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HEIGO REIMA

Colorectal cancer care and outcomes – evaluation and possibilities for improvement in Estonia

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Haematology and Oncology Clinic, Faculty of Medicine, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia

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“Nad võivad öelda, et arstiteaduslik doktoriväitekiri peab arstiteadust avardama ja üldiseks kasuks olema; eestlaste haigustest kirjutamine ei vääriks aga vaeva ja puudutaks üksnes selle provintsi elanikke.”

Carolus Ernestus Baer. Dissertatio Inauguralis Medica, De Morbis Inter Esthonos Endemicis. 1814.

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1. LIST OF ORIGINAL PUBLICATIONS

I. Innos K, **Reima H**, Baburin A, Paapsi K, Aareleid T, Soplepmann J. Subsite- and stage-specific colorectal cancer trends in Estonia prior to implementation of screening. *Cancer Epidemiol.* 2018;52:112–9.

II. **Reima H**, Soplepmann J, Innos K. Stage-specific survival differences between colon cancer subsites: a population-based study. *Acta Oncol.* 2021;60(12):1702–5.

III. **Reima H**, Soplepmann J, Elme A, Lõhmus M, Tiigi R, Uksov D. Changes in the quality of care of colorectal cancer in Estonia: a population-based high-resolution study. *BMJ Open.* 2020;10(10): e035556.

IV. **Reima H**, Saar H, Soplepmann J. Kolorektaalse kartsinoomi operatsioonipreparaatide ex vivo värvimine metüleensinisega lümfisõlmede tuvastamise parandamiseks. *Eesti Arst. 2011*;10.31.

V. **Reima H**, Saar H, Innos K, Soplepmann J. Methylene blue intra-arterial staining of resected colorectal cancer specimens improves accuracy of nodal staging: A randomized controlled trial. *Eur J Surg Oncol.* 2016;42(11):1642–6.

The author's personal contribution:

Paper I: Contributed to the interpretation of results, critically revised the manuscript and approved the final manuscript to be published.

Paper II: Contributed to the study concept and design, interpreted the results, prepared the first version of the manuscript, drafted the manuscript to which authors contributed, critically revised the manuscript and approved the final version to be published.

Paper III: Contributed to the study concept and design, participated in the acquisition of data, interpreted the results, prepared the first version of the manuscript, drafted the manuscript to which authors contributed, critically revised the manuscript and approved the final version to be published.

Paper IV: Contributed to the study concept and design, conducted the procedures (methylene blue intra-arterial staining of resected colorectal cancer specimens), participated in the acquisition of data, analysed the data, interpreted the results, prepared the first version of the manuscript, drafted the manuscript to which authors contributed, critically revised the manuscript and approved the final version to be published.

Paper V: Contributed to the study concept and design, conducted the procedures (methylene blue intra-arterial staining of resected colorectal cancer specimens), participated in the acquisition of data, interpreted the results, prepared the first version of the manuscript, drafted the manuscript to which authors contributed, critically revised the manuscript and approved the final version to be published.

2. ABBREVIATIONS

APC	annual percent change
CEA	carcino embryonic antigen
CI	confidence interval
CME	complete mesocolic excision
CRC	colorectal cancer
CT	computed tomography
DCO	death certificate only cases
ECR	Estonian Cancer Registry
EHR	excess hazard ratio
EoD	extent of disease
ESMO	European Society of Medical Oncology
HR	High Resolution
ICD	International Classification of Diseases
LCC	left-sided colon cancer
MDT	multidisciplinary team
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
RCC	right-sided colon cancer
RCT	randomised controlled trial
RSR	relative survival ratio
TME	total mesorectal excision
TNM	tumour, nodules, metastases staging system

3. INTRODUCTION

Colorectal cancer (CRC) is a malignant neoplasm arising from epithelial tissue of the large intestine. CRC is a major public health problem, being one of the leading causes of cancer incidence and mortality with increasing occurrence in the world and in Estonia (Arnold et al., 2017; National Institute for Health Development, 2022). However, the prognosis of CRC is excellent in early stages. Screening programs have proved to be effective in reducing incidence by the removal of premalignant lesions and in improving survival by early detection. Diagnosing and multimodal management of CRC has constantly evolved during the past decades, leading to improved survival (Ahmed et al., 2014). Surgery is a crucial part in curative treatment and there has also been significant advancement in operative techniques and perioperative care. At the same time, large disparities are seen not only globally, but also between European countries and between different socioeconomic population groups within the countries (Allemani et al., 2018; Carethers et al., 2020; Coughlin, 2020; De Angelis et al., 2014), therefore numerous people are not able to benefit from the progress.

WHO encourages the development and implementation of cancer control programs aiming to reduce the number of cancer cases and deaths and improve the quality of life of cancer patients (World Health Organisation, 2006). Europe's Beating Cancer Plan presented in 2021 represents a political commitment in the fight against cancer (European Commission, 2021). Aiming to tackle the entire disease pathway, the plan is structured around four key action areas: prevention, early detection, diagnosis and treatment, quality of life. Among other topics, the document highlights the following issues concerning CRC: improvement of screening with a goal to cover 90% of the target population, reducing inequalities in prevention and care across the EU and thereby increasing five-year survival rates. After the expiry of the previous Estonian National Cancer Strategy in 2015, there has been a period without official cancer policy in Estonia. Estonian Cancer Control Plan for the period of 2021–2030 was approved in April 2021 with priorities set for the next 10 years to move towards the general vision as follows: fewer people develop cancer, people live longer and healthier lives after a cancer diagnosis, people living with cancer have a better quality of life (National Institute for Health Development, 2021). Among other topics this document mentions tackling CRC risk factors, genetic consulting and surveillance in hereditary CRC syndromes, analysing results of CRC screening program and possible expansion of target group age range, ensuring timely diagnosis and treatment, and centralization of surgical care into officially recognized cancer centers.

CRC prognosis has been poor in Estonia in the past similarly to other countries in the Eastern Europe. Despite significant improvement, the five-year relative survival remains inferior compared to the countries of the Western and Northern Europe. This thesis contributes to a better understanding of the long-

term CRC trends by in-depth analysis of incidence and survival. It also includes a study examining the changes in CRC management patterns in Estonia and a randomized controlled trial examining the impact of intraarterial methylene blue staining of resected CRC specimens on the detection of lymph nodes. The results of the thesis have implications for CRC screening policy and development of diagnostics and care.

4. REVIEW OF THE LITERATURE

4.1. CRC epidemiology

4.1.1. CRC incidence

CRC is the third most common malignant tumour accounting for 10% of all cancer types worldwide (Arnold et al., 2017). There are estimated 1.93 million new CRC cases diagnosed in 2020 worldwide, the global new CRC cases is predicted to reach 3.2 million in 2040 (Xi et al., 2021). Incidence rates vary up to 10-fold, rising rapidly in many low-income and middle-income countries; stabilising or decreasing in highly developed countries where rates remain among the highest in the world (Center et al., 2009). CRC is considered a marker of socioeconomic development: in countries undergoing transition, incidence rates tend to rise uniformly with increasing human development index. The global burden of CRC is expected to increase by 60% to more than 2.2 million new cases by 2030.

The increase in incidence likely reflects changes in lifestyle factors and diet: obesity, physical inactivity, increased consumption of animal-source food coupled with low intake of cereals, vegetables and fruit, smoking and excess consumption of alcohol have been shown to be risk factors of CRC (Kerr et al., 2017). Some data suggest a role of gut microbiome imbalance in CRC carcinogenesis (Saus et al., 2019). Prospective studies have also suggested that vitamin D deficiency may contribute to CRC incidence (McCullough et al., 2019). Inflammatory bowel disease significantly increases the risk of CRC (Beaugerie et al., 2013). Age is the major unchangeable risk factor for sporadic CRC: nearly 70% of patients are >65 years of age and this disease is rare before the age of 40 years, even though data from Western registries show an increased incidence in the 40–44 years age group (Davis et al., 2011).

Overall CRC trend may mask divergent trends by subsite, as changing risk patterns and implementation of screening programs may affect subsite-specific trends in a different manner. Historically, the incidence of left-sided colon cancer (LCC) has been higher than right-sided colon cancer (RCC), however, the incidence of RCC has steadily increased over the years (Lee et al., 2015). A 30-year analysis of the SEER database between 1976 and 2005 showed an overall decrease in subsite-specific incidence of CRC except for RCC, which had an annual RCC percentage increase of 0.68% and overall percentage increase of 25% over 30 years (Cheng et al., 2011). A study in USA reported increasing rectal cancer incidence among younger adults for unknown reasons while decreased CRC incidence for all subsites was apparent in states who had higher CRC screening rates (Austin et al., 2014).

Although the lifetime risk of CRC is similar in men (4.4%) and women (4.1%) because women have a longer life expectancy, the incidence rate is 31% higher in men (Siegel et al., 2020). There is a recognised hereditary component of CRC as first-degree relatives of patients with colorectal adenomas or cancer

are at increased risk of CRC (Ahsan et al., 1998; Quintero et al., 2016). The most common genetically determined disorders associated with CRC are Lynch syndrome (1–3% of all CRC cases) and familial adenomatous polyposis (<1% of all CRC cases) (Stjepanovic et al., 2019). Therefore, all CRC patients should be queried regarding their family history for hereditary CRC risk assessment.

In Europe, CRC is the third most diagnosed cancer in men (after prostate and lung cancers) and the second one in women (after breast cancer) with the average estimated incidence rate of 91.6/100 000 for men and 56.3/100 000 for women in EU-27 in 2020 (European Cancer Information System, 2022). Five-fold variations between CRC incidence rates were observed across Europe in 2008 (Ferlay et al., 2018). The incidence of rectal cancer in the European Union is 35% of the total CRC incidence (Glynne-Jones et al., 2017).

In Estonia (population 1.33 million in 2021) CRC is the third leading cancer, exceeding 1000 new cases (incidence rates 51.1/100 000 for colon and 27.6/100 000 for rectal cancer) in 2019 (National Institute for Health Development, 2022). The incidence of CRC has been steadily rising since the beginning of cancer registration in Estonia in 1968 without any sign of stabilisation yet (National Institute for Health Development, 2022).

4.1.2. CRC mortality and survival

Worldwide, CRC is the second leading cause of cancer mortality with estimated 0.9 million deaths worldwide in 2020 (Xi et al., 2021). Mortality rates are rising in low- and middle-income countries and stabilising or decreasing in highly developed countries (Arnold et al., 2017; Center et al., 2009). Globally, the five-year relative survival for colon cancer ranged from below 30% in some African and South American countries to over 70% in Israel, Korea and Australia in 2010–2014, and a similar variation was seen for rectal cancer (Allemani et al., 2018). The stage of the disease at diagnosis highly affects survival. While the five-year survival rate was 90% for patients with localized disease (stages I–II), it was 71% for regional spread disease (stage III) and only 14% for advanced-stage patients with distant metastasis (stage IV) in the latest analysis of American Cancer Society (Siegel et al., 2020).

In Europe, CRC is the second leading cause of cancer-related death in men and the third in women (Ferlay et al., 2018). In EUROCARE-5 study (1999–2007) European average five-year relative survival for patients diagnosed with colon and rectal cancer was 57% and 56%, respectively. The analyses showed persistent differences in CRC survival across Europe with lowest survival rates observed in Eastern Europe similarly to previous studies (Holleczek et al., 2015).

Several studies have demonstrated reduced survival for RCC compared with LCC (Brungs et al., 2017; Petrelli et al., 2017). The possible explanations have been extensively discussed (Baran et al., 2018; Iacopetta, 2002). RCC and LCC have different embryologic origins, they exhibit different mutations, molecular characteristics, and histology. They also show differences in epidemiological

features, sensitivity to chemotherapy and pattern of metastatic spread. Nevertheless, information about the role of the more exact location of the tumour is limited. A Norwegian prospective study reported reduced survival among transverse colon, splenic flexure, and descending colon cancer patients compared with other colon subsites (Sjo et al., 2008). A Korean single-surgeon study described lower survival rates among ascending colon and hepatic flexure cancer (Lee et al., 2015).

In Estonia, CRC survival has been poor historically. In EUROCARE 3 (1990–1994), the five-year relative survival was below 40% for colon and around 30% for rectal cancer while the European average for both sites was close to 50% (Sant et al., 2003). Although the survival gap had narrowed considerably by the time EUROCARE-5 was conducted (1999–2007), the survival deficit in Estonia persisted as the five-year relative survival for colon cancer remained three percent units below European average (54% vs. 57%), and even further below the highest observed estimate (61%) seen for Central Europe (Holleczek et al., 2015). At the same time, survival for rectal cancer remained 8% below European average (50% vs. 58%) and further below the highest estimates (63%) for Belgium and Switzerland. However, Estonia was one of the countries of the largest survival gain.

4.2. CRC screening

A specific characteristic of CRC is slow development through the adenoma-carcinoma sequence, which often takes decades (Brenner et al., 2015). It may also take years for preclinical malignancy to advance clinically manifest CRC. This opens benefit of a broad time window for detecting and removing adenomas and preclinical CRC. The ultimate goal of CRC screening is to reduce mortality. A pooled analysis of randomised controlled trials showed mortality reduction by 15% in intention-to-screen analyses and 25% in per-protocol analyses (Hewitson et al., 2008). An International Agency for Research on Cancer (IARC) Working Group reported there was sufficient evidence that screening for CRC with faecal occult blood testing and colonoscopy reduces the risk of death from CRC and that the benefits outweigh the harms (Lauby-Secretan et al., 2018). CRC screening programs may increase incidence in the short term through the increased detection of prevalent cases and reduce the incidence in the long term through the removal of precancerous polyps. Thus, over time, screening lowers CRC mortality by reducing the incidence and by detecting tumours at earlier stages, which then have better prognoses (Center et al., 2009; Hewitson et al., 2008). The increased use of screening has been cited as one of the most important factors responsible for the recent decline in CRC rates in the United States (Levin et al., 2008; Siegel et al., 2020). CRC screening by colonoscopy has been shown to be beneficial for all topographies of colon cancer (Doubeni et al., 2018). Organised CRC screening programmes have been implemented in most European countries with the target population

mostly aged 50–74 years (Navarro et al., 2017; Ponti, 2017). The American Cancer Society's newest guidelines recommend that CRC screening age was lowered from 50 to 45 because CRC cases are on the rise among young and middle-aged people (Mehta et al., 2021). Estonia was one of the last in Europe to initiate CRC screening, which was started in 2016. The target age group is narrow compared to other European countries: men and women aged 60–69 are invited to participate in the screening every two years. Up until 2020, only persons with valid health insurance had access to free screening. From 2021, free screening is available also for persons without health insurance. Faecal occult blood test is carried out coordinated by family physicians, the subjects are referred to colonoscopy in case of a positive test (Estonian Health Insurance Fund, 2022). In 2020, the coverage by examination in target population was around 50% varying by regions (38%–63%) and by gender (44% for men and 54% for women) (National Institute for Health Development, 2022)

4.3. CRC diagnosis

In ICD-10 (WHO, 2004), CRC is categorised as colon cancer with further subclassification according to subsites (C18.0-C18.9), rectosigmoid junction (C19) and rectal cancer (C20) (Figure 1). In new ICD-11 (WHO, 2019), neoplasm of appendix is considered a separate entity while it was among CRC in ICD-10. Anal cancer (C21) is also a distinct malignancy with different aetiology, pathogenesis and treatment.

CRC patients can present with a wide range of symptoms such as rectal bleeding, change in bowel habits, weakness, anaemia, weight loss or abdominal pain (Dekker et al., 2019). However, CRC is largely an asymptomatic disease in early stages. The symptoms are common for both benign and malignant causes, therefore additional risk factors must be considered. New onset of symptoms should generally prompt colonoscopy to rule out CRC in individuals aged >45 years or younger persons with CRC family history. Low rectal cancers can be diagnosed by digital rectal examination.

Total colonoscopy is recommended for diagnosing CRC (Argilés et al., 2020). The procedure enables determination and marking of the exact tumour location and biopsy of the lesion as well as detection and removal of synchronous precancerous or cancerous lesions. If complete colonic exploration cannot be carried out before surgery (e.g. obstructive tumour), it should be done within 3–6 months. While identification of advanced tumour is straightforward, early cancers and premalignant adenomas appear as subtle mucosal lesions, therefore careful mucosal inspection after optimal bowel preparation is necessary to ensure their detection. Caecal intubation rate (≥90%), endoscope withdrawal time (>6 minutes) and adenoma detection rate (≥25% for screening colonoscopy) are used as quality indicators for colonoscopy (Lund et al., 2019). The diagnosis of CRC must be confirmed histologically.

