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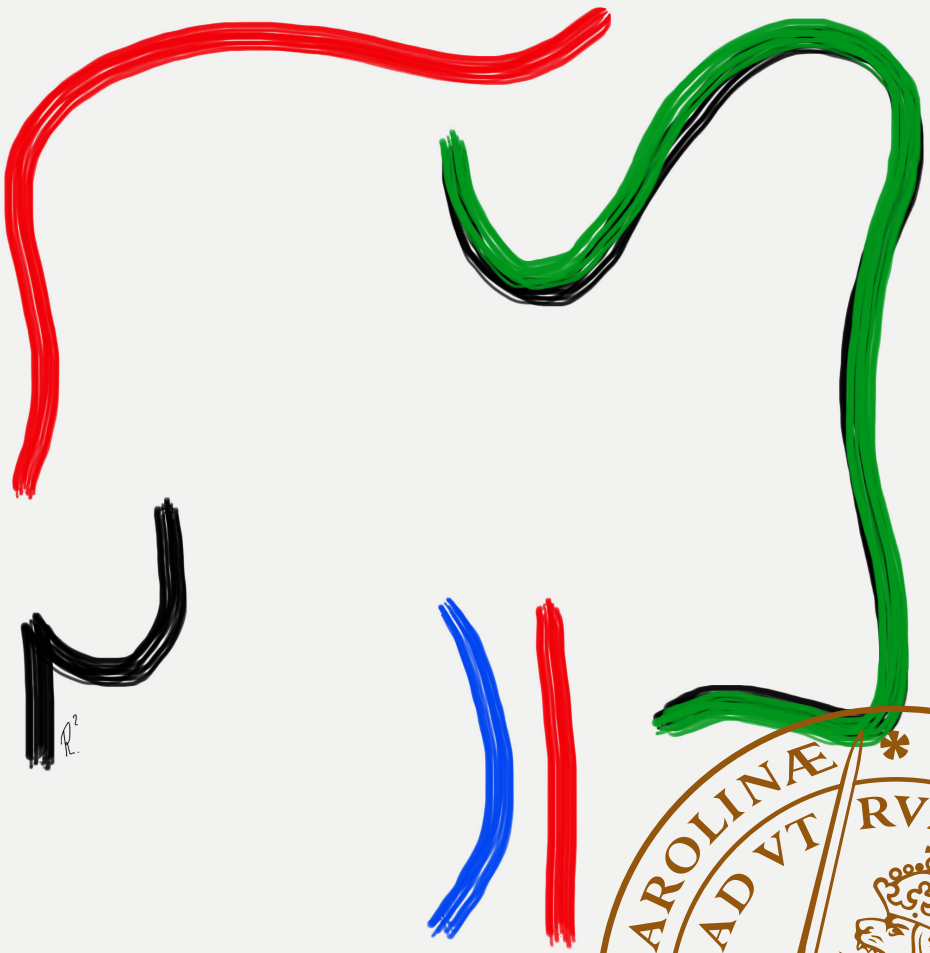

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Roberto Rosén

LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 5th of December at 09.00 in Agardhsalen, Clinical Research Centre
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Abstract:

Background: Work-up and management of patients with early colorectal cancer (CRC) is challenging and complex, striving to select patients for organ-sparing local resection instead of surgery. In addition, current risk assessment performed following local resection is insecure and results in overtreatment with surgery.

Aims: The overall aim of this thesis was to optimise work-up and management of patients with early CRC by (I) investigating the accuracy of tumour and nodal staging of CT for early colon cancer (CC) and (II) MRI for early rectal cancer (RC), (III) to determine costs associated with local and surgical treatments of early RC, exploring economic aspects of initiating treatment with local resection and (IV) to investigate impact of tumour location on risk of lymph node metastasis and recurrence in early RC.

Methods: Papers I, II and IV are retrospective multicentre cohort studies based on prospectively collected data from the Swedish colorectal cancer registry; (I) Patients with CC, staged as cT1-2 by CT or confirmed pT1 (2009-2018), (II) Patients with RC, staged as cT1-2 by MRI or confirmed pT1 (2009-2018), (IV) Patients with early (pT1-2) RC undergoing surgical resection (2009-2021). Paper III is a cost analysis on T1 RC, based on retrospective data from Skåne County 2011-2017 including surgically and locally resected patients. Paper III also comprises a hypothetical cost scenario based on data from the Swedish colorectal cancer registry including surgically treated T1 RC 2009-2017.

