ≥3 or have severe comorbidities, had significantly more complications than fit patients with CFS scores 1-2, whereas age did not affect postoperative outcomes. On the contrary, fit patients managed exceptionally well and showed a very low complication rate and mortality. Altogether these results emphasise the importance of patient assessment irrespective of chronological age (26).

The study sample represented only colon cancer patients as they have homogenous treatment strategies compared to rectum cancer patients. Our study showed higher frequency of right-sided colon cancers and female patients, which is in line with previously reported studies of aged patients (6,27). Colon cancer surgery is performed in Finland by surgeons specialised exclusively in colon operations following uniform, standardised protocols for colon cancer treatment (28). The study sample is nationally representative providing realistic and novel information on postoperative outcomes of aged patients.

Our study showed high morbidity rates in the early postoperative period. Almost 41% of the patients developed postoperative complications, and 15% had severe complications. These figures are comparable to other studies of colon cancer surgery in the aged (5,6,7). Complications were overrepresented in patients who were well-managing but inactive or mildly frail (CFS 3-4) and frail (CFS 5-9) compared to fit patients (CFS 1-2) with complication rates of 49% and 47% vs 16%. This indicates that fit aged patients can manage invasive surgical treatments like their younger counterparts (4). On the other hand, particularly vulnerable patients might benefit from preoperative medical optimisation and comprehensive geriatric assessment (29).

Previous studies verified that aged patients with severe complications have a disproportionately high risk of 30-day and 1-year mortality (3,6). In this study, the 30-day mortality rate was 1.9% and 8.3% in patients with severe complications, showing a remarkable decline from mortality rates previously reported in Finland and Netherlands (6,30). The enhanced recovery after surgery (ERAS) protocol and mini-invasive surgery were well-established in the recruiting hospitals (31,32). Thus, the significant improvement in mortality rates indicates improved preoperative risk assessment and optimisation, counselling and awareness of frailty together with nationwide standardisation and advancements in modern multidisciplinary treatment.

Nutritional prehabilitation was implemented at some of the study hospitals (33) but is not standard nationwide and may not cover all patients. This might explain excess complications with patients with mildly reduced albumin level (31-34 g/L) than patients with clearly abnormal albumin, suggesting probable malnutrition. On the other hand, BMI had no effect, and thus it should not be used alone for evaluation of nutritional state.

Frailty is identified as a significant predictor of postoperative complications leading to greater health care utilisation and higher mortality (8,14). Our study focused on the growing population of colon cancer patients aged 80 years or over with even more significant heterogeneity in physical and cognitive status. Notably, most patients lived at home before surgery, but only 56% returned directly to home after operative treatment emphasising the major impact of surgery on functional recovery. Our findings demonstrated that patients with pre-existing frailty and morbidity express an excess number of complications, corroborated by a recently published meta-analysis (34).

CFS approved to be a beneficial tool for assessing preoperative daily physical and cognitive activities and independence. At present, only few surgical units have readily available geriatric services for comprehensive assessment, so easily implemented frailty screening tools are helpful for surgeons. We grouped patients in three categories (CFS 1-2, 3-4 and 5-9), as we wanted to demonstrate the importance of identifying patients with possible vulnerable physical status. CFS ≥3 was the only screening parameter, which significantly showed association with adverse outcomes. Patients with CFS 3-4 can be challenging for a surgeon to identify, as they can manage well independently and live with mild frailty.

Although an observational study cannot answer the question if the surgery is beneficial or not, performing a randomised trial in this patient group is not realistic. Instead, it is clinically more relevant to study outcomes in an observational setting with less selection bias and more relevance to real-life settings. The strengths of this study included the fact that it examined a representative, nationwide cohort, treated at several secondary and tertiary care hospitals instead of single-centre analysis with uniform and standardised protocols during perioperative period (ERAS protocol).

There are some limitations to this study. It was acknowledged that the tests used (G-8, CFS and MNA-SF) represented screening tests, and geriatric evaluation would be needed for precise diagnosis of frailty and other geriatric syndromes. Although we did not do cognitive testing, CFS gives some insight into cognition, and it can be anticipated that patients with CFS 1-2 had no or only mild cognitive impairment. The sample size was not quite sufficient for the analysis of predictors of severe complications. More extensive patient data is needed to confirm the possible prognostic trends such as with CFS, ASA, MNA-SF and GFR. Moreover, a longer follow-up would be necessary to evaluate the complete impact of invasive cancer treatment (3,35). Future studies from this multicentre data will focus on long-term results with outcomes and especially functional recovery.

