



UNIVERSITY
OF TURKU

RECTAL CANCER SURGERY

Opportunities and Challenges
in the Modern Era

Anu Carpelan



UNIVERSITY
OF TURKU

RECTAL CANCER SURGERY

Opportunities and Challenges in the Modern Era

Anu Carpelan

University of Turku

Faculty of Medicine
Department of Surgery
Doctoral Programme in Clinical Research (DPCR)
Division of Digestive Surgery and Urology, Turku University Hospital

Supervised by

Professor Juha Grönroos, MD, PhD
Department of Surgery
Turku University Hospital
Turku, Finland

Docent Jukka Karvonen, MD, PhD
Department of Digestive Surgery
Turku University Hospital
Turku, Finland

Reviewed by

Docent Marja Hyöty, MD, PhD
Department of Gastroenterology and
Alimentary Tract Surgery
Tampere University Hospital
Tampere, Finland

Docent Monika Carpelan-Holmström,
MD, PhD
Department of Gastrointestinal Surgery
Helsinki University Hospital
Helsinki, Finland

Opponent

Docent Anna Lepistö, MD, PhD
Department of Gastrointestinal Surgery
Helsinki University Hospital
Helsinki, Finland

The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

ISBN 978-951-29-8311-7 (PRINT)
ISBN 978-951-29-8312-4 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama, Turku, Finland 2020

To Kim, Ilona and Amos

UNIVERSITY OF TURKU

Faculty of Medicine

Department of Surgery

Division of Digestive Surgery and Urology, Turku University Hospital

ANU CARPELAN: Rectal cancer surgery – opportunities and challenges in the modern era

Doctoral Dissertation, 136 pp.

Doctoral Programme in Clinical Research (DPCR)

January 2021

ABSTRACT

Aims: This thesis was designed to elucidate the opportunities and challenges faced by the surgeon and the patient in the era of modern rectal cancer surgery. Temporal changes in the treatment and survival of patients with rectal cancer during 2001-2012 were evaluated on the basis of a biobank database. The novel extralevator abdominoperineal excision (ELAPE) was compared to standard abdominoperineal excision (APE) in patients with locally advanced rectal cancer. The incidence, location and risk factors for local recurrence (LR) after modern multimodality treatment of rectal cancer were determined. To promote the assessment of postoperative bowel function in rectal cancer patients the low anterior resection syndrome (LARS) Score –questionnaire was translated to Finnish and validated.

Patients and Methods: The material consisted of patients treated for rectal cancer at Turku University Hospital between 2001 and 2016. Data was collected retrospectively from prospectively maintained electronic medical records. Answers to the LARS Score –questionnaire and quality of life (QoL) -questionnaires were collected by mail.

Results: The results of the current study showed that from 2001 to 2012, the overall survival and cancer specific survival of patients with stage I-III rectal cancer significantly increased. In locally advanced rectal cancer, patients operated with ELAPE did not have a better long-term survival than patients operated with APE. In stage I-III rectal cancer treated with curative intent, the incidence of LR was 11%. There was a slight predominance of lateral LRs. As a long term functional result 54% of rectal cancer patients that underwent continence preserving surgery had major LARS. The Finnish LARS Score –questionnaire was shown to be a valid test in the assessment of postoperative bowel function and its impact on the QoL.

Conclusions: With modern multimodality treatment the survival of patients with rectal cancer is excellent even though LR still sometimes occurs. Many of the survivors need guidance regarding LARS.

KEYWORDS: Combined modality therapy, local recurrence, proctectomy, quality of life, rectal neoplasms, risk factors, surveys and questionnaires, survival, translations.

TURUN YLIOPISTO

Lääketieteellinen tiedekunta

Kirurgian oppiaine

Vatsaelinkirurgian ja urologian klinikka, Turun yliopistollinen keskussairaala

ANU CARPELAN: Peräsuolisyöpäkirurgia – uusia mahdollisuuksia ja haasteita

Väitöskirja, 136 s.

Turun kliininen tohtoriohjelma (TKT)

Tammikuu 2021

TIIVISTELMÄ

Tavoitteet: Tämän väitöstutkimuksen tavoitteena oli selvittää nykyaikaiseen peräsuolisyöpäkirurgiaan liittyviä mahdollisuuksia ja haasteita sekä kirurgin että potilaan näkökulmasta. Muutoksia peräsuolisyövän hoidossa ja hoidon jälkeisessä elossaoloajassa vuosien 2001–2012 aikana tutkittiin biopankkiaineiston pohjalta. Paikallisesti edenneen peräsuolisyövän hoidoksi käyttöön otetun laajennetun peräsuolen poistoleikkauksen (ELAPE) pitkäaikaistuloksia verrattiin perinteisen peräsuolen poistoleikkauksen (APE) tuloksiin. Tutkimuksessa selvitettiin lisäksi peräsuolisyövän modernin hoidon jälkeen todettavien paikallisuusiutumien ilmaantuvuutta, sijaintia ja riskitekijöitä. Peräsuolisyöpäpotilaiden leikkauksen jälkeistä suolen toimintaa arvioimaan kehitetty LARS-kysely suomennettiin ja validoitiin.

Aineisto ja menetelmät: Tutkimuksen aineisto koostui Turun yliopistollisessa keskussairaalassa vuosien 2001 ja 2016 välillä hoidetuista peräsuolisyöpäpotilaista. Tiedot kerättiin takautuvasti sähköisestä sairauskertomuksesta. LARS-kyselyn ja elämänlaatukyselyiden vastaukset kerättiin potilailta postitse.

Tulokset: Tutkimuksessa todettiin, että vuosien 2001 ja 2012 välillä levinneisyysasteiden I–III peräsuolisyöpään sairastuneiden potilaiden kokonaisuossaolo ja tautispesifinen elossaolo paranivat merkitsevästi. ELAPE-tekniikalla leikattujen paikallisesti edennyttä syöpää sairastavien potilaiden pitkäaikaissennuste ei kuitenkaan ollut perinteisellä tekniikalla leikattuja parempi. Paikallisuusiutuma todettiin 11 %:lla radikaalitavoitteisesti hoidetuista levinneisyysasteen I-III peräsuolisyöpäpotilaista. Lantion sivuilla sijaitsevia uusiutumia oli hiukan muita sijainteja enemmän. Merkittäviä pitkäkestoisia ulostamiseen liittyviä oireita oli 54 %:lla potilaista, joiden peräaukko oli voitu peräsuolisyöpäleikkauksessa säästää. Suomennettu LARS-kysely todettiin validiksi leikkauksen jälkeisen suolen toiminnan ja sen elämänlaatuvaikutusten arvioinnissa.

Johtopäätökset: Peräsuolisyövän nykyaikaisen yhdistelmähoiton tulokset elossaolon perusteella arvioituna ovat erinomaisia, vaikka paikallisuusiutumia edelleen ilmaantuu. Monet peräsuolisyövästä selviytyneet tarvitsevat tukea toiminnallisten suolioireiden helpottamiseksi.

AVAINSANAT: Elossaolo, elämänlaatu, kysely, käänös, peräsuolisyöpä, peräsuolisyöpäleikkaus, riskitekijä, syövän paikallisuusiutuma, yhdistelmähoito.

Table of Contents

| | |
|--|-----------|
| Abbreviations | 8 |
| List of Original Publications | 10 |
| 1 Introduction | 11 |
| 2 Review of the Literature | 13 |
| 2.1 Epidemiology and clinical presentation of rectal cancer..... | 13 |
| 2.1.1 Incidence of rectal cancer | 13 |
| 2.1.2 Pathogenesis of rectal cancer | 13 |
| 2.1.3 Presentation and symptoms of rectal cancer..... | 14 |
| 2.2 Diagnosis and staging..... | 15 |
| 2.2.1 TNM staging of rectal cancer..... | 15 |
| 2.2.2 Clinical examination and colonoscopy | 15 |
| 2.2.3 Pathology | 15 |
| 2.2.4 Magnetic resonance imaging..... | 18 |
| 2.2.5 Contrast-enhanced computed tomography..... | 19 |
| 2.2.6 Positron emission tomography | 19 |
| 2.3 Treatment | 20 |
| 2.3.1 Choice of treatment..... | 20 |
| 2.3.2 Radiotherapy..... | 20 |
| 2.3.2.1 Short-course preoperative radiotherapy..... | 20 |
| 2.3.2.2 Long-course chemoradiotherapy | 21 |
| 2.3.2.3 Complications of radiotherapy | 21 |
| 2.3.3 Surgery | 22 |
| 2.3.3.1 History of rectal cancer surgery | 22 |
| 2.3.3.2 Total mesorectal excision | 22 |
| 2.3.3.3 Anterior resection | 23 |
| 2.3.3.4 Abdominoperineal excision..... | 24 |
| 2.3.3.5 Complications of surgery | 26 |
| 2.3.4 Adjuvant chemotherapy and chemoradiotherapy..... | 27 |
| 2.3.5 Treatment of metastatic and recurrent disease..... | 27 |
| 2.4 Prognosis and recurrent disease..... | 28 |
| 2.4.1 Prognosis of rectal cancer | 28 |
| 2.4.2 Distant recurrence..... | 28 |
| 2.4.3 Local recurrence | 28 |
| 2.4.3.1 Incidence of local recurrence | 28 |
| 2.4.3.2 Risk factors for local recurrence..... | 29 |
| 2.4.3.3 Location of local recurrence..... | 29 |
| 2.5 Long-term sequelae | 30 |

| | | |
|----------|--|-----------|
| 2.5.1 | Quality of life after treatment of rectal cancer | 30 |
| 2.5.2 | Low anterior resection syndrome (LARS) | 31 |
| 3 | Aims | 32 |
| 4 | Patients and Methods | 33 |
| 4.1 | Patients | 33 |
| 4.1.1 | Patients with rectal cancer identified through Auria Biobank (Study I)..... | 33 |
| 4.1.2 | Patients treated with abdominoperineal excision (Study II)..... | 34 |
| 4.1.3 | Patients followed up for local recurrence (Study III)..... | 34 |
| 4.1.4 | Patients evaluated for LARS (Study IV)..... | 34 |
| 4.2 | Methods | 36 |
| 4.2.1 | Preoperative evaluation and neoadjuvant treatment.... | 36 |
| 4.2.2 | Surgical technique..... | 37 |
| 4.2.3 | Adjuvant treatment | 37 |
| 4.2.4 | Follow-up regime..... | 37 |
| 4.2.5 | Translation of the LARS score..... | 38 |
| 4.2.6 | Testing the validity of the LARS score translation..... | 38 |
| 4.2.7 | Statistical analyses..... | 41 |
| 5 | Results | 43 |
| 5.1 | Temporal changes in the treatment and survival of rectal cancer patients (Study I)..... | 43 |
| 5.2 | Long-term results of extralevator abdominoperineal excision (Study II)..... | 46 |
| 5.3 | Location of local recurrence after modern multimodality treatment (Study III)..... | 51 |
| 5.4 | Validation of the Finnish LARS score questionnaire (Study IV) | 56 |
| 6 | Discussion | 59 |
| 6.1 | Improvement in quality of care and prognosis of rectal cancer | 59 |
| 6.2 | Role of extralevator abdominoperineal excision in the treatment of rectal cancer..... | 60 |
| 6.3 | Local recurrence in the modern era..... | 62 |
| 6.4 | Validity of the Finnish LARS-score questionnaire | 64 |
| 6.5 | Limitations of the study..... | 65 |
| 7 | Conclusions..... | 67 |
| | Acknowledgements | 68 |
| | References | 70 |
| | Original Publications..... | 91 |

Abbreviations

| | |
|--------|--|
| 5-FU | 5-fluorouracil |
| AFAP | Attenuated familial adenomatous polyposis |
| AL | Anastomotic leakage |
| APE | Abdominoperineal excision |
| CEA | Carcinoembryonic antigen |
| CI | Confidence interval |
| CIMP | CpG island methylator phenotype |
| CIN | Chromosomal instability |
| CRC | Colorectal cancer |
| CRM | Circumferential resection margin |
| CRT | Chemoradiotherapy |
| CSS | Cancer-specific survival |
| CT | Contrast-enhanced computed tomography |
| DFS | Disease free survival |
| DRE | Digital rectal examination |
| ELAPE | Extralevator abdominoperineal excision |
| EMVI | Extramural vascular invasion |
| EORTC | European Organisation for Research and Treatment of Cancer |
| FAP | Familial adenomatous polyposis |
| FIT | Fecal immunochemical test |
| gFOBT | Guaiac fecal occult blood test |
| HNPCC | Hereditary non-polyposis colorectal cancer |
| HR | Hazard ratio |
| ICD-10 | International Classification of Diseases 10 th Revision |
| IOP | Intraoperative perforation |
| LARS | Low anterior resection syndrome |
| LPLN | Lateral pelvic lymph node |
| LPLND | Lateral pelvic lymph node dissection |
| LR | Local recurrence |
| LRFS | Local recurrence free survival |
| LVI | Lymphovascular invasion |

| | |
|--------|--|
| MAP | MUTYH -associated polyposis |
| MDT | Multidisciplinary team |
| MINEN | Mixed neuroendocrine non-neuroendocrine neoplasm |
| MRF | Mesorectal fascia |
| MRI | Magnetic resonance imaging |
| MSI | Microsatellite instability |
| OS | Overall survival |
| pCR | Pathological complete response |
| PET-CT | Positron emission tomography-computed tomography |
| PME | Partial mesorectal excision |
| PNI | Perineural invasion |
| QLQ | Quality of life questionnaire |
| QoL | Quality of life |
| RT | Radiotherapy |
| SCPRT | Short-course preoperative radiotherapy |
| SEM | Standard error of the mean |
| TME | Total mesorectal excision |
| TNM | Tumor, Node, Metastasis |
| TRG | Tumour regression grade |

List of Original Publications

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

- I Heervä E, Carpelan A, Kurki S, Sundström J, Huhtinen H, Rantala A, Ålgars A, Ristamäki R, Carpén O, Minn H. Trends in presentation, treatment and survival of 1777 patients with colorectal cancer over a decade: a Biobank study. *Acta Oncol*, 2018; 57(6): 735-742.
- II Carpelan A, Karvonen J, Varpe P, Rantala A, Kaljonen A, Grönroos J, Huhtinen H. Extralevator versus standard abdominoperineal excision in locally advanced rectal cancer: a retrospective study with long-term follow-up. *Int J Colorectal Dis*, 2018; 33(4): 375-381.
- III Carpelan A, Heervä E, Kurki S, Varpe P, Rantala A, Grönroos J, Karvonen J, Huhtinen H. Local recurrence after modern multimodality treatment of rectal cancer: incidence, location and risk factors. *Submitted*.
- IV Carpelan A, Elamo E, Karvonen J, Varpe P, Elamo S, Vahlberg T, Grönroos J, Huhtinen H. Validation of the Low Anterior Resection Syndrome score in Finnish patients: preliminary results on quality of life in different LARS severity groups. *Scand J Surg*, 2020; *epub ahead of print*.

The original publications have been reproduced with the permission of the copyright holders.

1 Introduction

Surgery is the primary treatment of rectal cancer. Advances made in surgical techniques, especially the introduction of total mesorectal excision (TME) by Heald (Heald et al. 1982), have contributed to improved survival of rectal cancer patients (Guren et al. 2015, Kodeda et al. 2015). In many countries rectal cancer surgery has been centralised and multidisciplinary teams (MDTs) tailor the treatment, which selectively includes preoperative radiotherapy (RT), chemoradiotherapy (CRT) or adjuvant chemotherapy in addition to surgery (Brændengen et al. 2008, van Gijn et al. 2011, Guren et al. 2015, Zhao et al. 2016). During the 21st century enhanced preoperative assessment with magnetic resonance imaging (MRI) (MERCURY Study Group 2006) and standardised postoperative evaluation with histopathology (Quirke et al. 2009) have also dramatically modernised and specified the decision making process in the MDT meetings.

One of the recent changes in rectal cancer surgery is the introduction of extralevator abdominoperineal excision (ELAPE) in 2007 (Holm et al. 2007). The technique was advocated to overcome the problems encountered with standard abdominoperineal excision (APE), mainly positive circumferential resection margins (CRMs) and intraoperative perforations (IOPs), which hampered the oncological outcome of the patients with low rectal cancer (Eriksen et al. 2004, Wibe et al. 2004, Nagtegaal et al. 2005). ELAPE has become widely used, although the results of its superiority over APE are conflicting (Han et al. 2012, Zhou et al. 2015, Prytz et al. 2016, Bianco et al. 2017). In Finland, ELAPE is performed in approximately 50 % of the patients that require an APE (National Institute for Health and Welfare 2019).

Local recurrence (LR) of rectal cancer still occurs in 4-15 % of patients in spite of advances made in surgical techniques and neoadjuvant treatments (van Gijn et al. 2011, Glimelius et al. 2016, Poulsen et al. 2018, Peacock et al. 2019). Overall survival (OS) of patients with LR is often short and symptoms of pelvic pain, bleeding and fistula formation are difficult to palliate (Kodeda et al. 2012, Westberg et al. 2018). When LR is encountered, the chance for cure lies in radical surgery and the likelihood of its success is higher if the LR is situated axially or anteriorly in the pelvis (Moore et al. 2004, Westberg et al. 2018, Hagemans et al. 2019). Data on

location of LR after modern multimodality treatment is sparse, and has mainly been assessed in patient subgroups, for example in patients with cT3-T4 tumours only (Schaap et al. 2018, Ogura et al. 2019a) or in patients referred for surgery of LR (Denost et al. 2015).

As the survival of rectal cancer patients has increased, quality of life (QoL) after treatment is becoming increasingly important. Defecation disorders are frequent after anterior resection and the usual combination of symptoms (urgency, fragmentation, incontinence) is called low anterior resection syndrome (LARS) (Ortiz & Armendariz 1996). The long-term prevalence of LARS has been reported to be up to 41-56% (Chen et al. 2015, Croese et al. 2018, Pieniowski et al. 2019). The LARS score was developed in 2012 to ease the assessment of the severity of defecatory symptoms and their impact on QoL (Emmertsen & Laurberg 2012). It is a five item questionnaire, by which rectal cancer patients can be divided into having no, minor or major LARS. Although the LARS score has been widely adopted by the clinical and research communities, a recent study from the Netherlands still showed that postoperative bowel function is not routinely tested and more patient education is needed (Thomas et al. 2019).

In this thesis the temporal changes in the treatment and survival of patients with rectal cancer during 2001-2012 were evaluated. Special focus was directed to survival after ELAPE operation as well as to the incidence, location and risk factors of LR. Finally, validation of the translated Finnish LARS Score –questionnaire was performed to promote the evaluation and management of LARS in Finnish rectal cancer patients.

2 Review of the Literature

2.1 Epidemiology and clinical presentation of rectal cancer

2.1.1 Incidence of rectal cancer

Colorectal cancer (CRC) is the third most common cancer worldwide, with 1.8 million new cases diagnosed annually (IARC 2018). Rectal cancer represents one third of all CRC cases and its age standardised incidence in Finland in 2017 was 21.5/100 000/year (Finnish Cancer Registry). The incidence of CRC is higher in men and in older age groups, but lately the greatest increase in incidence has been seen in those under 50 years of age. This increase is mainly attributed to increasing number of rectal cancer in young patients. In age groups older than 50 years the incidence has, in fact, started to slowly decline, possibly due to CRC screening (Siegel et al. 2017, Kasi et al. 2019).

2.1.2 Pathogenesis of rectal cancer

The majority of CRCs develop from adenomatous polyps (Stryker et al. 1987, Fearon 2011) and the risk of developing CRC can be reduced by colonoscopic polypectomy (Winawer et al. 1993). Serrated sessile lesions or traditional serrated adenomas act as precursors in up to 25% of CRCs (Mäkinen et al. 2001, Crockett & Nagtegaal 2019). In chronic inflammatory bowel disease (ulcerative colitis and Crohn's disease), CRC is suspected to arise also from flat dysplastic mucosae without a visible precursor lesion (Itzkowitz & Harpaz 2004).

The formation of an adenoma and its subsequent progression to carcinoma are promoted by a series of mutations in tumour-suppressor genes (e.g. APC, p53) and oncogenes (e.g. KRAS, BRAF). This phenomenon is referred to as the chromosomal instability (CIN) pathway of CRC development and it accounts for more than 80% of CRCs. A minority of CRCs (15%) develop through the microsatellite instability (MSI) and CpG island methylator phenotype (CIMP) pathways, but these are more common in proximal colon than in rectum. (Fearon 2011, Muzny et al. 2012, Galon et al. 2014)

The majority of the genetic mutations leading to CRC are sporadic, while heritable factors account for 12 to 35% of CRC incidence (Lichtenstein et al. 2000, Czene et al. 2002). Family members of patients with CRC have an elevated risk for developing rectal cancer, even without the presence of a specific known hereditary cancer syndrome, which only account for 5 to 10 % of CRCs (Syngal et al. 2015). The most significant of these hereditary syndromes is the Lynch syndrome, formerly known as hereditary non-polyposis colorectal cancer (HNPCC) (Mecklin et al. 2007). Other hereditary conditions that substantially increase the risk of developing CRC are familial adenomatous polyposis (FAP), attenuated familial adenomatous polyposis (AFAP), MUTYH-associated polyposis (MAP), Peutz–Jeghers syndrome and juvenile polyposis syndrome.

Rectal cancer is more common in developed countries (IARC 2018), which has been largely attributed to dietary and lifestyle factors. Obesity, physical inactivity, smoking, excessive alcohol consumption and an unhealthy diet (low on fiber, fruits and vegetables and high on red and processed meat) are potentially modifiable risk factors for CRC, although the association of obesity and lack of physical exercise has been less pronounced in rectal than colon cancer (Aleksandrova et al. 2014). Recently, also gut microbiome and its alterations have been shown to have a role in colorectal carcinogenesis (Gagnière et al. 2016, Zhang et al. 2019).

2.1.3 Presentation and symptoms of rectal cancer

Rectal bleeding and change in bowel habits are the typical symptoms of rectal cancer (Hamilton et al. 2005). Up to 12-15 % of patients present in emergency setting with symptoms of bowel obstruction or perforation (Abel et al. 2015, Comber et al. 2016). Patients can also have weight loss and abdominal or pelvic pain, but although these symptoms sound alarming, they are not necessarily associated with a more advanced stage of disease (Stapley et al. 2006). Nevertheless, many of the patients are asymptomatic, especially in the early stages of the disease. Therefore screening programs have been started in many countries, based on showing blood in stools by either guaiac fecal occult blood test (gFOBT) or fecal immunochemical test (FIT) (Logan et al. 2012, Lauby-Secretan et al. 2018) or endoscopy without previous fecal testing (Brenner et al. 2014). Although screening has been shown to reduce CRC mortality by 9-32% in other countries (Lauby-Secretan et al. 2018) a previous gFOBT based screening program in Finland did not succeed in reducing mortality and was suspended (Pitkaniemi et al. 2015). The newer FIT is expected to perform better and therefore a randomised pilot study on CRC screening with FIT was started in Finland in 2019 (Heinävaara et al. 2019).

2.2 Diagnosis and staging

2.2.1 TNM staging of rectal cancer

Staging of rectal cancer is performed both in the diagnostic phase (to determine correct treatment) and postoperatively (to assess need for adjuvant treatment and follow-up based on risk of recurrence). The Tumour, Node, Metastasis (TNM) classification and staging of rectal cancer are presented in Tables 1 and 2 (UICC 2017). In case of clinical classification, prefix c is used (cTNM), for pathological classification the prefix is p (pTNM). An additional prefix y is added if staging is performed after neoadjuvant treatment (ypTNM). Patients who have a pathological complete response (pCR) to neoadjuvant treatment are classified as ypT0N0cM0.

2.2.2 Clinical examination and colonoscopy

The majority of rectal cancers are palpable on digital rectal examination (DRE), since less than one third of tumours are in the upper rectum (Augustad et al. 2018). Diagnosis is established by flexible endoscopy and the tumour is biopsied for pathological examination. Colonoscopy up to ceecal valve is recommended to rule out synchronous colon cancer, which is present in 2 – 6 % of the patients (Nikoloudis et al. 2004, Piñol et al. 2004, Latournerie et al. 2008, Mulder et al. 2011). Clinical examination by DRE can be complemented with endoscopic ultrasound imaging, which in expert hands can help in staging of distal T1-T2 early rectal cancer (Morino et al. 2015). Laboratory examinations include full blood count, renal and liver function test as well as carcinoembryonic antigen (CEA), which acts as a prognostic marker and has value in follow-up (Kim et al. 2015, Glynne-Jones et al. 2017). Clinical evaluation of the patient includes the assessment of functional status and physical performance as well as anal continence, in order to determine the extent of treatment feasible for the individual patient, especially in the case of elderly patients (Papamichael et al. 2015, Niemeläinen et al. 2020).

2.2.3 Pathology

Pathological examination of biopsies confirms the diagnosis of rectal cancer. The majority of the tumours are adenocarcinomas (90%) that originate from epithelial cells. Other histological types are mucinous, signet ring cell, medullary, micropapillary, serrated, cribriform comedo-type, adenosquamous, spindle cell, neuroendocrine, mixed neuroendocrine non-neuroendocrine (MINEN) and undifferentiated carcinoma (Galon et al. 2014).

Table 1. Tumour, Node, Metastasis (TNM) classification of rectal cancer (UICC 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 into 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 structures |

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 rectal cancer (UICC 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 |

Structured assessment and pathology report of the surgical specimen is recommended postoperatively (Glynne-Jones et al. 2017). Several important prognostic factors are assessed by the pathologist in addition to the pTNM staging. For a reliable evaluation of pN-stage, at least 12 nodes need to be dissected (Xu et al. 2017). CRM refers to the shortest distance of the tumour to the resection margin in cross-sectional plane. A CRM of ≤ 1 mm is independently associated with shorter disease free survival (DFS) and overall survival (OS) (Nagtegaal & Quirke 2008). The quality of mesorectal excision is reported as the plane of surgery being mesorectal, intramesorectal or exposing muscularis propria (Quirke et al. 2009). OS is also impaired in the presence of extramural vascular invasion (EMVI) also referred to as lymphovascular invasion (LVI) (Chand et al. 2015, McClelland & Murray 2015). Other prognostic factors to be reported include perineural invasion (PNI) (Song et al. 2019), tumour budding (Prall 2007), tumour deposits (Belt et al. 2010,

Shen & Hong 2019) and cellular mucin pools (Frankel & Jin 2015, Reggiani Bonetti et al. 2017). The response of the tumour to possible preoperative CRT is evaluated with the Dworak classification. Tumour regression grades (TRG) range from 0 to 4, where higher numbers refer to a better response and are a prognostic sign of better 5-year DFS (Dworak et al. 1997, Rödel et al. 2005).

2.2.4 Magnetic resonance imaging

MRI is the most accurate method for preoperative local staging of rectal cancer compared to DRE or endoscopic ultrasound (Brown et al. 2004). The importance of MRI in predicting the involvement of mesorectal fascia (MRF, distance ≤ 1 mm) or the intersphincteric plane by tumour has been shown to correlate with pCRM positivity as well as OS, DFS and LR rate (MERCURY Study Group 2006, MERCURY Study Group 2007, Taylor et al. 2014, Battersby et al. 2016). With MRI the cT3-stage of the tumour can also be subdivided to cT3a-d, where the extent of extramural growth of the tumour for more than 5 mm (cT3c/d) is a sign of worse prognosis (Table 3) (MERCURY Study Group 2007, Zinicola et al. 2017). The detection of EMVI in preoperative MRI implies a significant risk of development of distant metastases during follow up (OR=3.91, 95% CI 2.61-5.86, $p < 0.001$) (Bugg et al. 2014, Siddiqui et al. 2017).

After CRT, MRI is used in local restaging in cases where treatment response evaluation is needed before surgery. It is accurate in predicting pCRM positivity and thus helps in planning of the extent of surgery needed for radical removal of the tumour when MRF is threatened or involved (Battersby et al. 2016). TRG is also reported, with values from 1 to 5, where smaller numbers refer to a better response in contrast to the Dworak classification (Patel et al. 2012). However MRI alone is not sensitive and specific enough to reliably detect pCR (Sclafani et al. 2017).

For the evaluation of N-stage, MRI has shown conflicting results. Although the MERCURY study showed good sensitivity (85%) and specificity (97%) for detection of lymph node metastasis by MRI (Brown et al. 2003), these results have not been replicated by others (Kim et al. 2009, Park et al. 2014). A meta-analysis found a 77% sensitivity and 71% specificity for MRI to detect nodal metastasis and concluded MRI to be poor in rectal cancer N-staging (Al-Sukhni et al. 2012). In real life clinical practice, the sensitivity and positive predictive value of MRI in N-stage evaluation are closer to 50% (Brouwer et al. 2018). For the evaluation of lateral pelvic lymph nodes (LPLNs), MRI has shown promising results, which need to be verified in future studies (Schaap et al. 2018, Ogura et al. 2019b).

Current guidelines recommend the local staging to be performed by MRI and a structured report should be used by the radiologist (Glynne-Jones et al. 2017).

Table 3. Subdivision of the cT3-stage according to preoperative MRI (MERCURY Study Group 2007)

| cT3 subdivision | Depth of invasion beyond muscularis propria |
|-----------------|---|
| cT3a | < 1 mm |
| cT3b | 1–5 mm |
| cT3c | 5–15 mm |
| cT3d | > 15 mm |

2.2.5 Contrast-enhanced computed tomography

Contrast-enhanced computed tomography (CT) of the chest and abdomen is used in the evaluation of M-stage of rectal cancer (Tirumani et al. 2014, Glynne-Jones et al. 2017). At the time of diagnosis, 20% of patients have synchronous metastases, the most common site being the liver (Van der Geest et al. 2015, Riihimäki et al. 2016). CT has a sensitivity of 85% and a positive predictive value of 96% to detect liver metastases (Soyer et al. 2004). According to a meta-analysis, peritoneal metastases can be detected with a sensitivity of 83% and a specificity 86 % by CT (Laghi et al. 2017). The sensitivity of chest CT to detect pulmonary metastases is high (up to 99%) and isolated lung metastases are found in 3-12% of patients (Tan et al. 2009, Parnaby et al. 2012). However, it also detects a large number of small intermediate lung lesions, which cannot be classified as clearly benign or malignant. The percentage of such lesions varies between 4-42% in different studies, but is generally close to 20%. Approximately 30% of these small lesions will eventually turn out to be metastases (Parnaby et al. 2012, Lazzaron et al. 2015).