Results and conclusions: Clinical staging of early CRC dictates subsequent treatment and CT and MRI are pivotal in the work-up of CC and RC, respectively. In paper I, CT was found to frequently understage locally advanced CC as cT1-2 and pT1 tumours as cTx. In paper II, MRI was found to frequently understage pT3 RC and overstage pT1 tumours. In addition, both modalities were highly inaccurate in nodal staging. Based on our findings, CT and MRI are inaccurate in staging early CRC and should not dictate eligibility for local resection.

Health economic evaluations of different treatment alternatives for patients with early RC are necessary in times of escalating health care costs. In Paper III, total 1-year costs of T1 RC were investigated, and endoscopic submucosal dissection was significantly less expensive ($p<0.001$) compared to transanal endoscopic microsurgery and surgical resection techniques.

Risk factors for lymph node metastasis in T1 RC dictate whether local resection can be deemed as final treatment or subsequent surgical resection should be recommended. In Paper IV, distal tumour location was found to be an independent risk factor for recurrence in early RC (HR 2.051, CI 1.248–3.371, $P < 0.05$), which should be taken into account when managing early RC.

Key words: early colorectal cancer, lymph node metastases, recurrence, staging, diagnostic, cost analysis, location

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MADE IN SWEDEN

To my Family.

"The incision should be as long as necessary
and as short as possible."
Theodore Kocher (1841-1917)

Table of Contents

Original Papers

The present thesis is based on the following original papers, referred to by their Roman numeral, I-IV:

I. Wetterholm E, Rosén R, Rahman M, Rönnow CF. CT is unreliable in locoregional staging of early colon cancer: A nationwide registry-based study. Scand J Surg. 2023 Mar;112(1):33-40.

II. Rosén R, Nilsson E, Rahman M, Rönnow CF. Accuracy of MRI in early rectal cancer: national cohort study. Br J Surg. 2022 Jun 14;109(7):570-572.

III. Arthursson V, Rosén R, Norlin JM, Gralén K, Toth E, Syk I, Thorlacius H, Rönnow CF. Cost comparisons of endoscopic and surgical resection of stage T1 rectal cancer. Endosc Int Open. 2021 Sep 16;9(10):E1512-E1519.

IV. Rosén R, Thorlacius H, Rönnow CF. Is tumour location a dominant risk factor of recurrence in early rectal cancer? Surg Endosc. 2025 Feb;39(2):1056-1066.

Abbreviations

CC	Colon cancer
CI	Confidence interval
CRC	Colorectal cancer
CT	Computed tomography
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
FIT	Fecal Immunochemical Test
gFOBT	Faecal Occult Blood Test
HR	Hazards ratio
LNM	Lymph node metastases
LVI	Lymphovascular invasion
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
OR	Odds ratio
RC	Rectal cancer
SCRCR	Swedish Colorectal Cancer Registry
TEM	Transanal endoscopic microsurgery
TME	Total mesorectal excision

Background

Colorectal cancer

Anatomy

The colon, which is derived from the Greek word "koluein" meaning "to slow down," is a large-diameter hollow organ in continuity with the small intestine and follows a frame-like trajectory within the peritoneal cavity. The main physiological function of the colon is (re-)absorption of water and electrolytes, propulsion of its content towards the distality in addition to host bacteria responsible for production/transformation of vitamins. The rectum, in continuity with the colon, serves as a “reservoir” and provides mechanisms for continence and emptying, in coordination with the anal sphincter and the pelvic floor muscles.