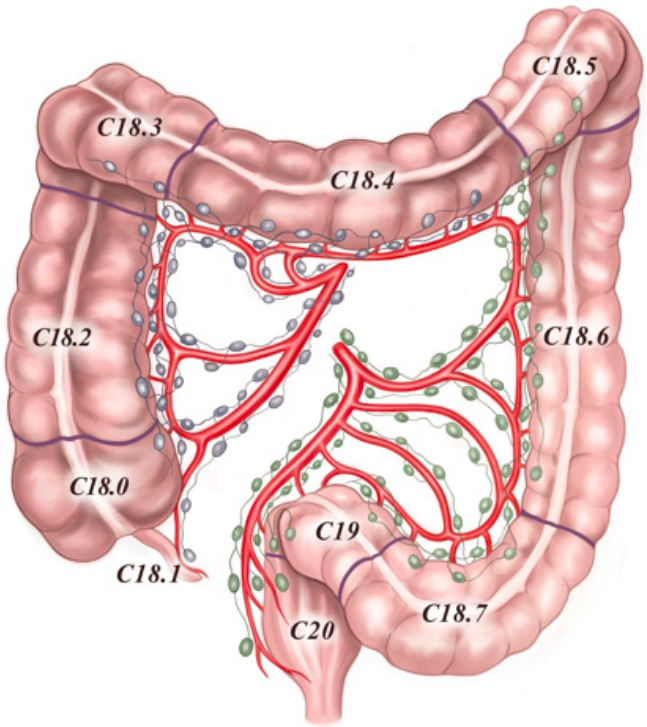

Figure 1. CRC division of subsites (ICD-10), their blood supply and lymphatic drainage. RCC including caecum (C18.0), ascending colon (C18.2), hepatic flexure (C18.3) and transverse colon (C18.4); LCC including splenic flexure (C18.5), descending colon (C18.6) and sigmoid colon (18.7); rectosigmoid junction (C19) and rectum (20). Drawn by Tatjana Veršinina.

4.4. CRC staging and treatment

4.4.1. Colon cancer staging and treatment

A complete work-up should be carried out as follows (Argilés et al., 2020). Comprehensive medical history, physical examination and laboratory tests must be conducted to provide assessment of patient status before deciding the definitive treatment approach. To determine the extent of the disease, thoracic, abdominal and pelvic imaging by contrast-enhanced computed tomography is required. In addition, serum level of carcinoembryonic antigen should be evaluated before surgery and monitored during the follow-up.

In case of *carcinoma in situ* or pT1 carcinoma confined in pedunculated polyp (Haggitt 1–3), endoscopic resection with clear margins and proper follow-up is sufficient in the absence of additional risk factors (Backes et al., 2018). For locally infiltrative tumours without distant metastases, curative surgery is indicated with the goal of wide resection of the involved bowel segment and its lymphatic drainage. The extent of resection is determined by the location of cancer and the pattern of potential lymphatic spread (Figure 1). With the standardised technique of complete mesocolic excision (CME), the mesocolic layer is separated from the parietal plane and central ligation of the supplying arteries and draining veins at their roots is performed producing a wide integrate specimen. After application of the CME technique, a German centre reported significant reduction of five-year local recurrence rates from 6.5% to 3.6% while cancer related five-year survival increased from 82% to 89% among colon cancer patients resected for cure (Hohenberger et al., 2009). In the absence of contraindications, laparoscopic resection offers reduced post-operative morbidity without compromising long-term outcomes when performed by experienced surgeons (Millo et al., 2013). In case of pT4b, *en bloc* resection of invaded adjacent organs must be carried out to ensure tumour-free margins. Complete removal of primary tumour and metastases in combination with systemic therapy offers the chance of cure for selected patients with oligometastatic disease (Kanas et al., 2012; Van Cutsem et al., 2016). The 30-day mortality rate after elective CRC surgery has decreased significantly (Iversen et al., 2014). Possibly reasons are improved patient optimisation, application of enhanced recovery protocol, advances in surgical techniques, more frequent use of minimally invasive surgery, improved complication prevention and management and advances in intensive care.

A standard pathological report should include specimen description, tumour site and size, macroscopic tumour perforation, histological type and grade, extension into the bowel wall and adjacent organs, distance of cancer from resected margins (proximal, distal and radial), presence or absence of tumour deposits, lymphovascular and/or perineural invasion, tumour budding, site and number of removed and involved regional lymph nodes (Washington et al., 2009). The pathological stage is reported according to the Union for Inter-

national Cancer Control (UICC) tumour, node, metastasis (TNM) classification, 8th edition is used since 2017 (James et al., 2017).

The risk of nodal metastases increases with higher T-stage, poor differentiation and more distal tumour location. An analysis of radically operated CRC patients reported the 34.5% overall proportion of lymph node metastases, being 8% for T1 tumours, 18.5% for T2 tumours, 42% for T3 tumours, and 50% for T4 tumours (Ricciardi et al., 2006). Patients with poorly differentiated tumours were much more likely to be node positive (52%) than patients with well-differentiated tumours (20%). Nodal metastases were noted in 7% of proximal T1 colon tumours, 7.5% of distal T1 colon tumours, and 10.1% of T1 rectal tumours.

Examination of ≥12 lymph nodes from resected CRC specimens is among the key quality measures to ensure accurate nodal staging. However, it is important to investigate as many lymph nodes as possible as the prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined (Elferink et al., 2011; Swanson et al., 2003). Lymph node count reflects the quality of surgery as well as pathology, but it is also dependent on patient characteristics (age, gender, tumour grade and location) and is affected by neoadjuvant therapy (de la Fuente, et al., 2009; Nathan et al., 2011). In case of a conventional pathologic examination, lymph nodes are detected from the mesocolon by manual palpation and visual inspection. As small lymph nodes are difficult to distinguish from the adipose tissue the pathologist might miss them. For enhancement of lymph node retrieval, different methods like fat clearance and sentinel node mapping have been examined (Bembenek, 2011; Gregurek et al., 2009). However, these methods were found to be ineffective and time consuming and their practical use is limited. Intra-arterial staining of surgical specimens with methylene blue, resulting in higher lymph node retrieval, was described in 2007 (Markl et al., 2007) and following studies confirmed this finding (Borowski et al., 2014; Kerwel et al., 2009; Klepšytė et al., 2012; Liu et al., 2014; Markl et al., 2008; Törnroos et al., 2011). Methylene blue staining is a simple technique with a short learning curve, low cost and only few minutes time consumption. However, this method is not widely incorporated into routine practice.

Adjuvant systemic therapy options should be considered for patients with high risk of recurrence evaluating expected survival benefit and risk of complications (Argilés et al., 2020). In general, most patients with stage III colon cancer should receive adjuvant therapy. For stage II, lymph nodes sampling <12 and pT4 stage including perforation are considered major risk factors while minor parameters are high grade tumour, vascular/lymphatic/perineural invasion, obstructive tumour and high preoperative carcino embryonic antigen (CEA) levels. Adjuvant chemotherapy in patients with T3N0 colon cancer with inadequate lymph node harvest is recommended as it significantly increased survival in a large-scale registry-based study (Wells et al., 2017). Adjuvant therapy decreases the risk of death by an absolute 3–5% in high-risk stage II colon cancer (with one major or multiple minor risk factors) with single-agent

5-fluorouracil and by 10%–15% in stage III disease with fluoropyrimidines alone, with a further 4%–5% improvement with oxaliplatin-containing combinations. Adjuvant treatment should start within eight weeks after surgery, duration of the therapy is 3–6 months (Argilés et al., 2020).

Patient follow-up for five years after curative treatment is recommended aiming to maximise survival by early detection of relapse (Pita-Fernández et al., 2015). Intensive follow-up regimen generally includes CEA monitoring, yearly CT-scans and colonoscopy in one year followed by 3–5 years. CRC survivors represent the third largest group of long-term cancer survivors in Western countries (Howell et al., 2012).

Palliative systemic therapy with the goal of disease control and prolonged survival is indicated for nonresectable metastatic CRC. The typical chemotherapy comprises a fluoropyrimidine (intravenous 5-FU or oral capecitabine) used in various combinations with irinotecan or oxaliplatin (Van Cutsem et al., 2016). The addition of targeted therapy with vascular endothelial growth factor (VGEF) or epidermal growth factor receptor (EGFR) antibodies can further prolong survival. A patient with metastatic CRC may typically achieve an overall survival of ∼30 months.

4.4.2. Rectal cancer staging and treatment

Tumours with distal extension to 15 cm from the anal margin measured by rigid endoscopy are classified as rectal. Another option to define rectal cancer is below the point of the sigmoid take-off as visualized on MRI imaging (D'Souza et al., 2018) or below the sacral promontory (Bagla et al., 2007). Rectal cancers are categorised as low (up to 5 cm), middle (from >5 to 10 cm) or high (from >10 up to 15 cm). Adenocarcinomas of the rectosigmoid junction (C19) represent up to ten percent of CRC (Falch et al., 2019). While the rectosigmoid junction is encoded as an independent segment of the large intestine in ICD-10, is not evaluated separately, but rather added to the rectum or colon in most studies on CRC. Rectosigmoid junction is accounted for rectal cancer in international incidence and survival analyses (Engholm et al., 2010; European Cancer Information System, 2022). A cohort study focusing on rectosigmoid junction reported more aggressive lymphatic spread, more frequent tumour perforations and higher rate of distant metastases compared to sigmoid colon or rectal cancers (Falch et al., 2019).

Principles for primary work-up, pathology, systemic therapy and follow-up of the rectal cancer are generally similar to those of colon cancer. The main difference for rectal cancer is the increased risk of local recurrence: as rectum is located extra-peritoneally in narrow pelvic cavity in close proximity of neighbouring pelvic organs, it is easier for a tumour to spread locally. More complex diagnostics, multimodal treatment and surgery are therefore required for rectal cancer compared to colon cancer. In addition, the issues of functional outcomes, sphincter preservation and prevention of surgical complications must be considered.

Pelvic MRI should be carried out to all patients with potentially curative rectal cancer to select patients who benefit from neoadjuvant treatment and to define the extent of surgery. High-quality MRI is an accurate locoregional staging tool for assessment of circumferential resection margin and can predict disease-free survival and local recurrence (Glynne-Jones et al., 2017; MERCURY Study Group, 2006; Taylor et al., 2014). MRI allows further subclassification of cT3 by evaluating the depth of invasion beyond the muscularis propria, assessment of the relationship between tumour and mesorectal fascia is crucial to decision-making. Clinical nodal staging is less reliable as lymph node size is poorly correlated with metastatic involvement, irregular border and heterogeneous signal provide more relevant additional information (Brown et al., 2003). Endoscopic rectal ultrasound is useful for defining treatment for the earliest (T1) tumours (Burdan et al., 2015).

Local excision by endoscopy or transanal surgery is appropriate for very early cancers (*in situ* or pT1 without adverse risk factors) (Glynne-Jones et al., 2017). For more advanced tumours, radical surgery is indicated. The standard of care in rectal cancer surgery is total mesorectal excision (TME), implying that all of the mesorectal fat, including all lymph nodes, should be meticulously excised while preserving the integrity of the surrounding mesorectal fascia. Since the introduction of this surgical technique by Bill Heald in 1986, local recurrence rates have reduced dramatically (Heald et al., 1986). A partial mesorectal excision with a distal margin of at least 5 cm of mesorectum can be considered in high rectal cancer. If anal sphincter and pelvic floor muscles are not involved, a sphincter preserving procedure with colorectal or coloanal anastomosis can be done providing better quality of life for the patients. Temporary defunctioning ileostomy is utilised for low colorectal anastomoses to mitigate the consequence of leak in selected high risk patients (Hanna et al., 2015). In case of low rectal tumour with levator or sphincter muscle involvement, an extralevator abdominoperineal excision with formation of end colostomy is indicated (De Nardi et al., 2015). Minimally invasive rectal cancer surgery reduces postoperative morbidity without compromising long term outcomes when performed by experienced and specialty trained surgeons (Hsieh et al., 2020). In the case of low rectal tumours, transanal TME may facilitate pelvic and distal mesorectal dissection (Penna et al., 2017).

In early rectal cancer, good quality surgery alone is the standard of care. Neoadjuvant treatment is indicated for locally advanced rectal cancer (cT3c or higher, extramural vascular invasion, threatened circumferential resection margin) aiming to reduce local recurrence (Glynne-Jones et al., 2017). Two different schedules of preoperative therapy are standards of care: short course radiotherapy with a 25 Gy total dose for one week, followed by immediate or delayed surgery and chemoradiotherapy with a dose of 45–50 Gy in 25–28 fractions. In addition, a new practise of short course radiotherapy followed by total neoadjuvant chemotherapy is recommended for selected very high risk patients (Bahadoer et al., 2021). Patient selection for surgery or different schedules of neoadjuvant therapy must be based on structured report of high

quality MRI imaging and made by joint decision making on multidisciplinary team (MDT) meeting. The standard methods of assessing treatment response following preoperative therapy are digital rectal examination, endoscopy, and re-imaging by MRI. These findings direct appropriate surgical strategy or the possibility of choosing a 'watch-and-wait' approach in case of clinical complete response (Dossa et al., 2017).

Adjuvant chemotherapy is generally indicated for stage III rectal cancer, but the evidence is more limited than for colon cancer as rectal cancer patients were excluded from most adjuvant studies (Glynne-Jones et al., 2017).

4.4.3. Quality of CRC care

To enhance the quality of care and patient outcomes, clinical practice guidelines are the most important documents for incorporating scientific evidence into healthcare decision-making through the formulation of recommendations (Franco et al., 2020; Graham et al., 2011). European Society of Medical Oncology (ESMO) has developed clinical guidelines for diagnosis, treatment and follow-up of colon and rectal cancers (Argilés et al., 2020; Glynne-Jones et al., 2017; Van Cutsem et al., 2016). Guidelines created by the National Comprehensive Cancer Network (NCCN) are followed in the United States (Benson et al., 2021; Engstrom et al., 2009), but this organisation has also active presence in Europe and has adapted the guidelines for some European countries (National Comprehensive Cancer Network, 2022). CRC management in Estonia is generally based on ESMO and NCCN guidelines.

In order to improve the quality of cancer care, patients must be centralized in high-volume centres providing expertise and access to all diagnostic and treatment modalities. This is particularly relevant for the complex surgical care: the effect of surgeon and hospital volumes on outcomes has increasingly become a focus of health care policy (National Institute for Health and Care Excellence, 2020). A Swedish population-based analysis observed significantly reduced local recurrence rate and prolonged overall survival for rectal cancer patients after centralization to colorectal unit with multidisciplinary management and increased subspecialisation (Khani et al., 2010). Improved survival for rectal cancer associated with centralisation was also seen in England and Denmark (Walters et al., 2015). In 1997, 61% of CRC patients in Estonia were treated at specialised hospitals (Innos et al., 2012).

A specialised and dedicated MDT including radiologists, surgeons, radiation oncologists, medical oncologists and pathologists should attend regular meetings and discuss CRC patients to identify the best possible treatment strategy in accordance with clinical guidelines (Fehervari et al., 2021; Glynne-Jones et al., 2017). The MDT should also audit whether their decisions are implemented and review patient outcomes with standardised quality assurance (Munro et al., 2015). A systemic review described limited impact of MDT on

patient survival, but patients discussed were more likely to receive complete preoperative staging and neoadjuvant/adjuvant treatment (Pillay et al., 2016).

As assessing the quality of cancer care has become increasingly important, a vast number of quality indicators have been developed reflecting process, outcome or structure measures to assess CRC diagnosis and treatment. A systemic review evaluating the scientific basis of CRC quality indicators analysed 41 articles with consensus-based, evidence-based and validation cohort studies (Keikes et al., 2017). From almost 400 total indicators described, they pointed out following most reported and validated indicators: pre- or post-operative colonoscopy, preoperative imaging for staging, pelvic imaging for rectal cancer, adequate staging (cTNM) before the start of treatment, presence of a MDT board, radiotherapy for rectal cancer if indicated, TME for low rectal cancer, quality of TME, surgeon caseload, abdominoperineal resection rate, anastomotic leakage rate, surgical re-intervention rate, 30-day mortality after surgery, tumour-free resection margins, minimum of examined lymph nodes, referral to medical oncologist if indicated, adjuvant chemotherapy for stage III colon cancer, considering adjuvant chemotherapy for high-risk stage II colon cancer, time between surgery and adjuvant chemotherapy, plan for follow up, CEA measuring on diagnosis and follow-up, overall survival. The authors of the systemic review conclude that CRC care is stuck in an abundance of quality indicators and there is a need to define a limited evidence-based set of validated quality indicators to facilitate the assessment. In Estonia, the following CRC quality indicators are currently recorded: postoperative 30-day mortality in patients operated with a diagnosis of CRC (with a target of <5% in elective and <15% in emergency surgery), proportion of patients receiving neoadjuvant radiotherapy (with or without chemotherapy) among locally advanced rectal cancer (with a target of 90%), the number of lymph nodes examined in patients undergoing primary radical CRC surgery (with a target of ≥12 lymph nodes examined in 80% of the patients) and the proportion of patients receiving adjuvant chemotherapy among colon cancer patients with high risk stage II (with a target of 50%) and stage III (with a target of 70%) (Estonian Health Insurance Fund, 2022).