After neoadjuvant CRT, a preoperative restaging CT reveals new metastases in 2-12% of patients. In one retrospective study, this changed the management of 11% of the patients. Others have found the impact of restaging CT to be lower and it might be that it has no effect on the OS of these patients. Therefore, restaging CT should probably be done only selectively (Bisschop et al. 2015, Liu et al. 2015, Park et al. 2018).

2.2.6 Positron emission tomography

Positron emission tomography-computed tomography (PET-CT) is not generally used for diagnostic staging of primary rectal cancer as the accuracy is inferior to CT and MRI (Brush et al. 2011, Balyasnikova & Brown 2016, Glynne-Jones et al. 2017). It has value in detecting metastases when raising CEA levels are discovered during follow-up of rectal cancer (Suga et al. 2010). It can also find extrahepatic metastases

in up to 32% of patients with liver metastases and thus affect the choice of treatment in up to 24% of patients when the extent of metastatic disease is being evaluated (Maffione et al. 2015).

2.3 Treatment

2.3.1 Choice of treatment

The choice of treatment for all rectal cancer patients should be made in an MDT meeting (Glynne-Jones et al. 2017). The MDT consists of dedicated surgeons, radiologists, radiation oncologists, medical oncologists and pathologists. During an MDT meeting, all new rectal cancer cases are presented and the CT and MRI images are reviewed to verify staging and risk assessment of each individual case. Based on this risk assessment, participants of the MDT make a decision on treatment modalities required for each patient. MDT meetings influence or change the treatment decisions of up to 26% of the rectal cancer patients (Karagkounis et al. 2018) and can have a positive effect on their survival (Munro et al. 2015).

2.3.2 Radiotherapy

2.3.2.1 Short-course preoperative radiotherapy

The use of RT as adjuvant treatment of rectal cancer was started in hope of reducing the number of LR's after rectal cancer surgery, already before the introduction of TME surgery. In the Stockholm I and II trials and the European Organisation for Research and Treatment of Cancer (EORTC) trial, the use of 25-34.5 Gy RT given in five to fifteen fractions and followed by surgery within a week, reduced the LR rate from 25-30% to 12-15% (Gérard et al. 1988, Cedermark et al. 1995, Martling et al. 2001). It was also shown that preoperative RT is better tolerated than postoperative RT (Påhlman & Glimelius 1990). When short-course preoperative radiotherapy (SCPRT) was combined with TME surgery of resectable rectal cancer in the Dutch TME trial, the five-year LR rate dropped from 10.9% to 5.6% (Peeters et al. 2007). Although the LR rate decreases with the use of SCPRT, OS is not improved (van Gijn et al. 2011).

Current recommendations state that SCPRT (consisting of a 25 Gy total dose at 5Gy/fraction during one week and followed by surgery within 10 days) should be given if the tumour is classified as cT3c/d, cN2 or EMVI+ but MRF is clear and downsizing of the tumour is not necessary (Glynne-Jones et al. 2017). If tumour regression is required but the patient is not fit for CRT, SCPRT with a 4-8 week

delay before surgery can be given (Erlandsson et al. 2019). Short course RT can also be used as single therapy for fragile patients that do not tolerate surgery or as a component of multimodal treatment in patients with stage IV disease (Holliday et al. 2017).

2.3.2.2 Long-course chemoradiotherapy

The addition of 5-fluorouracil (5-FU) based chemotherapy to preoperative RT can be used to downsize large rectal cancer tumours (Bosset et al. 2005). The use of CRT has decreased the LR rate from 17% to 8% compared to RT alone for stage II-III resectable rectal cancer (Bosset et al. 2006, Gérard et al. 2006). In locally advanced, at presentation inoperable rectal cancer, CRT increases the likelihood of radical resection and in resected patients decreases the LR rate from 7% to 5% compared to SCPRT (Brændengen et al. 2008). In this study, five year cancer-specific survival (CSS) was also increased from 55% to 72% with CRT. But like SCPRT, CRT does not significantly improve OS of rectal cancer patients (Bonnetain et al. 2012, Brændengen & Glimelius 2018).

In up to 25% of patients CRT can lead to pCR. To avoid surgery altogether, a ‘Watch and Wait’ strategy has been introduced (Habr-Gama et al. 2004). Of patients with clinical complete response treated without surgery, 25-30% develop local regrowth, which is often amenable to salvage surgery. The largest database study on the subject showed a 5-year OS of 85% and a 5-year DFS of 94% after ‘Watch and Wait’ (Van der Valk et al. 2018). However there are no clear criteria for patient selection and best follow-up scheme and therefore this strategy should still only be used in dedicated specialist centers or in context of a trial (Smith et al. 2018, Van der Valk et al. 2018).

Currently the use of oral capecitabine or intravenous 5-FU based CRT is recommended for locally advanced tumours with threatened or involved MRF, cT4 tumours or if there is suspicion of cancer in the LPLN (Glynne-Jones et al. 2017). Usually surgery is performed 6-8 weeks after the end of CRT, but longer waiting times can be used if pCR is sought for (Petrelli et al. 2016).

2.3.2.3 Complications of radiotherapy

Perioperative morbidity and mortality are slightly elevated when SCPRT or CRT is used. A large meta-analysis showed a hazard ratio (HR) of 1.25 (95 % CI 1.02–1.54; $p = 0.03$) for morbidity and a HR 1.48 (95 % CI 1.08–2.03; $p = 0.01$) for mortality when RT was used. The rate of AL was not increased (HR 0.96; 95 % CI 0.58–1.60; $p = 0.87$) (Rahbari et al. 2013). Acute side-effects include proctitis, dermatitis, nausea, fatigue, diarrhea and dysuria. With CRT also chemotherapy related side-

effect are possible, mainly stomatitis and hand-foot skin reaction (Ansari et al. 2017). Wound healing problems are also more frequent after RT with an odds ratio of 1.43 (95% CI 1.17–1.74, $p < 0.01$) for SCPRT and 1.52 (95% CI 1.08–2.16, $p = 0.02$) for CRT (Ma et al. 2017).

Long-term side-effects of RT include fecal incontinence and urgency to defecate, erectile dysfunction, vaginal dryness and pain in intercourse (Bregendahl et al. 2013, Wiltink et al. 2014, Chen et al. 2015, Ma et al. 2017). With modern RT techniques, the risk of urinary incontinence is not significantly elevated (Wiltink et al. 2014). There is an increased risk of pelvic insufficiency fractures (Kim et al. 2012, Jørgensen et al. 2018) and a slightly elevated risk (risk ratio 1.15, 95% CI 1.05-1.25) of secondary malignancy in the irradiated area (Berrington de Gonzalez et al. 2011).

2.3.3 Surgery

2.3.3.1 History of rectal cancer surgery

Rectal cancer was an incurable disease until the late 19th century, although especially French surgeons had performed perineal proctectomies already in the 18th century (Graney & Graney 1980). Mortality of these pelvic operations started to decline before the beginning of the 20th century, but most of the patients developed a cancer recurrence. The hallmark of the beginning of radical rectal cancer surgery was the description of APE by Miles in 1908 (Miles 1908). After the World War II, as many anesthesiological and aseptic advances were made, sphincter-saving procedures gained popularity. Especially after the report by Dixon in 1948 (Dixon 1948), which confirmed the safety of anterior resection and colorectal anastomosis, APE became the operation of choice only for tumours in the lowest part of the rectum. Use of circular staplers, first invented in Russia and further developed by Ravitch in the United States (Steichen & Ravitch 1982), enhanced the technical evolution of rectal cancer surgery.

The most important advancement of the 20th century in rectal cancer surgery was the discovery of “the holy plane” and TME by Heald (Heald et al. 1982). TME has become the gold standard of rectal cancer surgery.

2.3.3.2 Total mesorectal excision

TME refers to the removal of the rectum with its surrounding mesorectum, so that the embryological fascial plane around it remains intact (Heald et al. 1982). Compared to blunt dissection within the mesorectum practiced previously, this technique led to a dramatic fall in the rate of LR from over 20% to 5% and a clear advantage in OS (Heald et al. 1998). At the same time, it was noticed that lateral

spread of the tumour and a clear CRM, more often acquired by a colorectal surgeon trained in TME, were important prognostic factors after rectal cancer surgery (Quirke et al. 1986, Porter et al. 1998). It has also been shown, that the integrity of the MRF in the surgical specimen remains an independent prognostic factor for LR rate and DFS even if preoperative RT is used (Quirke et al. 2009).

2.3.3.3 Anterior resection

Surgical treatment of rectal cancer includes the removal of the diseased segment of bowel with the surrounding mesorectum and draining lymphatics. The lymphatic routes from high and middle rectum run alongside the inferior mesenteric vessels, and thus the inferior mesenteric artery is ligated close to its origin at the abdominal aorta (Augestad et al. 2018). For lower rectum, lymphatics drain also along the internal iliac vessels, but lateral pelvic lymph node dissection (LPLND) is not routinely practiced in Europe (Glynn-Jones et al. 2017). Pelvic dissection is performed in the TME plane leaving the hypogastric nerves intact (Acar & Kuzu 2012). In cases where the tumour grows through the MRF into adjacent organs, a multivisceral resection is needed in order to perform a radical operation with a clear CRM (The Beyond TME Collaborative 2013, Peacock et al. 2019).

In anterior resection (Figure 1a), the transection of the rectum is usually performed with a linear stapler at least 1 cm below the tumour. After RT, even a distal margin of 0,5 cm may be sufficient (Pahlman et al. 2013). For tumours in the upper rectum, the mesorectum and bowel can be transected 5 cm below the tumour. This is referred to as partial mesorectal excision (PME) and it has been shown to be oncologically adequate for tumours located above the peritoneal reflection (Lopez-Kostner et al. 1998).

After removal of the surgical specimen, an anastomosis is performed between the sigmoid colon and the rectal remnant. A straight end-to-end anastomosis can be performed after PME, but when the anastomosis is low a side-to-end anastomosis or a j-pouch formed from the distal colon is functionally better (Hüttner et al. 2015, Parc et al. 2019). Whatever technique is chosen, anastomotic leakage (AL) occurs in 19 – 28% of patients with a low rectal anastomosis (Hain et al. 2017, Pucciarelli et al. 2019). A defunctioning transversostomy or ileostomy is therefore often fashioned, as it reduces the rate of clinical AL and the need for early reoperations (Tan et al. 2009, Montedori et al. 2010). If the patient is too fragile to survive a possible AL, no anastomosis is made and the transected sigmoid is brought up as an end colostomy in Hartmann's operation (Sanderson 1980, Sverrisson et al. 2015). To avoid possible complications associated with the rectal stump after a low Hartmann's operation, an APE with intersphincteric dissection can also be used (Smedh et al. 2016). Intersphincteric resection on the other hand refers to an

operation where the internal anal sphincter is partly or entirely removed in order to radically dissect a low rectal cancer. Usually a coloanal handsewn anastomosis is performed (Rullier et al. 2013).

Anterior resection can be performed with similar oncological results either by conventional open surgery, laparoscopically (Vennix et al. 2014, Bonjer et al. 2015, Fleshman et al. 2019) or with robotic assistance (Jayne et al. 2017, Holmer & Kreis 2018). Transanal TME (TaTME) is a newer technically demanding operative technique, where the rectum is approached from above and below with laparoscopic instruments usually simultaneously by two surgical teams. Although good early results with this technique have been reported in expert centers, a larger randomised trial is needed to confirm its safety (Deijen et al. 2016, Aubert et al. 2019).

2.3.3.4 Abdominoperineal excision

APE is used when low rectal cancer either infiltrates the sphincter complex or the levator ani muscles, or is so close to them that a safe transection of the rectum below the tumour cannot be performed. In the operation the TME plane is followed down to the pelvic floor from the abdominal side after which the sphincter complex is dissected from a circular perineal incision. The dissection planes meet at the pelvic floor (Figure 1b) (Marr et al. 2005, Rullier et al. 2013). The perineum is reconstructed by suturing the remaining levator muscles together in the midline and then closing the skin. Like anterior resection, APE can be performed by open, laparoscopic or robotic approach (Jayne et al. 2017, Fleshman et al. 2019).

After the introduction of TME, the oncological results of anterior resection improved, but when APE was performed the rate of LR remained in 15-22% (Wibe et al. 2004, Marr et al. 2005). This was attributed mainly to the higher frequency of positive CRM and IOPs in APE (Eriksen et al. 2004, Wibe et al. 2004, Marr et al. 2005, Nagtegaal et al. 2005). To widen the resection margin, an extended resection currently referred to as ELAPE was described (Holm et al. 2007). In ELAPE, the dissection from the abdominal side is stopped at the upper border of the coccyx and just below the inferior hypogastric nerves and seminal vesicles or the cervix, clearly higher than in conventional APE. After forming the permanent colostomy and finishing the abdominal side of the operation, the patient is turned to prone position and the perineal dissection is performed from a tear-drop shaped incision. The levator muscles are included in the surgical specimen (Figure 1c) (Shihab et al. 2012). Due to the resulting larger tissue defect, the pelvic floor is often reconstructed using a biological mesh or a muscle flap, but primary closure with sutures only is also sometimes used (Musters et al. 2017, Foster et al. 2018).

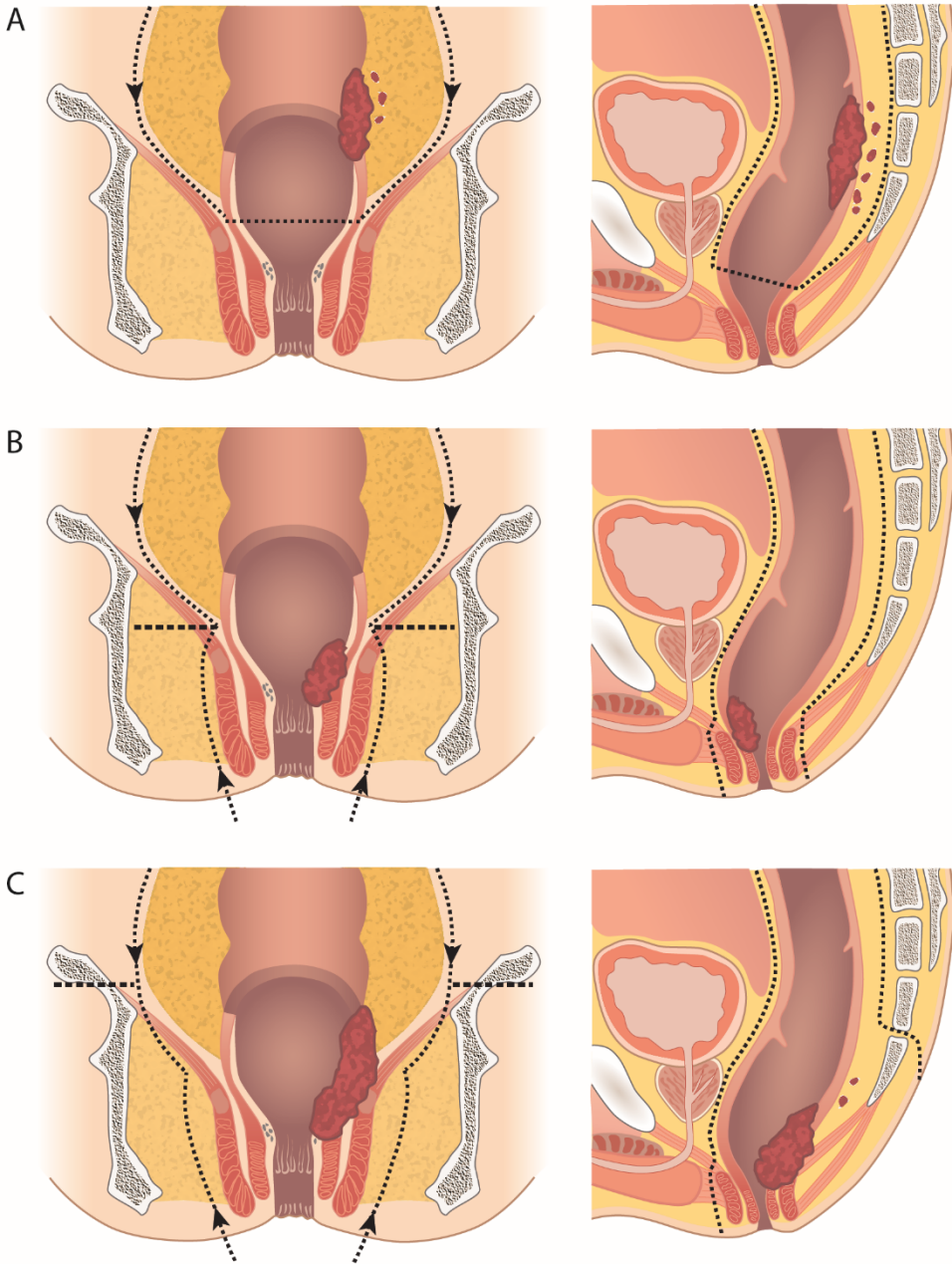


Figure 1. Resection lines in anterior resection (a), abdominoperineal excision, APE (b) and extralevator abdominoperineal excision, ELAPE (c).

Results on the superiority of ELAPE over APE in achieving a clear CRM and avoiding IOP are contradictory. Two randomized controlled studies have been conducted and both showed a significantly reduced CRM positivity rate in ELAPE (Han et al. 2012, Bianco et al. 2017). Han et al. also described a lower LR rate of 3% after ELAPE compared to 19% after APE during a median follow-up time of 29 months (Han et al. 2012). Several retrospective series have demonstrated similar results, with significant differences also in the number of IOPs (West et al. 2008, West et al. 2010, Stelzner et al. 2011, Perdawood & Lund 2015, Shen et al. 2015, Stelzner et al. 2016). On the other hand, large registry and population based studies have not been able to show any advantage of ELAPE over APE in CRM positivity, the number of IOPs or LR rates (Ortiz et al. 2014, Prytz et al. 2014, Klein et al. 2015, Klein et al. 2016, Prytz et al. 2016). The LR rate in different studies varies between 0-13% after ELAPE and between 3-19% after APE (Asplund et al. 2012, Han et al. 2012, Ortiz et al. 2014, Perdawood & Lund 2015, Shen et al. 2015, Stelzner et al. 2016).

During the past ten years, ELAPE has become widely used, with some centers performing exclusively ELAPE (Gravante et al. 2016, Stelzner et al. 2016) and others recommending the more radical approach only for selected cases with advanced tumours (Prytz et al. 2016). In spite of the increasing use of the more extensive procedure, none of the studies published so far have been able to show any OS benefit of ELAPE compared to APE (Klein et al. 2016, Prytz et al. 2016, Stelzner et al. 2016).

2.3.3.5 Complications of surgery

The postoperative mortality rate after rectal cancer surgery is 1% and overall morbidity rate varies from 27 to 40% (Van der Pas et al. 2013, Qiu et al. 2016, Sharp et al. 2020). Interventions are needed in approximately 15% of patients (Van der Pas et al. 2013). The most feared complication is AL. It occurs in 19 – 28% of patients with a low rectal anastomosis and can have a negative effect on the survival of these patients (Hain et al. 2017, Pucciarelli et al. 2019). In addition to AL, infectious complications include wound infection and dehiscence, intra-abdominal abscess formation, pneumonia and urinary tract infections. Healing of the perineal wound is delayed in 15-38% of patients undergoing APE or ELAPE and RT has clearly been shown to increase this risk (Musters et al. 2014). Some studies have also reported on more wound problems after ELAPE than APE (Prytz et al. 2014, Asplund et al. 2015) but data on this is inconclusive (Musters et al. 2014, Foster et al. 2018). Postoperative ileus develops in 5% of patients. Cardiac and thromboembolic events as well as renal failure are less frequent (Van der Pas et al. 2013, Qiu et al. 2016).

2.3.4 Adjuvant chemotherapy and chemoradiotherapy

After SCPRT or CRT, additional adjuvant chemotherapy for four months after surgery is currently recommended to patients with yp stage III disease and to patients with yp stage II disease who present with high risk features for disease recurrence. The level of evidence for the recommendation is not strong and the benefit may be to DFS only rather than OS (Zhao et al. 2016). Therefore the decision to give adjuvant chemotherapy has to be made on an individual basis with careful discussion with the patient. 5-FU alone or in combination with oxaliplatin is generally used (Glynne-Jones et al. 2017).

In cases where high risk features or extensive nodal disease are discovered at pathological examination and the patient has not received preoperative RT, postoperative CRT can be considered by the MDT. This is especially the case if positive CRM or tumour perforation has occurred and the risk of LR is elevated (Glynne-Jones et al. 2017).

2.3.5 Treatment of metastatic and recurrent disease

Patients who have synchronous metastases at time of diagnosis or who develop recurrent disease during follow-up, should be evaluated by a MDT for their potential to receive a curative resection (Van Cutsem et al. 2016). Radical resection of liver metastases leads to a 5-year OS of 40%. Surgery is also beneficial if conversion chemotherapy shrinks initially inoperable liver metastases to operable, since these patients have a 5 year OS of 33% (Adam et al. 2012). Patients with lung metastases also benefit from metastasectomy, with a 5-year OS of 40% for those patients in which radical resection can be performed (Pastorino et al. 1997, Nanji et al. 2018).

In case of isolated LR, radical surgery should be pursued. If CRT has not been given before the primary operation, it is recommended at this point (Glynne-Jones et al. 2017). Reirradiation can also sometimes be given preoperatively and in palliative setting it improves the symptoms of over 80% of patients (Guren et al. 2014). Operability of the LR is evaluated with the help of MRI and extensive resections involving adjacent organs are often required (Nielsen et al. 2011, Yeo & Paty 2014, Ganeshan et al. 2019). Only a minority (22-28%) of LRs are operable and the majority are thus managed with palliative care (Poulsen et al. 2018, Westberg et al. 2018).

Patients unsuitable for metastasis resection may undergo palliative treatments. Systemic chemotherapy is used to treat metastatic rectal cancer in first line, often combined with targeted biological agents (bevacizumab, panitumumab and cetuximab) (Van Cutsem et al. 2016). Local ablative therapies, such as radiofrequency ablation and targeted RT, can be used especially when the number

of metastases is small but they are inoperable. However although promising results have been reported, their effect on OS is uncertain (Ruers et al. 2012).

2.4 Prognosis and recurrent disease

2.4.1 Prognosis of rectal cancer

The 5-year OS of all patients with rectal cancer is in recent series 63-67% (Guren et al. 2015, Iversen et al. 2016, Siegel et al. 2017). For patients with localised stage I-II disease, 5-year OS is 88%, for stage III it is 70% but for patients with stage IV metastatic disease it is still only 14% (Siegel et al. 2017). Most CRC recurrences are detected within the first two to three years of surveillance (Baca et al. 2011, Räsänen et al. 2015).

2.4.2 Distant recurrence

According to large population based registry studies, 20-26 % of radically treated rectal cancer patients develop distant metastases during follow-up. Although the liver is the most common site of recurrence, especially for low rectal cancer with venous drainage also to iliac vessels, pulmonary metastases are almost as common (Guren et al. 2015, Riihimäki et al. 2016, Augestad et al. 2018). The median survival of all patients with metastatic disease has increased from 5 to 12 months in recent years, and for those who are able to undergo chemotherapy or metastasectomy, it has increased to 20-30 months (Lemmens et al. 2011, Mitry et al. 2013, Sorbye et al. 2013, Van der Geest et al. 2015, Heervä et al. 2018).

2.4.3 Local recurrence

2.4.3.1 Incidence of local recurrence

LR is defined as any recurrence within the pelvis after radical treatment of rectal cancer (Rullier et al. 2013). After modern multimodality treatment, the incidence of LR generally varies between 5 to 10 % (Kusters et al. 2009, Kulu et al. 2015, Hain et al. 2018, Ogura et al. 2019a). In recent population based registry studies from the Nordic countries, the 5-year rate of LR has been as low as 4% (Glimelius et al. 2016, Poulsen et al. 2018), but it might be that in such large registry based studies, some LRs are not detected (Moberger et al. 2018). In the TME trial the 5-year LR rate was 11% in the surgery-only group and 5% for those who received SCPRT (Peeters et al. 2007). These rates did not increase at the 10-year timepoint (van Gijn et al. 2011).

Lower 3-year LR rates between 2 and 5% have been reported in randomised controlled trials evaluating laparoscopic rectal cancer surgery (Jeong et al. 2014, Bonjer et al. 2015, Fleshman et al. 2019). These studies however had strict patient selection criteria, did not include T4 tumours, and the majority of the patients had received either CRT or SCPRT. On the other hand when only patients with more advanced tumours are analysed, the LR rate rises to 12-19% (Kusters et al. 2015, Kusters et al. 2017, Schaap et al. 2018, Peacock et al. 2019).

2.4.3.2 Risk factors for local recurrence

Significant risk factors for LR in previous literature have been CRM positivity (Wibe et al. 2002, Nagtegaal & Quirke 2008), higher T-stage of the tumour (Wibe et al. 2002), quality of TME surgery (intact mesorectal plane) (Quirke et al. 2009), LVI or PNI (Horn et al. 1991, Peacock et al. 2019), IOP (Bülow et al. 2011) and in some studies also AL (Hain et al. 2017, Wang et al. 2017).

2.4.3.3 Location of local recurrence

The location of LR is important when the possibility for surgery of LR is considered. In centrally or anteriorly located LRs, the likelihood of successful radical surgery is higher (Moore et al. 2004, Westberg et al. 2018, Hagemans et al. 2019) and the OS of patients with LR has been significantly longer if patients with LR are radically operated (Denost et al. 2015, The PelvEx Collaborative 2018, Westberg et al. 2018). Anatomically, the LR can be situated in the previous tumour bed, at the anastomosis after anterior resection or in the LPLNs (Denost et al. 2015). The topographic location of the LR in the pelvis is most often determined according to the Memorial Sloan-Kettering classification (Moore et al. 2004). It divides the pelvis into axial (anastomosis, perineum after APR, remaining mesorectum after PME), anterior (genital and urinary organs), posterior (or presacral, including sacrum and coccyx) and lateral compartments (LPLNs, iliac vessels, ureter, pelvic sidewalls including muscular, bony and nervous structures).

In previous literature the proportions of LRs in different locations vary considerably. In earlier studies with patient inclusion timeframe mainly in the 90's, the location of LR has been axial or anterior in 29-67%, posterior in 10-41% and lateral in 10-25% of patients (Enríquez-Navascués et al. 2011). Data on location of LR after modern multimodality treatment is sparse, and has mainly been assessed in patient subsets. According to a study of the Swedish Colorectal Cancer registry, the proportion of axial and anterior recurrences had declined during more recent years, but it still was 39% in patients without synchronous distant metastases (Westberg et al. 2018). The predominance of axial and anterior recurrences (50-70%) is also still

seen in studies evaluating patients that were operated for LR since these patients are more often referred for surgery (Denost et al. 2015, Kloose et al. 2015). In the TME-trial, 33% of LRs were posterior, 20% were lateral and 43% were axial or anterior. A tendency to greater proportion of posterior and lateral LR after RT compared to surgery only was noted (Kusters et al. 2010). In a recent large multicenter study that included patients with primarily cT3-4 low rectal tumours within 8 cm from the anal verge, 54% of LRs were lateral, 22% posterior and 24% axial or anterior (Ogura et al. 2019a).

2.5 Long-term sequelae

2.5.1 Quality of life after treatment of rectal cancer

Fecal and urinary incontinence are significantly more common among rectal cancer survivors than in age matched general population (Schiffmann et al. 2020). Although up to 80% of patients have genitourinary symptoms, their impact on QoL is lower than the impact of bowel dysfunction, which is present in 40-65% of patients (Eid et al. 2019, Kupsch et al. 2019).

After APE or ELAPE 50% of patients have perineal symptoms, mainly pain, tension and sitting disability. When present, these symptoms are associated with a lower QoL (Asplund et al. 2015). Generally the rectal cancer patients with a permanent ostomy have a similar QoL to those without an ostomy according to a large Cochrane review and a population-based Danish study (Pachler & Wille-Jorgensen 2012, Feddern et al. 2019). However, there are also studies which show the patients with an ostomy to have lower QoL, worse body image and lower levels of emotional, physical and mental functioning (Mols et al. 2014, Näsvalld et al. 2017). After anterior resection, constipation and diarrhea symptoms are more common than after APE (Feddern et al. 2019).

Incisional hernias have been described to develop in 18% of patients and bowel obstruction due to adhesions in 12%. Only a minority of these need surgical intervention as the reported rate of incisional hernia repair after rectal cancer treatment is 4% (Andersen et al. 2018, Petersson et al. 2019). Parastomal hernia develops in up to 50% of patients with permanent colostomy. When the colostomy is constructed, a prophylactic mesh is usually applied to prevent hernia formation, but results on its efficacy are inconclusive (Chapman et al. 2017, Mäkäräinen-Uhlbäck et al. 2020).

2.5.2 Low anterior resection syndrome (LARS)

LARS refers to the combination of functional defecatory symptoms that often diminish the QoL of patients after continence preserving rectal cancer surgery. Common symptoms include urgency, fragmentation and incontinence. The syndrome was already described in the 90's (Ortiz & Armendariz 1996) but the impact of it on the QoL of the patients was previously underestimated by surgeons (Chen et al. 2014). The development of the LARS score by Emmertsen and Laurberg in 2012 (Emmertsen & Laurberg 2012) and subsequent active research have led to increasing awareness of LARS among physicians who treat rectal cancer patients. The LARS score is an easy-to-fill, five item questionnaire, by which patients can be divided into having no, minor or major LARS. It has been translated and validated in many languages and it's nowadays actively used both in clinical practice and research (Juul et al. 2014a, Hou et al. 2015, Juul et al. 2015, Samalavicius et al. 2016, Akizuki et al. 2018, Hupkens et al. 2018, Liapi et al. 2019).