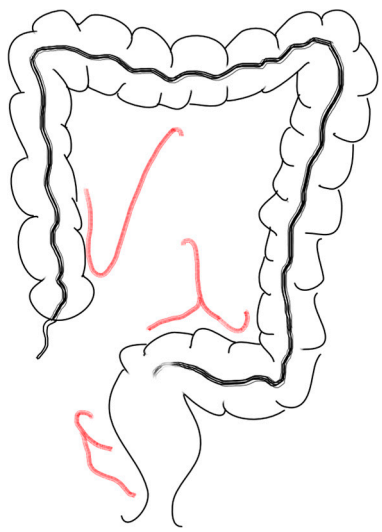

Figure 1. The colorectal tract
Schematic illustration of the colorectal tract and its arterial supply, with the superior mesenteric artery supplying the right and transverse colon, the inferior mesenteric artery supplying the left, sigmoid and proximal rectum, and the branches of the internal iliac artery supplying the mid and lower rectum.

During foetal life, the gut performs an anticlockwise rotation of 270 degrees, shaping the final disposition of the colon. Understanding this foetal rotation clarifies how the colorectal tract is fixed, its vascular supply, lymphatic drainage across different segments, and its anatomical relationships with other abdominal and pelvic organs.

The colon is divided in multiple segments as follows: the right or ascending colon, including the caecum and the appendix; the transverse colon running between the hepatic or right flexure and the splenic or left flexure; the left or descending colon and the sigmoid colon, in continuity with the rectum that follows distally. The rectum is proximally delimited by the sacral promontory and distally by the anus.

The wall of the colorectal tract is composed of, from the intraluminal surface to the extraluminal depth, a mucosa, a submucosa, a muscularis propria, a subserosa and a serosa.[1]

Aetiology

"The Hallmark of cancer", initially published in 2000[3] and updated in 2011[4], has defined general conditions needed to induce cancer. Environmental and genetic factors lead to the accumulation of genetic mutations and epigenetic alterations driving malignant transformation[5]. In colorectal cancer (CRC), two major pathways describing the sequence of genetic alterations leading to malignant transformation have been described, the adenoma-carcinoma pathway and the sessile-serrated pathway.

The pathways from polyp to adenocarcinoma

Lockhart-Mummery and *Dukes* initially suggested as early as 1927 that CRC was associated with polyps[6]. Further investigations led by *Morson*[7, 8] set the path to *Vogelstein*'s findings, who eventually described in 1988 the sequence of genetic mutational events leading to malignant degeneration of normal mucosal cells to adenocarcinoma[9]. The first step of the adenoma-carcinoma sequence consists of a mutation of the APC gene that promotes the formation of an adenomatous polyp, considered a precursor lesion. The second step is characterised by the activation of the K-RAS oncogene, which leads to the further development of the adenomatous polyp into an advanced adenoma. Finally, a mutation in the p53 tumour suppressor gene leads to cancerous transformation into CRC. *Vogelstein*'s findings were later demonstrated by the National Polyp Study Group in 1993[10], showing the preventive effect of polypectomy by colonoscopy on CRC incidence. In sporadic cases of CRC, approximately 10% of precursor lesions -adenoma- eventually undergo malignant transformation to CRC in a time span of 10 to 15 years[5].

However, approximately 10-30%[5, 11] of CRC arise from the sessile-serrated pathway, described later in 1990[12, 13]. The sessile-serrated pathway is characterized

by a BRAF mutation and hypermethylation in CpG islands, leading to the formation of microvesicular hyperplastic polyps and sessile serrated adenomas. Furthermore, the loss of DNA mismatch repair (MMR) mechanisms results in various degrees of microsatellite instability (MSI), which in turn leads to dysplasia and eventually the formation of high-frequency MSI CRC. Sessile serrated adenomas are usually found in the right colon[12], and, in contrast with the adenoma-carcinoma pathway, their formation occurs in a shorter timespan[14] in addition to higher proportion of malignant transformation[15].

The rarer traditional serrated adenomas are usually located in the left colon and occur by K-RAS mutation. Further hypermethylation in repair gene MGMT leads to formation of microsatellite low or stable CRC and CpG island methylator phenotype low CRC[16]. A "third pathway" has been more recently described consisting of CRC arising from gut-associated lymphoid tissue, a histotype involved in the absorption of luminal antigens.