While national cancer incidence and survival statistics are based on general population-based cancer registries, specific CRC quality-of-care registries containing detailed information on the diagnosis and treatment are useful for quality assurance and research. For example, Swedish National CRC Registry has operated since 1995 (Moberger et al., 2018) and Danish CRC Group Database since 1994 (Ingeholm et al., 2016). There has been no national CRC registry in Estonia and individual hospitals have (hopefully) analysed their performance and outcomes to the best of their ability. More detailed analysis of CRC care in Estonia has only been possible as part of European high-resolution studies for CRC patient cohorts in 1997 and 2011. The Estonian Society of Oncologists performed an audit of rectal cancer treatment in 2009 (Estonian Health Insurance Fund, 2010). The authors pointed out some shortcomings in staging, insufficient information about pre-treatment MDT decisions, lack of

relevant information in surgical protocols and pathology reports and low number of lymph nodes examined. They also suggested the need for further centralisation of rectal cancer care.

The aim of the EUROCARE project, currently including 116 European Cancer registries in 30 countries, is to analyse cancer survival in Europe. Large variations observed between different countries prompted the initiation of European High-Resolution (HR) studies to examine the patterns of cancer care. In the late 1990s, the proportion of radically operated patients with CRC varied from 44% to 86% among the participating 12 registries with the estimate for Estonia (56%) being one of the lowest (Gatta et al., 2010). Shortcomings in staging were evident as the proportion of patients resected radically who had ≥12 lymph nodes examined was below 2% in Estonia while the European average was 29%. A large variation (24%–73%) was also seen in the use of adjuvant chemotherapy in stage III colon cancer. A more detailed analysis of the 1997 Estonian CRC cohort showed extremely low quality of pathological examination, inadequate staging and insufficient use of neoadjuvant and adjuvant therapies (Innos et al., 2012).

4.5. Summary of the literature review

CRC is a major public health problem, being one of the leading causes of cancer incidence and mortality with increasing occurrence in the world. Increasing incidence is likely associated with changing risk profile related to "Westernization," including physical inactivity, obesity, and unfavourable dietary changes. Screening programs can reduce CRC mortality by decreasing incidence and diagnosing the disease at an early stage. CRC multimodal care has substantially evolved during the past decades and excellent survival rates can be achieved nowadays by early diagnosis and proper treatment. The diagnosis of CRC must be made on colonoscopy and confirmed pathologically. Surgery has a crucial role in curative treatment while survival can be further improved by neoadjuvant radiotherapy in locally advanced rectal cancer and adjuvant systemic therapy in patients with high risk of distant recurrence. Timely diagnosis and treatment, centralised care in high-volume centres with increased subspecialisation, multidisciplinary team management along with continuous monitoring of the process and outcomes are key measures to improve the quality of care.

In Estonia, the incidence of CRC has been steadily rising since the beginning of cancer registration in 1968 without any sign of stabilisation yet. Estonia was one of the last countries in Europe to initiate a CRC screening program. The current target age group is narrow (60–69 years) with coverage well below the recommended 70%. CRC prognosis has been historically poor in Estonia, the five-year relative survival was extremely low compared to European average in the first half of the 1990s, particularly for rectal cancer. Although Estonia was among the countries showing the largest survival gain in EUROCARE-5 (1999–

2007), the survival estimates remained considerably below the highest estimates observed in Europe. High-resolution studies have observed large variations in the patterns of cancer diagnosis and treatment across Europe, with particularly poor results for Estonia.

In order to better understand the population-based patterns of CRC care and outcomes, there has been a need for an in-depth analysis of long-term trends in CRC incidence, early detection and survival as well as the changes in CRC management. The results of the thesis have implications for health policy decisions and clinical practice.

5. AIMS OF THE STUDY

The general purpose of this study was to evaluate CRC incidence, quality of care and survival in Estonia and find possibilities to improve CRC care and outcomes.

The specific aims of the study were:

1. To examine the long-term incidence and survival trends of CRC prior to and after the implementation of screening in Estonia, with special emphasis on subsite and stage.
2. To analyse possible survival differences between detailed subsites of colon cancer, accounting for TNM stage.
3. To examine the changes in the patterns of diagnosis, staging and treatment of CRC in Estonia.
4. To assess the effect of intra-arterial staining of CRC specimens on nodal staging.

6. MATERIALS AND METHODS

6.1. Data collection

6.1.1. Estonian Cancer Registry

The ECR is a population-based registry covering the whole country (population 1.33 million in 2021) and has data since 1968. Reporting to the ECR is mandatory by law for all doctors in Estonia who diagnose or treat reportable tumours. Multiple sources are used for case ascertainment, including trace-back of cases first identified via death certificates as well as linkages with the electronic patient records of the cancer centres. The ECR uses ICD-O-3 for coding and follows international definitions and rules issued by the European Network of Cancer Registries and the International Association of Cancer Registries, for reporting incidence and survival.

To analyse CRC incidence and survival trends and the effect of different variables on survival, the ECR provided data on all adult (age ≥15 years) cases of CRC (ICD-10 codes C18–20) diagnosed in 1995–2019, regardless of cancer sequence (papers I and II). Percentage of microscopically verified cases, percentage of death certificate only (DCO) cases and percentage of cases discovered at autopsy were used as data quality indicators. For all cases, the ECR provided the following data: age, gender, date of diagnosis, topography, morphology, subsite, TNM stage, and follow-up for vital status.

6.1.2. Colorectal Cancer High Resolution Study

To examine the changes in CRC diagnosis and treatment patterns, data on two cohorts of CRC patients diagnosed in 1997 and 2011 were used (paper III). The study cohorts were initially formed for EUROCARE HR Studies, to compare cancer management practices across Europe (H. Brenner et al., 2012; De Angelis et al., 2014; Gatta et al., 2010; Sant et al., 2003). The study subjects were identified from the ECR and included all incident cases of cancer of colon ((International Classification of Diseases (ICD-10) C18) and rectum (ICD-10 C19-20), diagnosed in adults (age ≥15 years) in 1997 and 2011. DCO and autopsy cases (n=16 in 1997, n=13 in 2011) were excluded.

Data on diagnostic procedures, staging and treatment were gathered retrospectively from the patients' medical records by Estonian oncologists and colorectal surgeons, according to the study protocols of EUROCARE HR Studies (EUROCARE, 2022; Gatta et al., 2010).

6.1.3. Randomised controlled trial

A randomised controlled trial (RCT) was conducted to assess the effect of intra-arterial methylene blue staining of CRC specimens on nodal staging (paper V). In preparation for the RCT, a series of 60 consecutive staining procedures was performed as a pilot study to assess the feasibility of this technique (paper IV).

The staining procedure was performed in the operating theatre soon after specimens' removal to ensure staining of the fresh specimen. Depending on the type of resection, either the ileocolic, middle colic or inferior mesenteric artery was cannulated at the point of transection and cannula was fixed with ligature. Five ml of methylene blue was diluted in 15 ml of 0.9% saline and 10–15 ml of the solution was injected through the cannula; the success of the procedure was confirmed by the immediate blue staining of the vascular network and intestinal serosa (Figure 2).

After successful pilot study, an RCT was conducted with two parallel patient groups (Figure 3). The inclusion criteria were pathologically confirmed CRC and colorectal resection with curative intent. Resections with palliative intent, pre-malignant lesions and malignancies other than colorectal carcinoma were excluded. At the Department of Surgical Oncology, Tartu University Hospital, 266 patients were randomised into the intervention and control groups between March 2013 and April 2015. The sample size was sufficient to detect a difference in the proportion of subjects with ≥12 lymph nodes examined of 15% units, and a difference of 5 in mean lymph node count (SD 14), with two-sided alpha at 0.05 and statistical power at 0.8.

Informed consent was obtained from all patients. Allocation was done during operation, after abdominal exploration, when a radically unresectable disease was ruled out. Randomisation was performed by an independent person, using simple randomisation by the sequences produced by a random number calculator.

In the intervention group, the staining procedure was performed as for the pilot study above. In the control group, staining was not performed. Both the stained and non-stained CRC specimens were examined at the Department of Pathology after 24 hours of fixation in 10% formalin solution. Lymph nodes were detected by visual inspection and manual palpation of the mesocolon (Figure 4). The diameter of each lymph node cross-section was measured, and result rounded to 1 mm accuracy. Microscopic examination was performed, and metastatic involvement was described.

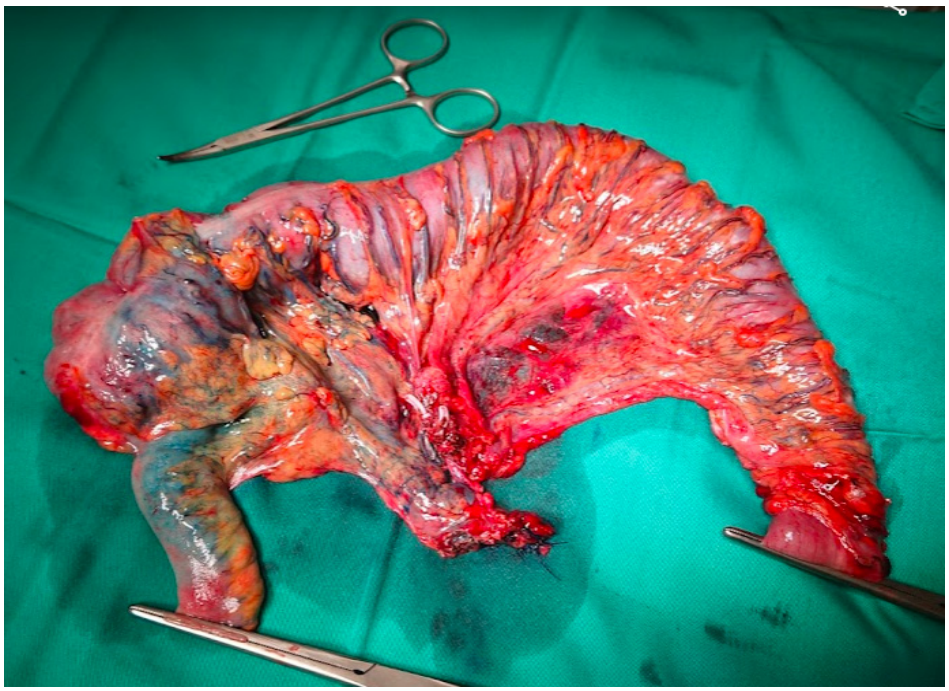

Figure 2. Methylene blue stained right hemicolectomy specimen

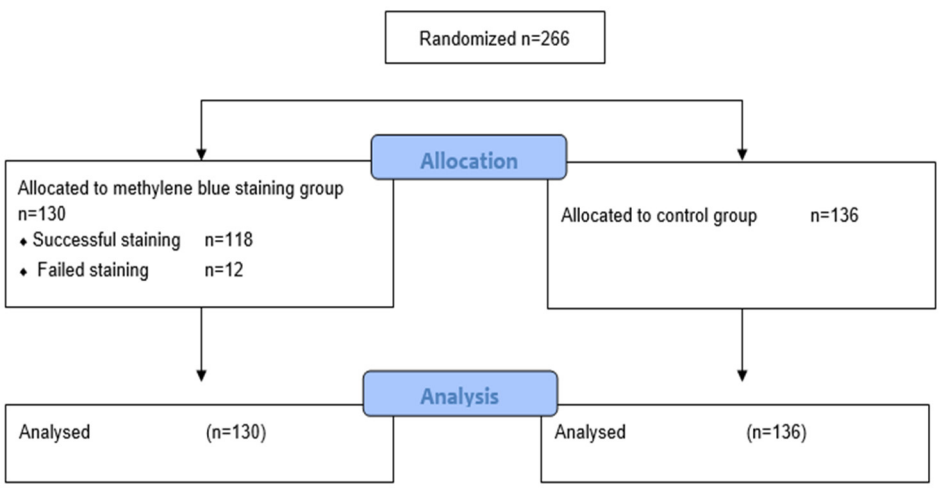

Figure 3. CONSORT flow diagram of study group allocation

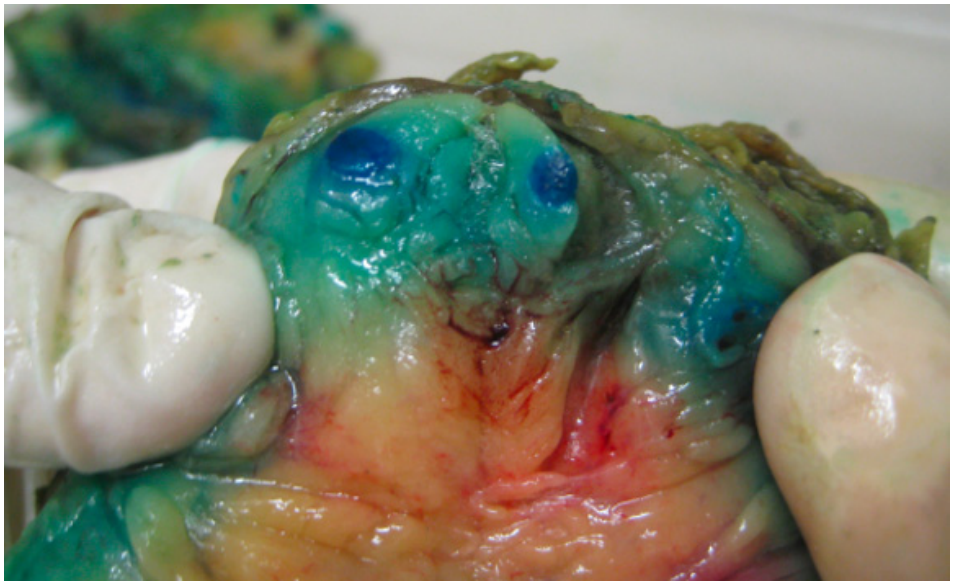

Figure 4. Stained lymph nodes in mesocolon

6.2. Data definitions

Patient age at diagnosis was categorised as follows: <55, 55–64, 65–74, ≥75 years (Papers I to III) and in 10-year age groups for the analysis presented in the thesis.

For analysis of incidence and survival trends in Estonia, time periods of 1995–1999, 2000–2004, 2005–2009, 2010–2014 and 2015–2019 were compared.

6.2.1. Subsites

In papers I and III, CRC subsites were categorised as follows: RCC, including appendix, caecum, ascending colon, hepatic flexure and transverse colon (ICD-10 C18.0–18.4), LCC, including splenic flexure, descending and sigmoid colon (C18.5–18.7), other or overlapping colon (C18.8–18.9), rectosigmoid junction and rectum (C19–20) (Figure 1).

In paper II, all detailed locations of colon cancer (ICD-10 C18.0–18.7) were analysed separately, excluding appendix (C18.1) and other or overlapping sites (C18.8–18.9).

6.2.2. Staging

In all papers, the stage was coded into grouped stage according to the Union for International Cancer Control version 7 of the TNM classification. The hospitals report stage information to the ECR according to one or more of the three following classifications: 1) component T, N and M codes; 2) grouped TNM stage; 3) extent of disease (EoD), categorised as local, spread to neighbouring tissues, regional lymph nodes, distant metastasis, unknown. Starting from 2012, TNM variables are routinely recorded at the ECR, and quality control procedures are applied. In case of conflicting information, component TNM codes take priority, and grouped stage and/or EoD are corrected accordingly.

For 1995–2011, TNM stage was coded as part of the study and similar rules were applied. If EoD was reported as distant metastasis and TNM variables were missing, stage IV was assumed. If grouped TNM stage was reported, but all or some component TNM values were missing, and the reported TNM values were not in conflict with the stage grouping, we assumed the grouped TNM stage to be correct.

Pathological TNM was used for staging primarily operated cases for the analysis based on EUROCARE HR studies (paper III). If pathological TNM was missing or patients received neoadjuvant treatment, clinical TNM stage was used for the 2011 cohort. The 1997 study protocol did not include data collection on clinical T and N stages.

In paper II, the T-category (T1-2, T3, T4) was analysed separately.

6.2.3. Diagnostic and treatment categories

In paper III, diagnostic exams (endoscopy and imaging) done within 3 months (before or after) from diagnosis were considered. The proportion of patients with ≥12 lymph nodes examined was estimated as an internationally established quality indicator for CRC care. Surgical treatment was categorised as shown in table 1. Information about the use of neoadjuvant radiotherapy for rectal cancer and adjuvant chemotherapy for colon cancer as indicators for treatment quality was also acquired.

In papers IV and V lymph nodes were categorised by diameter (mm) as follows: 0–2, >2–4, >4–6, >6–8, >8–10, >10. The primary outcome measures were total lymph node count, small-diameter (≤4mm) lymph node count and rate of finding ≥12 lymph nodes. The secondary outcome measures were metastatic lymph node count and rate by diameter and possible upstaging effect.