The long-term prevalence of LARS after anterior resection has been reported to be up to 41-56% (Chen et al. 2015, Croese et al. 2018, Pieniowski et al. 2019). Risk factors for major LARS include TME with an anastomosis closer to the anus compared to a higher anastomosis after PME (Bregendahl et al. 2013, Jimenez-Gomez et al. 2018, Kupsch et al. 2018), preoperative RT (Bregendahl et al. 2013, Bondeven et al. 2015, Hughes et al. 2017, Jimenez-Gomez et al. 2018, Nuytens et al. 2018), young age (Bregendahl et al. 2013, Kupsch et al. 2018) and formation or late closure of a protective ostomy (Wells et al. 2015, Hughes et al. 2017).

3 Aims

This thesis was designed to elucidate the opportunities and challenges faced by the surgeon and the patient in the era of modern rectal cancer surgery. The specific aims were as follows:

- I To evaluate temporal changes in the treatment and survival of patients with rectal cancer during 2001-2012.
- II To determine whether the more extensive ELAPE operation offers a better long-term survival than APE for patients with locally advanced rectal cancer.
- III To determine the incidence, location and risk factors of LR after modern multimodality treatment of rectal cancer.
- IV To evaluate the validity of the Finnish LARS Score –questionnaire.

4 Patients and Methods

4.1 Patients

4.1.1 Patients with rectal cancer identified through Auria Biobank (Study I)

Auria Biobank includes all biopsy and surgical samples from tumours of patients diagnosed with CRC in the Turku University Hospital region. All patients with a histologically confirmed diagnosis of colorectal adenocarcinoma between 2001 and 2012 were identified from Auria Biobank. Of these 1777 patients, 687 had rectal cancer. Clinical data (International Classification of Diseases 10th Revision (ICD-10) codes and chemotherapy data, since 2004) and RT records (since 2001) of the patients were linked from the hospital's electronic medical records to the pathology samples by the Biobank and a unanimous dataset was created. To identify patients with comorbidities, Charlson comorbidity index (Charlson et al. 1987) was calculated on the basis of ICD-10 codes given during hospital care. All tumour samples were staged according to the TNM classification. Metastatic disease was identified either as: (1) ICD-10 code for metastasis; (2) chemotherapy given for metastatic disease including the use of targeted therapy, or chemotherapy with non-adjuvant regimens; (3) palliative RT; or (4) histological confirmation of liver, lung, ovarian or peritoneal metastasis. Some patients had only a biopsy sample from the primary tumor without confirmation of distant metastases. This 'non-metastatic biopsy-only' category includes patients with inoperable locally advanced tumors, but also those who are unfit for any surgery or with missing ICD-10 codes for metastases. Biobank studies cannot specify the true reason for this.

Rectal cancer surgery was centralised in 2004 from several hospitals in the Turku region to the Turku University Hospital. Patients in this study were divided into three groups based on the year of diagnosis: 2001–2003 (before centralisation), 2004–2008 (after centralisation) and 2009–2012 (5 years after centralisation).

4.1.2 Patients treated with abdominoperineal excision (Study II)

All consecutive patients who underwent ELAPE (n = 42) for rectal adenocarcinoma between September 2009 and April 2016 in Turku University Hospital were retrospectively collected from the hospital's electronic patient records. Operations for locally recurrent rectal cancer were excluded. During this time period, ELAPE was selectively used for patients with locally advanced T3-T4 tumours in which the CRM would have been threatened using the traditional APE. Since ELAPEs were started in Turku University Hospital in 2009, the learning curve of the surgeons in this new technique is included in the time frame of Study II.

A historical comparison group (n = 27) was formed of patients who on the basis of imaging studies and clinical assessment would have been operated by ELAPE if the technique had already been in use. It comprised of patients who underwent APE between January 2004 and August 2009, excluding patients with T1-T2 tumours and patients with mobile T3 tumours in which only SCPRT was given before the operation.

4.1.3 Patients followed up for local recurrence (Study III)

All patients diagnosed with rectal cancer between 2007 and 2012 were retrospectively identified from electronic medical records of Turku University Hospital. Patients treated by local excision or with palliative intent only were excluded (figure 2). Of the 458 patients diagnosed with rectal cancer during the study period, 348 (147 [42%] women) were eligible. 320 of them had stage I-III disease. The 28 patients with primarily stage IV disease were analysed separately and only descriptively because of small numbers and shorter follow-up.

4.1.4 Patients evaluated for LARS (Study IV)

All patients who underwent an anterior resection for rectal cancer between 2007 and 2014 were collected from the Turku University Hospital's electronic patient records. Finnish speaking patients who were alive and living without an ostomy at the moment of the study were included. Those with cognitive impairment (for example dementia or major psychiatric disease) or LR of the cancer within the pelvis were excluded. Of the 641 patients diagnosed with rectal cancer in our unit during the study period, 159 were eligible. They were contacted by mail, and 104 (65%) of these patients participated in the study. The participants were similar to those not participating in regard to age, gender, operative details and the use of RT. Background information of the participating patients is presented in table 4.

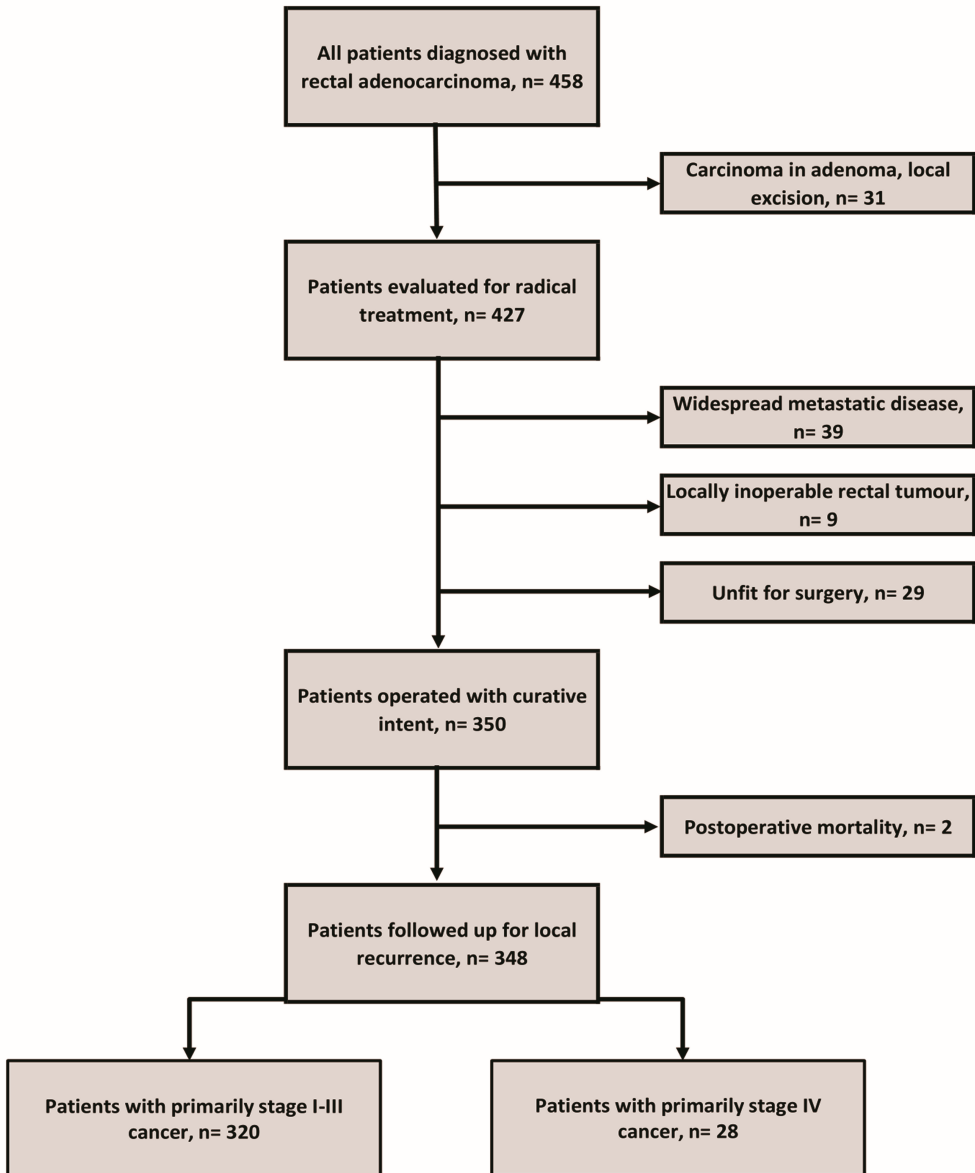


Figure 2. Study III flowchart

Table 4: Background information of the participating patients in Study IV (reproduced with the permission of the copyright holder).

| Variable | Study IV patients (n = 104) |
|--|-----------------------------|
| Age, years | 72 ± 8 |
| Gender (F/M) | 40/64 |
| Radiotherapy | |
| No radiotherapy | 72 (69) |
| Short 5 x 5 Gy | 26 (25) |
| Long 50.4 Gy with capecitabine | 4 (4) |
| Postoperative radiotherapy | 2 (2) |
| Type of operation | |
| TME | 61 (59) |
| PME | 43 (41) |
| Abdominal access | |
| Open | 94 (90) |
| Laparoscopic | 5 (5) |
| Laparoscopic converted to open | 5 (5) |
| Protective ostomy | 36 (35) |
| Time to closure of ostomy, months | 7,6 (5,3) |
| Anastomotic leakage | 11 (11) |

Values are given as mean ± SD, ratio, n (%) or median (interquartile range).

F/M, female/male ratio; Gy, gray; TME, total mesorectal excision; PME, partial mesorectal excision.

4.2 Methods

4.2.1 Preoperative evaluation and neoadjuvant treatment

Turku University Hospital is a tertiary referral center, to which rectal cancer treatment is centralised in Southwest Finland. Patients are managed by a MDT including experienced colorectal surgeons, radiation oncologists, medical oncologists, radiologists and pathologists. CT was performed to assess the presence of distant metastases at the time of diagnosis. MRI was used for local staging in the majority of the patients. Preoperative restaging MRI after CRT was not routinely

performed at the time of the studies. Either SCPRT or CRT was used selectively for cT3 high risk and cT4 mid and low rectal cancers.

4.2.2 Surgical technique

All patients were operated on by experienced colorectal consultant surgeons within the centralised colorectal unit of Turku University Hospital. According to tumour height, either anterior resection or APE was performed. ELAPE was used from 2009 onwards for tumours invading the levators. Perineal reconstruction after ELAPE was done using a biological mesh. Intersphincteric resections or LPLND for rectal cancer are not routinely performed at our unit. TME was performed for mid and low rectal cancers. For high tumours above the peritoneal reflection, PME with a 5 cm distal margin was considered sufficient.

Surgical complications were graded according to the Clavien–Dindo classification (Dindo et al. 2004).

4.2.3 Adjuvant treatment

During the study period, postoperative adjuvant chemotherapy was generally recommended by our MDT meeting for locally advanced or node-positive rectal cancer.

4.2.4 Follow-up regime

Follow-up consisted of clinical examination and laboratory tests (haemoglobin, CEA) every 6 months for 3 years and thereafter once a year until 5 years. Routine colonoscopy was performed at 3 years. For patients with stage III or high risk stage II disease, CT was performed at 2 years postoperatively. There were no changes to the follow-up routine during the study period.

DFS was calculated from the date of diagnosis (Study I) or the date of operation (studies II and III) to the date of diagnosis of metastatic disease or LR. OS was calculated from the date of diagnosis to death of any cause. CSS was calculated from diagnosis to date of death, where the cause of death was CRC.

In Study III, LR was defined as any recurrent rectal adenocarcinoma within the pelvis after previous surgery for rectal cancer. LRs were grouped according to the Memorial-Sloan Kettering classification as mainly axial, anterior, posterior or lateral (Moore et al. 2004). To specify the anatomic location of the LR, a further division into tumours located at the anastomosis, previous tumour bed or LPLNs was also made. Local recurrence free survival (LRFS) was calculated from the time of operation to the date of diagnosis of LR.

4.2.5 Translation of the LARS score

The previously validated English version of the LARS score questionnaire (Juul et al. 2015) was used as the template for the Finnish version. The translation process was performed according to previously published methodology for translating health status questionnaires (Bullinger et al. 1998, Kulis et al. 2017). Briefly, the English version was first translated to Finnish by two independent translators, whose mother tongue was Finnish. Possible differences between these translations were compared by a group of linguistics and colorectal surgeons and one consensus translation was agreed upon. This translation was backward translated to English by a third translator to check whether the original meaning of each question and answer had been retained. The third translator was unfamiliar with the original English version of the LARS score. The final translation (Figure 3, scoring instructions Figure 4) was pilot tested on a group of rectal cancer patients visiting the outpatient clinic.

4.2.6 Testing the validity of the LARS score translation

Validity of the translation was tested according to previously published methodology (Gandek & Ware 1998). To state that a translated health status questionnaire is valid in the target population, it needs to give similar results as other tests designed to measure the same construct. This convergent validity was tested by comparing results of previously validated QoL questionnaires (QLQs; EORTC QLQ-C30 and EORTC QLQ-CR29) to the results of the translated Finnish LARS score questionnaire. A valid test also needs to give different results when measuring different constructs. This discriminant validity was evaluated by comparing the severity of LARS of patient groups with and without risk factors for developing LARS. The test-retest reliability was assessed by repetition of the LARS score questionnaire in a two week interval on a subgroup of 23 patients. Study IV was conducted as a postal query by sending an information leaflet, a patient informed consent –form, the Finnish LARS score questionnaire, the EORTC QLQ-C30 (version 3.0) and the EORTC QLQ-CR29 with a prepaid return envelope to the eligible patients.

Low Anterior Resection Syndrome Score – LARS Score / suomennos**Kysely suolen toiminnasta**

Tämän kyselyn tavoite on arvioida suolen toimintaa. Rastita kunkin kysymyksen kohdalta vain yksi vastaus. Voi olla vaikeaa valita vain yksi, sillä oireet saattavat vaihdella päivästä toiseen. Valitse kuitenkin se vastaus, joka parhaiten kuvaa jokapäiväistä elämääsi. Jos sinulla on hiljattain ollut suolen toimintaan vaikuttanut tulehdus, älä ota sitä huomioon. Keskity vastaamaan kysymyksiin sen mukaan, miten suoli yleensä toimii.

Onko sinulla koskaan tilanteita, jolloin et pysty pidättämään ilmaa?

- Ei koskaan
- Kyllä, harvemmin kuin kerran viikossa
- Kyllä, ainakin kerran viikossa

Karkaako sinulta koskaan nestemäistä ulostetta?

- Ei koskaan
- Kyllä, harvemmin kuin kerran viikossa
- Kyllä, ainakin kerran viikossa

Kuinka usein ulostat?

- Yli 7 kertaa vuorokaudessa
- 4–7 kertaa vuorokaudessa
- 1–3 kertaa vuorokaudessa
- Harvemmin kuin kerran vuorokaudessa

Täytyykö sinun koskaan ulostaa uudelleen tunnin kuluessa edellisestä ulostuskerrasta?

- Ei koskaan
- Kyllä, harvemmin kuin kerran viikossa
- Kyllä, ainakin kerran viikossa

Onko sinulla koskaan niin voimakasta ulostustarvetta, että täytyy kiirehtiä vessaan?

- Ei koskaan
- Kyllä, harvemmin kuin kerran viikossa
- Kyllä, ainakin kerran viikossa

Figure 3. Finnish translation of the LARS score

| Low Anterior Resection Syndrome Score – LARS Score / Pisteytysohjeet | |
|--|---|
| Kokonaispistemäärän saat laskemalla yhteen 5 kysymyksestä saadut pisteet. | |
| <hr/> | |
| Onko sinulla koskaan tilanteita, jolloin et pysty pidättämään ilmaa? | |
| <input type="checkbox"/> Ei koskaan | 0 |
| <input type="checkbox"/> Kyllä, harvemmin kuin kerran viikossa | 4 |
| <input type="checkbox"/> Kyllä, ainakin kerran viikossa | 7 |
| Karkaako sinulta koskaan nestemäistä ulostetta? | |
| <input type="checkbox"/> Ei koskaan | 0 |
| <input type="checkbox"/> Kyllä, harvemmin kuin kerran viikossa | 3 |
| <input type="checkbox"/> Kyllä, ainakin kerran viikossa | 3 |
| Kuinka usein ulostat? | |
| <input type="checkbox"/> Yli 7 kertaa vuorokaudessa | 4 |
| <input type="checkbox"/> 4–7 kertaa vuorokaudessa | 2 |
| <input type="checkbox"/> 1–3 kertaa vuorokaudessa | 0 |
| <input type="checkbox"/> Harvemmin kuin kerran vuorokaudessa | 5 |
| Täytyykö sinun koskaan ulostaa uudelleen tunnin kuluessa edellisestä ulostuskerrasta? | |
| <input type="checkbox"/> Ei koskaan | 0 |
| <input type="checkbox"/> Kyllä, harvemmin kuin kerran viikossa | 9 |
| <input type="checkbox"/> Kyllä, ainakin kerran viikossa | 11 |
| Onko sinulla koskaan niin voimakasta ulostustarvetta, että täytyy kiirehtiä vessaan? | |
| <input type="checkbox"/> Ei koskaan | 0 |
| <input type="checkbox"/> Kyllä, harvemmin kuin kerran viikossa | 11 |
| <input type="checkbox"/> Kyllä, ainakin kerran viikossa | 16 |
| Kokonaispistemäärä: | _____ |
| Tulkinta: | 0–20: Ei LARSia 21–29: Lievä LARS 30–42: Vaikea LARS |

Figure 4. Finnish translation of the LARS score scoring instructions

4.2.7 Statistical analyses

Study I: Between groups 2001–2003, 2004–2008 and 2009–2012, the frequency of categorical covariates such as age group or gender was analysed using Pearson's chi-square test. OS, DFS and CSS were analyzed with Kaplan–Meier log-rank analysis. Since the last study cohort was from 2009 to 2012 and the study ended in 2016, the survival cutoff was set to 7 years, but occasionally a 10-year cutoff was used to calculate median survival. A cutoff of 5 years was used in metastatic disease. The effect of covariables on survival was analyzed with Cox regression analysis, first one covariable at time, followed by multivariable analysis. In multivariable analysis, the enter method was used with 95% confidence interval (CI). P-values of less than 0.05 were considered significant. Statistical analyses were performed with IBM SPSS statistics software version 21 (IBM SPSS Statistics, Armonk, NY).

Study II: The difference between the groups with regard to the distribution of baseline characteristics was analyzed for categorical variables by cross-tabulation and significances were tested with Pearson's chi-square test, or, in the case of small frequencies, with Fisher's exact test. For continuous variables the difference was analyzed by t-test for independent samples, or, for non-normally distributed continuous variables by Wilcoxon two sample test. The difference between groups in OS and DFS was studied by survival analysis, survival curves produced by Kaplan-Meier method and tested by Log-Rank test. Age and adjuvant treatment adjusted survival analyses were performed using the Cox proportional hazards model. P-values below 0.05 were considered statistically significant. Statistical analyses were done using SAS for Windows version 9.4.

Study III: Comparison between descriptive variables of LR and no LR groups was done with Pearson's chi-square analysis, or, in the case of small frequencies, with Fisher's exact test. OS and LRFS were analysed with Kaplan-Meier log-rank analysis. P-values of less than 0.05 were considered significant. When analysing risk factors for LR, univariable cox regression analysis was performed first using enter method and 95% CI. Subsequently, covariables with p-value below 0.1 were incorporated into final multivariable Cox regression model. Calculations were performed with IBM SPSS software version 26.

Study IV: Data analysis was performed after omission of identifying information. The differences in the gender, operative details or the use of CRT or SCPRT between the groups of responding and non-responding patients were compared with chi-square or Fisher's exact test. Two-sample t-test was used to test the difference in mean ages between responding and non-responding patients. Intraclass correlation coefficient was calculated to test the reliability of the Finnish LARS score in the test-retest group.

Global health status, functioning scales in the EORTC QLQ-C30 and symptomatic scales in QLQ-CR29 were compared between LARS severity groups

using Kruskal-Wallis test and further pairwise comparisons were done with Bonferroni-corrected Mann-Whitney U-test. Chi-square test was used to compare categorical variables between LARS severity groups. The difference in mean ages between LARS severity groups was tested with one-way analysis of variance.

P-values less than 0.05 were considered statistically significant. Statistical analyses were done using IBM SPSS Statistics 25.0 for Windows (IBM Corp. Armonk, NY).

5 Results

5.1 Temporal changes in the treatment and survival of rectal cancer patients (Study I)

The reliability of the population coverage of the Auria Biobank data was evaluated in comparison to regional rectal cancer incidence reported by the Finnish Cancer Registry (<https://syoparekisteri.fi/>). Compared to the registry data, the current Auria Biobank dataset contained 80% of rectal cancer samples from the Turku region in 2001–2003. From 2004 onwards, 94–99% of rectal cancer samples were included in the Auria Biobank highlighting the improved coverage due to centralisation of rectal cancer surgery. The remaining patients were operated in smaller regional hospitals in the Turku region, and were not included in this study.

The CSS data of Auria Biobank was validated by comparison to the official cause of death –data from Statistics Finland. According to Statistics Finland, the cause of death was CRC in 594 of the 1777 (33%) patients in the whole study. Based on Auria data, 587 patients either presented with or later progressed to stage IV disease or were never operated (non-metastatic biopsy-only disease), thus having a high probability of lethal disease. This figure was in close agreement with the 594 CRC deaths from records of Statistics Finland.

The minimum and median follow-up times were 3.3 and 8.6 years, respectively. Mean age of the patients was 70 years. The proportion of patients with comorbidities increased from 14% in 2004–2008 to 21% in 2009–2012 ($p = 0.001$). The stage distribution of rectal cancer remained essentially the same throughout 2001–2012. However, there was a significant decrease over time in the number of patients in whom the tumour was only biopsied ($p = 0.007$, Table 5).

For operated stage I–III rectal cancer patients, the mean number of lymph nodes dissected increased from 6 to 15 nodes during the study period ($p < 0.0001$) and the number of patients in whom <12 lymph nodes were dissected decreased from 83% to 21% ($p < 0.0001$). The proportion of emergently resected rectal cancers also fell from 5% in 2001–2003 to less than 1% in 2004–2012 ($p=0.02$). In 2001–2003, only 20% of the patients received preoperative RT. This increased to 51% in 2004–2012 ($p < 0.0001$). Correspondingly, the amount of post-operative RT decreased from 23

to 1% over the same period ($p < 0.0001$). There was no change in the ratio of SCPRT to CRT.

During the study period, 109 (19%) of the 564 patients with stage I–III rectal cancer developed metastatic disease. The majority of the recurrences occurred during the first 3 years of follow-up (Table 6).

Table 5. Staging of rectal cancer patients (n = 687) in Study I (reproduced with the permission of the copyright holder).

| Time interval | 2001-2003 (n = 118) | 2004-2008 (n = 309) | 2009-2012 (n = 260) |
|----------------------------|------------------------|------------------------|------------------------|
| Stage I | 28 (22) | 101 (33) | 80 (31) |
| Stage II | 29 (25) | 67 (22) | 62 (24) |
| Stage III | 30 (26) | 86 (28) | 81 (31) |
| Stage IV | 16 (14) | 31 (10) | 27 (11) |
| Non-metastatic biopsy-only | 15 (13) | 24 (8) | 10 (4) |

Values are given as n (%).

Table 6. Proportion of stage I-III patients who progressed to stage IV disease in Study I (reproduced with the permission of the copyright holder).

| | Patients (n) | 3-year | 5-year | End of study |
|-----------|--------------|---------|---------|--------------|
| Stage I | 209 | 14 (8) | 19 (9) | 20 (10) |
| Stage II | 158 | 27 (17) | 30 (19) | 33 (21) |
| Stage III | 197 | 45 (22) | 52 (26) | 56 (28) |

Values are given as n (%).

In survival analysis we found a significant improvement in OS and CSS of rectal cancer patients from 2004 onwards (Figure 5A). There was also a trend to an increase in DFS but the change remained non-significant. When survival was stratified by disease stage, OS and DFS were longer in stage I patients compared to stage II and stage III patients, but for CSS there was also a clear difference between node-negative and -positive patients (Figure 5B).

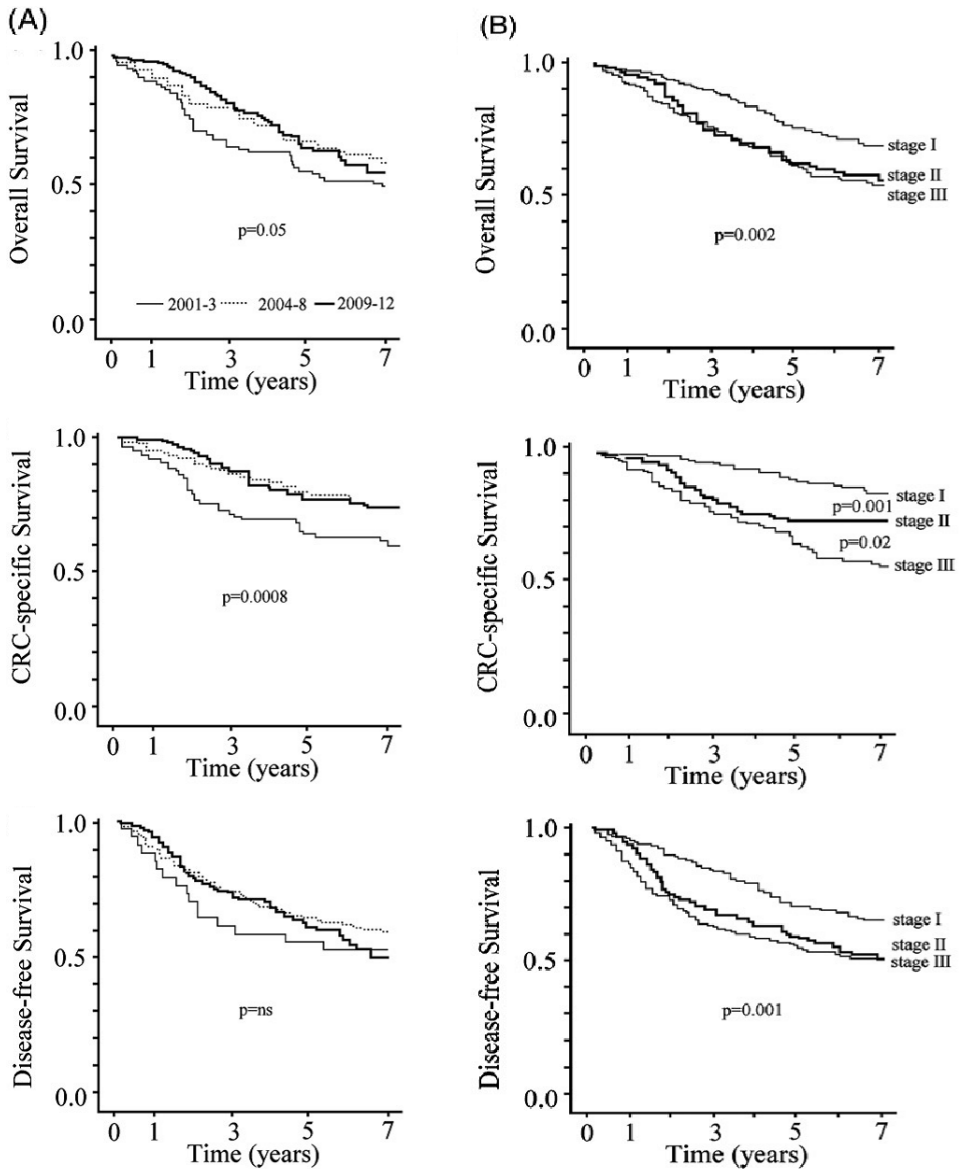


Figure 5. Kaplan–Meier analysis of 7-year survival in stage I-III rectal cancer stratified by the year of diagnosis (A) and the disease stage at the time of diagnosis (B). CRC, colorectal cancer. (Modified from Study I with the permission of the copyright holder).

Analysis of the factors associated with OS was also performed. In addition to age and comorbidities, T-stage (HR 1.6 [95% CI 1.1-2.4], $p = 0.03$), tumour grade (HR 1.6 [95% CI 1.1-2.4], $p = 0.02$) and R1 resection (HR 1.7 [95% CI 1.1-2.7], $p = 0.002$) were independent predictors of OS in stage I-III rectal cancer. No difference in survival was observed between patients with T4a and T4b tumors.

For patients under 70 years old, the use of oxaliplatin-based adjuvant therapy increased in stage III CRC during the study period (from 56 to 70%, $p = 0.002$), for stage II high risk patients it remained constant (76%). The proportion of patients who did not receive any adjuvant chemotherapy remained at 10–14% and a markedly higher comorbidity index was observed among them ($p < 0.0001$). They had a median CSS of 5.1 years, while the median CSS of patients who had received adjuvant chemotherapy was not reached ($p < 0.0001$). More than half of the patients in the adjuvant group were still alive at end of follow-up of 8.6 years.

OS of patients with stage IV disease did not change during the study period. For all stage IV CRC patients combined, the median OS was 18 months, for patients who were treated with chemotherapy it was 23 months. Stage IV patients who received bevacizumab in the first-line setting had a median OS of 34 months. Patients that did not receive any chemotherapy had a median OS of 6 months. In the subgroup of patients that progressed to stage IV disease after surgery, the median OS increased from 13 to 23 months between 2001–2008 and 2009–2012 ($p = 0.02$). 13% of patients underwent metastasectomy and this proportion remained constant. The proportion of stage IV patients who had received chemotherapy changed from 48 to 67% between 2004–2008 and 2009–2012 ($p < 0.0001$) and the amount of patients who received targeted therapy (bevacizumab, cetuximab or panitumumab) increased from 26 to 41% ($p = 0.006$).