Sporadic, familial and hereditary forms of CRC

CRC can be divided into three entities, which include sporadic, familial, and hereditary CRC. Sporadic CRC accounts for the majority of CRC and is not linked to any known genetic mutation or hereditary susceptibility. Familial CRC represents cases with familial occurrence, in absence of demonstrated associated genetic mutation. Hereditary CRC represents cases with genetic mutations such as Familial Adenomatous Polyposis (FAP) or Hereditary Non-Polyposis Colorectal Cancer (HNPCC). Familial CRC accounts for approximately 15-20% of CRC while hereditary CRC account for approximately 5-10%[5].

In FAP, mutations related to the APC gene promote the development of numerous adenomatous polyps throughout the colon, predisposing them to further malignant degeneration in CRC through the adenoma-carcinoma pathway. The large amount of adenomatous polyps generally developing before the age of 20[17, 18] and increases the risk of carcinoma formation before 40 years old[14]. Also known as *Lynch* syndrome, HNPCC is an autosomal dominant genetic mutation leading to microsatellite instability, which promotes the development of CRC through the sessile-serrated pathway. This provides an explanation for HNPCC-derived CRC to occur predominantly in the right colon.

Immunology and CRC

Cancer immunology has received increasing attention in recent decades due to the close interplay between certain forms of cancer and the immune system. In fact, density of tumour infiltrating T-cells lymphocytes (TILs) has been proposed as a prognostic marker in solid tumours, including CRC. Moreover, presence of lymph node metastasis (LNM) in CRC has been associated with a low count of TILs[19-22].

Incidence, risk factors and signs

Incidence

CRC is ranked third in terms of cancer incidence in both Sweden and worldwide, with more than 5300 and 2300 individuals diagnosed with colon and rectal cancer in Sweden during the year 2023, respectively [23-25]. CRC is principally prevalent in developed countries, with an incidence associated with the Human Development index (HDI), which takes into account life expectancy, education and income per capita[26]. In western countries, the lifetime risk of developing CRC is estimated up to 5%[5].

The implementation of screening programs, in combination with a widened treatment arsenal have reduced the overall incidence of CRC[27] and led to a decrease in CRC-related mortality over the last decades[28, 29]. In this context, it is interesting to note that the impact of screening programs on overall mortality has been debated[30].

There are raised concerns regarding an increase in incidence of early-onset CRC[31], thought to be linked to western lifestyle and obesity[28]. In fact, a higher proportion of patients with early onset CRC are diagnosed at an advanced stage and with more aggressive tumour biology, both yielding a higher mortality[26]. Similar observations have been reported in Sweden, with an increased proportion of younger patients presenting with an advanced stage at diagnosis[32]. As a result of this trend, the US Task Force Recommendations for CRC Screening recommend including individuals aged 45 and above[33].

Risk factors

Currently recognised risk factors for CRC are high age, inflammatory bowel diseases, lack of physical activity, low intake of fruit and vegetables, low-fibre diets, high intake of processed meat, overweight, and alcohol and tobacco consumption[34] in addition to hereditary forms and family history of CRC. Personal history of CRC or dysplastic colorectal lesions is also predisposing to CRC[35].

Inherited genetic factors contributing to development of CRC are estimated to account for up to 35% of cases of CRC, according to a study on twins[36], indicating the major impact of the environment on CRC development.

Conversely, non-steroidal anti-inflammatory drugs and low-dose aspirin have been shown to reduce the risk of adenoma formation and CRC, especially in secondary prevention[37, 38].

Symptoms and signs of CRC

The natural history of CRC makes it largely asymptomatic at its earlier stages[39]. Once prevalent, CRC manifestations may include blood in the stool, change in stool

size or bowel habits, anaemia and abdominal pain, while fatigue, bowel obstruction and palpable abdominal mass are principally seen in more advanced stages[40].

The appearance of "red flag" symptoms prompts a colonoscopy in a timely fashion to avoid any delay in a potential cancer diagnosis. In Sweden, for example, a standardized care path for CRC defines criteria for colonoscopy referral as well as aims regarding lead times for colonoscopy and diagnosis, work-up and staging, multidisciplinary team conference (MDT) discussion, treatment and follow-up[41].