Table 1. Algorithm for defining surgical treatment for the 1997 and 2011 cohorts of CRC patients

Surgical treatment	**1997**	**2011**
Radical surgery	Complete (R0) resection in stage I–III	Complete (R0) resection in stage I–IV
Not radical surgery	Palliative surgery, incl. colostomy only; Stage I–III, primary tumor not entirely resected; Stage IV operated cases	Palliative surgery, incl. colostomy only; Stage I–IV, primary tumor or metastases not entirely resected
Unknown	Surgery done but not known if radical or not radical; Unknown if surgery done or not	Surgery done but not known if radical or not radical; Unknown if surgery done or not

6.3. Statistical methods

6.3.1. Descriptive statistics

For the descriptive statistics, means, centiles and percentages were used. The significance of the difference between the groups was tested using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. Equality of the medians was compared with the chi-square median test. The equality of proportions in the 1997 and 2011 cohorts was tested with two-sample tests of proportions using large-sample statistics. A p-value less than 0.05 was considered significant.

6.3.2. Incidence

The incidence rate was calculated by dividing the annual number of incident cases by the average annual number of Estonian population in the given year and expressed per 100 000 person-years. Age-specific and age-standardized (world) CRC incidence rates were modelled and the estimated annual percentage change (APC) with 95% confidence intervals (CI) calculated with Joinpoint Regression Program (version 4.1.1.1) from the Surveillance Research Program of the US National Cancer Institute (http://surveillance.cancer.gov/joinpoint/). Permutation test was used to assess the statistical significance of the APCs, where APC is significantly different from zero at alpha=0.05.

6.3.3. Survival

Follow-up for vital status from the date of diagnosis until 31 December 2019 was conducted by the ECR at the Estonian Population Registry using unique personal identification numbers. In case of death or emigration, the respective dates were obtained. Survival time was accumulated from the date of diagnosis until the date of death; for patients who remained alive, survival time was censored at the time of emigration or at the end of follow-up.

Relative survival ratio (RSR), which captures both direct and indirect mortality due to cancer, was calculated as the ratio of observed survival and expected survival of the underlying general population. The latter was calculated according to Ederer II method (Ederer, 1959), based on national life tables of general-population survival probabilities, stratified by age (in 1-year increments from 0 to 99), sex and calendar year (in 1-year intervals). DCO and autopsy cases were excluded from survival analyses. Patients who were diagnosed and died on the same day were included with one day of survival time. Cohort method was used for patients diagnosed in 1995–1999, 2000–2004 and 2005–2009; period method for 2010–2014 (paper I) (H. Brenner, Gefeller, & Hakulinen, 2004). An updated survival analysis was done for the thesis, using cohort method for 2010–2014 and period method for 2015–2019. Complete analysis method was used for 2007–2016 colon cancer subsite analysis in paper II (Dickman et al., 2015). RSRs were calculated using the *strs* command in STATA 14 and 17 (Stata Corp, College Station, TX, USA) using actuarial method and are presented with 95% CI. Relative survival estimates were age standardised using direct standardisation with International Cancer Survival Standards (Corazziari et al., 2004).

In paper II, excess hazard ratios (EHR) of death within five years after diagnosis were estimated in the framework of generalised linear models using a Poisson assumption for the number of observed deaths (Dickman et al., 2015) for colon cancer subsites, adjusting for age, sex, period of diagnosis, and T category, based on complete analysis (2007–2016). All models included a year of follow-up. Lifetables for modelling were produced with the *strs* algorithm in STATA 14 (Stata Corp, College Station, TX, USA) (Dickman et al., 2015).

Cases with unknown stage or unknown T category were excluded from the models. The EHRs are presented with 95% confidence intervals (CI). Interactions between variables were tested with likelihood ratio test. As we found strong interactions between stage and all other variables, the EHRs are shown stratified by stage (because of small numbers, the results are not shown for stage I). No other significant interactions were detected.

6.4. Ethics

Study protocols were approved by the Tallinn Medical Research Ethics Committee (decision no. 556 (paper III), decision no. 2636 (papers I and II)) and Research Ethics Committee of the University of Tartu (protocol 198/T-23 (paper IV), protocol 222/T-13 (paper V)).

7. RESULTS

7.1. CRC incidence

The total number of CRC cases diagnosed in Estonia in 1995–2019 was 19 434 (Table 2). The average annual number of cases increased from 603 in 1995−1999 to 972 in 2015−2019. The proportion of microscopic verification increased and the proportion of DCO cases decreased. Age distribution shifted significantly towards the elderly while the proportion of men and women did not change. The proportion of colon cancer (particularly RCC) increased.

There were more women and elderly patients among RCC compared to LCC (Table 3; paper I, Table 3). Stage distribution changed significantly over the study period. The proportion of stage I increased throughout the study period, but the change was more pronounced comparing 2010−2014 to 2015−2019: from 10% to 13% ($p=0.025$) in RCC and from 11% to 17% ($p<0.001$) in LCC, respectively. The largest change in the stage distribution of rectal cancer was seen in stage III as the proportion of stage III increased from 17% in 1995–1999 to 26% in 2010–2014 and 35% in 2015–2019, while the proportion of stage II and stage IV decreased (Table 3; paper I, Table 3). In colon cancer, the proportion of stage III also increased significantly throughout the study period. The percentage of unknown stage decreased in all subsites.

Age-standardized incidence of colon cancer increased at a rate of 1.5% and 1.0% per year in men and women, respectively (Figure 5). The incidence of RCC increased significantly in both men and women, while the incidence of LCC increased significantly only in men during the last years of the study period. A significant increase was also seen in rectal cancer incidence for both men and women.

In age groups 70–79 and ≥80, increases were seen consistently for all subsites (Figures 6 and 7). In age group 60–69, changes in rates were seen for total colon cancer as well as for LCC, while a steady rise was seen for rectal cancer. In age group <50, significant increases were seen for total colon cancer and RCC in women, and for RCC in men.

Table 2. Incident cases of colon and rectal cancer in Estonia, 1995–2019

	Total		1995–1999		2000–2004		2005–2009		2010–2014		2015–2019		
	No	%[a]	No	%[a]	No	%[a]	No	%[a]	No	%[a]	No	%[a]	p-value[b]
Total	19434	100	3013	100	3440	100	3782	100	4339	100	4860	100	
Microscopic verification	17764	91	2684	89	3130	91	3443	91	4025	93	4482	92	p<0.001
Death certificate only	219	1.1	30	1.0	51	1.5	54	1.4	38	0.9	46	1.0	p=0.023
Autopsy	225	1.2	30	1.0	35	1.0	61	1.6	49	1.1	50	1.0	p=0.065
Sex													
Men	9018	46	1365	45	1569	46	1762	47	2004	46	2318	48	p=0.220
Women	10416	54	1648	55	1871	54	2020	53	2335	54	2542	52	
Age at diagnosis (years)													
<50	959	5	198	7	179	5	177	5	195	4	210	4	p<0.001
50–59	2218	11	437	15	397	12	467	12	461	11	456	9	
60–69	5251	27	1017	34	1003	29	962	25	983	23	1286	26	
70–79	6904	36	926	31	1363	40	1446	38	1608	37	1561	32	
≥80	4102	21	435	14	498	14	730	19	1092	25	1347	28	
Site													
Colon (C18)	12067	62	1860	62	2072	60	2336	62	2683	62	3116	64	p=0.007
Right-sided colon (C18.0–18.4)	5814	48[c]	802	43[c]	1003	48[c]	1118	48[c]	1367	51[c]	1524	49[c]	
Left-sided colon (C18.5–18.7)	5770	48[c]	963	52[c]	991	48[c]	1105	47[c]	1227	46[c]	1484	48[c]	
Other colon (C18.8–18.9)	483	4[c]	95	5[c]	78	4[c]	113	5[c]	89	3[c]	108	3[c]	
Rectum (C19–20)	7367	38	1153	38	1368	40	1446	38	1656	38	1744	36	

[a] due to rounding, the percentages may not sum up to 100%

[b] chi-square test comparing proportions over time periods

[c] proportion of colon cancers

Table 3. Sex, age and stage distribution of colorectal cancer by subsite in Estonia, 2010–2019

	Right-sided colon[a]			Left-sided colon[a]			Rectum[a]		
	2010–2014 (n=1340)	2015–2019 (n=1494)		2010–2014 (n=1202)	2015–2019 (n=1459)		2010–2014 (n=1627)	2015–2019 (n=1715)	
	%[b]	%[b]	p-value[c]	%[b]	%[b]	p-value[c]	%[b]	%[b]	p-value[c]
Sex									
Men	38	40	p=0.158	48	50	p=0.207	52	52	p=0.909
Women	62	60		52	50		48	48	
Age at diagnosis (years)									
<50	5	5	p<0.001	4	4	p=0.018	4	4	p=0.433
50–59	10	7		11	10		11	11	
60–69	17	22		23	27		28	30	
70–79	39	32		38	33		35	32	
≥80	28	34		23	25		23	23	
TNM stage group									
I	10	13	p=0.007	11	17	p=0.001	14	15	p<0.001
II	30	27		29	27		22	18	
III	23	25		21	21		26	35	
IV	27	27		27	26		25	22	
Unknown	11	8		11	9		14	11	

[a] death certificate only and autopsy cases excluded

[b] due to rounding, the percentages may not sum up to 100%

[c] chi-square test comparing proportions between 2010–2014 and 2015–2019

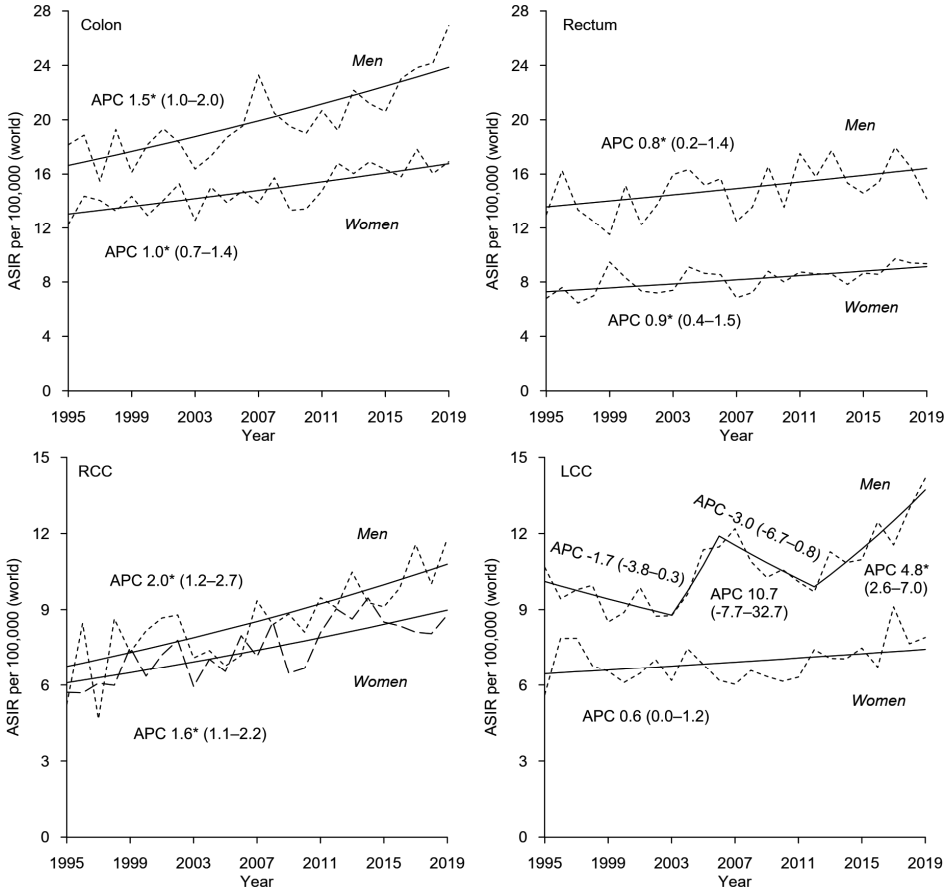

Figure 5. Observed (dashed line) and modelled (solid line) age-standardised (world) incidence rates (ASIR) and annual percentage change (APC) with 95% confidence intervals for trends in colon, rectal, right-sided colon cancer (RCC) and left-sided colon cancer (LCC) incidence in Estonia, 1995–2019. *The APC is significantly different from zero at alpha=0.05.

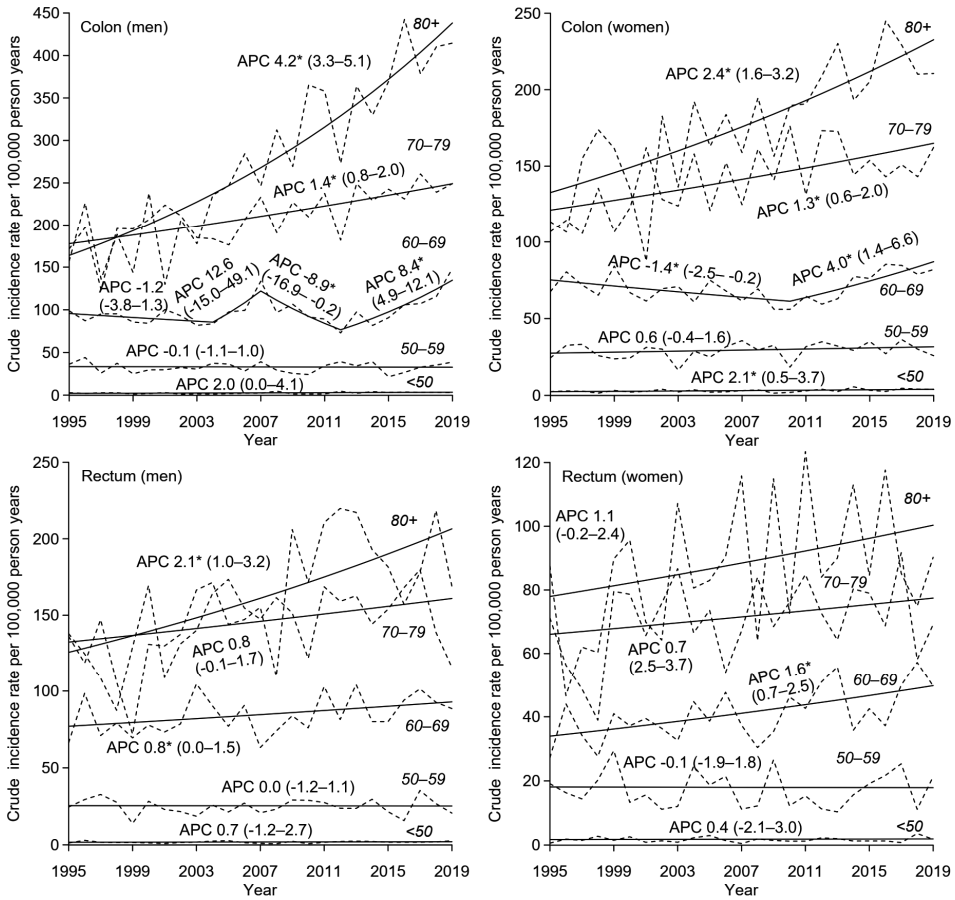

Figure 6. Observed (dashed line) and modelled (solid line) age-specific incidence rates and annual percentage change (APC) with 95% confidence intervals for trends in colon and rectal cancer incidence in Estonia, 1995–2019. *The APC is significantly different from zero at alpha=0.05.

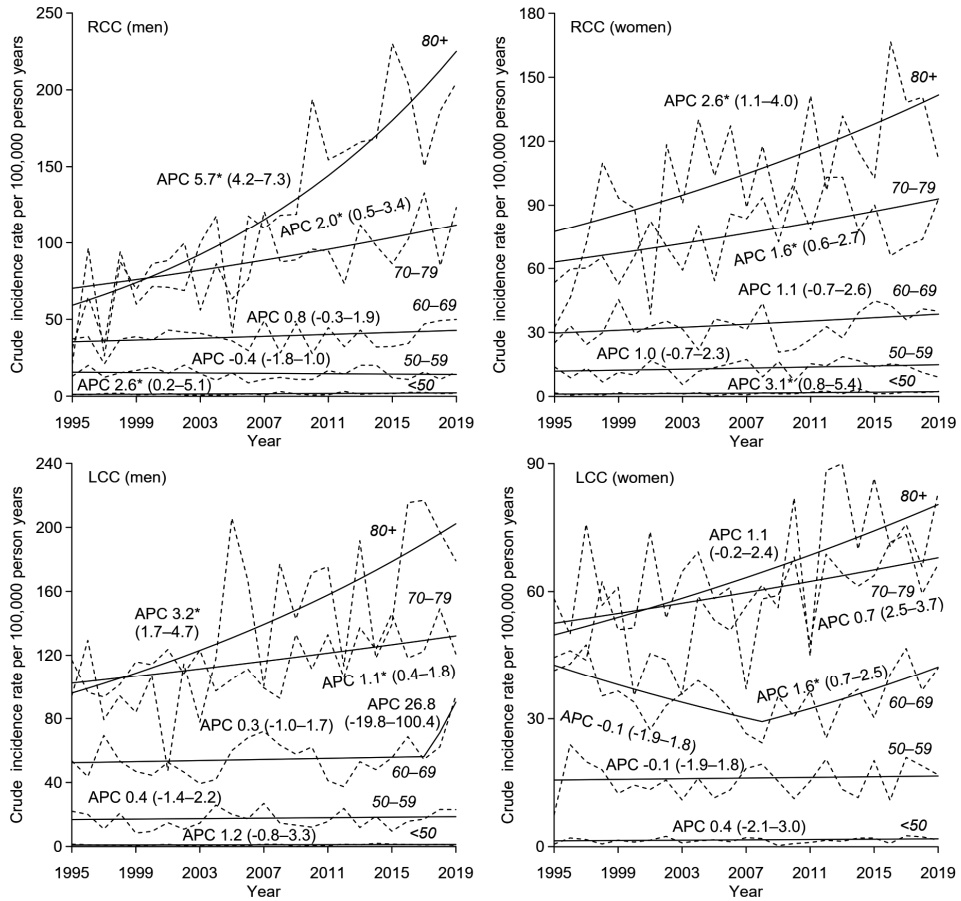

Figure 7. Observed (dashed line) and modelled (solid line) age-specific incidence rates and annual percentage change (APC) with 95% confidence intervals for trends in right-sided colon cancer (RCC) and left-sided colon cancer (LCC) incidence in Estonia, 1995–2019. *The APC is significantly different from zero at alpha=0.05.