5.2 Long-term results of extralevator abdominoperineal excision (Study II)

Demographic and clinical data on the study population is presented in Table 7. Patients in the APE group were slightly older and had higher American Society of Anesthesiology (ASA) –scores than patients in the ELAPE group but clinical T-staging of tumours was similar in both groups (Table 7). RT was not used for three patients in the ELAPE group and two in the APE group. One patient with a cT2 tumour was operated with ELAPE technique without RT, for him the choice of ELAPE was made because of obesity, prominent buttocks and anterior tumour location. For the remaining four patients, RT was omitted because of earlier pelvic RT for prostate cancer (3 patients) and age/comorbidities (1 patient). SCPRT was used in 7 patients in whom MRI showed the MRF to be threatened to the direction of the levators, but the tumour was clinically mobile or estimated by the surgeon to be radically operable with ELAPE. For 4 patients SCPRT was given because the MRF was threatened by large cT3 tumours anteriorly. In these patients the surgeon chose ELAPE as the operative technique for better visualisation of the anterior dissection plane in the perineal phase of the operation.

Table 7: Background information of the patients in Study II (reproduced with the permission of the copyright holder).

| | ELAPE (N=42) | APE (N=27) | P |
|--|---------------------|-------------------|---------------|
| Age, years | 61 (2) | 67 (2) | 0.0322 |
| BMI, kg/m² | 26 (1) | 27 (1) | 0.2269 |
| Gender (F/M) | 1:1.8 | 1:2.9 | 0.3945 |
| Smokers | 9 (21) | 11 (41) | 0.0844 |
| History of diabetes mellitus | 4 (10) | 7 (26) | 0.0709 |
| ASA score | | | 0.0037 |
| ASA I | 4 (10) | 0 (0) | |
| ASA II | 24 (57) | 8 (30) | |
| ASA III | 13 (31) | 13 (48) | |
| ASA IV | 1 (2) | 6 (22) | |
| Preoperative clinical T stage | | | 1.0000 |
| T2 | 1 (2) | 0 (0) | |
| T3 | 23 (55) | 15 (56) | |
| T4 | 18 (43) | 12 (44) | |
| Preoperative CEA, µg/l | 4.6 (2.5–8.9) | 6.5 (3.4–12.0) | 0.2481 |
| Preoperative radiotherapy | | | |
| No radiotherapy | 3 (7) | 2 (7) | 0.6554 |
| Short 5 x 5 Gy | 11 (26) | 0 (0) | 0.0023 |
| Long 50.4 Gy without chemotherapy | 0 (0) | 6 (22) | 0.0025 |
| Long 50.4 Gy with capecitabine | 28 (67) | 19 (70) | 0.7473 |

Values are given as mean (SEM), ratio, n (%) or median (interquartile range).

ASA, American Society of Anesthesiology; BMI, body mass index; ELAPE, extralevator abdominoperineal excision; APE, standard abdominoperineal excision; F/M, female/male ratio.

Operative details are presented in Table 8. ELAPE operations took longer but resulted in significantly less bleeding and thus fewer perioperative blood transfusions. Laparoscopic approach was increasingly used from 2010 onwards.

Table 8. Operative details of patients in Study II (reproduced with the permission of the copyright holder).

| | ELAPE (n = 42) | APE (n = 27) | P |
|---|----------------|--------------|-------------------|
| Surgical access in abdominal phase | | | <0.0001 |
| Open | 24 (57) | 27 (100) | |
| Laparoscopic | 18 (43) | 0 (0) | |
| Operative time, min | 237 (6) | 166 (9) | <0.0001 |
| Estimated blood loss, ml | 442 (42) | 1067 (178) | 0.0019 |
| Blood transfusion perioperatively | 10 (24) | 17 (63) | 0.0011 |
| IOP | 4 (10) | 6 (22) | 0.1336 |

Values are given as n (%) or mean (SEM). ELAPE, extralevator abdominoperineal excision; APE, standard abdominoperineal excision; IOP, intraoperative perforation.

The tumour staging was similar in the ELAPE and APE groups (Table 9). Patients with complete response after CRT were classified as ypT0 and stage 0. The proportions of patients with positive CRM and IOP were smaller in the ELAPE group but the differences did not reach statistical significance (Tables 8 and 9).

Complication profile of the Study II groups is presented in Table 10. The most common adverse event was perineal wound dehiscence and/or infection in both of the groups. Although the wound problems seemed to be more common and longer in duration after ELAPE, the differences were not statistically significant. Poor healing of the perineal wound inhibited the use of postoperative adjuvant chemotherapy only for two patients (5%) in the ELAPE group and for one patient (4%) in the APE group ($p=1.000$). More patients in the APE group needed perioperative blood transfusions, which explains the larger amount of grade II adverse events after APE. Two patients in the ELAPE group and one patient in the APE group had chronic perineal pain, while one patient in the ELAPE group developed a perineal hernia.

Three patients needed reoperations in the ELAPE group. One patient was reoperated for repair of vaginal wound dehiscence and one for abdominal wound dehiscence. One patient was reoperated twice, first for postoperative bleeding from inferior mesenteric vein and later for necrosis of colostomy. In the APE group, one patient was reoperated for small bowel obstruction. There was one postoperative death in the ELAPE group: the patient was disoriented immediately after the operation and was diagnosed with a brain metastasis. Metastasectomy was performed but the patient did not recover and was never discharged from the hospital.

Table 9. Histopathological classification and findings in Study II (reproduced with the permission of the copyright holder).

| | ELAPE (n = 42) | APE (n = 27) | P |
|----------------------------------|-----------------------|---------------------|----------|
| ypT staging | | | 0.6169 |
| pT0 | 4 (10) | 1 (4) | |
| pT1 | 2 (5) | 1 (4) | |
| pT2 | 6 (14) | 4 (15) | |
| pT3 | 20 (48) | 14 (52) | |
| pT4a | 3 (7) | 3 (11) | |
| pT4b | 7 (17) | 4 (15) | |
| ypN staging | | | 0.8172 |
| N0 | 26 (62) | 16 (59) | |
| N1a | 6 (14) | 2 (7) | |
| N1b | 1 (2) | 5 (19) | |
| N2a | 5 (12) | 1 (4) | |
| N2b | 4 (10) | 3 (11) | |
| ypM staging | | | 0.1554 |
| M0 | 36 (86) | 26 (96) | |
| M1a | 4 (10) | 1 (4) | |
| M1b | 2 (5) | 0 (0) | |
| Stage | | | 0.7343 |
| 0 | 4 (10) | 1 (4) | |
| I | 5 (12) | 2 (7) | |
| II | 16 (38) | 13 (48) | |
| III | 11 (26) | 10 (37) | |
| IV | 6 (16) | 1 (4) | |
| Number of nodes retrieved | 14 (6) | 12 (4) | 0.1020 |
| CRM involvement | 10 (24) | 11 (41) | 0.1358 |
| CRM, mm | 4.8 (0.7) | 3.6 (0.8) | 0.2672 |

Values are given as n (%) or mean (SEM). ELAPE, extralevator abdominoperineal excision; APE, standard abdominoperineal excision; CRM, circumferential resection margin.

Table 10. Adverse events in Study II (reproduced with the permission of the copyright holder).

| | ELAPE (N = 42) | APE (N = 27) | P |
|---|-----------------------|---------------------|----------|
| Clavien-Dindo grade | | | 0.3574 |
| 0 | 12 (29) | 6 (22) | |
| I | 7 (17) | 0 (0) | |
| II | 18 (43) | 20 (74) | |
| IIIa | 1 (2) | 0 (0) | |
| IIIb | 3 (7) | 1 (4) | |
| IV | 0 (0) | 0 (0) | |
| V | 1 (2) | 0 (0) | |
| Perineal wound dehiscence and/or infection | 19 (45) | 8 (30) | 0.1948 |
| Time to healing of perineal wound, weeks | 8.5 (1.92) | 3.5 (1.44) | 0.0731 |

Values are given as n (%) or mean (SEM). ELAPE, extralevator abdominoperineal excision; APE, standard abdominoperineal excision.

Adjuvant chemotherapy was administered to 31 (74%) and 17 (63%) patients in the ELAPE and APE groups, respectively ($p=0.3393$). For 6 (14%) and 2 (7%) patients it was deemed unnecessary by the MDT meeting. Old age and comorbidities prevented the use of chemotherapy significantly more often in the APE group than in the ELAPE group (7 [26%] versus 1 patients [2%], $p=0.0047$).

Survival was assessed for the patients with primarily non-metastatic disease to evaluate specifically the effect of operative technique (ELAPE) on survival. Therefore the patients with synchronous metastases were excluded. The mean follow-up times for the ELAPE and APE patients were 3.2 and 5.8 years, respectively. Kaplan-Meier curves of OS and DFS are presented in Figure 6. In statistical analyses, there were no differences between the two groups, even when adjusted for age and adjuvant treatment. There were 3 (7%) LRs in the ELAPE group and 5 (19%) in the APE group ($p=0.2473$).

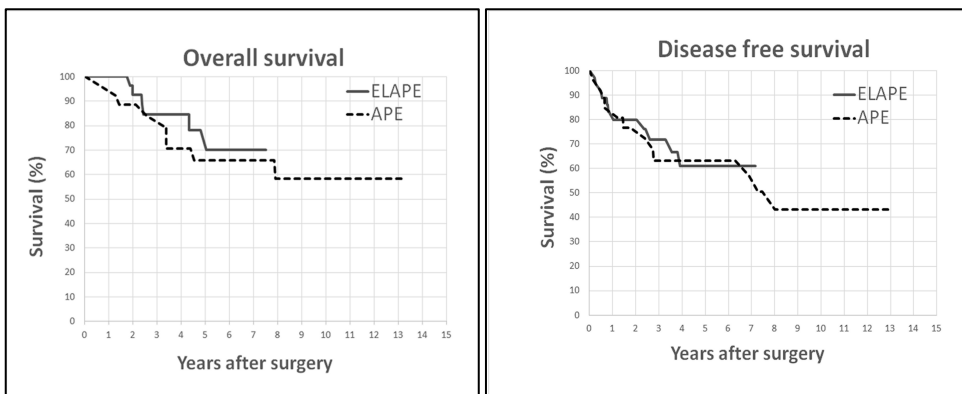


Figure 6. Overall survival ($p=0.8173$) and disease free survival ($p=0.6311$) of patients in ELAPE ($n = 36$) and APE ($n = 26$) groups in Study II. ELAPE, extralevator abdominoperineal excision; APE, standard abdominoperineal excision. (Reproduced with the permission of the copyright holder).

5.3 Location of local recurrence after modern multimodality treatment (Study III)

Clinical and pathological tumour staging, (neo)adjuvant treatments given and operative details of the 320 patients with stage I-III rectal cancer are shown in Tables 11 and 12.

During a median follow-up time of 5.5 years, 35 (11%) of the stage I-III patients developed LR. The median time from surgery to diagnosis of LR was 1.6 years (interquartile range 2.2). Altogether 25 (71%) of them were detected during scheduled follow-up visits, while the remaining 10 (29%) LRs caused symptoms which led to expedited diagnostic examinations. The LRs that were detected by routine follow-up were found by rising CEA level in 20 patients (80%), on clinical examination in 4 patients (16%) and by control CT in one patient (4%). The diagnosis of LR was verified by biopsy in 16 (46%) patients, in others the diagnosis was based on imaging, mainly PET-CT (11, 31%) but also CT and MRI. At the time of diagnosis of LR, 16 (46%) of the patients had also distant metastases. The majority of the isolated LRs (14, 74%) were either inoperable on the basis of imaging studies or the patient was unfit for redo surgery. Operative treatment of LR was attempted in the remaining five cases. One was radically resected, two had an R1 resection of their LR and two were found to be inoperable in laparotomy. Overall survival was significantly lower for patients with LR compared to those without LR (Figure 7a).

Table 11. Clinical and pathological features of patients in Study III.

| | All patients n = 320 | No LR n = 285 | LR n = 35 | P |
|--|---------------------------------|--------------------------|----------------------|-------------------|
| Preoperative clinical T-stage^{a,b} | | | | < 0.001 |
| cT1-2 | 76 (24) | 74 (97) | 2 (3) | |
| cT3 | 140 (44) | 124 (89) | 16 (11) | |
| cT4 | 27 (8) | 17 (63) | 10 (37) | |
| Missing | 77 (24) | 70 (91) | 7 (9) | |
| Location of primary tumour | | | | 0.075 |
| High rectum | 86 (27) | 81 (94) | 5 (6) | |
| Middle and low rectum | 234 (73) | 204 (87) | 30 (13) | |
| LPLN enlargement in preoperative MRI | 20 (8) | 15 (75) | 5 (25) | 0.063 |
| Perioperative radiotherapy | | | | 0.001 |
| No radiotherapy | 158 (49) | 142 (90) | 16 (10) | |
| Short 5 x 5 Gy | 103 (32) | 97 (94) | 6 (6) | |
| Long 50.4 Gy with capecitabine | 50 (16) | 37 (74) | 13 (26) | |
| Postoperative radiotherapy | 9 (3) | 9 (100) | 0 (0) | |
| Pathological T-stage^b | | | | 0.001 |
| (y)pT0 | 10 (3) | 10 (100) | 0 (0) | |
| (y)pT1 | 25 (8) | 25 (100) | 0 (0) | |
| (y)pT2 | 96 (30) | 89 (93) | 7 (7) | |
| (y)pT3 | 166 (52) | 145 (87) | 21 (13) | |
| (y)pT4 | 23 (7) | 16 (70) | 7 (30) | |
| Pathological N-stage^b | | | | 0.040 |
| (y)pN0 | 200 (63) | 179 (90) | 21 (10) | |
| (y)pN1 | 78 (24) | 73 (94) | 5 (6) | |
| (y)pN2 | 42 (13) | 33 (79) | 9 (21) | |
| Adjuvant chemotherapy | 145 (45) | 124 (86) | 21 (14) | 0.064 |

Values are given as n (%). First column (All patients) describes the frequency and proportion of the variable in the entire cohort. Percentages in no LR and LR groups represent the proportion within the row variable. LR, local recurrence; MRI, magnetic resonance imaging; LPLN, lateral pelvic lymph node; Gy, gray

^a Assessed by preoperative MRI

^b Staging according to UICC TNM 7th edition

Table 12. Operative details of stage I-III patients in Study III.

| Variable | All patients n = 320 | No LR n = 285 | LR n = 35 | P |
|-----------------------------------|-------------------------|------------------|--------------|---------|
| Operation | | | | 0.462 |
| Anterior resection | 188 (59) | 169 (90) | 19 (10) | |
| APE | 98 (30) | 87 (89) | 11 (11) | |
| ELAPE | 21 (7) | 17 (81) | 4 (19) | |
| Hartmann's operation | 13 (4) | 12 (92) | 1 (8) | |
| Intraoperative perforation | 23 (7) | 13 (57) | 10 (43) | < 0.001 |
| Anastomotic leakage | 13 (7) | 7 (54) | 6 (46) | < 0.001 |
| Radicality of operation | | | | < 0.001 |
| R0 | 291 (91) | 267 (92) | 24 (8) | |
| R1^a | 23 (7) | 17 (74) | 6 (26) | |
| R2^b | 6 (2) | 1 (17) | 5 (83) | |

Values are given as n (%). First column (All patients) describes the frequency and proportion of the variable in the entire cohort. Percentages in no LR and LR groups represent the proportion within the row variable. LR, local recurrence; APE, abdominoperineal excision; ELAPE, extralevator abdominoperineal excision.

^a Circumferential resection margin \leq 1 mm

^b Circumferential resection margin 0 mm assessed by the pathologist or clinical suspicion of residual tumour reported by the surgeon at the primary operation

The LR was axial in 9 (26%), anterior in 5 (14%), posterior in 9 (26%) and lateral in 12 (34%) of the patients. Most of the LRs appeared in the previous tumour bed (22, 63%). After an IOP, the LR occurred in the previous tumour bed in 9 (90%) cases. The majority of the tumour bed LRs were posterior (8, 36%) and axial (7, 32%) with smaller numbers in anterior (3, 14%) and lateral (4, 18%) locations.

Only six LRs occurred in the anastomosis and three of these patients had had an AL. Anastomotic LRs were found in all of the four locations: two were axial, two anterior, one posterior and one was lateral. When compared to patients with tumour bed or LPLN LR, anastomotic LRs were more often isolated (83% vs 50% of tumour bed and 43% of LPLN LRs), i.e. no distant metastases were detected at the time of diagnosis of LR.

Seven patients developed a LR in LPLN, but only three of them had had a clearly enlarged LPLN at the preoperative MRI. Of the other five lateral LRs, four were tumour bed LRs, while one originated from the anastomosis.

The incidence of LR did not differ according to the type of operation used (Table 12). The R0 resection rate was 91% and LR occurred in 24 (8%) of the radically operated patients. Of the 23 patients with an R1 resection, six (26%) developed a

LR. There were altogether six patients with an R2 operation, five of whom developed a LR. The sixth patient, an 84-year-old man, died two years after the primary operation, with no signs of LR or metastatic disease at autopsy.

In the entire study population, R1 or R2 operation, IOP, AL and LVI were identified as significant risk factors for LR (Table 13, Figure 7 b-g). Pathological T-stage 3-4 and preoperative LPLN enlargement were also significant risk factors in univariable, but not in multivariable analysis. Altogether 56 out of the 320 stage I-III patients in our study had either an IOP, AL or a positive CRM. 27 (77%) of the LRs developed to these high risk patients. The number of patients with LR was too small to perform subgroup analyses of risk factors for LR in different locations of LR.

For the 28 patients with primarily stage IV disease, the median (range) OS was only 16 (2-120) months. Two (7%) of these patients developed a LR during follow-up. One was a posterior tumour bed LR and the other was a lateral LPLN LR.

Table 13. Cox univariable and multivariable analysis of risk factors for local recurrence in Study III.

| | Univariable analysis HR (95% CI), p | Multivariable analysis HR (95% CI), p |
|---------------------------------------|--|--|
| Age over 70 years | 1.5 (0.8-2.9), p = 0.251 | |
| Male gender | 0.8 (0.4-1.6), p = 0.582 | |
| Pathological stage | | |
| (y)pT3-4 | 3.2 (1.4-7.3) p = 0.006 | 1.9 (0.4 - 9.3), p = 0.397 |
| (y)pN1-2 | 0.9 (0.4-1.7) p = 0.685 | |
| Poorly differentiated, grade 3 tumour | 1.0 (0.5-2.3) p = 0.943 | |
| Lymphovascular invasion | 2.0 (1.0-4.0) p = 0.048 | 5.7 (1.3 - 25.0), p = 0.022 |
| LPLN enlargement in preop MRI | 2.8 (1.1-7.3) p = 0.039 | 1.3 (0.2 - 6.8), p = 0.766 |
| Position in middle or low rectum | 2.4 (0.9-6.3) p = 0.065 | 1.7 (0.4 - 7.5), p = 0.468 |
| Abdominoperineal excision | 1.4 (0.7-2.7) p = 0.331 | |
| Radicality of operation | | |
| CRM ≤1mm (R1-2) | 6.3 (3.1-13.0) p < 0.001 | 25.0 (5.2 - 125.0), p < 0.001 |
| Intraoperative perforation | 7.0 (3.4-14.7) p < 0.001 | 50.0 (6.6 - 333.3), p < 0.001 |
| Anastomotic leakage | 7.1 (2.7-18.5) p < 0.001 | 7.6 (1.9 - 29.4), p = 0.003 |

CRM, circumferential resection margin; LPLN, lateral pelvic lymph node; MRI, magnetic resonance imaging

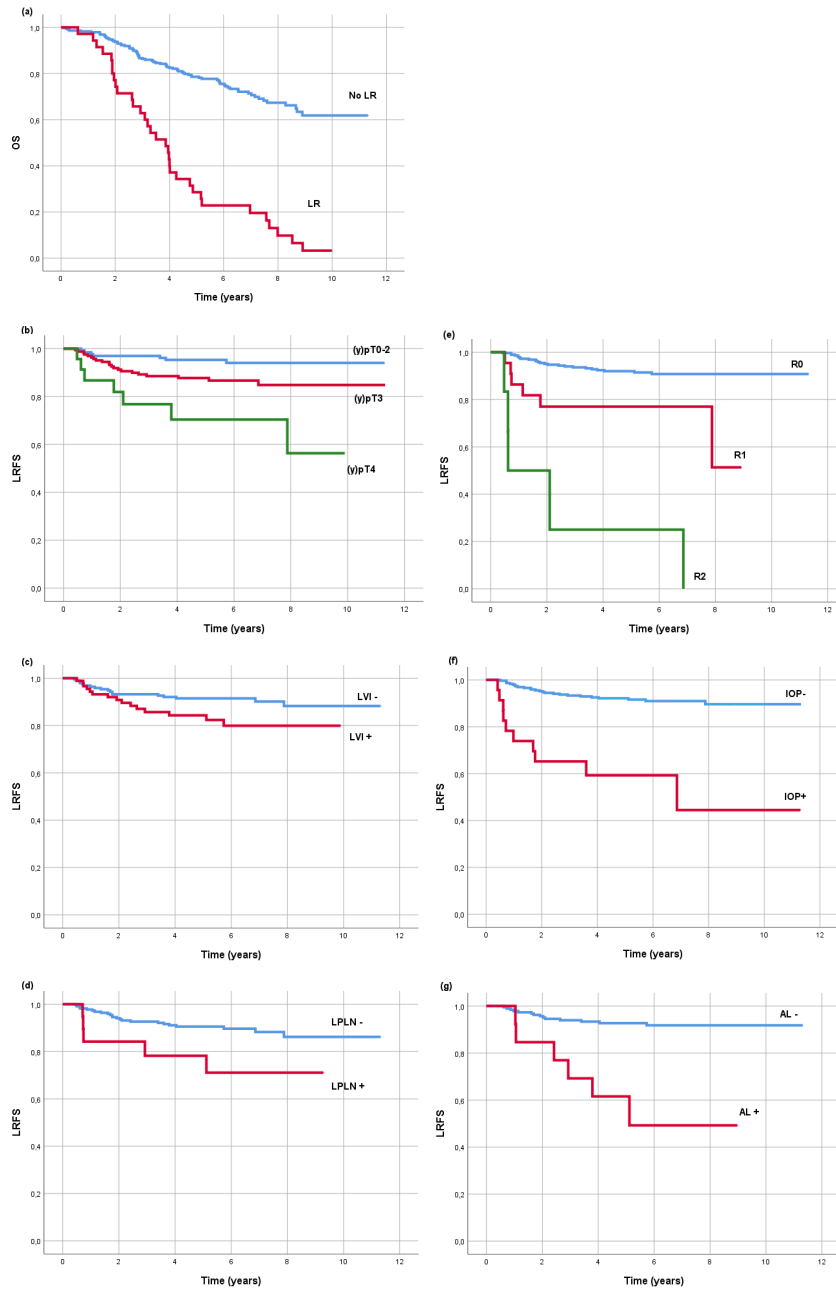


Figure 7. Kaplan-Meier analysis of overall survival (OS, a) and local recurrence free survival (LRFS, b-g) stratified by different risk factors. (a) Local recurrence (LR), $p < 0.001$. (b) T-stage, $p < 0.001$. (c) Lymphovascular invasion (LVI), $p = 0.044$. (d) Lateral pelvic lymph node (LPLN) enlargement in preoperative MRI, $p = 0.031$. (e) Radicality of operation, $p < 0.001$. (f) Intraoperative perforation (IOP), $p < 0.001$. (g) Anastomotic leakage (AL), $p < 0.001$.

5.4 Validation of the Finnish LARS score questionnaire (Study IV)

The participants filled the questionnaires at a mean time of 6.6 years (range 2.8-11.6 years, SD 2.4) after the anterior resection or closure of protective ostomy. 56 (54%) of the patients had major LARS (LARS score 30-42), 26 (25%) had minor LARS (LARS score 21-29) and 22 (21%) had no LARS (LARS score 0–20).

There was a clear, clinically and statistically significant association of the LARS severity groups and QoL, as measured with the EORTC QLQ-C30 and QLQ-CR29 questionnaires (Table 14). This means, that the convergent validity of the translation is good. When compared to patients with no LARS, those with major LARS had significantly lower scores (i.e. lower QoL and lower level of functioning) on global health status/QoL scale as well as on role, cognitive and social functioning scales. Patients with major LARS also had higher scores (i.e. more symptoms) for symptomatic scales in CR29. The only significant difference between those with no LARS and those with minor LARS was in stool frequency. There was also no significant difference in the global QoL of those with minor and those with major LARS, although the patients with major LARS had more flatulence and fecal incontinence as well as embarrassment of their bowel function.

To assess the discriminant validity of the translation, we compared groups which were expected to differ in the severity of LARS. Patients operated with TME had significantly higher LARS scores (median 32, interquartile range 15) than patients operated with PME (median 29, interquartile range 11; $p=0.037$). There was also a tendency to higher LARS scores for patients treated with CRT or SCPRT ($p = 0.132$) and patients younger than 70 years ($p = 0.080$), but these differences were not significant (Figure 8). When comparisons were made between these risk factors and LARS severity groups, the proportion of patients with major LARS was slightly higher after RT (19 out of 32 patients, 59%) than after operative treatment only (37 out of 72 patients, 51%), but the difference was not significant. The mean ages of patients with major LARS (71 years), minor LARS (72 years) and no LARS (73 years) were similar. When analysed separately for groups of patients under and over 70 years of age, 26 (63%) of the younger patients had major LARS compared to 30 (48%) of the older patients, but this small difference was not significant.

Table 14. Comparison of global health status/quality of life (QoL) and functional scales on EORTC QLQ-C30 and symptom scales relating to bowel functioning on EORTC QLQ-CR29 between different LARS severity groups (reproduced with the permission of the copyright holder).

| Variable | No LARS (n = 22) | Minor LARS (n = 26) | Major LARS (n = 56) | P (all groups) |
|---------------------------------------|---------------------|------------------------|------------------------|-------------------|
| EORTC QLQ-C30 | | | | |
| Global health status/QoL (QL2) | 80/ 83 (31) | 76/ 75 (21) | 67/ 67 (33) | 0.012* |
| Physical functioning (PF2) | 87/ 93 (17) | 81/ 80 (22) | 78/ 87 (38) | 0.175 |
| Role functioning (RF2) | 92/ 100 (8) | 87/ 92 (21) | 82/ 83 (33) | 0.035# |
| Emotional functioning (EF) | 90/ 92 (17) | 85/ 83 (29) | 85/ 92 (25) | 0.616 |
| Cognitive functioning (CF) | 94/ 100 (17) | 88/ 83 (17) | 84/ 83 (33) | 0.039# |
| Social functioning (SF) | 97/ 100 (0) | 91/ 100 (17) | 84/ 100 (33) | 0.015§ |
| EORTC QLQ-CR29 | | | | |
| Flatulence (FL) | 32/ 33 (33) | 33/ 33 (0) | 51/ 33 (33) | 0.006# |
| Fecal incontinence (FI) | 4/ 0 (0) | 16/ 0 (33) | 31/ 33 (0) | <0.001† |
| Sore skin (SS) | 0/ 0 (0) | 14/ 0 (33) | 22/ 33 (33) | <0.001¶ |
| Stool frequency (SFr) | 13/ 17 (17) | 29/ 17 (17) | 39/ 33 (33) | 0.001* |
| Embarrassment (EMB) | 7/ 0 (0) | 14/ 0 (33) | 38/ 33 (50) | <0.001§ |

Values are given as mean/median (interquartile range).

* Significant difference in pairwise comparison between no LARS vs major LARS (p=0.018)

Significant difference in pairwise comparison between no LARS vs major LARS (p=0.033)

Significant difference in pairwise comparison between no LARS vs major LARS (p=0.039)

§ Significant difference in pairwise comparison between no LARS vs major LARS (p=0.018)

* Significant differences in pairwise comparisons between no LARS vs major LARS (p=0.030) and between minor LARS vs major LARS (p=0.039)

† Significant differences in pairwise comparisons between no LARS vs major LARS (p<0.001) and between minor LARS vs major LARS (p=0.012)

¶ Significant difference in pairwise comparison between no LARS vs major LARS (p<0.001)

* Significant differences in pairwise comparisons between no LARS vs major LARS (p<0.001) and between no LARS vs minor LARS (p=0.024)

§ Significant differences in pairwise comparisons between no LARS vs major LARS (p<0.001) and between minor LARS vs major LARS (p=0.003)

In the test-retest subgroup the second LARS questionnaire was returned by 22 of the 23 patients. 17 (77%) of them were grouped to the same LARS severity category at both time points. Intraclass correlation coefficient was 0.77 (95% CI 0.51-0.90), which shows good reliability of the Finnish LARS score.

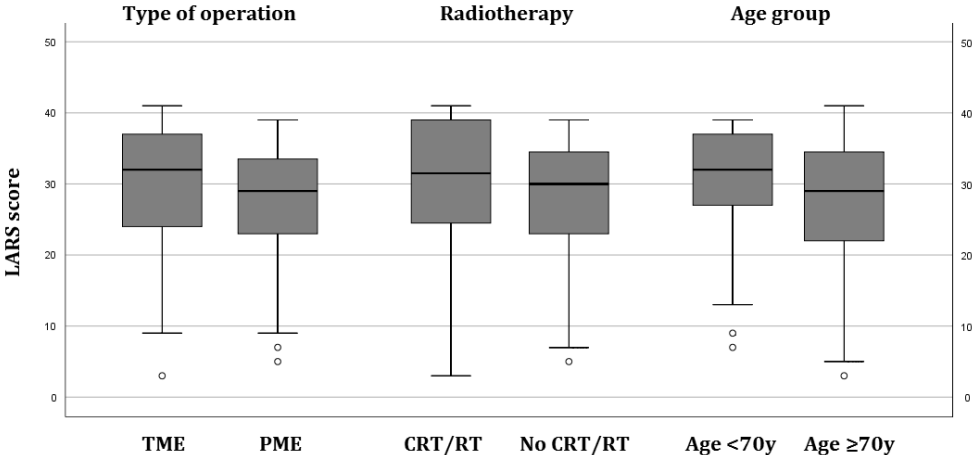


Figure 8. Distribution of the LARS score in different risk groups. A significant difference was found between TME and PME ($p=0.037$), but not between radiotherapy ($p=0.132$) or age groups ($p=0.080$). TME, total mesorectal excision; PME, partial mesorectal excision; CRT, chemoradiotherapy; RT, radiotherapy (reproduced with the permission of the copyright holder).