Screening

Duke's classification of rectal cancer (RC) was published as early as 1932, reporting a survival benefit for distal CRC diagnosed at an early stage[42]. Initiated in 1948, the first study evaluating the use of rigid proctosigmoidoscopy as CRC screening with polypectomy reported a decrease in incidence of distal CRC[43]. The use of the guaiac-based faecal occult blood test (gFOBT) was first reported in the 1960s on an asymptomatic population for potential detection of early colorectal polyps[44, 45]. The development of endoscopes[46] in the 1960s, in addition to the development of polypectomy techniques in the early 1970s[45, 47] revolutionised CRC screening strategies and paved the way for the first randomised trials[45]. Initiated in the 1970s, trials of CRC screening investigated gFOBT-based screening with completion colonoscopy in positive cases, showing a decrease in CRC incidence and CRC-related mortality, but no impact on overall mortality [45, 48-50].

The long subclinical phase[51] of established CRC offers a window of opportunity to detect precursor lesions prior to their malignant transformation. Implementation of screening programmes for CRC has allowed detection of precancerous lesions as well as a two-fold increase in detection of stage I CRC, thereby increasing the proportion of lesions amenable to local resection[52, 53]. Notably, according to analyses using a model based on the natural history of CRC, the identification of premalignant colorectal lesions, and not the detection of prevalent CRC, appears to be the major contributor of CRC-mortality reduction in screening[54].

Screening for CRC has been shown to significantly reduce the incidence of CRC as well as CRC-related mortality[55]. However, evidence regarding its impact on overall mortality is weaker[30]. Adherence to screening for CRC represents a major challenge. In fact, it is estimated that less than two-thirds of the invited population do effectively undergo screening[30, 56, 57] which impedes the protective effect of screening. Moreover, failure in the screening process has been shown to contribute to more than 60% of CRC-mortality[58]. Hence, interpretations of screening trials vary greatly based on a per-protocol or intention-to-treat analysis, the latter corresponding to a more realistic setting[30, 59].

CRC screening can be performed using either stool-based methods or image-based methods, as described below.

Stool-based tests

gFOBT was developed in the 1960s[44] as a qualitative method for detecting the heme group in stools using hydrogen peroxidase. The method does not specifically detect human haemoglobin, which impairs its diagnostic performance and requires avoidance of certain food and medication prior to its use[60].

The Faecal Immunochemical Test (FIT), developed in the late 1970s using goat antibodies against human blood[61], allows for specific detection of human blood at a lower threshold than gFOBT. In addition to having superior diagnostic performance[60], FIT does not impose any dietary or medicational restriction prior to testing, thereby increasing screening adherence rates[62]. Qualitative FIT allows for office-based analysis but requires a visual interpretation, with high interobserver agreement but poor inter-test agreement owing to different cut-off values[60, 63]. Quantitative FIT, on the other hand, performed using automated analysis, minimises interobserver variation, allows a higher volume of testing[60] and has an adjustable cut-off value which impacts rates of referral for colonoscopy, thereby being adaptable to fit available healthcare resources[60, 64, 65].

Later developed stool-based DNA tests detect specific genetic alterations involved in the adenoma-carcinoma sequence as well as markers of hypermethylation[60] expressed in the serrated polyp pathway. Combining these tests with FIT increases the sensitivity for detection of serrated polyps[66, 67], usually located in the proximal colon and reported to rarely exhibit bleeding, which explains the lower sensitivity of FIT alone for these lesions[67].

Colonoscopy

Bozzini, considered the "father of endoscopy", presented the *Lichtleiter* in 1806, a device consisting of a light candle container with an optical device connected to a set of speculums[68, 69] for examination of various body cavities. *Desormeaux*, a French urologist, pursued the development of *Bozzini*'s concept and introduced it into his clinical practice at the *Hôpital Necker* during the second half of the 1860s for examination of the lower urinary tract[70, 71] and baptizing it the "*endoscope"*. Since then, tremendous developments in endoscopic technology and techniques have been made thanks to more than two centuries of dedication and perseverance[45, 72].

Currently, colonoscopy is considered the gold standard for assessing a wide range of colorectal pathologies (including CRC), allowing for both diagnosis and (advanced) interventions such as polypectomy, argon-plasma coagulation or even stenting. Colonoscopy requires prior full bowel preparation in addition to varying degrees of sedation. Complications are estimated to occur in less than 1% of screening colonoscopies[73, 74] and include cardiopulmonary complications, bowel perforation (with or without prior polypectomy), post-polypectomy syndrome and bleeding[74].