7.2. CRC survival

7.2.1. CRC survival changes in 1995–2019

The age-standardised five-year RSR for colon cancer increased from 50% in 1995–1999 to 59% in 2015–2019 (Figure 8; Table 4; paper I, table 4). Women had larger survival gain than men (from 49% to 60% and from 52% to 58% respectively). Survival gain was more pronounced for younger patients. Among subsites of colon cancer, only LCC showed significant survival increase (from 51% to 60%). Significant increase in stage-specific survival was seen for stage IV (Figure 9). No significant changes were seen between last time periods (2010–2014 and 2015–2019).

For rectal cancer, the age-standardised five-year RSR increased from 38% in 1995–1999 to 63% in 2015–2019 (Figure 8; Table 4; paper I, table 5). Significant survival gain was seen in nearly all subgroup analyses. An increase of 39 percent units (from 34% to 73%) was apparent for stage III rectal cancer (Figure 10). No significant changes were seen between last time periods (2010–2014 and 2015–2019).

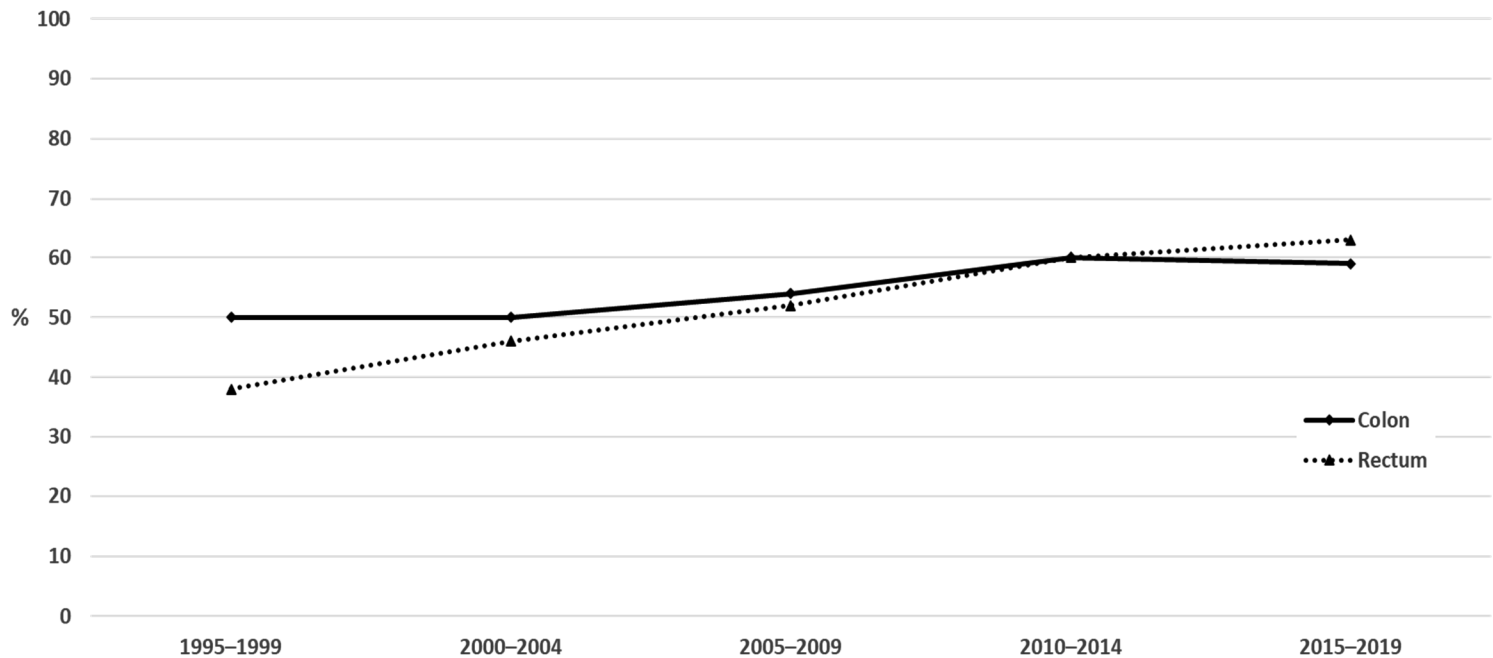

Figure 8. Age-standardised five-year relative survival for colon and rectal cancer, Estonia 1995–2019.

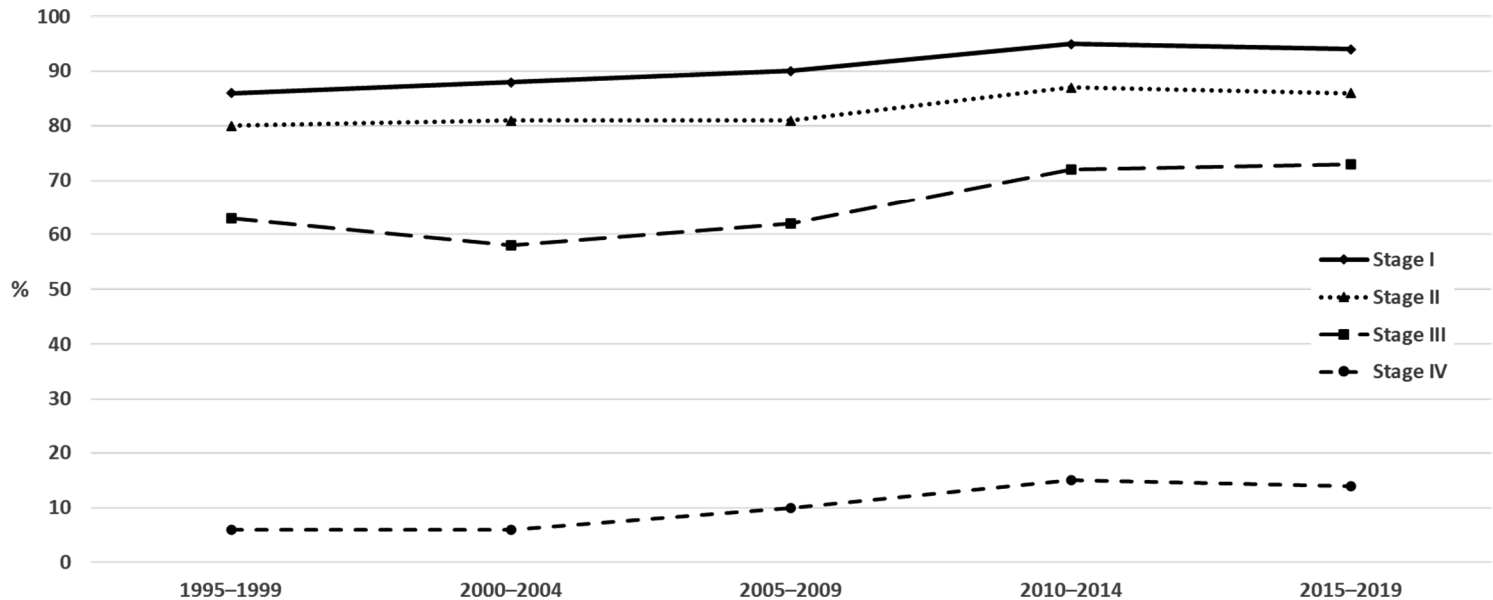

Figure 9. Stage-specific age-standardised five-year relative survival for colon cancer, Estonia 1995–2019.

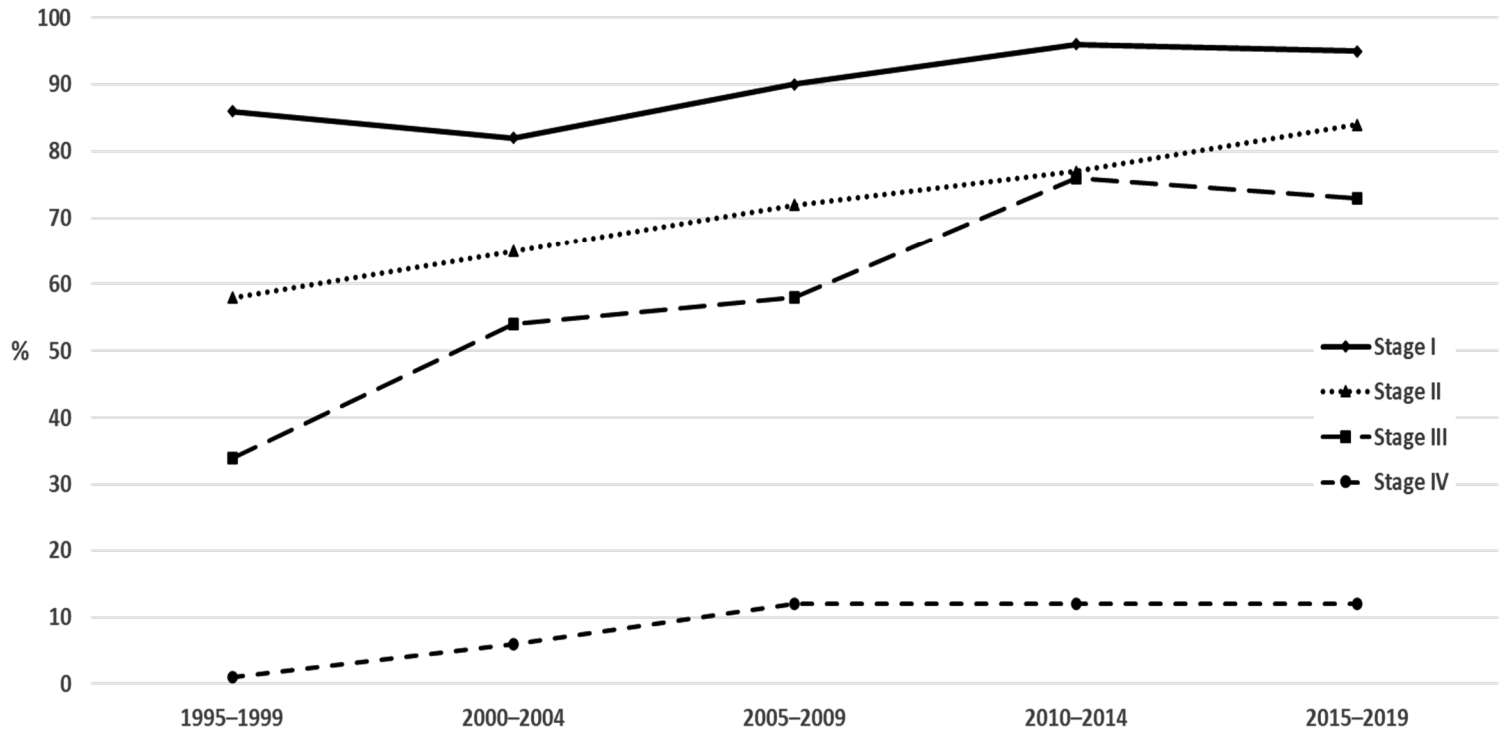

Figure 10. Stage-specific age-standardised five-year relative survival for rectal cancer, Estonia 1995–2019.

Table 4. Five-year relative survival ratio (RSR) for colon and rectal cancer in Estonia, by sex, age, stage, and subsite, 2010–2019

	Colon				Rectum			
	2010–2014		2015–2019		2010–2014		2015–2019	
	five-year RSR	95% CI	five-year RSR	95% CI	five-year RSR	95% CI	five-year RSR	95% CI
Total (age-standardised)	60	57–62	59	57–61	60	57–63	63	60–65
Sex (age-standardised)								
Men	58	54–61	58	54–61	59	54–63	60	55–64
Women	62	58–65	60	57–63	61	57–65	66	62–70
Age at diagnosis (years)								
<50	70	61–78	64	55–71	67	54–77	66	54–76
50–59	59	53–65	61	54–66	67	59–74	73	65–79
60–69	63	58–67	62	58–66	60	55–65	66	61–71
70–79	59	55–62	57	53–61	59	54–64	64	59–69
≥80	50	44–56	51	45–56	45	38–53	41	34–48
TNM stage group (age-standardised)								
I	95	85–99	94	86–97	96	83–99	95	85–98
II	87	83–90	86	81–89	77	69–83	84	77–88
III	72	67–76	73	69–77	76	70–81	73	67–77
IV	15	12–18	14	11–17	12	9–17	12	9–16
Unknown	44	37–51	46	38–54	51	44–59	61	23–69
Subsite (age-standardised)								
Right-sided colon (C18.0–18.4)	59	56–62	59	55–62				
Left-sided colon (C18.5–18.7)	61	58–65	60	56–63				
Other colon (C18.8–18.9)[a]	41	29–55	42	29–55				

[a] not age-standardised

7.2.2. Stage-specific survival differences between colon cancer subsites

A total of 4913 colon cancer cases were included in the analysis of colon cancer subsites (paper II, Table 1). The total numbers differed by subsite, ranging from 1854 cases for sigmoid colon to 231 cases for splenic flexure. Five-year RSR was the highest for ascending colon (58%) and sigmoid colon (57%), and the lowest for hepatic flexure cancer (48%) (paper II, Table 2).

In univariate analysis, hepatic flexure cancer showed 1.38 (95% CI 1.08–1.75) times higher EHR of death compared with sigmoid colon cancer patients (paper II, Table 2). In stratified multivariate analysis, there were no significant differences between subsites in stage II, but in stage III, hepatic flexure cancer patients showed 1.90 (95% CI 1.17–3.07) times higher EHR of death compared with sigmoid colon cancer patients. In stage IV, significantly higher EHR of death was seen for ascending colon and hepatic flexure cancer patients (1.40 (95% CI 1.12–1.74) and 1.51 (95% CI 1.11–2.04) respectively). In addition, patient age ≥75 years and T4 tumour were also independent prognostic factors.

7.3. CRC diagnosis and treatment

The number of newly diagnosed CRC cases in Estonia was 546 in 1997 and 847 in 2011 (paper III, Table 1). Significant changes observed in diagnosis and treatment are shown in Figures 11 and 12. The use of colonoscopy increased significantly in colon cancer patients (paper III, Table 2). Liver and pulmonary imaging increased significantly both in colon and rectal cancer patients. The 1997 study protocol did not differentiate between imaging modalities, but abdominal CT was performed 86% in colon and 89% in rectal cancer patients while thoracic CT was performed 77% in colon and 83% in rectal cancer patients in 2011. Pelvic MRI was not available in 1997, but it was used 36% in rectal cancer patients in 2011. MDT meetings were not practiced routinely in 1997, but the proportion of patients discussed in MDT was 65% for colon and 86% for rectal cancer among elective surgery patients in 2011. The use of neoadjuvant radiotherapy among stage II and III rectal cancer patients increased significantly (paper III, Table 4).