6 Discussion

6.1 Improvement in quality of care and prognosis of rectal cancer

In Study I, a clear increase over time in OS and CSS of patients with stage I-III rectal cancer was found. This coincides with the introduction of MDT meetings, centralisation of rectal cancer surgery, increase in the use of preoperative RT and implementation of standardised pathology examination and reporting. The use of adjuvant chemotherapy in stage III CRC also became slightly more frequent. OS of patients with stage IV disease remained constant, with the exception of the subgroup of patients who developed metachronous metastases in whom OS increased over time.

The 5-year survival rates in Study I are comparable to those in larger studies reported previously (Gunderson et al. 2010, Li et al. 2016). A major improvement in OS and CSS occurred during 2004–2008, but DFS did not show a statistical improvement at the time. One reason for this may be the incomplete information of ICD10 codes or contemporary chemotherapy, on which DFS was based, in 2001–2003. In recent years, several changes in the treatment of rectal cancer have been linked with improved survival, including centralised and improved surgery, MDTs (Guren et al. 2015, Kodeda et al. 2015), preoperative RT in rectal cancer (Peeters et al. 2007, Brændengen et al. 2008), increase in the number of lymph nodes examined (Xu et al. 2017) and more precise adjuvant treatments (Van Steenberghe et al. 2010, André et al. 2015). These changes also took place in Turku university hospital, resulting in improved survival and also a relatively low recurrence risk, especially after 3 years of follow-up, as compared to previously published studies (Guren et al. 2015, Riihimäki et al. 2016, Augestad et al. 2018). Although it is not possible to analyse the impact of one specific change per se on the basis of Study I, it is likely that the introduction of preoperative CRT in 2004 contributed to the significant decrease in the number of patients with unresectable rectal cancer.

The results of Study I suggest that the clinical presentation of rectal cancer at the time of histological diagnosis remained essentially the same between 2001 and 2012. It should be noted that some tumours may be down-staged following preoperative CRT. However, since no stage migration was observed, it is estimated that the study

cohort and its improved survival are not affected by the possibly earlier detection of CRC in Finland. Of note is that comprehensive screening of CRC was not performed in the Turku region during 2001–2012. The mean age of the patients only increased from 70 to 71 years during the two later periods of Study I, but the proportion of patients with comorbidities increased from 14 to 21 %. In spite of this, survival did not decrease. This might reflect better treatment of the patients but it can also be that the observed rise in comorbidities is biased by more precise reporting of ICD-10 codes in the most recent years of the study.

Only a limited number of patients with stage IV rectal cancer had received targeted therapy in the first-line setting, representing clinical practice at the time of the Study I. However, 13% of them still underwent metastasectomy. The OS of stage IV patients with metachronous metastases improved in 2009, at the same time when the use of targeted therapy became more frequent, similar to findings observed elsewhere (Hammerman et al. 2015, Stein et al. 2015). It should be noted that a specialised liver surgeon began to work in Turku university hospital starting from year 2012. After this recruitment, an increase in successful metastasectomy rates and earlier use of targeted therapy in stage IV disease have taken place (Heervä et al. 2018).

The strength of Study I as a Biobank based study is the combination of multiple electronic databases into one dataset which covers the majority of the population in the region. The dataset allows the analysis of survival and prognostic factors based on real-life data. Since the Finnish electronic medical records system tracks every patient until death, no patients in Study I were lost during follow-up.

6.2 Role of extralevator abdominoperineal excision in the treatment of rectal cancer

In Study II, no difference in the DFS or OS of patients operated by ELAPE or APE could be demonstrated. Similar results have been reported in earlier studies (Klein et al. 2016, Prytz et al. 2016, Stelzner et al. 2016). The median follow-up time of the patients in the ELAPE group was slightly over 3 years, which is still quite short but sufficient as most CRC recurrences occur within the first 3 years of follow-up (Baca et al. 2011). The survival rates did not differ even though the patients in the APE group were older and had more comorbidities. According to Study II, it seems that the ELAPE technique offers no survival benefit for the patient when compared to APE.

Although there seemed to be fewer IOPs and less CRM positivity in the ELAPE group, the differences were not statistically significant. Recently a Finnish study group found a significantly reduced rate of IOP and CRM positivity in a slightly larger study population including all patients undergoing APE or ELAPE in their

institution, but neither that study showed any increase in OS or CSS of the patients in the ELAPE era (Lehtonen et al. 2019). In Study II, the IOP rates were similar to their study, but the CRM positivity rates were higher in both groups, which reflects the advanced stage of the tumours in the Study II cohort. The proportions of patients in the ELAPE group with IOP (10%) and positive CRM (24%) were similar to those published recently by professor Holm's group (IOP 10%, CRM positivity 20%) (Palmer et al. 2014). The majority of their patients had T3–T4 tumours, similarly to the Study II cohort. On the contrary, in the RELAPe randomised controlled trial (Bianco et al. 2017) that reported a significantly reduced rate of CRM positivity (ELAPE 6%, APE 41%), the majority of the patients in the ELAPE group had T1–T2 tumours after CRT. In the population based studies which did not find any advantage of ELAPE over APE (Ortiz et al. 2014, Prytz et al. 2014, Klein et al. 2015), the IOP rates have varied from 4 to 11% and CRM positivity from 6 to 16% with both operative techniques. Lower rates represent both the inclusion of less advanced tumours and the time frame of the studies. With current attention to resection planes in APE, the surgical results of standard APE have improved (Klein et al. 2015). The historical comparison group is in this regard a limitation of Study II, which can be seen especially in the amount of blood loss in APE patients of Study II. Although the difference in blood loss between the study groups can to some extent be explained by the more frequent use of laparoscopy in the ELAPE group, it can be speculated that with modern insight of pelvic anatomy the blood loss during APE is nowadays much smaller. Because all advanced tumours have been operated with ELAPE in Turku University hospital since 2009, a contemporary comparison group with similar tumours could unfortunately not be collected.

LR occurred in 7% of the ELAPE patients versus 19% of APE group, but this difference was not statistically significant. In previous literature, LR rates of 0–13% after ELAPE have been reported (Asplund et al. 2012, Han et al. 2012, Ortiz et al. 2014, Perdawood & Lund 2015, Shen et al. 2015) and some studies have reached significant differences when compared to rates of LR after APE (15–19%) (Han et al. 2012, Shen et al. 2015, Stelzner et al. 2016). On the other hand, some studies report LR rates as low as 3–9% after standard APE (Asplund et al. 2012, Ortiz et al. 2014). In clinical practice, the possible decrease in LR rate is very significant for the patients, as LR after APE is often inoperable and can cause severe pelvic pain and persisting fistulae.

An important novel finding in Study II was that the tendency to prolonged healing of the perineal wound did not inhibit the use of postoperative adjuvant chemotherapy. There were no statistical differences in the frequency and grade of adverse events, but as perineal wound healing problems are common (45% in ELAPE and 30% in APE group), all patients undergoing ELAPE or APE should be

informed preoperatively of the high likelihood of wound dehiscence, especially after CRT.

Even though the survival of patients with advanced tumours was relatively high and the rate of LR tolerable in Study II, the rates of IOP and positive CRM were still rather high. It has recently been shown that especially for anterior tumours with threatened MRF, ELAPE does not increase the CRM compared to APE and that in these instances a pelvic exenteration might be more appropriate (How et al. 2014). It has also been suggested that for tumours infiltrating the levators, ischioanal fat or perianal skin, an ischioanal APE should be performed, extending the dissection even more laterally to include the fatty tissue around the sphincters (Holm 2014). Further research will be needed in the future to assess the benefits of these even more extensive procedures.

6.3 Local recurrence in the modern era

In Study III, it was demonstrated that in an unselected cohort of stage I-III rectal cancer patients who received modern multimodality treatment, the incidence of LR was 11%. Although there was a slight predominance of lateral LRs, axial and anterior LRs still occur. The majority of the LRs originated from the previous tumour bed. Positive CRM, IOP, AL and LVI were identified as independent risk factors for LR.

Most of the literature assessing the location of LR stems from studies conducted in the 90's and they show a tendency to more lateral recurrences after the use of SCPRT or CRT (Enríquez-Navascués et al. 2011). A continuing shift to fewer axial and anterior LRs over time was also shown by a recent Swedish registry based study including patients from 1995 to 2007 (Westberg et al. 2018). The few studies conducted on patients treated within the same contemporary timeframe as Study III, included patients with cT3-T4 tumours only (Kusters et al. 2017, Schaap et al. 2018, Ogura et al. 2019a). In these studies, the proportions of lateral and posterior LRs were similar to those of Study III. The large proportion of lateral LR in these studies has led to further research by the Lateral Node Study Consortium to advocate LPLND especially if there are enlarged lymph nodes in the lateral compartment after preoperative CRT (Ogura et al. 2019a, Ogura et al. 2019b). In Study III only 7 of the 35 LRs were located in LPLN and less than half of them had had LPLN enlargement in preoperative MRI. On the basis of this retrospective study it is impossible to state whether these patients would have benefited from LPLND in the primary operation. In the future LPLND should be considered in patients with LPLN enlargement in preoperative MRI. If pursued, the dissection should be radical, since selective removal of bulky nodes only seems to result in an unacceptably high rate of LR of over 50% (Schaap et al. 2018, Ogura et al. 2019a).

Even though lateral LRs were most common in the Study III cohort, a substantial portion of tumour bed and anastomotic LRs were still axial or anterior. It would be important to diagnose these central LRs at an early stage since the likelihood of curative surgery for LR is much higher in this scenario (Moore et al. 2004, Denost et al. 2015, Westberg et al. 2018, Hagemans et al. 2019). The LRs in Study III were diagnosed at a median of 1.6 years after surgery, slightly later than in a study with a more frequent endoscopic follow-up regime (Räsänen et al. 2015). By focusing more intensive follow-up on patients at higher risk for LR, especially those who are younger and fit enough for often extensive redo surgery, it might be possible to find the central LRs before they metastasise or become inoperable.

CRM involvement and LVI have been clearly shown to be important prognostic factors for LR (Nagtegaal & Quirke 2008, Peacock et al. 2019) and this holds true also in Study III. IOP is also a known risk factor for LR (Bülow et al. 2011). Although the patients in Study III were operated by experienced colorectal surgeons as demonstrated by the high rate of R0 resections, IOP still sometimes occurred. Perforation was an independent risk factor in the multivariable analysis, but actually four out of ten patients with a LR after a perforation were also in the R2 resection category. Contrary to this, the patients with a LR after an AL were all R0 resected. In previous literature the association of AL and LR has been debatable. In registry based studies from Belgium (Van de Putte et al. 2017), Denmark (Bertelsen et al. 2010) and Spain (Espín et al. 2015) AL has not been an independent risk factor for LR. On the other hand two meta-analyses and a recent French study (Mirnezami et al. 2011, Hain et al. 2017, Wang et al. 2017) found an increased risk of LR after an AL. The Study III results are in concert with the latter studies and add to previous knowledge by defining the location of LR after AL, which tended to be more often anastomotic and central. A tight rectoscopy surveillance schedule for all rectal cancer patients was recently shown to be unnecessary (Tronstad et al. 2019). This holds true also in the Study III cohort, since only six (3%) of the 188 patients who underwent anterior resection developed an anastomotic LR, potentially detectable by routine endoscopy. It is an aim for future studies to show whether endoscopic surveillance of patients with AL will result in earlier diagnosis of LR and thus better chance for cure of the recurring disease.

The incidence of LR in Study III was slightly higher than expected. This can be affected by the possibly better coverage of follow-up than in other registry based studies, where some LRs might go unnoticed. Data on LRs was meticulously collected from prospectively maintained electronic medical records which include also results of radiological examinations conducted by primary health care providers because of centralised imaging facilities. The postoperative mortality was also surprisingly low allowing more patients to be followed-up.

6.4 Validity of the Finnish LARS-score questionnaire

In Study IV, the Finnish translation of the LARS score was shown to have good psychometric properties. Convergent validity and test-retest reliability were excellent. When considering discriminant validity, the Finnish LARS score expectedly gave clearly differentiating results for patients operated with TME and PME. Patients with TME operation had significantly higher LARS scores than those operated with PME, which is in line with findings from previous studies (Bregendahl et al. 2013, Jimenez-Gomez et al. 2018, Kupsch et al. 2018). LARS scores and LARS severity were also higher for patients treated with RT and in younger patients, but without statistical significances.

Previous studies reporting age to be a significant factor in LARS severity have included younger patients with age limit set to 64 years (Bregendahl et al. 2013, Kupsch et al. 2018). On the other hand, in two recent studies with mean ages of 63 and 70 years, age was not an independent risk factor (Jimenez-Gomez et al. 2018, Nuytens et al. 2018). Altogether, of the seven published LARS score translation validation studies, only two have reported significant correlations between age and LARS score (Juul et al. 2014a, Hou et al. 2015, Juul et al. 2015, Samalavicius et al. 2016, Akizuki et al. 2018, Hupkens et al. 2018, Liapi et al. 2019). Thus the results of previous studies regarding age as a risk factor are inconsistent, although it would be logical for younger working aged patients to experience more disturbance to their QoL from LARS symptoms than for retired patients with more flexible time tables. As the mean age in Study IV was 72 years and only 20 patients were under 65 years old, it is possible to speculate that not enough young patients were included to show a significant correlation. On the other hand, even with this sample size the directions of correlation between the Finnish LARS scores and risk factor groups were as anticipated. Thus the discriminant validity of the translation can be considered as satisfactory.

As the included patients were long-term survivors of rectal cancer, the proportion of patients who had received CRT (4%) or SCPRT (25%) in Study IV was unusually low (Table 4). During the same timeframe 51% of all patients with rectal cancer treated in Turku University hospital received RT (Study I). This reflects the correct use of RT for patients with bad and ugly tumours only (Glynne-Jones et al. 2017), who unfortunately also have shorter OS or need an APE instead of anterior resection. A follow-up study of the TME trial found a 56% prevalence of major LARS in irradiated patients 14 years after the treatment (Chen et al. 2015). This percentage is in concert with the prevalence of major LARS after RT in Study IV. The reason for the surprisingly high proportion of major LARS in the group of patients treated without RT is unclear. It can be speculated, that a patient who has major defecatory

symptoms, is more likely to fill in and return the questionnaires than a patient who is satisfied with his or her bowel movements.

Some of the previous LARS score translation validation studies have used the EORTC QLQs to assess convergent validity (Hou et al. 2015, Juul et al. 2015, Hupkens et al. 2018). Results have shown significant differences in the QoL of patients with no LARS and major LARS. On the other hand, pairwise comparisons of differences between all three LARS severity groups have seldom been made. Only an international multicenter study analysed the impact on QoL of minor LARS in comparison to no LARS and major LARS (Juul et al. 2014b). In this study, authors presented significant differences between those with minor and major LARS, but the differences between patients with no LARS and minor LARS were small and clinically irrelevant although statistically significant. In Study IV, further pairwise comparisons of EORTC QLQ scores between the different LARS severity groups were performed. Special interest was placed in the symptom scales of EORTC QLQ-CR29, which have not been previously analysed to this extent in relation to all three LARS severity groups. Like in the above mentioned studies, the differences between those with no LARS and major LARS were significant. But although the EORTC QLQ-C30 could not pick up significant differences in the global QoL between those with no and minor LARS or minor and major LARS, there was a clear progression of defecatory symptoms when stepping up from no to minor LARS and from minor to major LARS. Differences in the mean symptom scores of 10 or more like in Study IV are also considered clinically significant (Fayers et al. 2001). Therefore the division of patients to no, minor and major LARS groups according to the Finnish LARS score can be considered valid.

6.5 Limitations of the study

Study I: Major limitation of Study I is its retrospective setting. There can also be selection bias affecting the OS results, since comorbidities had an effect on survival. Rectal cancer patients need to be fit enough for surgery and those with biopsy-only were left out of survival analyses since disease stage was determined by the postoperative pathology report. Since less patients with comorbidities were operated in the 2001-2003 interval and more were only biopsied, the effect of the selection bias is probably highest in this earliest study group.

Study II: In addition to the historical comparison group, limitations of Study II include its retrospective setting and relatively small sample size. For a single-center study, it would require a much longer time period to include more patients. On the other hand it is a strength of this study that all patients in both study groups have been operated in a single center by the same experienced surgeons during a time frame in which there were no significant changes in the adjuvant therapy regimes.

All data were collected retrospectively, but from prospectively maintained electronic medical records. Finnish cause of death records are also very precise and accurate, so survival analyses can be considered very reliable.

Study III: The major limitations of Study III are its single center setting and retrospective nature. The number of LRs in different locations within the pelvis was also too low to make firm conclusions on the risk factors for LR in these subsets. Therefore, for example the association of AL and anastomotic LR needs to be confirmed in future studies.

Study IV: Limitations of Study IV are its relatively small sample size and the fact that patients from a long period of time needed to be included to reach even this sample size. This may have caused bias to the LARS severity profile of the responding patient group. With a larger patient sample, the results on discriminant validity of the translation might have been stronger.

7 Conclusions

The conclusions of this study were as follows:

- I During 2001-2012, the OS and CSS of patients with stage I-III rectal cancer clearly increased. This was facilitated by the introduction of MDT meetings, centralisation of rectal cancer surgery, increase in the use of preoperative RT and implementation of standardised pathology examination and reporting.
- II In locally advanced rectal cancer, patients operated with ELAPE do not have a better long-term survival than patients operated with APE.
- III In the modern era, the incidence of rectal cancer LR was 11%. There was a slight predominance of lateral LRs. Positive CRM, IOP, AL and LVI were independent risk factors for LR.
- IV The Finnish LARS Score –questionnaire is a valid test in the assessment of postoperative bowel function and its impact on the QoL.

Acknowledgements

This thesis was carried out at the Department of Digestive Surgery, Turku University Hospital, and Department of Surgery, University of Turku, Finland during the years 2016-2020.

Research is team work and this thesis would not have been completed without the invaluable help of many colleagues and friends. I am sincerely grateful to my official supervisors, Professor Juha Grönroos and Docent Jukka Karvonen for giving me excellent guidance and clear pragmatic advice, just the kind of help a straightforward surgeon needs to finalise a thesis. I owe my deepest debt of gratitude to Docent Heikki Huhtinen, the true mastermind behind this project, not only for his contributions to the current work but also for the contagious enthusiasm for clinical research in the field of colorectal surgery. And although this book has been written to demonstrate research skills learned as a PhD student, the motivation to finish it stems from a will to become a skillful surgeon. Therefore I wish to especially thank Pirita Varpe and Heikki Sarparanta who in addition to Jukka and Heikki have shown me the mastery of colorectal surgery.

I am very grateful to Docent Monika Carpelan-Holmström and Docent Marja Hyöty for their perceptive comments on the manuscript and instructive discussions during the review process.

I want to thank all my co-authors and the whole Colorectal Cancer Biobank research group, especially Eetu Heervä, Raija Ristamäki and Annika Ålgars, for taking me along and for the enlightening multidisciplinary discussions during our research meetings, you have taught me a lot. I am very grateful to Eeva Elamo and Sami Elamo for the brilliant idea to translate the LARS questionnaire and for acquainting me with the translation process and personnel.

I highly value the research-friendly atmosphere of the Department of Digestive Surgery and I am grateful to Docent Arto Rantala for supporting it. I have felt welcome to this work community from the very first days I started my residency almost ten years ago and therefore I wish to express my appreciation to all my colleagues, both past and present. My special thanks go to Elina Lietzen for the joyful shared moments as trainees, to Maija Lavonius for teaching me the challenging and

diverse role of a surgical consultant in gynecological operations and to Simo Laine for sharing his skills in operative endoscopy.

I am obliged to my beloved parents, Jorma and Leila Mäkinen for supporting me in all possible ways in everything I have embarked on and to my wonderful children Ilona and Amos for putting things in life to a perspective. Above all, I am grateful to my dear husband Kim for his patience with me when my thoughts have been on this thesis project, thanks for standing by me through both good and difficult days.

This work was financially supported by the Finnish government research funding (EVO), the Mary and Georg C. Ernroth Foundation, the Cancer Society of Southwest Finland, the Finnish Society of Surgery, the Turunmaa Duodecim Society and the TYKS Foundation.

December 2020

Anu Carpelan

References

- Abel, G. A., Shelton, J., Johnson, S., Elliss-Brookes, L. & Lyratzopoulos, G. 2015. Cancer-specific variation in emergency presentation by sex, age and deprivation across 27 common and rarer cancers. *British Journal of Cancer*, 112(1), p. S129-S136. <<http://doi.org/10.1038/bjc.2015.52>>.
- Acar, H. I. & Kuzu, M. A. 2012. Important points for protection of the autonomic nerves during total mesorectal excision. *Diseases of the Colon and Rectum*, 55(8), p. 907–912. <<http://doi.org/10.1097/DCR.0b013e318259b44f>>.
- Adam, R., De Gramont, A., Figueras, J., Guthrie, A., Kokudo, N., Kunstlinger, F., Loyer, E., Poston, G., Rougier, P., Rubbia-Brandt, L., Sobrero, A., Tabernero, J., Teh, C., Van Cutsem, E. & Vauthey J-N of the EGOSLIM (Expert Group on OncoSurgery management of Liver Metastases) group 2012. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *The Oncologist*, 17(10), p. 1225–1239. <<http://doi.org/10.1634/theoncologist.2012-0121>>.
- Akizuki, E., Matsuno, H., Satoyoshi, T., Ishii, M., Usui, A., Ueki, T., Nishidate, T., Okita, K., Mizushima, T., Mori, M. & Takemasa, I. 2018. Validation of the Japanese version of the low anterior resection syndrome score. *World Journal of Surgery*, 42(8), p. 2660–2667. <<http://doi.org/10.1007/s00268-018-4519-8>>.
- Al-Sukhni, E., Milot, L., Fruitman, M., Beyene, J., Victor, J. C., Schmocker, S., Brown, G., McLeod, R. & Kennedy, E. 2012. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. *Annals of Surgical Oncology*, 19(7), p. 2212–2223. <<http://doi.org/10.1245/s10434-011-2210-5>>.
- Aleksandrova, K., Pischon, T., Jenab, M., Bueno-de-Mesquita, H. B., Fedirko, V., Norat, T., Romaguera, D., Knüppel, S., Boutron-Ruault, M.-C., Dossus, L., Dartois, L., Kaaks, R., Li, K., Tjønneland, A., Overvad, K., Quirós, J. R., Buckland, G., Sánchez, M. J., Dorransoro, M., Chirlaque, M.-D., et al. 2014. Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study. *BMC Medicine*, 12(1), p. 168. <<http://doi.org/10.1186/s12916-014-0168-4>>.
- Andersen, P., Erichsen, R., Froslev, T., Madsen, M. R., Laurberg, S. & Iversen, L. H. 2018. Open versus laparoscopic rectal cancer resection and risk of subsequent incisional hernia repair and paracolostomy hernia repair: a nationwide population-based cohort study. *Surgical Endoscopy*, 32(1), p. 134–144. <<http://doi.org/10.1007/s00464-017-5648-0>>.
- André, T., de Gramont, A., Vernerey, D., Chibaudel, B., Bonnetain, F., Tijeras-Raballand, A., Scriver, A., Hickish, T., Tabernero, J., Van Laethem, J. L., Banzi, M., Maartense, E., Shmueli, E., Carlsson, G. U., Scheithauer, W., Papamichael, D., Möehler, M., Landolfi, S., Demetter, P., Colote, S., et al. 2015. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-Year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. *Journal of Clinical Oncology*, 33(35), p. 4176–4187. <<http://doi.org/10.1200/jco.2015.63.4238>>.
- Ansari, N., Solomon, M. J., Fisher, R. J., Mackay, J., Burmeister, B., Ackland, S., Heriot, A., Joseph, D., McLachlan, S.-A., McClure, B. & Ngan, S. Y. 2017. Acute adverse events and postoperative

- Brush, J., Boyd, K., Chappell, F., Crawford, F., Dozier, M., Fenwick, E., Glanville, J., McIntosh, H., Renehan, A., Weller, D. & Dunlop, M. 2011. The value of FDG positron emission tomography/computerised tomography (PET/CT) in pre-operative staging of colorectal cancer: a systematic review and economic evaluation. *Health Technology Assessment*, 15(35). <<http://doi.org/10.3310/hta15350>>.
- Bugg, W. G., Andreou, A. K., Biswas, D., Toms, A. P. & Williams, S. M. 2014. The prognostic significance of MRI-detected extramural venous invasion in rectal carcinoma. *Clinical Radiology*, 69(6), p. 619–623. <<http://doi.org/https://doi.org/10.1016/j.crad.2014.01.010>>.
- Bullinger, M., Alonso, J., Apolone, G., Lepège, A., Sullivan, M., Wood-Dauphinee, S., Gandek, B., Wagner, A., Aaronson, N., Bech, P., Fukuhara, S., Kaasa, S. & Ware, J. E. 1998. Translating health status questionnaires and evaluating their quality: the IQOLA project approach. *Journal of Clinical Epidemiology*, 51(11), p. 913–923. <[http://doi.org/https://doi.org/10.1016/S0895-4356\(98\)00082-1](http://doi.org/https://doi.org/10.1016/S0895-4356(98)00082-1)>.
- Bülow, S., Christensen, I. J., Iversen, L. H., Harling, H. & Danish Colorectal Cancer Group 2011. Intra-operative perforation is an important predictor of local recurrence and impaired survival after abdominoperineal resection for rectal cancer. *Colorectal Disease*, 13(11), p. 1256–1264. <<http://doi.org/10.1111/j.1463-1318.2010.02459.x>>.
- Cedermarck, B., Johansson, H. & Rutqvist, L. E. 1995. The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. *Cancer*, 75(9), p. 2269–2275. <[http://doi.org/10.1002/1097-0142\(19950501\)75:9<2269::aid-cnrcr2820750913>3.0.co;2-i](http://doi.org/10.1002/1097-0142(19950501)75:9<2269::aid-cnrcr2820750913>3.0.co;2-i)>.
- Chand, M., Evans, J., Swift, R. I., Tekkis, P. P., West, N. P., Stamp, G., Heald, R. J. & Brown, G. 2015. The prognostic significance of postchemoradiotherapy high-resolution MRI and histopathology detected extramural venous invasion in rectal cancer. *Annals of Surgery*, 261(3), p. 473–479. <<http://doi.org/10.1097/SLA.0000000000000848>>.
- Chapman, S. J., Wood, B., Drake, T. M., Young, N. & Jayne, D. G. 2017. Systematic review and meta-analysis of prophylactic mesh during primary stoma formation to prevent parastomal hernia. *Diseases of the Colon & Rectum*, 60(1), p. 107–115. <<http://doi.org/10.1097/dcr.0000000000000670>>.
- 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. *J Chronic Dis*, 40(5), p. 373–383. <[http://doi.org/10.1016/0021-9681\(87\)90171-8](http://doi.org/10.1016/0021-9681(87)90171-8)>.
- Chen, T. Y.-T., Emmertsen, K. J. & Laurberg, S. 2014. Bowel dysfunction after rectal cancer treatment: a study comparing the specialist's versus patient's perspective. *BMJ Open*, 4(1), p. e003374. <<http://doi.org/10.1136/bmjopen-2013-003374>>.
- Chen, T. Y., Wiltink, L. M., Nout, R. A., Meershoek-Klein Kranenbarg, E., Laurberg, S., Marijnen, C. A. & van de Velde, C. J. 2015. Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomized trial. *Clinical Colorectal Cancer*, 14(2), p. 106–114. <<http://doi.org/10.1016/j.clcc.2014.12.007>>.
- Comber, H., Sharp, L., de Camargo Cancela, M., Haase, T., Johnson, H. & Pratschke, J. 2016. Causes and outcomes of emergency presentation of rectal cancer. *International Journal of Cancer*, 139(5), p. 1031–1039. <<http://doi.org/10.1002/ijc.30149>>.
- Crockett, S. D. & Nagtegaal, I. D. 2019. Terminology, molecular features, epidemiology, and management of serrated colorectal neoplasia. *Gastroenterology*, 157(4), p. 949–966.e944. <<http://doi.org/10.1053/j.gastro.2019.06.041>>.
- Croese, A. D., Lonie, J. M., Trollope, A. F., Vangaveti, V. N. & Ho, Y. H. 2018. A meta-analysis of the prevalence of low anterior resection syndrome and systematic review of risk factors. *International Journal of Surgery*, 56, p. 234–241. <<http://doi.org/10.1016/j.ijsu.2018.06.031>>.
- Czene, K., Lichtenstein, P. & Hemminki, K. 2002. Environmental and heritable causes of cancer among 9.6 million individuals in the Swedish family-cancer database. *International Journal of Cancer*, 99(2), p. 260–266. <<http://doi.org/10.1002/ijc.10332>>.
- Deijen, C. L., Velthuis, S., Tsai, A., Mavrouli, S., de Lange-de Klerk, E. S., Sietses, C., Tuynman, J. B., Lacy, A. M., Hanna, G. B. & Bonjer, H. J. 2016. COLOR III: a multicentre randomised clinical

- Bondeven, P., Emmertsen, K. J., Laurberg, S. & Pedersen, B. G. 2015. Neoadjuvant therapy abolishes the functional benefits of a larger rectal remnant, as measured by magnetic resonance imaging after restorative rectal cancer surgery. *European Journal of Surgical Oncology*, 41(11), p. 1493–1499. <<http://doi.org/10.1016/j.ejso.2015.07.003>>.
- Bonjer, H. J., Deijen, C. L., Abis, G. A., Cuesta, M. A., van der Pas, M. H. G. M., de Lange-de Klerk, E. S. M., Lacy, A. M., Bemelman, W. A., Andersson, J., Angenete, E., Rosenberg, J., Fuerst, A., Haglund, E. & COLOR II Study Group 2015. A randomized trial of laparoscopic versus open surgery for rectal cancer. *The New England Journal of Medicine*, 372(14), p. 1324–1332. <<http://doi.org/10.1056/NEJMoa1414882>>.
- Bonnetain, F., Bosset, J. F., Gerard, J. P., Calais, G., Conroy, T., Mineur, L., Bouché, O., Maingon, P., Chapet, O., Radošević-Jelic, L., Methy, N. & Collette, L. 2012. What is the clinical benefit of preoperative chemoradiotherapy with 5FU/leucovorin for T3-4 rectal cancer in a pooled analysis of EORTC 22921 and FFCO 9203 trials: surrogacy in question? *European Journal of Cancer*, 48(12), p. 1781–1790. <<http://doi.org/10.1016/j.ejca.2012.03.016>>.
- Bosset, J.-F., Calais, G., Mineur, L., Maingon, P., Radošević-Jelic, L., Daban, A., Bardet, E., Beny, A., Briffaux, A. & Collette, L. 2005. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results—EORTC 22921. *Journal of Clinical Oncology*, 23(24), p. 5620–5627. <<http://doi.org/10.1200/jco.2005.02.113>>.
- Bosset, J.-F., Collette, L., Calais, G., Mineur, L., Maingon, P., Radošević-Jelic, L., Daban, A., Bardet, E., Beny, A. & Ollier, J.-C. 2006. Chemotherapy with preoperative radiotherapy in rectal cancer. *The New England Journal of Medicine*, 355(11), p. 1114–1123. <<http://doi.org/10.1056/NEJMoa060829>>.
- Brændengen, M. & Glimelius, B. 2018. Preoperative radiotherapy or chemoradiotherapy in rectal cancer – Is survival improved? An update of the “Nordic” LARC study in non-resectable cancers. *Radiotherapy and Oncology*, 127(3), p. 392–395. <<http://doi.org/https://doi.org/10.1016/j.radonc.2018.05.004>>.
- Brændengen, M., Tveit, K. M., Berglund, Å., Birkemeyer, E., Frykholm, G., Pålman, L., Wiig, J. N., Byström, P., Bujko, K. & Glimelius, B. 2008. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. *Journal of Clinical Oncology*, 26(22), p. 3687–3694. <<http://doi.org/10.1200/jco.2007.15.3858>>.
- Bregendahl, S., Emmertsen, K. J., Lous, J. & Laurberg, S. 2013. Bowel dysfunction after low anterior resection with and without neoadjuvant therapy for rectal cancer: a population-based cross-sectional study. *Colorectal Disease*, 15(9), p. 1130–1139. <<http://doi.org/10.1111/codi.12244>>.
- Brenner, H., Stock, C. & Hoffmeister, M. 2014. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. *British Medical Journal*, 348, p. g2467. <<http://doi.org/10.1136/bmj.g2467>>.
- Brouwer, N. P. M., Stijns, R. C. H., Lemmens, V. E. P. P., Nagtegaal, I. D., Beets-Tan, R. G. H., Fütterer, J. J., Tanis, P. J., Verhoeven, R. H. A. & de Wilt, J. H. W. 2018. Clinical lymph node staging in colorectal cancer; a flip of the coin? *European Journal of Surgical Oncology*, 44(8), p. 1241–1246. <<http://doi.org/https://doi.org/10.1016/j.ejso.2018.04.008>>.
- Brown, G., Richards, C. J., Bourne, M. W., Newcombe, R. G., Radcliffe, A. G., Dallimore, N. S. & Williams, G. T. 2003. Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. *Radiology*, 227(2), p. 371–377. <<http://doi.org/10.1148/radiol.2272011747>>.
- Brown, G., Davies, S., Williams, G. T., Bourne, M. W., Newcombe, R. G., Radcliffe, A. G., Blethyn, J., Dallimore, N. S., Rees, B. I., Phillips, C. J. & Maughan, T. S. 2004. Effectiveness of preoperative staging in rectal cancer: digital rectal examination, endoluminal ultrasound or magnetic resonance imaging? *British Journal of Cancer*, 91(1), p. 23–29. <<http://doi.org/10.1038/sj.bjc.6601871>>.