Post-colonoscopy CRC is defined as CRC diagnosed after a negative colonoscopy, with non-interval cancer representing CRC diagnosed at or after the recommended screening or surveillance period, while interval cancer represents cases diagnosed within the screening or surveillance period[75, 76]. Post-colonoscopy CRC is estimated to be at the origin of up to 9%[76] of cases of CRC and is associated with missed lesions, incomplete colonoscopy and aggressive tumour biology.

Adenoma Detection Rate (ADR) is defined as the proportion of screening colonoscopies performed by a physician detecting at least one adenoma (or CRC). ADR is considered a quality indicator, shown to be inversely related to post-colonoscopy CRC[77, 78]. Bowel preparation, reported using the Boston Bowel Preparation Scale, is also a quality indicator, reducing ADR by nearly 50% when inadequate[79]. Shorter duration of colonoscope retraction has also been shown to be associated with post-colonoscopy CRC[80]. Artificial intelligence-based detection systems have been shown to increase the ADR, with the exception of sessile serrated lesions[81] which are believed to be responsible for post-colonoscopy CRC.

CT-colonography

The development of fibercolonoscopy in the 1970s as a screening modality caused discordance between radiologists and gastroenterologists performing colonoscopies[82], since barium enema was the preferred work-up modality in case of a positive faecal occult blood test or finding at sigmoidoscopy. The question was formally addressed as late as the 2000s by the first blinded comparative study that demonstrated the superiority of colonoscopy over double barium enema as follow-up after polypectomy[83].

Described in the 1980s[84], CT colonography (CTC) comprises administration of bowel contrast and insufflation prior to CT scanning of the abdomen and pelvis. CTC provides information regarding size, morphology and location of colorectal lesions[85] but is limited by the size of detectable mucosal lesions in addition to not allowing removal of polyps or biopsies of CRC.

While colorectal lesions greater than 10 mm are detected equally to colonoscopy[86, 87], sensitivity is slightly reduced for polyps smaller than 10 mm and significantly reduced for polyps smaller than 6 mm compared to colonoscopy[87]. However, polyps smaller than 10 mm detected by CTC have a low risk of high-grade dysplasia or CRC[88], which is why a threshold of 10 mm has been suggested for referral colonoscopy in the context of CTC-based screening.

Use of rectal contrast administration and air insufflation constitutes a risk of bowel perforation reported in less than 0.1%[89] of performed CTC. The potential harmful effect of ionising radiation on a population level is mitigated by the age categories included in screening programs[90]. Thus, the estimated lifetime risk of radiation-induced cancer has been reported to be lower than 1% at 50 years old and half as much by the age of 70 years old[91]. Current techniques allow for radiation doses as

low as 4.5 mSv using low-dose protocols and new dose-modulation techniques[87], which should be put in perspective with the annual background radiation ranging from 1 to 13 mSv[92].