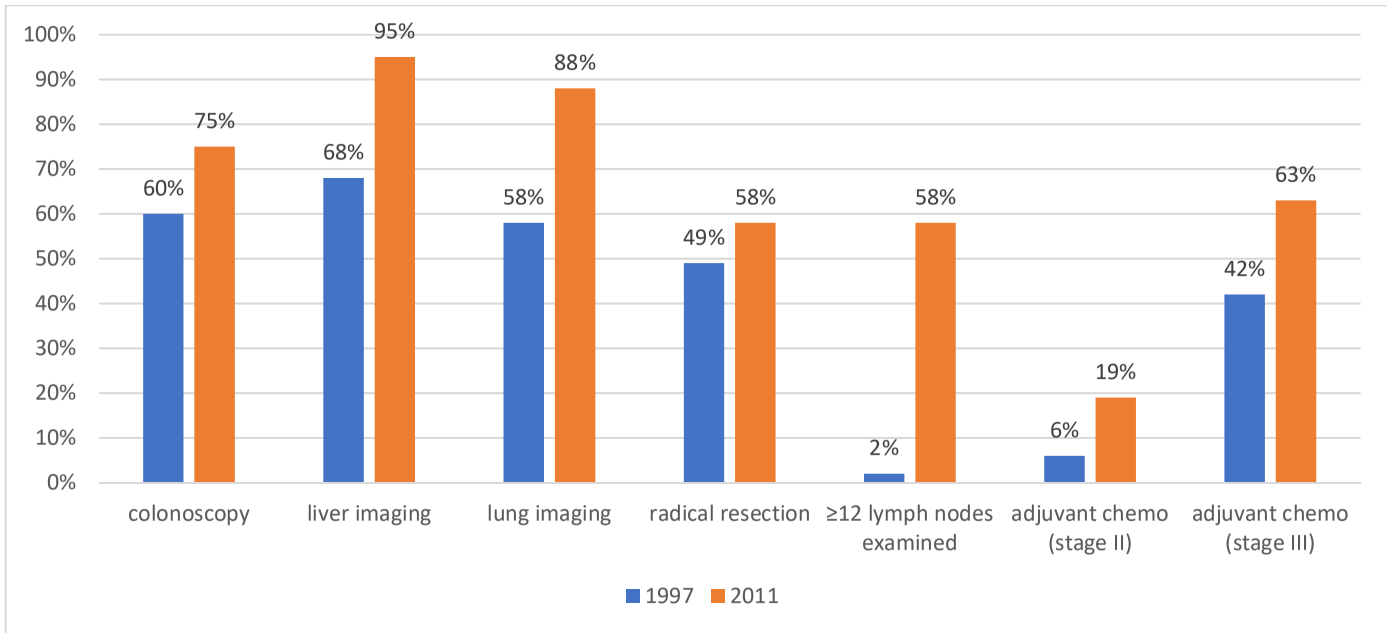

Figure 11. Changes in colon cancer diagnosis and treatment

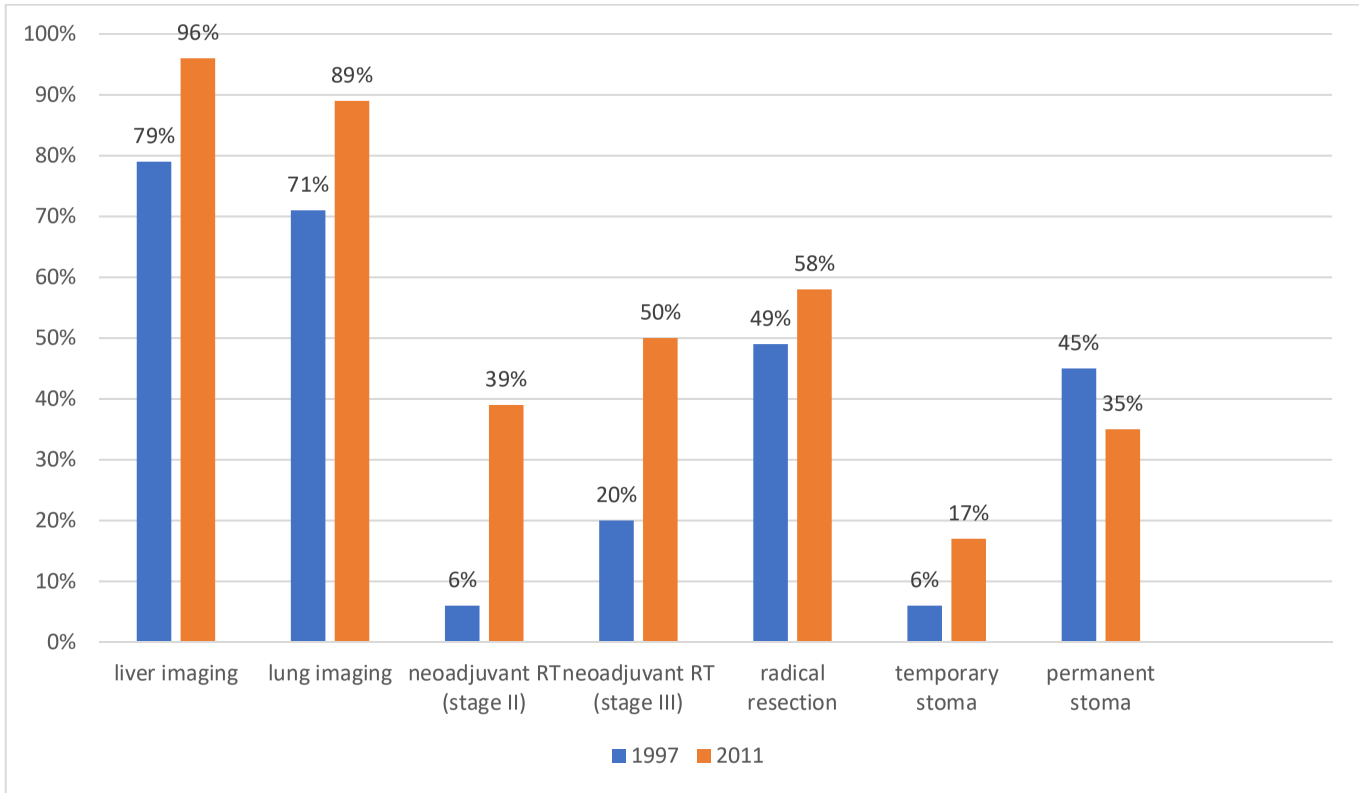

Figure 12. Changes in rectal cancer diagnosis and treatment

Radical resection rate increased significantly in colon and rectal cancer patients (paper II, Table 3). At the same time, there was an increase in the proportion of emergency surgery among surgically treated patients from 18% to 26% (p=0.017) in colon and from 7% to 14% (p=0.02) in rectal cancer. The use of temporary stomas among rectal cancer surgery patients increased while the use of permanent stomas decreased significantly. All resections were done by laparotomy in 1997, whereas the proportion of laparoscopic surgery among elective patients was 12% in colon and 8% in rectal cancer in 2011. In 2011, 5% of rectal cancer patients had their tumour removed by local excision. Complete removal of metastases was performed 13% among stage IV CRC patients in 2011. Postoperative 30-day mortality decreased from 4% to 1% (p=0.021) among radically treated colon cancer patients but was not changed significantly among radically treated rectal cancer (from 1% to 2% (p=0.412) respectively).

The proportion of patients who had ≥12 lymph nodes examined increased significantly among radically operated colon and rectal cancer patients (paper III, Table 2). The use of adjuvant chemotherapy increased significantly among stage II and III colon cancer patients (paper III, Table 4).

7.4. Methylene blue intra-arterial staining of resected colorectal cancer specimens

In the pilot study (paper IV), the median number of lymph nodes examined was 27 (ranging from 0 to 80) and 88% (53/60) of the patients had ≥12 lymph nodes examined. The proportion of patients with metastatic lymph nodes was 47% (28/60). It was more likely to find metastases in larger lymph nodes (paper III, Figure 1).

The RCT included 266 patients, of whom 130 were randomised into the intervention group (methylene blue staining) and 136 into the control group (paper V, Table 1). In 12 patients (9% of the intervention group) the staining procedure was not successful. Patient characteristics (age, gender, neoadjuvant therapy, procedure type, length of surgical specimen, T-stage) were similar between the groups.

The median number of lymph nodes examined was 27 (95% CI 23–31) in the intervention group and 16 (95% CI 14–19) in the control group (p<0.001). In the staining group more small (≤4 mm diameter) lymph nodes were examined (median number 20.5 vs. 10, p< 0.001) (paper V, Figure 1).

The proportion of patients who had ≥12 lymph nodes examined was 86% in the intervention group and 69% in the control group (p=0.001) (paper V, Table 2).

The proportion of patients with metastatic lymph nodes was 42% in the staining group and 43% in the control group (NS) (paper V, Table 2).

In the staining group 50% of the metastases were in small (≤4 mm diameter) lymph nodes, the proportion of patients who had metastases in small lymph nodes only was 8% in both groups (paper V, Figure 2).

8. DISCUSSION

This thesis provides a population-based analysis of the long-term CRC incidence and survival trends in Estonia and an analysis of survival differences between detailed colon cancer subsites stratified by stage. We observed an overall increase in CRC incidence with divergent trends across subsites, sex and age groups. The recent increase in colon cancer incidence observed in age group 60–69 along with the simultaneous rise in the proportion of stage I tumours suggest an effect of the introduction of screening. There was a considerable increase in five-year relative survival for both colon and rectal cancers with substantial heterogeneity across subsites, age and stage groups. The role of colon cancer sidedness as a prognostic factor was not consistent across RCC subsites as we found a distinct survival disadvantage among stage III hepatic flexure cancer patients.

The thesis also examined the changes in the diagnosis, staging and multimodality treatment of CRC in Estonia. Major advancements were seen, which have likely contributed to the improvement of survival. However, our analysis revealed several possibilities for further improvement.

As we detected a substantial shortcoming in the examination of the lymph nodes, we conducted an RCT to test if implementing methylene blue staining procedure of CRC specimens would improve nodal staging. This simple intervention significantly increased the number of lymph nodes examined through detecting more small diameter nodes and enabled to examine ≥12 lymph nodes in most cases. However, the proportions of patients with lymph node metastases were similar between the groups and no upstaging effect was revealed.

8.1. Strengths and limitations of the thesis

This is the first in-depth overview of CRC care and outcomes in Estonia with a focus on various aspects of diagnosis and treatment, using different study designs, including an experimental study. The main strength of the register-based studies was the ability to use long-term population-based nation-wide cancer incidence and survival data collected uniformly over the study period and the availability of information on detailed subsite and TNM stage. A large study group allowed us to perform detailed survival analyses based on subsites and stratified by TNM stages. EUROCARE HR study protocols enabled uniform and reliable data gathering from patient records by specialised doctors, therefore we could directly compare complete cohorts of two incidence years. The randomised study with a substantial sample size enabled a detailed analysis of the impact of the methylene blue staining procedure on nodal staging.

One of the weaknesses was possible misclassification of stage, particularly during earlier periods, due to less rigorous diagnostic examinations and missed regional and/or distant metastases. Stage-specific survival estimates may therefore be somewhat underestimated in the earlier periods. The overall proportion

of unknown stage was between 10−15%, but higher among the elderly. The main weakness of the study comparing detailed colon cancer subsites was the lack of characteristics beyond localisation and stage as the information about treatment details and patient comorbidities was not available in the registry data. Lack of up-to-date data on CRC diagnosis, staging and treatment was also a limitation of the dissertation. As there is no CRC quality-of-care registry in Estonia, it was only possible to analyse the data acquired from the EUROCARE HR survey. Another weakness was the retrospective nature of data collection: inaccurate or missing data in medical records could have led to some bias. Owing to certain differences between 1997 and 2011 study protocols, we were not able to compare all the parameters directly. According to the 1997 study protocol, data on clinical T and N status were not collected. Thus, the proportion of unknown stage was considerably higher for the 1997 cohort. For the RCT, a weakness was the 9% failure rate of the staining procedure. The causes of the failure were inability to cannulate the artery, perforation of the artery and leakage of dye. This could be explained with the learning curve as staining was performed by different surgeons and surgical residents.

8.2. CRC incidence and survival

The most recent trends in CRC incidence indicate a consistent increase in colon and rectal cancer in both sexes, likely due to the increasing prevalence of risk factors while the effectiveness of CRC screening program is limited. A recent study reported the rise in population-level mean BMI and prevalence of obesity in Estonia, most likely driven by overall behavioural and environmental changes that affect the whole population (Reile et al., 2020). Social inequality, tobacco smoking and excessive alcohol consumption are also problems in Estonia (National Institute for Health Development, 2021). A recent research reported divergent trends in CRC incidence across European countries associated to CRC screening (Cardoso et al., 2021). In countries with long-standing screening programmes, CRC incidence decreased substantially over time. In countries where screening programmes were implemented during the study period, CRC incidence either remained stable or increased up to the year screening was implemented. Where high screening coverage and uptake were rapidly achieved, incidence rates initially increased but then subsequently decreased. Conversely, CRC increased in countries where no large-scale screening programmes were available. The study suggests that screening has contributed substantially to the progress achieved in reducing the CRC burden and the absence of progress found for countries with no screening programmes strongly calls for their implementation. The paper points out that Estonia and Norway have recently developed efforts to make screening accessible to their populations, and other countries should follow their suit. The recent rapid rise in the incidence of CRC in screening age group presented in this thesis is consistent with the initial screening effect. However, the narrow target group (60–

69 years) and low coverage of only 50% (National Institute for Health Development, 2022) may hinder the rapid achievement of the preventive effect of CRC screening in Estonia.

Colon cancer incidence increased throughout the study period in both sexes, being more rapid in men. Rectal cancer incidence increased equally in both sexes through the study period. RCC increased through the study period in both sexes but increase of LCC was seen only in the last period for men. As shown elsewhere, overall CRC incidence may conceal divergent trends by subsite, a shift towards right-sided colon cancer has been described elsewhere (McDevitt et al., 2017). CRC subsites may have different aetiology in terms of inherited and environmental factors (Lee et al., 2015). In the United States, decreasing incidence trends were seen for both RCC and LCC, but the decline started much later for RCC (Siegel et al., 2012).

In our analyses, incidence increase was mostly limited to older age groups throughout the study period. The shift in age distribution of CRC patients towards the elderly is a common phenomenon associated with the aging society. The recent increase in colon cancer incidence observed in age group 60–69 suggests an effect of the introduction of screening. In age group <50, significant increases were seen for RCC in both sexes. In all Nordic countries, a slight increase in colon cancer incidence in men and women below 55 years of age has been apparent (Engholm et al., 2010). In the United States, an increase in CRC incidence in young men and women not covered by screening was observed (Bhandari et al., 2017), while another study found a rise particularly in RCC incidence (Austin et al., 2014).

The recent rise in the proportion of stage I tumours suggest an effect of the introduction of screening. The observed shift in stage distribution from stage II to stage III over the study period may be explained by stage migration due to improved lymph node assessment and increased use of imaging (Derwinger et al., 2007; McDevitt et al., 2017; Snaebjornsson et al., 2017). However, as lymph node size is poorly correlated with metastatic involvement (Brown et al., 2003), clinical nodal staging may result in flawed estimation of stage III in rectal cancer patients receiving neoadjuvant treatment. Although the proportion of stage IV cancer remained rather constant throughout the study period, stage migration may also have occurred as the use of CT became more prevalent leading to improved detection of distant metastases. In late 1990s, Eastern Europe countries including Estonia showed high proportion of metastatic CRC (34%) compared to Western Europe countries (24%) and USA (23% in California) (Allemani et al., 2013). The proportion of cases with distant metastasis at primary diagnosis was higher in Estonia in 2010–2014 compared to Norway, Canada or UK in 2000–2007 (Maringe et al., 2013) or in Iceland in 1997–2004 (Snaebjornsson et al., 2017), which may partly explain poorer overall survival. Decrease of metastatic CRC at diagnosis can be achieved by increasing the effectiveness of the screening programme and also by timely presentation and referral of symptomatic patients.

Colon cancer five-year RSR in Estonia increased 9% units (from 50% to 59%) over the study period. By 2015–2019, colon cancer survival in Estonia was 60% for women while it exceeded 70% in Finland, Norway, Sweden and Denmark in the same period (Engholm et al., 2010). Survival rate for men was 58% in Estonia while it was 72% in Denmark and 68% in Norway and Sweden in the same period. Our further in-depth survival analysis of detailed colon cancer subsites stratified by stage revealed no significant differences in stage II but found 1.9 times higher EHR of death for hepatic flexure cancer patients in stage III. To our knowledge, this finding has not previously been described in the literature. The diagnostic approach, indications for surgery, adjuvant treatment, and follow-up regimens are similar for different colon cancer subsites and no distinctions in tumour biology are known between the RCC subgroups. Therefore, the only likely explanation for reduced survival in stage III hepatic flexure cancer patients could be the surgical factor. Lymphatic drainage of hepatic flexure differs from the other subsites and more complex surgery is required for proper lymph node clearance. Caecal and ascending colon cancers tend to metastasise into the ileocolic lymph nodes while transverse colon cancer may spread to the lymph nodes along the middle colic artery and metastases have also been observed in the lymph nodes of gastroepiploic-omental region, infrapyloric and infrapancreatic areas (Hohenberger et al., 2009). However, hepatic flexure cancer is located between these lymph node regions and can spread towards all aforementioned pathways (Figure 1). Extended right hemicolectomy is therefore recommended for hepatic flexure cancer to remove lymph nodes from all above-mentioned areas. Regardless, some surgeons could be tempted to perform standard right hemicolectomy not only for caecal and ascending colon but also for hepatic flexure cancer, leaving behind potentially metastatic lymph nodes of the middle colic and gastroepiploic regions. Therefore, suboptimal surgery may result in recurrence and reduced survival among stage III patients of this specific location. We also detected significant survival disadvantage among ascending colon and hepatic flexure cancer patients in stage IV. Previous studies have reported reduced survival particularly in late stages of RCC (Baran et al., 2018), but we are not able to explain the finding of better survival for caecal and transverse cancer compared with other RCC subsites.