In conclusion, this study showed that aged patients have high morbidity rates after curative colon cancer surgery. However, the fittest patients had excellent operative outcomes, like younger counterparts. Surgeons should not abstain from curative surgery based only on age or comorbidities. Conversely, modern treatment decision-making should complement preoperative risk assessment with the considered use of CFS and counselling jointly with patients and their family.

Acknowledgements

The authors warmly thank M.D Kirk Langley Fremantle Hospital, WA Australia, for his help in editing the English language.

Funding information

Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital partly supported this study financially. Cancer Foundation Finland obtained external funding by awarding a grant, but they did not have any role in designing the study, collection, analysis, interpretation of the data or writing the manuscript.

References

1. Global Burden of Disease Cancer Collaboration et al. Global, regional and national cancer incidence, mortality, years of life lost, years lived with disability and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: A systematic analysis for the global burden of disease study. JAMA Oncol 2019; **5**:1749-68.
2. Jafari MD, Jafari F, Halabi WJ, Nguyen VQ, Pigazzi A, Carmichael JC et al. Colorectal cancer resections in the ageing US population: a trend toward decreasing rates and improved outcomes. JAMA Surg 2014;**149**: 557–64.
3. Duraes LC, Stocchi L, Dietz D, Kalady MF, Kessler H, Schroeder D et al. The disproportionate effect of perioperative complications on mortality within 1 year after colorectal cancer resection in octogenarians. Ann Surg Oncol 2016; **23**:4293–301.
4. 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**:477-84.
5. Allardyce RA, Bagshaw PF, Frampton CM, Frizelle FA, Hewett PJ, Rieger NA et al. Australasian Laparoscopic Colon Cancer Study shows that elderly patients may benefit from lower postoperative complication rates following laparoscopic versus open resection. Br J Surg 2010; **97**: 86-91.
6. Niemeläinen S, Huhtala H, Ehrlich A, Kössi J, Jämsen E, Hyöty M. Risk factors of short-term survival in the aged in elective colon cancer surgery: a population-based study. Int J Colorectal Dis 2020;**35**: 307-15.
7. Fagard K, Leonard S, Deschodt M, Devriendt E, Wolthuis A, Prenen H et al. The Impact of Frailty on Postoperative Outcomes in Individuals Aged 65 and Over Undergoing Elective Surgery for Colorectal Cancer: A Systematic Review. J Geriatr Oncol. 2016; **7**:479-491.

8. Pandit V, Khan M, Martinez C, Jehan F, Zeeshan M, Koblinski J et al. A modified frailty index predicts adverse outcomes among patients with colon cancer undergoing surgical intervention. Am J Surg 2018; **216**: 1090-94.
9. Papamichael D, Audisio RA, Glimelius B, de Gramont A, Glynne-Jones R, Haller D et al. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2015. Ann Oncol 2015; **26:**463-76.
10. Ghignone F, Hernandez P, Mahmoud NN, Ugolini G. Functional recovery in senior adults undergoing surgery for colorectal cancer: Assessment tools and strategies to preserve functional status. Eur J Surg Oncol 2020; **46**: 387-93.
11. Montroni I, Rostoft S, Spinelli A, Van Leeuwen BL, Ercolani G, Saur NM et al. GOSAFE - Geriatric Oncology Surgical Assessment and Functional rEcovery After Surgery: Early Analysis on 977 Patients. J Geriatr Oncol 2020; **11:** 244-55.
12. Huisman MG, Kok M, de Bock GH, van Leeuwen BL. Delivering Tailored Surgery to Older Cancer Patients: Preoperative Geriatric Assessment Domains and Screening Tools - A Systematic Review of Systematic Reviews. Eur J Surg Oncol 2017; **43**: 1-14.
13. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005; **173**:489-95.
14. Okabe H, Ohsaki T, Ogawa K, Ozaki N, Hayashi H, Akahoshi S et al. Frailty predicts severe postoperative complications after elective colorectal surgery. Am J Surg 2019; **217**: 677-81.
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. Lancet. 2007; **370**:1453–7.
16. https://www.project-redcap.org/.
17. Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M et al. Screening Older Cancer Patients: First Evaluation of the G-8 Geriatric Screening Tool. Ann Oncol 2012; **23**: 2166-72.
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; **240**:205-13.
19. Brierley JD, Gospodarowicz MK, Wittekind CH. TNM Classification of Malignant Tumours. 8. Edition. Wiley-Blackwell, Hoboken (New Jersey), US 2016.
20. Vaccaro CA, Im V, Rossi GL, Quintana GO, Benati ML, Perez de Arenaza D et al. Lymph node ratio as prognosis factor for colon cancer treated by colorectal surgeons. Dis Colon Rectum 2009; **52**: 1244-50.
21. Suominen MH, Jyväkorpi SK, Pitkälä KH, Finne-Soveri H, Hakala P, Männisto S et al. Nutritional guidelines for older people in Finland. J Nutr Health Aging 2014; **18**:861-7.
22. Owens WD, Felts JA, Spitznagel EL Jr. ASA Physical Status Classifications: A Study of Consistency of Ratings. Anesthesiology 1978; **49**:239-43.
23. Chang CM, Yin WY, Wei CK, Wu CC, Su YC, Yu CH et al. Adjusted Age-Adjusted Charlson Comorbidity Index Score as a Risk Measure of Perioperative Mortality before Cancer Surgery. PloS One 2016; **11**, e0148076.doi: 10.1371/journal.pone.0148076.

24. Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederholm T et al. Validation of the Mini Nutritional Assessment short-form (MNA-SF): a practical tool for identification of nutritional status. J Nutr Health Aging 2009; **13**:782-8.
25. CKD Evaluation and Management. Available at CKD Evaluation and Management – KDIGO. Accessed 28 Jan 2021.
26. Fagard K, Casaer J, Wolthuis A, Flamaing J, Milisen K, Lobelle JP et al. Postoperative complications in individuals aged 70 and over undergoing elective surgery for colorectal cancer. Colorectal Dis 2017;**19**: O329-38.
27. Reif de Paula T, Simon HL, Profeta da Luz MM, Keller DS. Right sided colorectal cancer increases with age and screening should be tailored to reflect this: a national cancer database study. Tech Coloproctol. 2021; **25:81**-89.
28. National guidelines for colorectal cancer treatment in Finland. https://www.terveysportti.fi/dtk/ltk/koti?p_artikkeli =hsu00007. Accessed 28 Jan 2021.
29. Partridge JSL, Harari D, Martin FC, Dhesi JK. The impact of pre-operative comprehensive geriatric assessment on postoperative outcomes in older patients undergoing scheduled surgery: a systematic review. Anaesthesia 2014; **69**:8-16.
30. Brouwer NPM, Heil TC, Olde Rikkert MGM, Lemmens VEPP, Rutten JHT, de Wilt JHW et al. The gap in postoperative outcome between older and younger patients with stage I-III colorectal cancer has been bridged: results from the Netherlands cancer registry. Eur J Cancer 2019;**116**: 1-9.
31. Seishima R, Okabayashi K, Hasegawa H, Tsuruta M, Shigeta K, Matsui S et al. Is laparoscopic colorectal surgery beneficial for elderly patients? A systematic review and meta-analysis. J Gastrointest Surg 2015; **19**:756-65.
32. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS ®) Society Recommendations: 2018. World J Surg 2019; **43**:659-95.
33. Gillis C, Buhler K, Bresee L, Carli F, Gramlich L, Culos-Reed N et al. Effects of Nutritional Prehabilitation, With and Without Exercise, on Outcomes of Patients Who Undergo Colorectal Surgery: A Systematic Review and Meta-analysis. Gastroenterology 2018; **155**:391-410.
34. Boakye D, Rillmann B, Walter V, Jansen L, Hoffmeister M, Brenner H. Impact of comorbidity and frailty on prognosis in colorectal cancer patients: A systematic review and meta-analysis. Cancer Treat Rev 2018; **64:30**-39.
35. Niemeläinen S, Huhtala H, Ehrlich A, Kössi J, Jämsen E, Hyöty M. Long-term survival following elective colon cancer surgery in the aged. A population-based cohort study. Colorectal Dis. 2020; **22**:1585-1596.

PUBLICATION
IV

One-year outcomes for colon cancer surgery in octogenarians: A prospective, multicentre observational study.

Susanna Niemeläinen, Heini Huhtala, Esa Jämsen, Jyrki Kössi, Jan Andersen, Anu Ehrlich, Eija Haukijärvi, Suvi Koikkalainen, Selja Koskensalo, Anne Mattila, Tarja Pinta, Mirjami Uotila-Nieminen, Hanna Vihervaara, Marja Hyöty

Submitted.