- Brush, J., Boyd, K., Chappell, F., Crawford, F., Dozier, M., Fenwick, E., Glanville, J., McIntosh, H., Renehan, A., Weller, D. & Dunlop, M. 2011. The value of FDG positron emission tomography/computerised tomography (PET/CT) in pre-operative staging of colorectal cancer: a systematic review and economic evaluation. *Health Technology Assessment*, 15(35). <<http://doi.org/10.3310/hta15350>>.
- Bugg, W. G., Andreou, A. K., Biswas, D., Toms, A. P. & Williams, S. M. 2014. The prognostic significance of MRI-detected extramural venous invasion in rectal carcinoma. *Clinical Radiology*, 69(6), p. 619–623. <<http://doi.org/https://doi.org/10.1016/j.crad.2014.01.010>>.
- Bullinger, M., Alonso, J., Apolone, G., Lepège, A., Sullivan, M., Wood-Dauphinee, S., Gandek, B., Wagner, A., Aaronson, N., Bech, P., Fukuhara, S., Kaasa, S. & Ware, J. E. 1998. Translating health status questionnaires and evaluating their quality: the IQOLA project approach. *J Clin Epidemiol*, 51(11), p. 913–923. <[http://doi.org/https://doi.org/10.1016/S0895-4356\(98\)00082-1](http://doi.org/https://doi.org/10.1016/S0895-4356(98)00082-1)>.
- Bülow, S., Christensen, I. J., Iversen, L. H., Harling, H. & Danish Colorectal Cancer Group 2011. Intra-operative perforation is an important predictor of local recurrence and impaired survival after abdominoperineal resection for rectal cancer. *Colorectal Disease*, 13(11), p. 1256–1264. <<http://doi.org/10.1111/j.1463-1318.2010.02459.x>>.
- Cedermarck, B., Johansson, H. & Rutqvist, L. E. 1995. The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. *Cancer*, 75(9), p. 2269–2275. <[http://doi.org/10.1002/1097-0142\(19950501\)75:9<2269::aid-cnrcr2820750913>3.0.co;2-i](http://doi.org/10.1002/1097-0142(19950501)75:9<2269::aid-cnrcr2820750913>3.0.co;2-i)>.
- Chand, M., Evans, J., Swift, R. I., Tekkis, P. P., West, N. P., Stamp, G., Heald, R. J. & Brown, G. 2015. The prognostic significance of postchemoradiotherapy high-resolution MRI and histopathology detected extramural venous invasion in rectal cancer. *Annals of Surgery*, 261(3), p. 473–479. <<http://doi.org/10.1097/SLA.0000000000000848>>.
- Chapman, S. J., Wood, B., Drake, T. M., Young, N. & Jayne, D. G. 2017. Systematic review and meta-analysis of prophylactic mesh during primary stoma formation to prevent parastomal hernia. *Diseases of the Colon & Rectum*, 60(1), p. 107–115. <<http://doi.org/10.1097/dcr.0000000000000670>>.
- 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. *J Chronic Dis*, 40(5), p. 373–383. <[http://doi.org/10.1016/0021-9681\(87\)90171-8](http://doi.org/10.1016/0021-9681(87)90171-8)>.
- Chen, T. Y.-T., Emmertsen, K. J. & Laurberg, S. 2014. Bowel dysfunction after rectal cancer treatment: a study comparing the specialist's versus patient's perspective. *BMJ Open*, 4(1), p. e003374. <<http://doi.org/10.1136/bmjopen-2013-003374>>.
- Chen, T. Y., Wiltink, L. M., Nout, R. A., Meershoek-Klein Kranenbarg, E., Laurberg, S., Marijnen, C. A. & van de Velde, C. J. 2015. Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomized trial. *Clinical Colorectal Cancer*, 14(2), p. 106–114. <<http://doi.org/10.1016/j.clcc.2014.12.007>>.
- Comber, H., Sharp, L., de Camargo Cancela, M., Haase, T., Johnson, H. & Pratschke, J. 2016. Causes and outcomes of emergency presentation of rectal cancer. *International Journal of Cancer*, 139(5), p. 1031–1039. <<http://doi.org/10.1002/ijc.30149>>.
- Crockett, S. D. & Nagtegaal, I. D. 2019. Terminology, molecular features, epidemiology, and management of serrated colorectal neoplasia. *Gastroenterology*, 157(4), p. 949–966.e944. <<http://doi.org/10.1053/j.gastro.2019.06.041>>.
- Croese, A. D., Lonie, J. M., Trollope, A. F., Vangaveti, V. N. & Ho, Y. H. 2018. A meta-analysis of the prevalence of low anterior resection syndrome and systematic review of risk factors. *International Journal of Surgery*, 56, p. 234–241. <<http://doi.org/10.1016/j.ijssu.2018.06.031>>.
- Czene, K., Lichtenstein, P. & Hemminki, K. 2002. Environmental and heritable causes of cancer among 9.6 million individuals in the Swedish family-cancer database. *International Journal of Cancer*, 99(2), p. 260–266. <<http://doi.org/10.1002/ijc.10332>>.
- Deijen, C. L., Velthuis, S., Tsai, A., Mavrouli, S., de Lange-de Klerk, E. S., Sietses, C., Tuynman, J. B., Lacy, A. M., Hanna, G. B. & Bonjer, H. J. 2016. COLOR III: a multicentre randomised clinical

- trial comparing transanal TME versus laparoscopic TME for mid and low rectal cancer. *Surgical Endoscopy*, 30(8), p. 3210–3215. <<http://doi.org/10.1007/s00464-015-4615-x>>.
- Denost, Q., Faucheron, J. L., Lefevre, J. H., Panis, Y., Cotte, E., Rouanet, P., Jafari, M., Capdepon, M., Rullier, E. & Association Française de Chirurgie 2015. French current management and oncological results of locally recurrent rectal cancer. *European Journal of Surgical Oncology*, 41(12), p. 1645–1652. <<http://doi.org/10.1016/j.ejso.2015.09.019>>.
- Dindo, D., Demartines, N. & Clavien, P. A. 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), p. 205–213. <<http://doi.org/10.1097/01.sla.0000133083.54934.ac>>.
- Dixon, C. F. 1948. Anterior resection for malignant lesions of the upper part of the rectum and lower part of the sigmoid. *Annals of Surgery*, 128(3), p. 425–442. <<http://doi.org/10.1097/00000658-194809000-00009>>.
- Dworak, O., Keilholz, L. & Hoffmann, A. 1997. Pathological features of rectal cancer after preoperative radiochemotherapy. *International Journal of Colorectal Disease*, 12(1), p. 19–23. <<http://doi.org/10.1007/s003840050072>>.
- Eid, Y., Bouvier, V., Menahem, B., Thobie, A., Dolet, N., Finochi, M., Renier, M., Gardy, J., Launoy, G., Dejardin, O., Morello, R. & Alves, A. 2019. Digestive and genitourinary sequelae in rectal cancer survivors and their impact on health-related quality of life: Outcome of a high-resolution population-based study. *Surgery*, 166(3), p. 327–335. <<http://doi.org/10.1016/j.surg.2019.04.007>>.
- Emmertsen, K. J. & Laurberg, S. 2012. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. *Annals of Surgery*, 255(5), p. 922–928. <<http://doi.org/10.1097/SLA.0b013e31824f1c21>>.
- Enriquez-Navascués, J. M., Borda, N., Lizerazu, A., Placer, C., Elosegui, J. L., Ciria, J. P., Lacasta, A. & Bujanda, L. 2011. Patterns of local recurrence in rectal cancer after a multidisciplinary approach. *World Journal of Gastroenterology*, 17(13), p. 1674–1684. <<http://doi.org/10.3748/wjg.v17.i13.1674>>.
- Eriksen, M. T., Wibe, A., Syse, A., Haffner, J., Wiig, J. N., Norwegian Rectal Cancer Group & Norwegian Gastrointestinal Cancer Group 2004. Inadvertent perforation during rectal cancer resection in Norway. *British Journal of Surgery*, 91(2), p. 210–216. <<http://doi.org/10.1002/bjs.4390>>.
- Erlandsson, J., Löhrinc, E., Ahlberg, M., Pettersson, D., Holm, T., Glimelius, B. & Martling, A. 2019. Tumour regression after radiotherapy for rectal cancer - Results from the randomised Stockholm III trial. *Radiotherapy and Oncology*, 135, p. 178–186. <<http://doi.org/10.1016/j.radonc.2019.03.016>>.
- Espin, E., Ciga, M. A., Pera, M., Ortiz, H. & Spanish Rectal Cancer Project 2015. Oncological outcome following anastomotic leak in rectal surgery. *British Journal of Surgery*, 102(4), p. 416–422. <<http://doi.org/10.1002/bjs.9748>>.
- Fayers, P., Aaronson, N., Bjordal, K., Groenvold, M., Curran, D. & Bottomley A. on behalf of the EORTC Quality of Life Group 2001. The EORTC QLQ-C30 Scoring Manual (3rd Edition). *Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001*.
- Fearon, E. R. 2011. Molecular Genetics of Colorectal Cancer. *Annual Review of Pathology: Mechanisms of Disease*, 6(1), p. 479–507. <<http://doi.org/10.1146/annurev-pathol-011110-130235>>.
- Feddern, M.-L., Emmertsen, K. J. & Laurberg, S. 2019. Quality of life with or without sphincter preservation for rectal cancer. *Colorectal Disease*, 21(9), p. 1051–1057. <<http://doi.org/10.1111/codi.14684>>.
- Finnish Cancer Registry <<https://cancerregistry.fi/statistics/cancer-statistics/>>. Accessed January 2020.
- Fleshman, J., Branda, M. E., Sargent, D. J., Boller, A. M., George, V. V., Abbas, M. A., Peters, W. R., Jr., Maun, D. C., Chang, G. J., Herline, A., Fichera, A., Mutch, M. G., Wexner, S. D., Whiteford, M. H., Marks, J., Birnbaum, E., Margolin, D. A., Larson, D. W., Marcello, P. W., Posner, M. C.,

- et al. 2019. Disease-free survival and local recurrence for laparoscopic resection compared with open resection of stage II to III rectal cancer: follow-up results of the ACOSOG Z6051 randomized controlled trial. *Annals of Surgery*, 269(4), p. 589–595. <<http://doi.org/10.1097/SLA.0000000000003002>>.
- Foster, J. D., Tou, S., Curtis, N. J., Smart, N. J., Acheson, A., Maxwell-Armstrong, C., Watts, A., Singh, B. & Francis, N. K. 2018. Closure of the perineal defect after abdominoperineal excision for rectal adenocarcinoma – ACPGBI Position Statement. *Colorectal Disease*, 20(S5), p. 5–23. <<http://doi.org/10.1111/codi.14348>>.
- Frankel, W. L. & Jin, M. 2015. Serosal surfaces, mucin pools, and deposits, oh my: challenges in staging colorectal carcinoma. *Modern Pathology*, 28 Suppl 1, p. S95–S108. <<http://doi.org/10.1038/modpathol.2014.128>>.
- Gagnière, J., Raisch, J., Veziat, J., Barnich, N., Bonnet, R., Buc, E., Bringer, M.-A., Pezet, D. & Bonnet, M. 2016. Gut microbiota imbalance and colorectal cancer. *World Journal of Gastroenterology*, 22(2), p. 501–518. <<http://doi.org/10.3748/wjg.v22.i2.501>>.
- Galon, J., Mlecnik, B., Bindea, G., Angell, H. K., Berger, A., Lagorce, C., Lugli, A., Zlobec, I., Hartmann, A., Bifulco, C., Nagtegaal, I. D., Palmqvist, R., Masucci, G. V., Botti, G., Tatangelo, F., Delrio, P., Maio, M., Laghi, L., Grizzi, F., Asslaber, M., et al. 2014. Towards the introduction of the 'Immunoscore' in the classification of malignant tumours. *The Journal of pathology*, 232(2), p. 199–209. <<http://doi.org/10.1002/path.4287>>.
- Gandek, B. & Ware, J. E. 1998. Methods for validating and norming translations of health status questionnaires: the IQOLA project approach. *Journal of Clinical Epidemiology*, 51(11), p. 953–959. <[http://doi.org/10.1016/S0895-4356\(98\)00086-9](http://doi.org/10.1016/S0895-4356(98)00086-9)>.
- Ganeshan, D., Nougaret, S., Korngold, E., Rauch, G. M. & Moreno, C. C. 2019. Locally recurrent rectal cancer: what the radiologist should know. *Abdominal Radiology*, 44(11), p. 3709–3725. <<http://doi.org/10.1007/s00261-019-02003-5>>.
- Gérard, A., Buyse, M., Nordlinger, B., Loygue, J., Pène, F., Kempf, P., Bosset, J. F., Gignoux, M., Arnaud, J. P. & Desai, C. 1988. Preoperative radiotherapy as adjuvant treatment in rectal cancer. Final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). *Annals of Surgery*, 208(5), p. 606–614. <<http://doi.org/10.1097/0000658-198811000-00011>>.
- Gérard, J.-P., Conroy, T., Bonnetain, F., Bouché, O., Chapet, O., Cluson-Dejardin, M.-T., Untereiner, M., Leduc, B., Francois, É., Maurel, J., Seitz, J.-F., Buecher, B., Mackiewicz, R., Ducreux, M. & Bedenne, L. 2006. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *Journal of Clinical Oncology*, 24(28), p. 4620–4625. <<http://doi.org/10.1200/jco.2006.06.7629>>.
- Glimelius, B., Myklebust, T. A., Lundqvist, K., Wibe, A. & Guren, M. G. 2016. Two countries - two treatment strategies for rectal cancer. *Radiotherapy and Oncology*, 121(3), p. 357–363. <<http://doi.org/10.1016/j.radonc.2016.11.010>>.
- Glynn-Jones, R., Wyrwicz, L., Tiret, E., Brown, G., Rodel, C., Cervantes, A. & Arnold, D. 2017. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 28(suppl_4), p. iv22–iv40. <<http://doi.org/10.1093/annonc/mdx224>>.
- Graney, M. J. & Graney, C. M. 1980. Colorectal surgery from antiquity to the modern era. *Diseases of the Colon & Rectum*, 23(6), p. 432–441. <<http://doi.org/10.1007/bf02586797>>.
- Gravante, G., Miah, A., Mann, C. D., Stephenson, J. A., Gani, M. A., Sharpe, D., Norwood, M., Boyle, K., Miller, A. & Hemingway, D. 2016. Circumferential resection margins and perineal complications after neoadjuvant long-course chemoradiotherapy followed by extralevator abdominoperineal excision of the rectum: Five years of activity at a single institution. *Journal of Surgical Oncology*, 114(1), p. 86–90. <<http://doi.org/10.1002/jso.24257>>.
- Gunderson, L. L., Jessup, J. M., Sargent, D. J., Greene, F. L. & Stewart, A. 2010. Revised tumor and node categorization for rectal cancer based on surveillance, epidemiology, and end results and

- rectal pooled analysis outcomes. *Journal of Clinical Oncology*, 28(2), p. 256–263. <<http://doi.org/10.1200/jco.2009.23.9194>>.
- Guren, M. G., Undseth, C., Rekstad, B. L., Brændengen, M., Dueland, S., Spindler, K.-L. G., Glynne-Jones, R. & Tveit, K. M. 2014. Reirradiation of locally recurrent rectal cancer: A systematic review. *Radiotherapy and Oncology*, 113(2), p. 151–157. <<http://doi.org/https://doi.org/10.1016/j.radonc.2014.11.021>>.
- Guren, M. G., Korner, H., Pfeffer, F., Myklebust, T. A., Eriksen, M. T., Edna, T. H., Larsen, S. G., Knudsen, K. O., Nesbakken, A., Wasmuth, H. H., Vonen, B., Hofslie, E., Faerden, A. E., Brændengen, M., Dahl, O., Steigen, S. E., Johansen, M. J., Lindsetmo, R. O., Drolsum, A., Tollali, G., et al. 2015. Nationwide improvement of rectal cancer treatment outcomes in Norway, 1993–2010. *Acta Oncologica*, 54(10), p. 1714–1722. <<http://doi.org/10.3109/0284186x.2015.1034876>>.
- Habr-Gama, A., Perez, R. O., Nadalin, W., Sabbaga, J., Ribeiro, U., Jr., Silva e Sousa, A. H., Jr., Campos, F. G., Kiss, D. R. & Gama-Rodrigues, J. 2004. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Annals of Surgery*, 240(4), p. 711–717; discussion 717–718. <<http://doi.org/10.1097/01.sla.0000141194.27992.32>>.
- Hagemans, J. A. W., van Rees, J. M., Alberda, W. J., Rothbarth, J., Nuyttens, J. J. M. E., van Meerten, E., Verhoef, C. & Burger, J. W. A. 2019. Locally recurrent rectal cancer; long-term outcome of curative surgical and non-surgical treatment of 447 consecutive patients in a tertiary referral centre. *European Journal of Surgical Oncology*. <<http://doi.org/10.1016/j.ejso.2019.10.037>>.
- Hain, E., Maggiori, L., Manceau, G., Mongin, C., Prost à la Denise, J. & Panis, Y. 2017. Oncological impact of anastomotic leakage after laparoscopic mesorectal excision. *British Journal of Surgery*, 104(3), p. 288–295. <<http://doi.org/10.1002/bjs.10332>>.
- Hain, E., Maggiori, L., Zappa, M., Prost, A. I. D. J. & Panis, Y. 2018. Anastomotic leakage after side-to-end anastomosis for rectal cancer: does leakage location matter? *Colorectal Disease*, 20(3), p. O55–O60. <<http://doi.org/10.1111/codi.14005>>.
- Hamilton, W., Round, A., Sharp, D. & Peters, T. J. 2005. Clinical features of colorectal cancer before diagnosis: a population-based case–control study. *British Journal of Cancer*, 93(4), p. 399–405. <<http://doi.org/10.1038/sj.bjc.6602714>>.
- Hammerman, A., Greenberg-Dotan, S., Battat, E., Feldhamer, I., Bitterman, H. & Brenner, B. 2015. The 'real-life' impact of adding bevacizumab to first-line therapy in metastatic colorectal cancer patients: a large Israeli retrospective cohort study. *Acta Oncologica*, 54(2), p. 164–170. <<http://doi.org/10.3109/0284186x.2014.958532>>.
- Han, J. G., Wang, Z. J., Wei, G. H., Gao, Z. G., Yang, Y. & Zhao, B. C. 2012. Randomized clinical trial of conventional versus cylindrical abdominoperineal resection for locally advanced lower rectal cancer. *American Journal of Surgery*, 204(3), p. 274–282. <<http://doi.org/10.1016/j.amjsurg.2012.05.001>>.
- Heald, R. J., Husband, E. M. & Ryall, R. D. 1982. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? *British Journal of Surgery*, 69(10), p. 613–616. <<http://doi.org/10.1002/bjs.1800691019>>.
- Heald, R. J., Moran, B. J., Ryall, R. D. H., Sexton, R. & MacFarlane, J. K. 1998. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978–1997. *Archives of Surgery*, 133(8), p. 894–898. <<http://doi.org/10.1001/archsurg.133.8.894>>.
- Heervä, E., Lavonius, M., Jaakkola, P., Minn, H. & Ristamäki, R. 2018. Overall survival and metastasis resections in patients with metastatic colorectal cancer using electronic medical records. *Journal of Gastrointestinal Cancer*, 49(3), p. 245–251. <<http://doi.org/10.1007/s12029-017-9927-8>>.
- Heinävaara, S., Jäntti, M., Färkkilä, M., Hyöty, M., Kairaluoma, M., Rautio, T., Voutilainen, M., Malila, N. & Sarkeala, T. 2019. Screening for colorectal cancer is being reformed. *Lääketieteellinen Aikakauskirja Duodecim*, 135(19), p. 1920–1927. <<https://www.duodecimlehti.fi/lehti/2019/1919/duo15151>>.

- Holliday, E. B., Hunt, A., You, Y. N., Chang, G. J., Skibber, J. M., Rodriguez-Bigas, M. A., Bednarski, B. K., Eng, C., Koay, E. J., Minsky, B. D., Taniguchi, C., Krishnan, S., Herman, J. M. & Das, P. 2017. Short course radiation as a component of definitive multidisciplinary treatment for select patients with metastatic rectal adenocarcinoma. *Journal of Gastrointestinal Oncology*, 8(6), p. 990–997. <<http://doi.org/10.21037/jgo.2017.09.02>>.
- Holm, T., Ljung, A., Haggmark, T., Jurell, G. & Lagergren, J. 2007. Extended abdominoperineal resection with gluteus maximus flap reconstruction of the pelvic floor for rectal cancer. *British Journal of Surgery*, 94(2), p. 232–238. <<http://doi.org/10.1002/bjs.5489>>.
- Holm, T. 2014. Controversies in abdominoperineal excision. *Surgical Oncology Clinics of North America*, 23(1), p. 93–111. <<http://doi.org/10.1016/j.soc.2013.09.005>>.
- Holmer, C. & Kreis, M. E. 2018. Systematic review of robotic low anterior resection for rectal cancer. *Surgical Endoscopy*, 32(2), p. 569–581. <<http://doi.org/10.1007/s00464-017-5978-y>>.
- Horn, A., Dahl, O. & Morild, I. 1991. Venous and neural invasion as predictors of recurrence in rectal adenocarcinoma. *Diseases of the Colon & Rectum*, 34(9), p. 798–804. <<http://doi.org/10.1007/BF02051074>>.
- Hou, X. T., Pang, D., Lu, Q., Yang, P., Jin, S. L., Zhou, Y. J. & Tian, S. H. 2015. Validation of the Chinese version of the low anterior resection syndrome score for measuring bowel dysfunction after sphincter-preserving surgery among rectal cancer patients. *European Journal of Oncology Nursing*, 19(5), p. 495–501. <<http://doi.org/10.1016/j.ejon.2015.02.009>>.
- How, P., West, N. P. & Brown, G. 2014. An MRI-based assessment of standard and extralevator abdominoperineal excision specimens: time for a patient tailored approach? *Annals of Surgical Oncology*, 21(3), p. 822–828. <<http://doi.org/10.1245/s10434-013-3378-7>>.
- Hughes, D. L., Cornish, J. & Morris, C. 2017. Functional outcome following rectal surgery—predisposing factors for low anterior resection syndrome. *International Journal of Colorectal Disease*, 32(5), p. 691–697. <<http://doi.org/10.1007/s00384-017-2765-0>>.
- Hupkens, B. J. P., Breukink, S. O., Olde Reuver Of Briel, C., Tanis, P. J., de Noo, M. E., van Duijvendijk, P., van Westreenen, H. L., Dekker, J. W. T., Chen, T. Y. T. & Juul, T. 2018. Dutch validation of the low anterior resection syndrome score. *Colorectal Disease*, 20(10), p. 881–887. <<http://doi.org/10.1111/codi.14228>>.
- Hüttner, F. J., Tenckhoff, S., Jensen, K., Uhlmann, L., Kulu, Y., Büchler, M. W., Diener, M. K. & Ulrich, A. 2015. Meta-analysis of reconstruction techniques after low anterior resection for rectal cancer. *British Journal of Surgery*, 102(7), p. 735–745. <<http://doi.org/10.1002/bjs.9782>>.
- IARC 2018. International Agency for Research on Cancer. World Health Organisation. Global Cancer Observatory. <https://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf>. Accessed January 2020.
- Itzkowitz, S. H. & Harpaz, N. 2004. Diagnosis and management of dysplasia in patients with inflammatory bowel diseases. *Gastroenterology*, 126(6), p. 1634–1648. <<http://doi.org/https://doi.org/10.1053/j.gastro.2004.03.025>>.
- Iversen, L. H., Green, A., Ingeholm, P., Østerlind, K. & Gögenur, I. 2016. Improved survival of colorectal cancer in Denmark during 2001–2012 – The efforts of several national initiatives. *Acta Oncologica*, 55(sup2), p. 10–23. <<http://doi.org/10.3109/0284186X.2015.1131331>>.
- Jayne, D., Pigazzi, A., Marshall, H., Croft, J., Corrigan, N., Copeland, J., Quirke, P., West, N., Rautio, T., Thomassen, N., Tilney, H., Gudgeon, M., Bianchi, P. P., Edlin, R., Hulme, C. & Brown, J. 2017. Effect of robotic-assisted vs conventional laparoscopic surgery on risk of conversion to open laparotomy among patients undergoing resection for rectal cancer: the ROLARR randomized clinical trial. *JAMA*, 318(16), p. 1569–1580. <<http://doi.org/10.1001/jama.2017.7219>>.
- Jeong, S.-Y., Park, J. W., Nam, B. H., Kim, S., Kang, S.-B., Lim, S.-B., Choi, H. S., Kim, D.-W., Chang, H. J., Kim, D. Y., Jung, K. H., Kim, T.-Y., Kang, G. H., Chie, E. K., Kim, S. Y., Sohn, D. K., Kim, D.-H., Kim, J.-S., Lee, H. S., Kim, J. H., et al. 2014. Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival

- outcomes of an open-label, non-inferiority, randomised controlled trial. *The Lancet Oncology*, 15(7), p. 767–774. <[http://doi.org/10.1016/S1470-2045\(14\)70205-0](http://doi.org/10.1016/S1470-2045(14)70205-0)>.
- Jimenez-Gomez, L. M., Espin-Basany, E., Trenti, L., Martí-Gallostra, M., Sánchez-García, J. L., Vallribera-Valls, F., Kreisler, E., Biondo, S. & Armengol-Carrasco, M. 2018. Factors associated with low anterior resection syndrome after surgical treatment of rectal cancer. *Colorectal Disease*, 20(3), p. 195–200. <<http://doi.org/10.1111/codi.13901>>.
- Juul, T., Ahlberg, M., Biondo, S., Emmertsen, K. J., Espin, E., Jimenez, L. M., Matzel, K. E., Palmer, G., Sauermann, A., Trenti, L., Zhang, W., Laurberg, S. & Christensen, P. 2014a. International validation of the low anterior resection syndrome score. *Annals of Surgery*, 259(4), p. 728–734. <<http://doi.org/10.1097/SLA.0b013e31828fac0b>>.
- Juul, T., Ahlberg, M., Biondo, S., Espin, E., Jimenez, L. M., Matzel, K. E., Palmer, G. J., Sauermann, A., Trenti, L., Zhang, W., Laurberg, S. & Christensen, P. 2014b. Low anterior resection syndrome and quality of life: an international multicenter study. *Diseases of the Colon and Rectum*, 57(5), p. 585–591. <<http://doi.org/10.1097/dcr.0000000000000116>>.
- Juul, T., Battersby, N. J., Christensen, P., Janjua, A. Z., Branagan, G., Laurberg, S., Emmertsen, K. J. & Moran, B. 2015. Validation of the English translation of the low anterior resection syndrome score. *Colorectal Disease*, 17(10), p. 908–916. <<http://doi.org/10.1111/codi.12952>>.
- Jørgensen, J. B., Bondeven, P., Iversen, L. H., Laurberg, S. & Pedersen, B. G. 2018. Pelvic insufficiency fractures frequently occur following preoperative chemo-radiotherapy for rectal cancer – a nationwide MRI study. *Colorectal Disease*, 20(10), p. 873–880. <<http://doi.org/10.1111/codi.14224>>.
- Karagkounis, G., Stocchi, L., Lavery, I. C., Liska, D., Gorgun, E., Veniero, J., Plesec, T., Amarnath, S., Khorana, A. A. & Kalady, M. F. 2018. Multidisciplinary conference and clinical management of rectal cancer. *Journal of the American College of Surgeons*, 226(5), p. 874–880. <<http://doi.org/10.1016/j.jamcollsurg.2018.01.056>>.
- Kasi, P. M., Shahjehan, F., Cochuyt, J. J., Li, Z., Colibaseanu, D. T. & Merchea, A. 2019. Rising proportion of young individuals with rectal and colon cancer. *Clinical Colorectal Cancer*, 18(1), p. e87–e95. <<http://doi.org/https://doi.org/10.1016/j.clcc.2018.10.002>>.
- Kim, C. H., Lee, S. Y., Kim, H. R. & Kim, Y. J. 2015. Prognostic effect of pretreatment serum carcinoembryonic antigen level: a useful tool for prediction of distant metastasis in locally advanced rectal cancer following neoadjuvant chemoradiotherapy and total mesorectal excision. *Medicine*, 94(31), p. e1291–e1291. <<http://doi.org/10.1097/MD.0000000000001291>>.
- Kim, H. J., Boland, P. J., Meredith, D. S., Lis, E., Zhang, Z., Shi, W., Yamada, Y. J. & Goodman, K. A. 2012. Fractures of the sacrum after chemoradiation for rectal carcinoma: incidence, risk factors, and radiographic evaluation. *International Journal of Radiation Oncology*Biophysics*, 84(3), p. 694–699. <<http://doi.org/https://doi.org/10.1016/j.ijrobp.2012.01.021>>.
- Kim, Y.-W., Cha, S.-W., Pyo, J., Kim, N.-K., Min, B.-S., Kim, M.-J. & Kim, H. 2009. Factors related to preoperative assessment of the circumferential resection margin and the extent of mesorectal invasion by magnetic resonance imaging in rectal cancer: a prospective comparison study. *World Journal of Surgery*, 33(9), p. 1952–1960. <<http://doi.org/10.1007/s00268-009-0126-z>>.
- Klein, M., Fischer, A., Rosenberg, J., Gogenur, I. & Danish Colorectal Cancer, G. 2015. Extralevatory abdominoperineal excision (ELAPE) does not result in reduced rate of tumor perforation or rate of positive circumferential resection margin: a nationwide database study. *Annals of Surgery*, 261(5), p. 933–938. <<http://doi.org/10.1097/SLA.0000000000000910>>.
- Klein, M., Colov, E. & Gogenur, I. 2016. Similar long-term overall and disease-free survival after conventional and extralevator abdominoperineal excision—a nationwide study. *International Journal of Colorectal Disease*, 31(7), p. 1341–1347. <<http://doi.org/10.1007/s00384-016-2596-4>>.
- Klose, J., Tarantino, I., Schmidt, T., Bruckner, T., Kulu, Y., Wagner, T., Schneider, M., Buchler, M. W. & Ulrich, A. 2015. Impact of anatomic location on locally recurrent rectal cancer: superior

- outcome for intraluminal tumour recurrence. *Journal of Gastrointestinal Surgery*, 19(6), p. 1123–1131. <<http://doi.org/10.1007/s11605-015-2804-5>>.
- Kodeda, K., Derwinger, K., Gustavsson, B. & Nordgren, S. 2012. Local recurrence of rectal cancer: a population-based cohort study of diagnosis, treatment and outcome. *Colorectal Disease*, 14(5), p. e230–237. <<http://doi.org/10.1111/j.1463-1318.2011.02895.x>>.
- Kodeda, K., Johansson, R., Zar, N., Birgisson, H., Dahlberg, M., Skullman, S., Lindmark, G., Glimelius, B., Pählman, L. & Martling, A. 2015. Time trends, improvements and national auditing of rectal cancer management over an 18-year period. *Colorectal Disease*, 17(9), p. O168–179. <<http://doi.org/10.1111/codi.13060>>.
- Kulis, D., Bottomley, A., Velikova, G., Greimel, E. & Koller, M. 2017. EORTC quality of life group Translation manual, fourth edition. Available at <https://qol.eortc.org/app/uploads/sites/2/2018/02/translation_manual_2017.pdf> Accessed May 2018.
- Kulu, Y., Tarantio, I., Warschkow, R., Kny, S., Schneider, M., Schmied, B. M., Buchler, M. W. & Ulrich, A. 2015. Anastomotic leakage is associated with impaired overall and disease-free survival after curative rectal cancer resection: a propensity score analysis. *Annals of Surgical Oncology*, 22(6), p. 2059–2067. <<http://doi.org/10.1245/s10434-014-4187-3>>.
- Kupsch, J., Jackisch, T., Matzel, K. E., Zimmer, J., Schreiber, A., Sims, A., Witzigmann, H. & Stelzner, S. 2018. Outcome of bowel function following anterior resection for rectal cancer-an analysis using the low anterior resection syndrome (LARS) score. *International Journal of Colorectal Disease*, 33(6), p. 787–798. <<http://doi.org/10.1007/s00384-018-3006-x>>.
- Kupsch, J., Kuhn, M., Matzel, K. E., Zimmer, J., Radulova-Mauersberger, O., Sims, A., Witzigmann, H. & Stelzner, S. 2019. To what extent is the low anterior resection syndrome (LARS) associated with quality of life as measured using the EORTC C30 and CR38 quality of life questionnaires? *International Journal of Colorectal Disease*, 34(4), p. 747–762. <<http://doi.org/10.1007/s00384-019-03249-7>>.
- Kusters, M., Beets, G. L., van de Velde, C. J. H., Beets-Tan, R. G. H., Marijnen, C. A. M., Rutten, H. J. T., Putter, H. & Moriya, Y. 2009. A comparison between the treatment of low rectal cancer in Japan and the Netherlands, focusing on the patterns of local recurrence. *Annals of Surgery*, 249(2), p. 229–235. <<http://doi.org/10.1097/SLA.0b013e318190a664>>.
- Kusters, M., Marijnen, C. A. M., van de Velde, C. J. H., Rutten, H. J. T., Lahaye, M. J., Kim, J. H., Beets-Tan, R. G. H. & Beets, G. L. 2010. Patterns of local recurrence in rectal cancer; a study of the Dutch TME trial. *European Journal of Surgical Oncology*, 36(5), p. 470–476. <<http://doi.org/10.1016/j.ejso.2009.11.011>>.
- Kusters, M., Austin, K. K. S., Solomon, M. J., Lee, P. J., Nieuwenhuijzen, G. A. P. & Rutten, H. J. T. 2015. Survival after pelvic exenteration for T4 rectal cancer. *The British Journal of Surgery*, 102(1), p. 125–131. <<http://doi.org/10.1002/bjs.9683>>.
- Kusters, M., Slater, A., Muirhead, R., Hompes, R., Guy, R. J., Jones, O. M., George, B. D., Lindsey, I., Mortensen, N. J. & Cunningham, C. 2017. What to do with lateral nodal disease in low locally advanced rectal cancer? A call for further reflection and research. *Diseases of the Colon and Rectum*, 60(6), p. 577–585. <<http://doi.org/10.1097/dcr.0000000000000834>>.
- Laghi, A., Bellini, D., Rengo, M., Accarpio, F., Caruso, D., Biacchi, D., Di Giorgio, A. & Sammartino, P. 2017. Diagnostic performance of computed tomography and magnetic resonance imaging for detecting peritoneal metastases: systematic review and meta-analysis. *Radiologia Medica*, 122(1), p. 1–15. <<http://doi.org/10.1007/s11547-016-0682-x>>.
- Latournerie, M., Jooste, V., Cottet, V., Lepage, C., Faivre, J. & Bouvier, A.-M. 2008. Epidemiology and prognosis of synchronous colorectal cancers. *British Journal of Surgery*, 95(12), p. 1528–1533. <<http://doi.org/10.1002/bjs.6382>>.
- Lauby-Secretan, B., Vilahur, N., Bianchini, F., Guha, N. & Straif, K. 2018. The IARC perspective on colorectal cancer screening. *The New England Journal of Medicine*, 378(18), p. 1734–1740. <<http://doi.org/10.1056/NEJMs1714643>>.

- Lazzaron, A. R., Vieira, M. V. & Damin, D. C. 2015. Should preoperative chest computed tomography be performed in all patients with colorectal cancer? *Colorectal Disease*, 17(10), p. O184–O190. <<http://doi.org/10.1111/codi.13071>>.
- Lehtonen, T., Räsänen, M., Carpelan-Holmström, M. & Lepistö, A. 2019. Oncological outcomes before and after the extralevator abdominoperineal excision era in rectal cancer patients treated with abdominoperineal excision in a single centre, high volume unit. *Colorectal Disease*, 21(2), p. 183–190. <<http://doi.org/10.1111/codi.14468>>.
- Lemmens, V. E. P. P., de Haan, N., Rutten, H. J. T., Martijn, H., Loosveld, O. J. L., Roumen, R. M. H. & Creemers, G. J. M. 2011. Improvements in population-based survival of patients presenting with metastatic rectal cancer in the south of the Netherlands, 1992–2008. *Clinical & Experimental Metastasis*, 28(3), p. 283–290. <<http://doi.org/10.1007/s10585-010-9370-8>>.
- Li, J., Yi, C. H., Hu, Y. T., Li, J. S., Yuan, Y., Zhang, S. Z., Zheng, S. & Ding, K. F. 2016. TNM staging of colorectal cancer should be reconsidered according to weighting of the T stage: verification based on a 25-year follow-up. *Medicine*, 95(6), p. e2711. <<http://doi.org/10.1097/md.0000000000002711>>.
- Liapi, A., Mavrantonis, C., Lazaridis, P., Kourkouni, E., Zevlas, A., Zografos, G. & Theodoropoulos, G. 2019. Validation and comparative assessment of low anterior resection syndrome questionnaires in Greek rectal cancer patients. *Annals of Gastroenterology*, 32(2), p. 185–192. <<http://doi.org/10.20524/aog.2019.0350>>.
- Lichtenstein, P., Holm, N. V., Verkasalo, P. K., Iliadou, A., Kaprio, J., Koskenvuo, M., Pukkala, E., Skytthe, A. & Hemminki, K. 2000. Environmental and heritable factors in the causation of cancer — analyses of cohorts of twins from Sweden, Denmark, and Finland. *New England Journal of Medicine*, 343(2), p. 78–85. <<http://doi.org/10.1056/nejm200007133430201>>.
- Liu, G.-C., Zhang, X., Xie, E., An, X., Cai, P.-Q., Zhu, Y., Tang, J.-H., Kong, L.-H., Lin, J.-Z., Pan, Z.-Z. & Ding, P.-R. 2015. The value of restaging with chest and abdominal CT/MRI scan after neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Medicine*, 94(47), p. e2074–e2074. <<http://doi.org/10.1097/MD.0000000000002074>>.
- Logan, R. F. A., Patnick, J., Nickerson, C., Coleman, L., Rutter, M. D. & von Wagner, C. 2012. Outcomes of the bowel cancer screening programme (BCSP) in England after the first 1 million tests. *Gut*, 61(10), p. 1439–1446. <<http://doi.org/10.1136/gutjnl-2011-300843>>.
- Lopez-Kostner, F., Lavery, I. C., Hool, G. R., Rybicki, L. A. & Fazio, V. W. 1998. Total mesorectal excision is not necessary for cancers of the upper rectum. *Surgery*, 124(4), p. 612–617; discussion 617–618. <<http://doi.org/10.1067/msy.1998.91361>>.
- Ma, B., Gao, P., Wang, H., Xu, Q., Song, Y., Huang, X., Sun, J., Zhao, J., Luo, J., Sun, Y. & Wang, Z. 2017. What has preoperative radio(chemo)therapy brought to localized rectal cancer patients in terms of perioperative and long-term outcomes over the past decades? A systematic review and meta-analysis based on 41,121 patients. *International Journal of Cancer*, 141(5), p. 1052–1065. <<http://doi.org/10.1002/ijc.30805>>.
- Maffione, A. M., Lopci, E., Bluemel, C., Giammarile, F., Herrmann, K. & Rubello, D. 2015. Diagnostic accuracy and impact on management of (18)F-FDG PET and PET/CT in colorectal liver metastasis: a meta-analysis and systematic review. *European Journal of Nuclear Medicine and Molecular Imaging*, 42(1), p. 152–163. <<http://doi.org/10.1007/s00259-014-2930-4>>.
- Marr, R., Birbeck, K., Garvican, J., Macklin, C. P., Tiffin, N. J., Parsons, W. J., Dixon, M. F., Mapstone, N. P., Sebag-Montefiore, D., Scott, N., Johnston, D., Sagar, P., Finan, P. & Quirke, P. 2005. The modern abdominoperineal excision: the next challenge after total mesorectal excision. *Annals of Surgery*, 242(1), p. 74–82. <<http://doi.org/10.1097/01.sla.0000167926.60908.15>>.
- Martling, A., Holm, T., Johansson, H., Rutqvist, L. E., Cedermark, B. & Stockholm Colorectal Cancer Study Group 2001. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. *Cancer*, 92(4), p. 896–902. <[http://doi.org/10.1002/1097-0142\(20010815\)92:4<896::aid-cnrc1398>3.0.co;2-r](http://doi.org/10.1002/1097-0142(20010815)92:4<896::aid-cnrc1398>3.0.co;2-r)>.

- McClelland, D. & Murray, G. I. 2015. A comprehensive study of extramural venous invasion in colorectal cancer. *PLoS One*, 10(12). <<http://doi.org/10.1371/journal.pone.0144987>>.
- Mecklin, J. P., Aarnio, M., Läärä, E., Kairaluoma, M. V., Pylvänäinen, K., Peltomäki, P., Aaltonen, L. A. & Järvinen, H. J. 2007. Development of colorectal tumors in colonoscopic surveillance in Lynch syndrome. *Gastroenterology*, 133(4), p. 1093–1098. <<http://doi.org/10.1053/j.gastro.2007.08.019>>.
- MERCURY Study Group 2006. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *British Medical Journal*, 333(7572), p. 779. <<http://doi.org/10.1136/bmj.38937.646400.55>>.
- MERCURY Study Group 2007. Extramural depth of tumor invasion at thin-section MR in patients with rectal cancer: results of the MERCURY study. *Radiology*, 243(1), p. 132–139. <<http://doi.org/10.1148/radiol.2431051825>>.
- Miles, E. W. 1908. A method of performing abdomino-perineal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon. *The Lancet*, 172(4451), p. 1812–1813. <[http://doi.org/10.1016/S0140-6736\(00\)99076-7](http://doi.org/10.1016/S0140-6736(00)99076-7)>.
- Mirnezami, A., Mirnezami, R., Chandrakumaran, K., Sasapu, K., Sagar, P. & Finan, P. 2011. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. *Annals of Surgery*, 253(5), p. 890–899. <<http://doi.org/10.1097/SLA.0b013e3182128929>>.
- Mitry, E., Rollot, F., Jooste, V., Guiu, B., Lepage, C., Ghiringhelli, F., Faivre, J. & Bouvier, A. M. 2013. Improvement in survival of metastatic colorectal cancer: are the benefits of clinical trials reproduced in population-based studies? *European Journal of Cancer*, 49(13), p. 2919–2925. <<http://doi.org/10.1016/j.ejca.2013.04.001>>.
- Moberger, P., Skoldberg, F. & Birgisson, H. 2018. Evaluation of the Swedish Colorectal Cancer Registry: an overview of completeness, timeliness, comparability and validity. *Acta Oncologica*, 57(12), p. 1611–1621. <<http://doi.org/10.1080/0284186x.2018.1529425>>.
- Mols, F., Lemmens, V., Bosscha, K., van den Broek, W. & Thong, M. S. Y. 2014. Living with the physical and mental consequences of an ostomy: a study among 1–10-year rectal cancer survivors from the population-based PROFILES registry. *Psycho-Oncology*, 23(9), p. 998–1004. <<http://doi.org/10.1002/pon.3517>>.
- Montedori, A., Cirocchi, R., Farinella, E., Sciannameo, F. & Abraha, I. 2010. Covering ileo- or colostomy in anterior resection for rectal carcinoma. *The Cochrane Database of Systematic Reviews*, (5), p. Cd006878. <<http://doi.org/10.1002/14651858.CD006878.pub2>>.
- Moore, H. G., Shoup, M., Riedel, E., Minsky, B. D., Alektiar, K. M., Ercolani, M., Paty, P. B., Wong, W. D. & Guillem, J. G. 2004. Colorectal cancer pelvic recurrences: determinants of resectability. *Diseases of the Colon and Rectum*, 47(10), p. 1599–1606. <<http://doi.org/10.1007/s10350-004-0677-x>>.
- Morino, M., Risio, M., Bach, S., Beets-Tan, R., Bujko, K., Panis, Y., Quirke, P., Rembacken, B., Rullier, E., Saito, Y., Young-Fadok, T. & Allaix, M. E. 2015. Early rectal cancer: the European Association for Endoscopic Surgery (EAES) clinical consensus conference. *Surgical Endoscopy*, 29(4), p. 755–773. <<http://doi.org/10.1007/s00464-015-4067-3>>.
- Mulder, S. A., Kranse, R., Damhuis, R. A., de Wilt, J. H. W., Ouwendijk, R. J. T., Kuipers, E. J. & van Leerdam, M. E. 2011. Prevalence and prognosis of synchronous colorectal cancer: A Dutch population-based study. *Cancer epidemiology*, 35(5), p. 442–447. <<http://doi.org/https://doi.org/10.1016/j.canep.2010.12.007>>.
- Munro, A., Brown, M., Niblock, P., Steele, R. & Carey, F. 2015. Do Multidisciplinary Team (MDT) processes influence survival in patients with colorectal cancer? A population-based experience. *BMC Cancer*, 15(1), p. 686. <<http://doi.org/10.1186/s12885-015-1683-1>>.
- Musters, G. D., Buskens, C. J., Bemelman, W. A. & Tanis, P. J. 2014. Perineal wound healing after abdominoperineal resection for rectal cancer: a systematic review and meta-analysis. *Diseases of the Colon and Rectum*, 57(9), p. 1129–1139. <<http://doi.org/10.1097/dcr.000000000000182>>.

- Musters, G. D., Klaver, C. E. L., Bosker, R. J. I., Burger, J. W. A., van Duijvendijk, P., van Etten, B., van Geloven, A. A. W., de Graaf, E. J. R., Hoff, C., Leijtens, J. W. A., Rutten, H. J. T., Singh, B., Vuylsteke, R. J. C. L. M., de Wilt, J. H. W., Dijkgraaf, M. G. W., Bemelman, W. A. & Tanis, P. J. 2017. Biological mesh closure of the pelvic floor after extralevator abdominoperineal resection for rectal cancer: a multicenter randomized controlled trial (the BIOPEX-study). *Annals of Surgery*, 265(6), p. 1074–1081. <<http://doi.org/10.1097/sla.0000000000002020>>.
- Muzny, D. M., Bainbridge, M. N., Chang, K., Dinh, H. H., Drummond, J. A., Fowler, G., Kovar, C. L., Lewis, L. R., Morgan, M. B., Newsham, I. F., Reid, J. G., Santibanez, J., Shinbrot, E., Trevino, L. R., Wu, Y.-Q., Wang, M., Gunaratne, P., Donehower, L. A., Creighton, C. J., Wheeler, D. A., et al. 2012. Comprehensive molecular characterization of human colon and rectal cancer. *Nature*, 487(7407), p. 330–337. <<http://doi.org/10.1038/nature11252>>.
- Mäkinen, M. J., George, S. M., Jernvall, P., Mäkelä, J., Vihko, P. & Karttunen, T. J. 2001. Colorectal carcinoma associated with serrated adenoma--prevalence, histological features, and prognosis. *The Journal of pathology*, 193(3), p. 286–294. <[http://doi.org/10.1002/1096-9896\(2000\)9999:9999::Aid-path800>3.0.Co;2-2](http://doi.org/10.1002/1096-9896(2000)9999:9999::Aid-path800>3.0.Co;2-2)>.
- Mäkäräinen-Uhlbäck, E. J., Klintrop, K. H. B., Vierimaa, M. T., Carpelan-Holmström, M. A., Kössi, J. A. O., Kairaluoma, M. V., Ohtonen, P. P., Tahvonen, P. R. & Rautio, T. T. 2020. Prospective, randomized study on the use of prosthetic mesh to prevent a parastomal hernia in a permanent colostomy: results of a long-term follow-up. *Diseases of the Colon and Rectum*, 63(5), p. 678–684. <<http://doi.org/10.1097/dcr.0000000000001599>>.
- Nagtegaal, I. D. & Quirke, P. 2008. What is the role for the circumferential margin in the modern treatment of rectal cancer? *Journal of Clinical Oncology*, 26(2), p. 303–312. <<http://doi.org/10.1200/jco.2007.12.7027>>.
- Nagtegaal, I. D., van de Velde, C. J., Marijnen, C. A., van Krieken, J. H. & Quirke, P. 2005. Low rectal cancer: a call for a change of approach in abdominoperineal resection. *Journal of Clinical Oncology*, 23(36), p. 9257–9264. <<http://doi.org/10.1200/JCO.2005.02.9231>>.
- Nanji, S., Karim, S., Tang, E., Brennan, K., McGuire, A., Pramesh, C. S. & Booth, C. M. 2018. Pulmonary metastasectomy for colorectal cancer: predictors of survival in routine surgical practice. *The Annals of Thoracic Surgery*, 105(6), p. 1605–1612. <<http://doi.org/https://doi.org/10.1016/j.athoracsur.2018.02.007>>.
- National Institute for Health and Welfare 2019. Specialised somatic health care. Care periods in 2018. Finnish official statistics. Available in Finnish and Swedish at <https://sampon.thl.fi/pivot/prod/fi/thil/perus01/fact_thil_perus01?&row=operation_type-187706&column=time-6656> Accessed 26th of October 2020.
- Nielsen, M. B., Laurberg, S. & Holm, T. 2011. Current management of locally recurrent rectal cancer. *Colorectal Disease*, 13(7), p. 732–742. <<http://doi.org/10.1111/j.1463-1318.2009.02167.x>>.
- Niemeläinen, S., Huhtala, H., Ehrlich, A., Kössi, J., Jämsen, E. & Hyöty, M. 2020. Long-term survival following elective colon cancer surgery in the aged. A population-based cohort study. *Colorectal Disease*. <<http://doi.org/10.1111/codi.15242>>.
- Nikoloudis, N., Saliangas, K., Economou, A., Andreadis, E., Siminou, S., Manna, I., Georgakis, K. & Chrissidis, T. 2004. Synchronous colorectal cancer. *Techniques in Coloproctology*, 8(1), p. s177–s179. <<http://doi.org/10.1007/s10151-004-0149-2>>.
- Nuytens, F., Develtere, D., Sergeant, G., Parmentier, I., D'Hoore, A. & D'Hondt, M. 2018. Perioperative radiotherapy is an independent risk factor for major LARS: a cross-sectional observational study. *International Journal of Colorectal Disease*, 33(8), p. 1063–1069. <<http://doi.org/10.1007/s00384-018-3043-5>>.
- Näsvall, P., Dahlstrand, U., Lowenmark, T., Rutegard, J., Gunnarsson, U. & Strigard, K. 2017. Quality of life in patients with a permanent stoma after rectal cancer surgery. *Quality of Life Research*, 26(1), p. 55–64. <<http://doi.org/10.1007/s11136-016-1367-6>>.
- Ogura, A., Konishi, T., Cunningham, C., Garcia-Aguilar, J., Iversen, H., Toda, S., Lee, I. K., Lee, H. X., Uehara, K., Lee, P., Putter, H., van de Velde, C. J. H., Beets, G. L., Rutten, H. J. T. & Kusters,

- M. 2019a. Neoadjuvant (chemo)radiotherapy with total mesorectal excision only is not sufficient to prevent lateral local recurrence in enlarged nodes: results of the multicenter lateral node study of patients with low cT3/4 rectal cancer. *Journal of Clinical Oncology*, 37(1), p. 33–43. <<http://doi.org/10.1200/jco.18.00032>>.
- Ogura, A., Konishi, T., Beets, G. L., Cunningham, C., Garcia-Aguilar, J., Iversen, H., Toda, S., Lee, I. K., Lee, H. X., Uehara, K., Lee, P., Putter, H., van de Velde, C. J. H., Rutten, H. J. T., Tuynman, J. B. & Kusters M. for the Lateral Node Study Consortium 2019b. Lateral nodal features on restaging magnetic resonance imaging associated with lateral local recurrence in low rectal cancer after neoadjuvant chemoradiotherapy or radiotherapy. *JAMA Surgery*, 154(9), p. e192172–e192172. <<http://doi.org/10.1001/jamasurg.2019.2172>>.
- Ortiz, H. & Armendariz, P. 1996. Anterior resection: do the patients perceive any clinical benefit? *International Journal of Colorectal Disease*, 11(4), p. 191–195. <<http://doi.org/10.1007/s003840050042>>.
- Ortiz, H., Ciga, M. A., Armendariz, P., Kreisler, E., Codina-Cazador, A., Gomez-Barbadillo, J., Garcia-Granero, E., Roig, J. V. & Biondo S. on behalf of the Spanish Rectal Cancer Project 2014. Multicentre propensity score-matched analysis of conventional versus extended abdominoperineal excision for low rectal cancer. *British Journal of Surgery*, 101(7), p. 874–882. <<http://doi.org/10.1002/bjs.9522>>.
- Pachler, J. & Wille-Jørgensen, P. 2012. Quality of life after rectal resection for cancer, with or without permanent colostomy. *Cochrane Database Systemic Reviews*, 12, p. Cd004323. <<http://doi.org/10.1002/14651858.CD004323.pub4>>.
- Pahlman, L., Bujko, K., Rutkowski, A. & Michalski, W. 2013. Altering the therapeutic paradigm towards a distal bowel margin of < 1 cm in patients with low-lying rectal cancer: a systematic review and commentary. *Colorectal Disease*, 15(4), p. e166–e174. <<http://doi.org/10.1111/codi.12120>>.
- Palmer, G., Anderin, C., Martling, A. & Holm, T. 2014. Local control and survival after extralevator abdominoperineal excision for locally advanced or low rectal cancer. *Colorectal Disease*, 16(7), p. 527–532. <<http://doi.org/10.1111/codi.12610>>.
- Papamichael, D., Audisio, R. A., Glimelius, B., de Gramont, A., Glynne-Jones, R., Haller, D., Köhne, C. H., Rostoft, S., Lemmens, V., Mitry, E., Rutten, H., Sargent, D., Sastre, J., Seymour, M., Starling, N., Van Cutsem, E. & Aapro, M. 2015. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. *Annals of Oncology*, 26(3), p. 463–476. <<http://doi.org/https://doi.org/10.1093/annonc/mdu253>>.
- Parc, Y., Ruppert, R., Fuerst, A., Golcher, H., Zutshi, M., Hull, T., Tiret, E., Hemminger, F., Galandiuk, S., Fender, S., Weber, K., Zimmerman, A., Aiello, A. & Fazio, V. 2019. Better function with a colonic j-pouch or a side-to-end anastomosis?: a randomized controlled trial to compare the complications, functional outcome, and quality of life in patients with low rectal cancer after a j-pouch or a side-to-end anastomosis. *Annals of Surgery*, 269(5), p. 815–826. <<http://doi.org/10.1097/sla.0000000000003249>>.
- Park, H. J., Jang, J. K., Park, S. H., Park, I. J., Kim, J. H., Baek, S. & Hong, Y. S. 2018. Restaging abdominopelvic computed tomography before surgery after preoperative chemoradiotherapy in patients with locally advanced rectal cancer. *JAMA oncology*, 4(2), p. 259–262. <<http://doi.org/10.1001/jamaoncol.2017.4596>>.
- Park, J. S., Jang, Y. J., Choi, G. S., Park, S. Y., Kim, H. J., Kang, H. & Cho, S. H. 2014. Accuracy of preoperative MRI in predicting pathology stage in rectal cancers: Nodefor- Node matched histopathology validation of MRI features. *Diseases of the Colon and Rectum*, 57(1), p. 32–38. <<http://doi.org/10.1097/DCR.0000000000000004>>.
- Parnaby, C. N., Bailey, W., Balasingam, A., Beckert, L., Eglinton, T., Fife, J., Frizelle, F. A., Jeffery, M. & Watson, A. J. M. 2012. Pulmonary staging in colorectal cancer: a review. *Colorectal Disease*, 14(6), p. 660–670. <<http://doi.org/10.1111/j.1463-1318.2011.02601.x>>.