Rectal cancer survival in Estonia has gone through remarkable changes, increasing 25% units (from 38% to 63%) over the study period. In men, the five-year RSR increased from 38% in 1995–1999 to 60% in 2015–2019, whereas the change over the same period was from 46% to 72% in Denmark and from 57% to 71% in Norway (Engholm et al., 2010). An even larger increase (from 37% to 66%) was seen in women in Estonia while the change was from 52% to 74% in Denmark and from 56% to 72.5% in Finland (Engholm et al., 2010). Survival for rectal cancer was lower than for colon cancer in earlier periods of the study but has surpassed colon cancer in 2015–2019. Improved staging, better quality of TME surgery along with increasing

use of neoadjuvant and adjuvant therapies have likely contributed to the dramatic increase in the survival of rectal cancer in Estonia.

Age-related survival difference increased for both colon and rectal cancer similarly to previous findings (Brenner et al., 2004; Gondos et al., 2007). More limited treatment options and increased complication rate due to co-morbidities and frailty, diminished access to care resulting in late presentation with more advanced stage at diagnosis are but a few possible explanations for these age gradients. Larger proportion of unknown stage among the elderly suggests less thorough diagnostic process in our analysis. As the proportion of elderly patients is increasing, improving their outcomes could contribute significantly towards better overall survival. There is substantial evidence that mini-invasive surgery is associated with reduced postoperative mortality among elderly patients (Antoniou et al., 2015).

The accuracy of staging influences subsequent treatment choices and would therefore be expected to lead to improved survival. According to a CRC quality registry (Regionalt Cancercentrum Norr, 2017), the five-year RSR for stage I CRC patients diagnosed in Sweden in 2007–2016 was around 95% (91% in Estonia 2010–2014, data not shown), nearly 90% for stage II (83% in Estonia), nearly 70% for stage III (71% in Estonia), and around 15% for stage IV (13% in Estonia). This comparison suggests a slight survival deficit for Estonian patients diagnosed at stages I and II, but not at later stages. In our study, the five-year RSR for stage IV improved from 6% to 14% for colon and from 1% to 12% for rectal cancer, data from the later period is comparable with respective estimate from Sweden (15%) (Regionalt Cancercentrum Norr, 2017). Increased survival for stage IV can be explained by the change in treatment paradigm for oligo-metastatic disease with increasing application of surgery and other local therapies combined with systemic therapy to eradicate the disease (Van Cutsem et al., 2016).

8.3. CRC diagnosis and treatment

The low use of colonoscopy in 1997 could probably be explained by limited availability. Barium enema as an accessible alternative was used instead in 28% of colon cancer patients in 1997 (data not shown), but the disadvantage of this method was poor sensitivity. The use of endoscopy was significantly improved in 2011 and barium enema utilized rarely. In emergency cases (around 20% in our data), diagnosis is based on CT and these patients receive surgery without prior endoscopy. Among patients who underwent elective colon cancer surgery, colonoscopy use exceeded 90% in 2011. This result is like that shown for Switzerland (Spitale et al., 2017).

In our findings, the use of thoracic and liver imaging improved significantly. Contrast-enhanced CT is the preferred imaging modality (Horton et al., 2000). Thoracic X-ray and abdominal ultrasound were used historically in 1990s but were abandoned due to poor sensitivity. The 1997 study protocol did not

differentiate between imaging modalities, but the use of thoracic and abdominal CT exceeded 80% in 2011. MRI was not used in Estonia in 1997 and only 36% of rectal cancer patients underwent MRI in 2011. This was probably a consequence of still low availability as well as underestimating the importance of this imaging modality.

MDTs were not the routine practice in Estonia in 1997, but in 2011, 65% of elective colon and 86% of elective rectal cancer patients were discussed at MDT. This indicator is comparable with data shown for Sweden in the same year (around 60% for colon and 90% for rectal cancer) (Kolonrapport, 2018; Rektalrapport, 2018).

In 1997 only 6% of stage II and 20% of stage III rectal cancer patients received neoadjuvant radiotherapy. The receipt of radiotherapy has been affected by limited availability as the relative number of linear accelerators in Estonia has been one of the lowest in Europe according to the ESTRO-HERO survey (Grau et al., 2014). This situation had improved by 2011 when 39% of stage II and 50% of stage III rectal cancer patients received neoadjuvant radiotherapy in Estonia. An officially established CRC quality indicator in Estonia aims to measure the proportion of patients receiving neoadjuvant radiotherapy (with or without chemotherapy) among locally advanced rectal cancer with a target of 90% (Estonian Health Insurance Fund, 2022). Though, it is difficult to interpret this indicator as early stage II (T3a and T3b) rectal cancers with low risk of local recurrence may receive upfront surgery according to ESMO rectal cancer guidelines, neoadjuvant treatment decision is based on individual risk assessment analysing MRI findings on MDT meeting (Glynne-Jones et al., 2017). The use of neoadjuvant radiotherapy among radically operated rectal cancer patients was 29% in Denmark (Poulsen et al., 2018) and 39% in Norway (Guren et al., 2015) for the same period.

In our study, curative resection rate increased from 49% to 58% in colon and from 47% to 60% in rectal cancer. The proportion of CRC patients receiving surgery was 92% in Italian analysis, but it also included palliative procedures (Minicozzi et al., 2014). The largest increase in the proportion of radically operated patients was seen in age group ≥75 years (from 30% to 53%, $p<0.001$; data not shown). Reduced survival among elderly patients in early stages described in paper II can partly be explained by still high proportion of patients not receiving radical surgery. Thirty-day postoperative mortality rate among radically operated colon cancer patients decreased from 4% to 2% although significantly more elderly (≥75) patients were operated in the latter period. The reduction of postoperative CRC mortality has been described elsewhere (Iversen et al., 2014). The 2% rectal cancer 30-day mortality in our study in 2011 is comparable with data shown for Norway (1.4% in 2007–2010). As expected, mortality was much higher after emergency surgery compared with elective surgery (10% vs 2%, data not shown). In a Swiss CRC quality report, emergency surgery showed 10-fold higher (20% vs 2%) 30-day postoperative mortality rate in 2011–2012 (Spitale et al., 2017).

In our study, significantly more sphincter-preserving operations were done for rectal cancer patients as the use of temporary stomas increased and the proportion of patients with permanent stomas decreased, which is consistent with literature data (Tilney et al., 2008). In addition, in 5% of rectal cancer cases, the tumour was removed by local trans-anal excision in 2011. This less invasive and function-sparing approach is indicated in selected cases T1 cancer without adverse risk factors (Junginger et al., 2016). With gradual expansion of CRC screening programme in Estonia, we expect to diagnose more T1 cancers suitable for local excision. All CRC resections were done by open surgery in Estonia in 1997. In 2011, the proportion of laparoscopic operations was 12% in among elective surgeries in colon and 8% in rectal cancer, which is comparable to Swedish and Norwegian data at that time (Guren et al., 2015; Kolonrapport, 2018; Rektalrapport, 2018). The use of minimally invasive CRC resection is increasing in Europe, but large variation between countries and clinical centres prevails (Babaei et al., 2016). An analysis of 2017 data showed that at Tartu University Hospital, 45% of CRC resections were done laparoscopically (data not published). The 1997 study protocol did not include data collection on the resection of metastases in stage IV CRC. In 2011, complete resection rate for metastatic disease was 14% in colon and 13% in rectal cancer in Estonia. In a systematic review resection rates of CRC liver metastases ranged from 10% to 30% (Kanas et al., 2012). We observed an unexpected unfavourable trend as the proportion of emergency surgeries increased significantly. In 2011, every fourth colon cancer surgery was performed after emergency admission, a similar estimate was reported for Sweden (Kolonrapport, 2018). The main reason for both the persistently high proportion of stage IV patients and the observed increase in emergency surgery is probably delay in diagnosis. This could be caused by lack of screening program and low awareness about CRC symptoms among public as well as primary care doctors resulting in delayed presentation and referral (Courtney et al., 2012; Domínguez-Ayala et al., 2012). Another problem could be the delay of treatment due to waiting period for consultation, staging procedures, MDT and waiting list for treatment.

In 1997, the standard of examining ≥12 lymph nodes was not adopted in Estonia and only 2% of radically operated patients had sufficient number of lymph nodes examined. In a previous survey of 1997 CRC cohort in Estonia, most patients with available pathological information had one to four lymph nodes examined, therefore a significant proportion of patients were probably understaged (Innos et al., 2012). Higher lymph node yield reclassifies cancers that have just barely formed lymph node metastases to stage III. As a result, the remaining stage II cancers carry improved survival and the survival carried by the stage III cancers is also improved because of reclassification of “formerly stage II” cancers with minimal nodal burden. This type of stage migration has been referred to as the Will Rogers phenomenon (Feinstein et al., 1985). In colon cancer, upstaging of patients from stage II to stage III may improve survival by more patients being offered adjuvant chemotherapy (Goldstein, 2002; Wells et al., 2017). By 2011, the quality of pathology had significantly

improved in Estonia as 58% patients with colon cancer and 50% patients with rectal cancer had ≥12 lymph nodes examined. Nevertheless, these results remain considerably worse than those shown for Norway (78%) (Årsrapport, 2015) or Switzerland (86%) (Spitale et al., 2017) for the same period.

The poor state of lymph node examination in Estonia prompted us to conduct a trial to explore a possible method to improve the situation. Our RCT showed a significant increase of the total number of lymph nodes examined in the methylene blue staining group compared to the control group (median lymph node count 27 vs. 16 respectively) clearly confirming the results of previous studies, where similar gains were reported (Borowski et al., 2014; Kerwel et al., 2009; Klepšytė et al., 2012; Liu et al., 2014; Markl et al., 2008; Törnroos et al., 2011). We found a significant difference in lymph node count between the staining and non-staining groups among smaller lymph nodes with a diameter of ≤4 mm while the number of larger nodes was similar for the groups. Markl et al. reported a similar effect for the group of <6 mm diameter lymph nodes (Markl et al., 2008). This can be explained by the fact that larger lymph nodes are detectable from the mesocolon/mesorectum more easily by visual inspection and manual palpation while small lymph nodes are difficult to distinguish from the adipose tissue and the effect of staining is particularly important to notice them (Markl et al., 2013). Yet the clinical role of small lymph nodes is not irrelevant, in our study 8% of all patients had metastases in small-diameter (≤4 mm) lymph nodes only. In our trial the staining procedure enabled to identify 17% more patients fulfilling the standard of ≥12 lymph node count, which can be considered highly significant improvement. Staining has increased lymph node yield to a roughly similar degree in other randomized trials (Borowski et al., 2014; Liu et al., 2014; Markl et al., 2008). Methylene blue staining procedure could change practice by refining risk assessment and therefore allowing to omit unnecessary adjuvant chemotherapy for a number of stage II CRC patients.

The proportion of patients receiving adjuvant chemotherapy increased significantly in our study, probably due to stage migration caused by dramatically improved nodal staging and improved adherence of evidence-based guidelines. Among radically resected stage III colon cancer patients, this proportion was 69% in 2011 (data not shown), while it was 59% in Switzerland in 2011–2012 (Spitale et al., 2017). In comparison of 6 European countries, the proportion of resected stage III colon cancer receiving chemotherapy in Estonia was not inferior to Western European countries in 2011 (Minicozzi et al., 2020).

9. CONCLUSIONS

This thesis provides an in-depth overview of long-term CRC incidence, care, and survival in Estonia, showing divergent trends across subsites, age, and stage groups. The study identified several shortcomings in early detection, care, and survival, enabling us to give recommendations for further practice and health care policy.

1. CRC incidence in Estonia is steadily rising with no sign of stabilisation yet. We observed divergent incidence trends across subsites, sex and age groups. The recent increase in colon cancer incidence observed in age group 60–69 along with the simultaneous rise in the proportion of stage I tumours suggest an effect of the introduction of screening. Five-year RSR improved significantly for both colon and rectal cancer patients but remained lower than in Northern Europe. We observed substantial survival heterogeneity across subsites, age and stage groups. Diagnosis delay is a major obstacle as the proportion of CRC cases diagnosed at stage IV remained high.
2. The role of colon cancer side as a prognostic factor was not consistent across RCC subsites. We observed a distinct survival disadvantage among stage III hepatic flexure cancer patients, further research is required to identify the underlying reasons.
3. Major improvements were seen in the diagnosis, staging and treatment of CRC in Estonia from 1997 to 2011 contributing to better outcomes, however there is substantial room for further progress. Increase in emergency surgery indicates shortcomings in timely diagnosis and treatment.
4. Methylene blue staining of resected CRC specimens significantly improves staging accuracy by finding more small-diameter lymph nodes and enables to detect ≥12 lymph nodes in most cases. Through precise risk stratification for stage II CRC patients, the staining procedure could avoid unnecessary adjuvant chemotherapy.

10. IMPLICATIONS FOR PRACTICE AND HEALTH POLICY

To reduce CRC incidence in Estonia, tackling risk factors and increasing screening effectiveness is necessary. The quality of screening needs to be assessed through regular monitoring. There is also a need to expand the target group of the screening program and improve its coverage.

To improve early detection, raising awareness about CRC symptoms among the public is necessary. Oncologic watchfulness among primary care doctors must result in timely referral of symptomatic patients to colonoscopy. A more efficient screening program would also improve early detection.

To improve the quality of diagnosis and treatment, Estonian cancer care system must adapt to rising CRC incidence, ensuring timely diagnosis and optimal treatment for all patients regardless of age. Routine monitoring of performance and outcomes is necessary to find the areas for improvement. Ad-hoc studies such as used in this thesis are not a sustainable solution, there is a need for a national CRC quality-of-care registry in Estonia. Hepatic flexure cancer must be managed with special attention. Extended right hemicolectomy with proper lymph node clearance is mandatory as a curative surgical procedure for this subsite; if the experience of laparoscopic approach is limited, it should be performed in an open manner. Methylene blue staining has been introduced in clinical practise in Tartu University Hospital since the completion of the trial, we suggest routine use of this technique for all CRC resections with curative intent.

Several issues raised in this thesis have been addressed by the Estonian Cancer Control Plan 2021–2030 but proposed actions need to be effectively implemented. Implications of this thesis are likely to be relevant for other Eastern Europe countries with economic transition, in view of persisting inequalities in CRC outcomes across Europe.

11. FUTURE DIRECTIONS

Further studies are warranted to examine the effect of diagnosis and treatment delays on CRC outcomes in Estonia. It is also necessary to evaluate the centralization of surgical treatment and compare treatment outcomes in different cancer centres in Estonia. Estonia should participate in international comparative studies in the future. Detailed analysis of the surgical care and other treatment-related factors of hepatic flexure cancer is required to look for the underlying reasons for reduced survival of this subsite. Further studies on stage-specific survival differences between detailed colon cancer subsites based on larger number of patients are required to confirm our findings in international context.

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13. SUMMARY IN ESTONIAN

Kolorektaalvähi ravi ja tulemite hindamine ning nende parandamise võimalused Eestis

Taust

Kolorektaalvähk ehk käär- ja pärasoolevähk on pahaloomuline kasvaja, mis saab alguse jämesoole limaskestast. See haigus on oluline rahvatervishoiu probleem, olles üks sagedasemaid vähihaigestumuse ja -surma põhjuseid maailmas. Haigestumus on kõrgeim arenenud riikides, ent tõuseb kiiresti arenevates riikides. Selle põhjuseks on ilmselt muutused rahvastiku tervisekäitumises: kolorektaalvähi riskitegurid on vähene füüsiline aktiivsus, rasvumine, rohkelt lihatooteid ning vähe juurvilju, puuvilju ja kiudaineid sisaldav dieet, samuti suitsetamine ja liigne alkoholi tarbimine. Kolorektaalvähi sagedamateks sümptomiteks on veritsus, sooletegevuse muutused, nõrkus, aneemia, kaalulangus, kõhuvalu. Samas on need sümptomid mittespetsiifilised ja varane kolorektaalvähk on sageli asümptomaatiline. Kolorektaalvähi ennetamiseks ja varaseks avastamiseks on välja töötatud tõenduspõhine sõeluuring, mis võimaldab efektiivselt vähendada suremust. Multimodaalne ravi on pidevalt arenenud, tuues kaasa ravitulemuste paranemise. Varase avastamise ja kaasaegse raviga on võimalik saavutada kõrget elulemust. Kolorektaalvähi peamine diagnoosimismeetod on koloskoopia, diagnoosi kinnitamiseks on vajalik histoloogiline uuring. Kuratiivses ravis on kesksel kohal kirurgiline ravi, kuid tulemusi parandab neoadjuvantne kiiritusravi lokaalselt levinud pärasoole vähi korral ja adjuvantne süsteemravi patsientidel, kellel on suur kaugleviku risk. Hea ravikvaliteedi võtmekomponendid on varane diagnoosimine, tsentraliseeritud ravi täiendava subspetsialiseerumise ja suurte ravimahtudega, multidistsiplinaarne käsitlus ning raviprotsessi ja -tulemuste järjepidev monitoorimine.

Eestis on kolorektaalvähi haigestumus püsiva tõusutrendiga alates vähiregistri algusaastatest. Eesti oli üks viimaseid Euroopa riike, kus alustati kolorektaalvähi sõeluuringuga (2016). Hetkeseisuga ei saa sõeluuringuprogrammi pidada optimaalseks, sest sihtrühma vanusevahemik on kitsam kui enamikus Euroopa riikides (Eestis 60–69, mujal 50–75) ja hõlmatus on ligikaudu 50% (soovitatud vähemalt 70%). Kolorektaalvähi ravitulemused on varasematel perioodidel olnud halvad: EUROCARE-3 (1990–1994) uuringus oli Eesti kolorektaalvähi viie aasta suhteline elulemus märgatavalt alla Euroopa keskmise, eriti pärasoolevähi korral. Hilisemas EUROCARE-5 (1999–2007) uuringus oli Eesti enim elulemust parandanud riikide hulgas, kuid siiski jäid tulemused alla Euroopa keskmise ja oluliselt madalamaks võrreldes parimate riikide tulemustega. Üleeuroopaliste elulemuserinevuste selgitamiseks on läbi viidud süvauuringud (*EUROCARE High Resolution Studies*), milles analüüsiti detailselt diagnostikat ja ravi eri riikides. Eesti 1997. aasta kolorektaalvähi patsientide kohordi analüüs tõi välja olulised puudujäägid patoloogilises uurimises ja

staadiumide määramises, aga ka puuduliku neoadjuvantse ning adjuvantse ravi rakendamise.

Töö eesmärgid

Doktoritöö peamine eesmärk oli hinnata kolorektaalvähki haigestumust, ravikvaliteeti ja elulemust Eestis ning leida võimalusi tulemuste parandamiseks.
Töö alaeesmärgid:

1. Hinnata kolorektaalvähi pikaajalisi haigestumuse ja elulemuse trende Eestis enne ja pärast sõeluuringuprogrammi alustamist, keskendudes alapaikmetele ja staadiumidele.
2. Analüüsida võimalikke elulemuse erinevusi käärsoolevähi detailsete alapaikmete vahel, võttes arvesse TNM staadiumi.
3. Hinnata muutusi kolorektaalvähi diagnostikas ja ravikäsitluses Eestis.
4. Hinnata kolorektaalvähi operatsioonipreparaatide intraarteriaalse metüleensinisega värvimise mõju lümfisõlmede leidmisele.

Metoodika

Eesti Vähiregistrist päriti andmed ajavahemikul 1995–2019 Eestis täiskasvanutel (vanus ≥15 aastat) diagnoositud kolorektaalvähi juhtude kohta, tuginedes Rahvusvahelise Haiguste Klassifikatsiooni 10. versioonile (RHK-10 koodid C18–20). Käärsoolevähk (C18) rühmitati parempoolseks (C18.0–18.4), vasakpoolseks (C18.5–18.7) ja muuks (C18.8–18.9) käärsoolevähiks. Pärasoolevähk hõlmas RHK-10 koodid C19–20. Staadium klassifitseeriti vastavalt TNM klassifikatsioonile. Haigestumuskordajad arvutati kasutades aastakeskmist rahvastikku ja väljendati 100 000 inimaasta kohta. Vanusestandardimiseks kasutati maailma standardrahvastikku. Kordajate modelleerimiseks ja aastase protsentuaalse muutuse (koos 95% usaldusvahemikuga) arvutamiseks kasutati *joinpoint* regressioonanalüüsi. Elulemuse analüüsimiseks jälgiti patsientide elustaatust kuni 31.12.2019, linkides vähiregistri andmed Rahvastikuregistri andmetega. Analüüsist jäeti välja lahangul diagnoositud ja ainult surmatunnistuse alusel registreeritud juhud. Isiku surma või emigreerumise korral tuvastati vastav kuupäev. Viie aasta suhteline elulemusmäär koos 95% usaldusvahemikuga saadi tegeliku elulemuse jagamisel eeldatava elulemusega, viimane leiti Ederer II meetodil rahvastiku elutabelite põhjal. Varasemate perioodide puhul kasutati kohort-analüüsi, hilisemate perioodide korral, kui patsiendid ei olnud veel läbinud viieaastast jälgimisperioodi, kasutati perioodmeetodit. Vanusele kohandatud elulemusmäärade arvutamiseks kasutati rahvusvahelisi standardeid. Käärsoolevähi alapaikmete elulemuse võrdlemiseks arvutati liigriskisuhted (*excess hazard ratio, EHR*) generaliseeritud lineaarmudeli abil kihitatuna staadiumi järgi. Analüüs kohandati vanusele, soole, diagnoosiperioodile ja T kategooriale.

Diagnostika ja ravi analüüsimiseks kasutati kolorektaalvähi patsientide 1997. ja 2011. aasta kohortide andmeid, mis olid algselt kogutud üleeuroopaliste EUROCARE süvauuringute raames. Vähiregistri abil tuvastatud patsientide

detailsed diagnostika- ja raviandmed koguti retrospektiivselt patsientide haiguslugudest lähtuvalt rahvusvahelisest uuringuprotokollist.

Randomiseeritud sekkumisuuringus hinnati kolorektaalvähi operatsioonipreparaatide intraarteriaalse metüleensinisega värvimise mõju lümfisõlmede leidmisele. Uuring viidi läbi Tartu Ülikooli Kliinikumis ja uuringusse kaasati 266 kolorektaalvähi patsienti, kellele tehti sooleresektsioon kuratiivsel eesmärgil ajavahemikus märts 2013 kuni aprill 2015. Patsiendid randomiseeriti sekkumisrühma (teostati värvimine) ja kontrollrühma. Värvimise protseduur teostati operatsioonitoas pärast preparaadi eemaldamist. Formaliin-fiksatsiooni järel leiti patoloogilisel uuringul soolekinnistist lümfisõlmed, mikroskoopilisel uuringul hinnati iga lümfisõlme diameetrit ja metastaatilist haaratust.

Rühmade võrdlemiseks kasutati kirjeldava statistika meetodeid. Kõik statistilised analüüsid viidi läbi programmiga STATA (Stata, College Station, Texas, USA). Uuringuprotokollid kooskõlastati Tallinna Meditsiiniuuringute Eetikakomitee või Tartu Ülikooli Inimuuringute Eetikakomitee poolt.

Tulemused ja arutelu

Kokku diagnoositi aastatel 1995–2019 Eestis 19434 kolorektaalvähi juhtu. Kui perioodil 1995–1999 diagnoositi keskmiselt 603 juhtu aastas, siis perioodiks 2015–2019 oli aastakeskmine juhtude arv suurenenud 972 juhuni. Vanemate vanuserühmade osakaal suurenes uuringuperioodil olulisel määral, ent sooline jaotus ei muutunud. Parempoolse käärsoolevähiga patsientide seas oli oluliselt rohkem naisi ja eakaid patsiente.

Pikaajaline haigestumustrend näitab haigestumuse jätkuvat tõusu nii käärkui pärasoolevähi puhul, kusjuures enim suurenes parempoolse käärsoolevähi haigestumus. Põhjuseks võib tõenäoliselt pidada riskitegurite levimuse suurenemist rahvastikus. Hiljuti avaldatud 21 Euroopa riigi analüüsis näidati, et haigestumus väheneb riikides, kus on pikka aega rakendatud efektiivset sõeluuringuprogrammi, kuid suureneb riikides, kus sõeluuring puudub. Eestis alustati kolorektaalvähi skriininguga 2016. aastal, ent sihtrühma vanusevahemik on kitsam kui enamikus Euroopa riikides ja sihtrühma hõlmatus on vaid 50%. Viimastel aastatel täheldatud haigestumuse tõus vanuserühmas 60–69 koos I staadiumi suurenenud osakaaluga viitavad sõeluuringu mõjule.

Käärsoolevähi viie aasta suhteline elulemus oli 50% aastatel 1995–1999 ja 59% aastatel 2015–2019, tulemus paranes enam naistel. Siiski jäi see näitaja ligikaudu kümne protsendi võrra madalamaks võrreldes Põhjamaadega, mis võib olla põhjustatud kaugelearenenud kasvajate püsivalt suurest osakaalust. Märgatav oli elulemuse tõus IV staadiumi korral, mida võib seostada paradigmamuutusega oligometastaatilise haiguse ravis. Käärsoolevähi alapaikmete staadiumipõhises analüüsis leiti, et III staadiumi vähi korral on maksanurgavähi elulemus 1.9 korda halvem võrreldes sigmasoole vähiga. Meile teadaolevalt ei ole sarnast leidu kirjanduses varem mainitud. Kuna diagnostika, näidustus operatsiooniks ning adjuvantravi ja jälgimine on kõikide alapaikmete puhul

sarnased, siis põhjuseks võib olla operatsiooni kvaliteet. Maksanurga kasvajad võivad erinevalt teistest käärsoole parema poole alapaikmetest levida nii ileokoolilistesse kui ka keskmise käärsoolearteri ja maolukuti piirkonna lümfisõlmedesse. Seetõttu on selle kasvajapaikme korral näidustatud laiendatud parempoolne hemikolektoomia kõigi nende lümfisõlmede eemaldamisega, siiski piirdutakse sageli tavapärase parempoolse hemikolektoomiaga.

Pärasoolevähi prognoos paranes Eestis märkimisväärselt: elulemus tõusis uuringuperioodil koguni 25% võrra (38% vs 63%), suurem oli tõus naistel. Siiski jäi see näitaja madalamaks võrreldes Põhjamaadega, põhjuseks võib taaskord olla IV staadiumi kasvajate suur osakaal. Elulemuse tõus oli märgatav peaaegu kõigis alarühmades, kusjuures III staadiumis paranes elulemus uuringuperioodil lausa 39% võrra (34% vs 73%). Elulemuse paranemise põhjusteks on tõenäoliselt korrektsem staadiumi määramine, kvaliteetsem kirurgiline ravi ning suurem neoadjuvantse ja adjuvantse ravi kasutus.

1997. ja 2011. aasta kohortide võrdluses suurenes oluliselt koloskoopia kasutus esmases diagnostikas, mis asendas varem kasutatud röntgenkontrastuuringu, mille puudujäägiks oli vähene tundlikkus. Oluliselt paranes piltdiagnostika kasutus staadiumi määramiseks – kompuuteruuringut kasutati 2011. aastal enam kui 80% juhtudel. Pärasoolevähi lokaalset levikut hakati hindama magnettomograafia abil, kuid uuringu kasutus jäi siiski tagasihoidlikuks (36%). Kasutusele võeti multidistsiplinaarne otsustusprotsess: 86% pärasoolevähi patsientidest tehti raviotsus konsiiliumis. Neoadjuvantse kiiritusravi kasutus pärasoolevähi korral tõusis 6%-lt 39%-ni II staadiumi korral ja 26%-lt 50%-ni III staadiumi korral. Meetodi kasutust piiras varasemalt lineaarkiirendite vähesus Eestis, kuid hilisemal perioodil oli kiiritusravi kasutus Eestis kõrgem kui Norras või Taanis. Radikaalse kirurgia osakaal tõusis 49%-lt 58%-ni, suurim oli tõus ≥75 vanuserühmas. Operatsioonijärgne suremus vähenes käärsoolevähi patsientidel 4%-lt 2%-ni, olles võrreldav Norra või Šveitsi andmetega. Kasutusele võeti laparoskoopiline kirurgia ja pärasoolevähi korral kasutati sagedamini sfinkterit säilitavaid operatsioonimeetodeid. Ebasoodsaks trendiks oli erakorraliste operatsioonide sageduse tõus, mille põhjuseks võib tõenäoliselt pidada viivitusi vähi diagnoosimisel ja ravis. Kui 1997. aastal uuriti vähemalt 12 lümfisõlme vaid 2% juhtudest, siis see näitaja paranes 2011. aastaks 50%-ni pärasoolevähi ja 58%-ni käärsoolevähi patsientidel. Siiski jäi näitaja oluliselt madalamaks võrrelduna Norra või Šveitsi vastavate näitajatega samal perioodil. Lümfisõlmede diagnostika paranemise tulemusena toimus staadiumi nihe II staadiumist III staadiumi ning ühtlasi suurenes adjuvantse keemiaravi osakaal. Radikaalselt opereeritud käärsoolevähi III staadiumi patsientidest said keemiaravi 69%, mis on võrreldav mitmete Lääne-Euroopa riikidega samal perioodil.

Lümfisõlmede uurimise parandamiseks läbiviidud randomiseeritud uuringus leiti, et metüleensinisega värvimise meetod parandab oluliselt staadiumi määramist, tagades suurema hulga väikse diameetriga lümfisõlmede leidmise ja võimaldades enamikul juhtudest uurida ≥12 lümfisõlme. Meetodi praktiline väärtus seisneb selles, et tänu riskihinnangu täpsustamisele on võimalik osadel juhtudel loobuda adjuvantravist.

Järeldused

Doktoritöö annab põhjaliku ülevaate kolorektaalvähi pikaajalistest haigestumuse ja elulemuse trendidest ning ravikäsitluse muutustest Eestis. Töö käigus tuvastatud probleemid võimaldavad anda soovitusi tervishoiupoliitika ja kliinilise praktika tõhustamiseks Eestis.

1. Kolorektaalvähi haigestumus Eestis suureneb jätkuvalt, kuid trendid erinevad alapaikme, soo ja vanuse lõikes. Hiljutine haigestumuse tõus vanuserühmas 60–69 koos I staadiumi suurenenud osakaaluga viitavad sõeluuringu mõjule. Viie aasta suhteline elulemus paranes oluliselt nii käärsoole- kui ka pärasoolevähi patsientidel, kuid jäi madalaks võrreldes Põhjamaade näitajatega. Elulemuse mahajäämus on tõenäoliselt tingitud diagnoosi hilinemisest, sest IV staadiumis diagnoositud juhtude osakaal on jätkuvalt suur.
2. Parempoolse käärsoolevähi halvem prognoos ei ilmnenud kõigi alapaikmete korral. Oluliselt madalam elulemus ilmnes III staadiumi maksanurga kasvajate puhul, mille põhjuste selgitamiseks on vaja täiendavaid uuringuid.
3. 1997. ja 2011. aasta võrdluses on Eestis oluliselt paranenud kolorektaalvähi diagnostika, staadiumi määramine ja ravi, kuid leiti siiski mitmeid probleeme, mis jätavad ruumi edasiseks arenguks. Suurenenud erakorraliste operatsioonide hulk viitab viivitustele vähi diagnoosimisel ja ravis.
4. Kolorektaalvähi operatsioonipreparaatide värvimine intraarteriaalse metüleensinisega parandas oluliselt staadiumi määramist võimaldades enamikul juhtudest tuvastada ≥12 lümfisõlme. Meetodi kasutamisel on tänu riskihinnangu täpsustamisele osadel juhtudel võimalik loobuda adjuvantravist.

Praktilised soovitused ja edasised uurimissuunad

Kolorektaalvähi haigestumuse vähendamiseks tuleb keskenduda elustiiliga seotud riskitegurite levimuse langetamisele rahvastikus ja tõhustada sõeluuringut. Tuleb pidevalt monitoorida sõeluuringu kvaliteeti, laiendada sihtrühma vanusevahemikku ja parandada hõlmatust.

Varase avastamise tõhustamiseks on vajalik elanikkonna ja esmatasandi meedikute teadlikkuse suurendamine kolorektaalvähi sümptomitest, et sümptomaatilised patsiendid jõuaksid õigeaegselt koloskoopiale. Varasele avastamisele aitab kaasa ka tõhus sõeluuring.

Et tagada õigeaegne ja kvaliteetne diagnoosimine ja ravi igas vanuses patsientidele, peab tervishoiusüsteem kohanema üha suureneva kolorektaalvähi patsientide arvuga. Kvaliteedi tagamiseks on vajalik raviprotsessi ja -tulemuste pidev hindamine. Käesolevas töös kasutatud ad-hoc uuringud ei ole selleks jätkusuutlik lahendus, vajalik on üleriigiline kolorektaalvähi kvaliteediregister. Maksanurga vähi kirurgilises ravis tuleb regionaalsete lümfisõlmede eemaldamiseks teha laiendatud parempoolne hemikolektoomia. Kui laparoskoopiline

kogemus on piiratud, tuleb selleks eelistada avatud meetodit. Operatsioonipreparaatide metüleensinisega värvimise protseduur on Tartu Ülikooli Kliinikumis rutiinses kasutuses, soovitame seda kasutada kõigil radikaalselt opereeritud kolorektaalvähi patsientidel.

Mitmed käesolevas töös väljatoodud probleemid on leidnud käsitlust ka vähitõrje tegevuskavas, ent võtmeküsimus on soovitatud tegevuste efektiivne rakendamine praktikasse.

Edaspidi tuleb uurida diagnostika ja ravi viivituse mõju vähitulemitele Eestis. Samuti on vajalik hinnata kirurgilise ravi tsentraliseeritust ja ravitulemusi eri vähikeskustes. Eesti peaks jätkuvalt osalema rahvusvahelistes võrdlusuuringutes. Et uurida maksanurga vähi halvema elulemuse põhjuseid, on vajalik detailne kirurgilise ravi analüüs. Töö tulemuste kinnitamiseks rahvusvahelises kontekstis on vajalik uuringut korrata suuremates patsiendirühmades.

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15. PUBLICATIONS

16. CURRICULUM VITAE

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Publikatsioonid:

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