- Pastorino, U., Buyse, M., Friedel, G., Ginsberg, R. J., Girard, P., Goldstraw, P., Johnston, M., McCormack, P., Pass, H. & Putnam, J. B. 1997. Long-term results of lung metastasectomy: Prognostic analyses based on 5206 cases. *The Journal of Thoracic and Cardiovascular Surgery*, 113(1), p. 37–49. <[http://doi.org/https://doi.org/10.1016/S0022-5223\(97\)70397-0](http://doi.org/https://doi.org/10.1016/S0022-5223(97)70397-0)>.
- Patel, U. B., Blomqvist, L. K., Taylor, F., George, C., Guthrie, A., Bees, N. & Brown, G. 2012. MRI after treatment of locally advanced rectal cancer: how to report tumor response—The MERCURY experience. *American Journal of Roentgenology*, 199(4), p. W486-W495. <<http://doi.org/10.2214/AJR.11.8210>>.
- Peacock, O., Waters, P. S., Bressel, M., Lynch, A. C., Wakeman, C., Eglinton, T., Koh, C. E., Lee, P. J., Austin, K. K., Warriar, S. K., Solomon, M. J., Frizelle, F. A. & Heriot, A. G. 2019. Prognostic factors and patterns of failure after surgery for T4 rectal cancer in the beyond total mesorectal excision era. *The British Journal of Surgery*, 106(12), p. 1685–1696. <<http://doi.org/10.1002/bjs.11242>>.
- Peeters, K. C., Marijnen, C. A., Nagtegaal, I. D., Kranenbarg, E. K., Putter, H., Wiggers, T., Rutten, H., Pahlman, L., Glimelius, B., Leer, J. W. & van de Velde C. J. for the Dutch Colorectal Cancer Group 2007. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Annals of Surgery*, 246(5), p. 693–701. <<http://doi.org/10.1097/01.sla.0000257358.56863.ce>>.
- Perdawood, S. K. & Lund, T. 2015. Extralevator versus standard abdominoperineal excision for rectal cancer. *Techniques in Coloproctology*, 19(3), p. 145–152. <<http://doi.org/10.1007/s10151-014-1243-8>>.
- Pettersson, J., Koedam, T. W., Bonjer, H. J., Andersson, J., Angenete, E., Bock, D., Cuesta, M. A., Deijen, C. L., Furst, A., Lacy, A. M., Rosenberg, J. & Haglund, E. 2019. Bowel obstruction and ventral hernia after laparoscopic versus open surgery for rectal cancer in a randomized trial (COLOR II). *Annals of Surgery*, 269(1), p. 53-57. <<http://doi.org/10.1097/sla.0000000000002790>>.
- Petrelli, F., Sgroi, G., Sarti, E. & Barni, S. 2016. Increasing the interval between neoadjuvant chemoradiotherapy and surgery in rectal cancer: a meta-analysis of published studies. *Annals of Surgery*, 263(3), p. 458–464. <<http://doi.org/10.1097/sla.0000000000000368>>.
- Pieniowski, E. H. A., Palmer, G. J., Juul, T., Lagergren, P., Johar, A., Emmertsen, K. J., Nordenvall, C. & Abraham-Nordling, M. 2019. Low anterior resection syndrome and quality of life after sphincter-sparing rectal cancer surgery: a long-term longitudinal follow-up. *Diseases of the Colon and Rectum*, 62(1), p. 14-20. <<http://doi.org/10.1097/dcr.0000000000001228>>.
- Piñol, V., Andreu, M., Castells, A., Payá, A., Bessa, X. & Jover, R. 2004. Synchronous colorectal neoplasms in patients with colorectal cancer: Predisposing individual and familial factors. *Diseases of the Colon and Rectum*, 47(7), p. 1192–1200. <<http://doi.org/10.1007/s10350-004-0562-7>>.
- Pitkaniemi, J., Seppä, K., Hakama, M., Malminiemi, O., Palva, T., Vuoristo, M. S., Järvinen, H., Paimela, H., Pikkarainen, P., Anttila, A., Elovainio, L., Hakulinen, T., Karjalainen, S., Pylkkänen, L., Rautalahti, M., Sarkeala, T., Vertio, H. & Malila, N. 2015. Effectiveness of screening for colorectal cancer with a faecal occult-blood test, in Finland. *BMJ Open Gastroenterol*, 2(1), p. e000034. <<http://doi.org/10.1136/bmjgast-2015-000034>>.
- Porter, G. A., Soskolne, C. L., Yakimets, W. W. & Newman, S. C. 1998. Surgeon-related factors and outcome in rectal cancer. *Annals of Surgery*, 227(2), p. 157–167. <<http://doi.org/10.1097/0000658-199802000-00001>>.
- Poulsen, L. O., Yilmaz, M. K., Ljungmann, K., Jespersen, N., Wille-Jørgensen, P., Petersen, L. N. & Falkmer, U. G. 2018. Local recurrence rate in a national Danish patient cohort after curative treatment for rectal cancer. *Acta Oncologica*, 57(12), p. 1639–1645. <<http://doi.org/10.1080/0284186x.2018.1497299>>.
- Prall, F. 2007. Tumour budding in colorectal carcinoma. *Histopathology*, 50(1), p. 151–162. <<http://doi.org/10.1111/j.1365-2559.2006.02551.x>>.

- Prytz, M., Angenete, E., Ekelund, J. & Haglind, E. 2014. Extralevator abdominoperineal excision (ELAPE) for rectal cancer--short-term results from the Swedish Colorectal Cancer Registry. Selective use of ELAPE warranted. *International Journal of Colorectal Disease*, 29(8), p. 981–987. <<http://doi.org/10.1007/s00384-014-1932-9>>.
- Prytz, M., Angenete, E., Bock, D. & Haglind, E. 2016. Extralevator abdominoperineal excision for low rectal cancer--extensive surgery to be used with discretion based on 3-year local recurrence results: a registry-based, observational national cohort study. *Annals of Surgery*, 263(3), p. 516–521. <<http://doi.org/10.1097/SLA.0000000000001237>>.
- Pucciarelli, S., Del Bianco, P., Pace, U., Bianco, F., Restivo, A., Maretto, I., Selvaggi, F., Zorcolo, L., De Franciscis, S., Asteria, C., Urso, E. D. L., Cuicchi, D., Pellino, G., Morpurgo, E., La Torre, G., Jovine, E., Belluco, C., La Torre, F., Amato, A., Chiappa, A., et al. 2019. Multicentre randomized clinical trial of colonic J pouch or straight stapled colorectal reconstruction after low anterior resection for rectal cancer. *British Journal of Surgery*, 106(9), p. 1147–1155. <<http://doi.org/10.1002/bjs.11222>>.
- Påhlman, L. & Glimelius, B. 1990. Pre- or postoperative radiotherapy in rectal and rectosigmoid carcinoma. Report from a randomized multicenter trial. *Annals of Surgery*, 211(2), p. 187–195. <<http://doi.org/10.1097/0000658-199002000-00011>>.
- Qiu, Y., Liu, Q., Chen, G., Wang, W., Peng, K., Xiao, W. & Yang, H. 2016. Outcome of rectal cancer surgery in obese and nonobese patients: a meta-analysis. *World Journal of Surgical Oncology*, 14(1), p. 23–23. <<http://doi.org/10.1186/s12957-016-0775-y>>.
- Quirke, P., Durdey, P., Dixon, M. F. & Williams, N. S. 1986. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet*, 2(8514), p. 996–999. <[http://doi.org/10.1016/s0140-6736\(86\)92612-7](http://doi.org/10.1016/s0140-6736(86)92612-7)>.
- Quirke, P., Steele, R., Monson, J., Grieve, R., Khanna, S., Couture, J., O'Callaghan, C., Myint, A. S., Bessell, E., Thompson, L. C., Parmar, M., Stephens, R. J., Sebag-Montefiore, D., MRC CR07/NCIC-CTG CO16 Trial Investigators & NCRI Colorectal Cancer Study Group 2009. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet*, 373(9666), p. 821–828. <[http://doi.org/10.1016/S0140-6736\(09\)60485-2](http://doi.org/10.1016/S0140-6736(09)60485-2)>.
- Rahbari, N. N., Elbers, H., Askoxylakis, V., Motschall, E., Bork, U., Büchler, M. W., Weitz, J. & Koch, M. 2013. Neoadjuvant Radiotherapy for Rectal Cancer: Meta-analysis of Randomized Controlled Trials. *Annals of Surgical Oncology*, 20(13), p. 4169–4182. <<http://doi.org/10.1245/s10434-013-3198-9>>.
- Reggiani Bonetti, L., Lioni, S., Domati, F. & Barresi, V. 2017. Do pathological variables have prognostic significance in rectal adenocarcinoma treated with neoadjuvant chemoradiotherapy and surgery? *World Journal of Gastroenterology*, 23(8), p. 1412–1423. <<http://doi.org/10.3748/wjg.v23.i8.1412>>.
- Riihimäki, M., Hemminki, A., Sundquist, J. & Hemminki, K. 2016. Patterns of metastasis in colon and rectal cancer. *Scientific Reports*, 6, p. 29765–29765. <<http://doi.org/10.1038/srep29765>>.
- Ruers, T., Punt, C., Van Coevorden, F., Pierie, J. P. E. N., Borel-Rinkes, I., Ledermann, J. A., Poston, G., Bechstein, W., Lentz, M. A., Mauer, M., Van Cutsem, E., Lutz, M. P. & Nordlinger, B. 2012. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). *Annals of Oncology*, 23(10), p. 2619–2626. <<http://doi.org/https://doi.org/10.1093/annonc/mds053>>.
- Rullier, E., Denost, Q., Vendrely, V., Rullier, A. & Laurent, C. 2013. Low rectal cancer: classification and standardization of surgery. *Diseases of the Colon and Rectum*, 56(5), p. 560–567. <<http://doi.org/10.1097/DCR.0b013e31827c4a8c>>.
- Räsänen, M., Carpelan-Holmström, M., Mustonen, H., Renkonen-Sinisalo, L. & Lepistö, A. 2015. Pattern of rectal cancer recurrence after curative surgery. *International Journal of Colorectal Disease*, 30(6), p. 775–785. <<http://doi.org/10.1007/s00384-015-2182-1>>.

- Rödel, C., Martus, P., Papadopoulos, T., Füzesi, L., Klimpfinger, M., Fietkau, R., Liersch, T., Hohenberger, W., Raab, R., Sauer, R. & Wittekind, C. 2005. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *Journal of Clinical Oncology*, 23(34), p. 8688–8696. <<http://doi.org/10.1200/jco.2005.02.1329>>.
- Samalavicius, N. E., Dulskas, A., Lasinskas, M. & Smailyte, G. 2016. Validity and reliability of a Lithuanian version of low anterior resection syndrome score. *Techniques in Coloproctology*, 20(4), p. 215–220. <<http://doi.org/10.1007/s10151-015-1424-0>>.
- Sanderson, E. R. 1980. Henri Hartmann and the Hartmann Operation. *Archives of Surgery*, 115(6), p. 792–793. <<http://doi.org/10.1001/archsurg.1980.01380060088026>>.
- Schaap, D. P., Ogura, A., Nederend, J., Maas, M., Cnossen, J. S., Creemers, G. J., van Lijnschoten, I., Nieuwenhuijzen, G. A. P., Rutten, H. J. T. & Kusters, M. 2018. Prognostic implications of MRI-detected lateral nodal disease and extramural vascular invasion in rectal cancer. *British Journal of Surgery*, 105(13), p. 1844–1852. <<http://doi.org/10.1002/bjs.10949>>.
- Schiffmann, L., Kostev, K. & Kalder, M. 2020. Fecal and urinary incontinence are major problems associated with rectal cancer. *International Journal of Colorectal Disease*, 35(1), p. 35–40. <<http://doi.org/10.1007/s00384-019-03450-8>>.
- Sclafani, F., Brown, G., Cunningham, D., Wotherspoon, A., Mendes, L. S. T., Balyasnikova, S., Evans, J., Peckitt, C., Begum, R., Tait, D., Taberner, J., Glimelius, B., Roselló, S., Thomas, J., Oates, J. & Chau, I. 2017. Comparison between MRI and pathology in the assessment of tumour regression grade in rectal cancer. *British Journal of Cancer*, 117(10), p. 1478–1485. <<http://doi.org/10.1038/bjc.2017.320>>.
- Sharp, S. P., Malizia, R., Skancke, M., Arsoniadis, E. G., Ata, A., Stain, S. C., Valerian, B. T., Lee, E. C. & Wexner, S. D. 2020. A NSQIP analysis of trends in surgical outcomes for rectal cancer: What can we improve upon? *American Journal of Surgery*. <<http://doi.org/10.1016/j.amjsurg.2020.01.004>>.
- Shen, F. & Hong, X. 2019. Prognostic value of N1c in colorectal cancer: a large population-based study using propensity score matching. *International Journal of Colorectal Disease*, 34(8), p. 1375–1383. <<http://doi.org/10.1007/s00384-019-03328-9>>.
- Shen, Z., Ye, Y., Zhang, X., Xie, Q., Yin, M., Yang, X., Jiang, K., Liang, B. & Wang, S. 2015. Prospective controlled study of the safety and oncological outcomes of ELAPE procure with definitive anatomic landmarks versus conventional APE for lower rectal cancer. *European Journal of Surgical Oncology*, 41(4), p. 472–477. <<http://doi.org/10.1016/j.ejso.2015.01.017>>.
- Shihab, O. C., Heald, R. J., Holm, T., How, P. D., Brown, G., Quirke, P. & Moran, B. J. 2012. A pictorial description of extralevator abdominoperineal excision for low rectal cancer. *Colorectal Disease*, 14(10), p. e655–660. <<http://doi.org/10.1111/j.1463-1318.2012.03181.x>>.
- Siddiqui, M. R. S., Simillis, C., Hunter, C., Chand, M., Bhoday, J., Garant, A., Vuong, T., Artho, G., Rasheed, S., Tekkis, P., Abulafi, A. M. & Brown, G. 2017. A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. *British Journal of Cancer*, 116(12), p. 1513–1519. <<http://doi.org/10.1038/bjc.2017.99>>.
- Siegel, R. L., Miller, K. D., Fedewa, S. A., Ahnen, D. J., Meester, R. G. S., Barzi, A. & Jemal, A. 2017. Colorectal cancer statistics, 2017. *CA: A Cancer Journal for Clinicians*, 67(3), p. 177–193. <<http://doi.org/10.3322/caac.21395>>.
- Smedh, K., Sverrisson, I., Chabok, A., Nikberg, M. & HAPIrect Collaborative Study Group 2016. Hartmann's procedure vs abdominoperineal resection with intersphincteric dissection in patients with rectal cancer: a randomized multicentre trial (HAPIrect). *BMC Surgery*, 16(1), p. 43. <<http://doi.org/10.1186/s12893-016-0161-2>>.
- Smith, F. M., Cresswell, K., Myint, A. S. & Renehan, A. G. 2018. Is “watch-and-wait” after chemoradiotherapy safe in patients with rectal cancer? *British Medical Journal*, 363, p. k4472. <<http://doi.org/10.1136/bmj.k4472>>.

- Song, J. H., Yu, M., Kang, K. M., Lee, J. H., Kim, S. H., Nam, T. K., Jeong, J. U., Jang, H. S., Lee, J. W. & Jung, J. H. 2019. Significance of perineural and lymphovascular invasion in locally advanced rectal cancer treated by preoperative chemoradiotherapy and radical surgery: Can perineural invasion be an indication of adjuvant chemotherapy? *Radiotherapy and Oncology*, 133, p. 125–131. <<http://doi.org/10.1016/j.radonc.2019.01.002>>.
- Sorbye, H., Cvancarova, M., Qvortrup, C., Pfeiffer, P. & Glimelius, B. 2013. Age-dependent improvement in median and long-term survival in unselected population-based Nordic registries of patients with synchronous metastatic colorectal cancer. *Annals of Oncology*, 24(9), p. 2354–2360. <<http://doi.org/10.1093/annonc/mdt197>>.
- Soyer, P., Pocard, M., Boudiaf, M., Abitbol, M., Hamzi, L., Panis, Y., Valleur, P. & Rymer, R. 2004. Detection of hypovascular hepatic metastases at triple-phase helical CT: sensitivity of phases and comparison with surgical and histopathologic findings. *Radiology*, 231(2), p. 413–420. <<http://doi.org/10.1148/radiol.2312021639>>.
- Stapley, S., Peters, T. J., Sharp, D. & Hamilton, W. 2006. The mortality of colorectal cancer in relation to the initial symptom at presentation to primary care and to the duration of symptoms: a cohort study using medical records. *British Journal of Cancer*, 95(10), p. 1321–1325. <<http://doi.org/10.1038/sj.bjc.6603439>>.
- Steichen, F. M. & Ravitch, M. M. 1982. History of mechanical devices and instruments for suturing. *Current problems in surgery*, 19(1), p. 1–52. <[http://doi.org/10.1016/0011-3840\(82\)90004-1](http://doi.org/10.1016/0011-3840(82)90004-1)>.
- Stein, A., Petersen, V., Schulze, M., Seraphin, J., Hoeffkes, H. G., Valdix, A. R., Schroeder, J., Herrenberger, J., Boxberger, F., Leutgeb, B., Hinke, A., Kutscheidt, A. & Arnold, D. 2015. Bevacizumab plus chemotherapy as first-line treatment for patients with metastatic colorectal cancer: results from a large German community-based observational cohort study. *Acta Oncologica*, 54(2), p. 171–178. <<http://doi.org/10.3109/0284186x.2014.961649>>.
- Stelzner, S., Hellmich, G., Schubert, C., Puffer, E., Haroske, G. & Witzigmann, H. 2011. Short-term outcome of extra-levator abdominoperineal excision for rectal cancer. *International Journal of Colorectal Disease*, 26(7), p. 919–925. <<http://doi.org/10.1007/s00384-011-1157-0>>.
- Stelzner, S., Hellmich, G., Sims, A., Kittner, T., Puffer, E., Zimmer, J., Bleyl, D. & Witzigmann, H. 2016. Long-term outcome of extralevator abdominoperineal excision (ELAPE) for low rectal cancer. *International Journal of Colorectal Disease*, 31(10), p. 1729–1737. <<http://doi.org/10.1007/s00384-016-2637-z>>.
- Stryker, S. J., Wolff, B. G., Culp, C. E., Libbe, S. D., Ilstrup, D. M. & MacCarty, R. L. 1987. Natural history of untreated colonic polyps. *Gastroenterology*, 93(5), p. 1009–1013. <[http://doi.org/https://doi.org/10.1016/0016-5085\(87\)90563-4](http://doi.org/https://doi.org/10.1016/0016-5085(87)90563-4)>.
- Suga, T., Nakamoto, Y., Saga, T., Higashi, T., Hara, T., Ishizu, K., Nishizawa, H. & Togashi, K. 2010. Prevalence of positive FDG-PET findings in patients with high CEA levels. *Annals of Nuclear Medicine*, 24(6), p. 433–439. <<http://doi.org/10.1007/s12149-010-0387-5>>.
- Sverrisson, I., Nikberg, M., Chabok, A. & Smedh, K. 2015. Hartmann's procedure in rectal cancer: a population-based study of postoperative complications. *International Journal of Colorectal Disease*, 30(2), p. 181–186. <<http://doi.org/10.1007/s00384-014-2069-6>>.
- Syngal, S., Brand, R. E., Church, J. M., Giardiello, F. M., Hampel, H. L. & Burt, R. W. 2015. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. *American Journal of Gastroenterology*, 110(2), p. 223–262. <<http://doi.org/10.1038/ajg.2014.435>>.
- Tan, K. K., Lopes Jr., G. d. L. & Sim, R. 2009. How uncommon are isolated lung metastases in colorectal cancer? A review from database of 754 patients over 4 years. *Journal of Gastrointestinal Surgery*, 13(4), p. 642–648. <<http://doi.org/10.1007/s11605-008-0757-7>>.
- Tan, W. S., Tang, C. L., Shi, L. & Eu, K. W. 2009. Meta-analysis of defunctioning stomas in low anterior resection for rectal cancer. *British Journal of Surgery*, 96(5), p. 462–472. <<http://doi.org/10.1002/bjs.6594>>.

- Taylor, F. G., Quirke, P., Heald, R. J., Moran, B. J., Blomqvist, L., Swift, I. R., Sebag-Montefiore, D., Tekkis, P. & Brown, G. 2014. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. *Journal of Clinical Oncology*, 32(1), p. 34–43. <<http://doi.org/10.1200/jco.2012.45.3258>>.
- The Beyond TME Collaborative 2013. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. *British Journal of Surgery*, 100(8), p. 1009–1014. <<http://doi.org/10.1002/bjs.9192>>.
- The PelvEx Collaborative 2018. Factors affecting outcomes following pelvic exenteration for locally recurrent rectal cancer. *British Journal of Surgery*, 105(6), p. 650–657. <<http://doi.org/10.1002/bjs.10734>>.
- Thomas, G., van Heinsbergen, M., van der Heijden, J., Slooter, G., Konsten, J. & Maaskant, S. 2019. Awareness and management of low anterior resection syndrome: A Dutch national survey among colorectal surgeons and specialized nurses. *European Journal of Surgical Oncology*, 45(2), p. 174–179. <<http://doi.org/10.1016/j.ejso.2018.11.001>>.
- Tirumani, S. H., Kim, K. W., Nishino, M., Howard, S. A., Krajewski, K. M., Jagannathan, J. P., Cleary, J. M., Ramaiya, N. H. & Shinagare, A. B. 2014. Update on the role of imaging in management of metastatic colorectal cancer. *Radiographics*, 34(7), p. 1908–1928. <<http://doi.org/10.1148/rg.347130090>>.
- Tronstad, P. K., Simpson, L. V. H., Olsen, B., Pfeffer, F. & Karliczek, A. 2019. Low rate of local recurrence detection by rectoscopy in follow-up of rectal cancer. *Colorectal Disease*. <<http://doi.org/10.1111/codi.14858>>.
- UICC 2017. TNM Classification of malignant tumours, 8th edition. John Wiley & Sons Ltd, UK.
- Van Cutsem, E., Cervantes, A., Adam, R., Sobrero, A., Van Krieken, J. H., Aderka, D., Aranda Aguilar, E., Bardelli, A., Benson, A., Bodoky, G., Ciardiello, F., D'Hoore, A., Diaz-Rubio, E., Douillard, J. Y., Ducreux, M., Falcone, A., Grothey, A., Gruenberger, T., Haustermans, K., Heinemann, V., et al. 2016. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Annals of Oncology*, 27(8), p. 1386–1422. <<http://doi.org/https://doi.org/10.1093/annonc/mdw235>>.
- Van de Putte, D., Van Daele, E., Willaert, W., Pattyn, P., Ceelen, W. & Van Nieuwenhove, Y. 2017. Effect of abdominopelvic sepsis on cancer outcome in patients undergoing sphincter saving surgery for rectal cancer. *Journal of Surgical Oncology*, 116(6), p. 722–729. <<http://doi.org/10.1002/jso.24706>>.
- Van der Geest, L. G. M., Lam-Boer, J. t., Koopman, M., Verhoef, C., Elferink, M. A. G. & de Wilt, J. H. W. 2015. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. *Clinical & Experimental Metastasis*, 32(5), p. 457–465. <<http://doi.org/10.1007/s10585-015-9719-0>>.
- Van der Pas, M. H., Haglind, E., Cuesta, M. A., Furst, A., Lacy, A. M., Hop, W. C. & Bonjer, H. J. 2013. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. *Lancet Oncol*, 14(3), p. 210–218. <[http://doi.org/10.1016/s1470-2045\(13\)70016-0](http://doi.org/10.1016/s1470-2045(13)70016-0)>.
- Van der Valk, M. J. M., Hilling, D. E., Bastiaannet, E., Meershoek-Klein Kranenbarg, E., Beets, G. L., Figueiredo, N. L., Habr-Gama, A., Perez, R. O., Renchan, A. G., van de Velde, C. J. H., Ahlberg, M., Appelt, A., Asoglu, O., Bär, M.-T., Barroca, R., Beets-Tan, R. G. H., Belgers, E. H. J., Bosker, R. J. I., Breukink, S. O., Bujko, K., et al. 2018. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *The Lancet*, 391(10139), p. 2537–2545. <[http://doi.org/https://doi.org/10.1016/S0140-6736\(18\)31078-X](http://doi.org/https://doi.org/10.1016/S0140-6736(18)31078-X)>.
- van Gijn, W., Marijnen, C. A. M., Nagtegaal, I. D., Kranenbarg, E. M.-K., Putter, H., Wiggers, T., Rutten, H. J. T., Pählman, L., Glimelius, B., van de Velde, C. J. H. & Dutch Colorectal Cancer Group 2011. Preoperative radiotherapy combined with total mesorectal excision for resectable

- rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncology*, 12(6), p. 575–582. <[http://doi.org/10.1016/S1470-2045\(11\)70097-3](http://doi.org/10.1016/S1470-2045(11)70097-3)>.
- Van Steenberghe, L. N., Elferink, M. A. G., Krijnen, P., Lemmens, V., Siesling, S., Rutten, H. J. T., Richel, D. J., Karim-Kos, H. E. & Coebergh, J. W. W. 2010. Improved survival of colon cancer due to improved treatment and detection: a nationwide population-based study in the Netherlands 1989–2006. *Annals of Oncology*, 21(11), p. 2206–2212. <<http://doi.org/10.1093/annonc/mdq227>>.
- Wang, S., Liu, J., Wang, S., Zhao, H., Ge, S. & Wang, W. 2017. Adverse effects of anastomotic leakage on local recurrence and survival after curative anterior resection for rectal cancer: a systematic review and meta-analysis. *World Journal of Surgery*, 41(1), p. 277–284. <<http://doi.org/10.1007/s00268-016-3761-1>>.
- Wells, C. I., Vather, R., Chu, M. J., Robertson, J. P. & Bissett, I. P. 2015. Anterior resection syndrome—a risk factor analysis. *Journal of Gastrointestinal Surgery*, 19(2), p. 350–359. <<http://doi.org/10.1007/s11605-014-2679-x>>.
- Vennix, S., Pelzers, L., Bouvy, N., Beets, G. L., Pierie, J. P., Wiggers, T. & Breukink, S. 2014. Laparoscopic versus open total mesorectal excision for rectal cancer. *Cochrane Database of Systematic Reviews*, (4), p. Cd005200. <<http://doi.org/10.1002/14651858.CD005200.pub3>>.
- West, N. P., Finan, P. J., Anderin, C., Lindholm, J., Holm, T. & Quirke, P. 2008. Evidence of the oncologic superiority of cylindrical abdominoperineal excision for low rectal cancer. *Journal of Clinical Oncology*, 26(21), p. 3517–3522. <<http://doi.org/10.1200/JCO.2007.14.5961>>.
- West, N. P., Anderin, C., Smith, K. J., Holm, T., Quirke, P. & European Extralevator Abdominoperineal Excision Study Group 2010. Multicentre experience with extralevator abdominoperineal excision for low rectal cancer. *British Journal of Surgery*, 97(4), p. 588–599. <<http://doi.org/10.1002/bjs.6916>>.
- Westberg, K., Palmer, G., Hjern, F., Johansson, H., Holm, T. & Martling, A. 2018. Management and prognosis of locally recurrent rectal cancer – A national population-based study. *European Journal of Surgical Oncology*, 44(1), p. 100–107. <<http://doi.org/10.1016/j.ejso.2017.11.013>>.
- Wibe, A., Rendedal, P. R., Svensson, E., Norstein, J., Eide, T. J., Myrvold, H. E. & Søreide, O. 2002. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. *British Journal of Surgery*, 89(3), p. 327–334. <<http://doi.org/10.1046/j.0007-1323.2001.02024.x>>.
- Wibe, A., Syse, A., Andersen, E., Tretli, S., Myrvold, H. E., Søreide, O. & Norwegian Rectal Cancer Group 2004. Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior vs. abdominoperineal resection. *Diseases of the Colon and Rectum*, 47(1), p. 48–58. <<http://doi.org/10.1007/s10350-003-0012-y>>.
- Wiltink, L. M., Chen, T. Y. T., Nout, R. A., Kranenbarg, E. M.-K., Fiocco, M., Laurberg, S., van de Velde, C. J. H. & Marijnen, C. A. M. 2014. Health-related quality of life 14years after preoperative short-term radiotherapy and total mesorectal excision for rectal cancer: Report of a multicenter randomised trial. *European Journal of Cancer*, 50(14), p. 2390–2398. <<http://doi.org/https://doi.org/10.1016/j.ejca.2014.06.020>>.
- Winawer, S. J., Zauber, A. G., Ho, M. N., O'Brien, M. J., Gottlieb, L. S., Sternberg, S. S., Wayne, J. D., Schapiro, M., Bond, J. H., Panish, J. F., Ackroyd, F., Shike, M., Kurtz, R. C., Hornsby-Lewis, L., Gerdes, H. & Stewart, E. T. 1993. Prevention of colorectal cancer by colonoscopic polypectomy. *The New England Journal of Medicine*, 329(27), p. 1977–1981. <<http://doi.org/10.1056/nejm199312303292701>>.
- Xu, Z., Berho, M. E., Becerra, A. Z., Aquina, C. T., Hensley, B. J., Arsalanizadeh, R., Noyes, K., Monson, J. R. T. & Fleming, F. J. 2017. Lymph node yield is an independent predictor of survival in rectal cancer regardless of receipt of neoadjuvant therapy. *Journal of Clinical Pathology*, 70(7), p. 584–592. <<http://doi.org/10.1136/jclinpath-2016-203995>>.
- Yeo, H. L. & Paty, P. B. 2014. Management of recurrent rectal cancer: Practical insights in planning and surgical intervention. *Journal of Surgical Oncology*, 109(1), p. 47–52. <<http://doi.org/10.1002/jso.23457>>.

- Zhang, J., Haines, C., Watson, A. J. M., Hart, A. R., Platt, M. J., Pardoll, D. M., Cosgrove, S. E., Gebo, K. A. & Sears, C. L. 2019. Oral antibiotic use and risk of colorectal cancer in the United Kingdom, 1989–2012: a matched case–control study. *Gut*, 68(11), p. 1971–1978. <<http://doi.org/10.1136/gutjnl-2019-318593>>.
- Zhao, L., Liu, R., Zhang, Z., Li, T., Li, F., Liu, H. & Li, G. 2016. Oxaliplatin/fluorouracil-based adjuvant chemotherapy for locally advanced rectal cancer after neoadjuvant chemoradiotherapy and surgery: a systematic review and meta-analysis of randomized controlled trials. *Colorectal Disease*, 18(8), p. 763–772. <<http://doi.org/10.1111/codi.13381>>.
- Zhou, X., Sun, T., Xie, H., Zhang, Y., Zeng, H. & Fu, W. 2015. Extralevator abdominoperineal excision for low rectal cancer: a systematic review and meta-analysis of the short-term outcome. *Colorectal Disease*, 17(6), p. 474–481. <<http://doi.org/10.1111/codi.12921>>.
- Zinicola, R., Pedrazzi, G., Haboubi, N. & Nicholls, R. J. 2017. The degree of extramural spread of T3 rectal cancer: an appeal to the American Joint Committee on Cancer. *Colorectal Disease*, 19(1), p. 8–15. <<http://doi.org/10.1111/codi.13565>>.



**UNIVERSITY
OF TURKU**

ISBN 978-951-29-8311-7 (PRINT)
ISBN 978-951-29-8312-4 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)