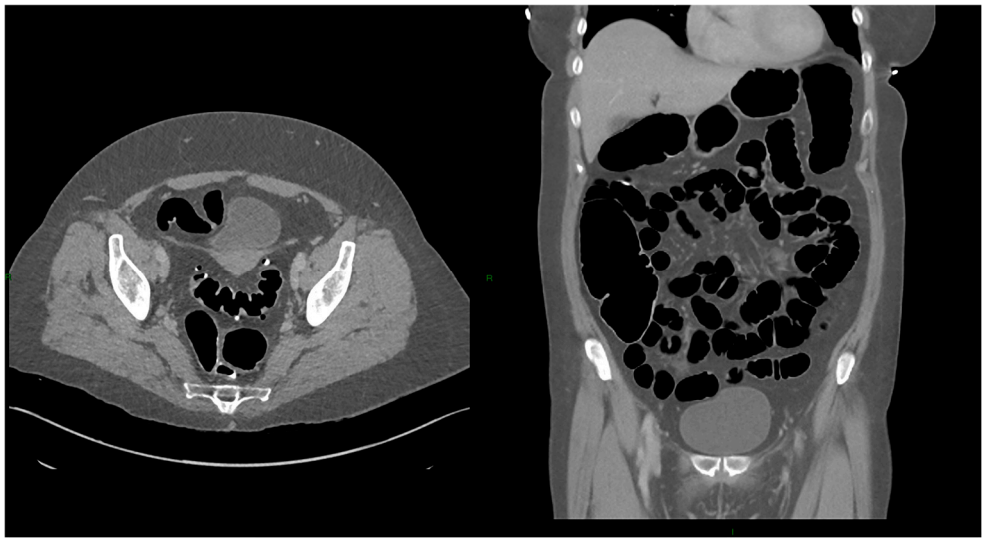

Figure 2. CT colonography after incomplete screening colonoscopy.
CT colonography with normal findings in a patient with incomplete screening colonoscopy due to inability passing sigmoid diverticulosis. Case courtesy of Calum Worsley, Radiopaedia.org, rID: 88385. Reproduced under Creative Commons CC BY-NC-SA 3.0.

The net benefit of extracolonic incidental findings found in up to 27% of CTC requiring further work-up is unclear[55]. However, use of a robust reporting classification (C-RADS) allows to mitigate the potential consequences of these incidental findings[93].

Currently, CTC is recommended in cases of incomplete colonoscopy or when colonoscopy is not feasible[94].

CRC Surveillance

While screening covers a large group of asymptomatic individuals at normal risk for CRC, surveillance interests a limited group of asymptomatic individuals with a significant increased risk for developing CRC.

Individuals subject to an increased risk of CRC include those with a personal or familial history of CRC, individuals with hereditary syndrome and individuals with inflammatory bowel disease.

TNM classification and prognosis

Duke introduced the first classification nomenclature for RC in the 1930s, which was later generalised for CRC[95, 96] and revised in the 1970s allowing better correlation with survival[97]. However, *Dukes* modified classification was successively abandoned at the benefit of the TNM classification which was first described by *Denoix* in the 1940s and early 1950s [98].

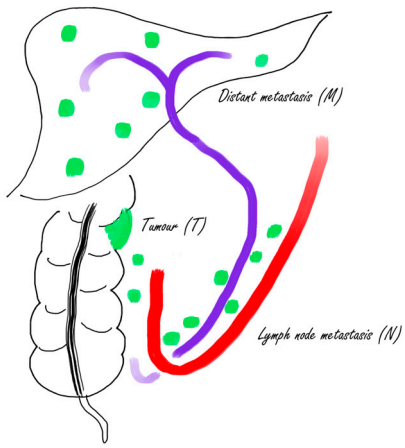

Figure 3. The extent of a colon cancer
Schematic illustration of the correspondence of TNM according in a colon cancer located in the right (or ascending) colon with lymph node metastases as well as liver metastases. Copyright Roberto Rosén © 2025.

The TNM classification reflects the anatomical extent of a tumoral disease with regard to the depth of invasion of the primary tumour across the layers of the bowel wall (T-stage, Table 1), the presence and number of LNM (N-stage, Table 2) and the presence of distant metastases (M). The combined TNM classification is further stratified into stages (Table 3), which correlate to prognosis. Currently, the TNM classification is at its 8th edition and is maintained by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC).

For patients diagnosed with CRC in Sweden after 2019, the age-standardised 5-year survival has increased from approximately 50% before 1988 to currently approximately 70%[99].

Table 1 Classification of the primary tumour (T-stage)
Classification of the primary tumour (T-stage) according according to AJCC/UICC 8th version of TNM classification.

T-stage	Description
Tx	Unassessable tumour
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Submucosal invasion
T1 Sm1	1/3 superficial submucosal invasion
T1 Sm2	2/3 submucosal invasion
T1 Sm3	Deep 3/3 submucosal invasion
T2	Muscular invasion
T3	Invasion beyond muscularis propria in pericolic/perirectal tissue
T4	Invasion beyond the visceral peritoneum or to an adjacent organ or structure

Table 2. Classification of regional lymph node (N-stage)
Classification of the primary tumour (N-stage) according according to AJCC/UICC 8th version of TNM classification.

N-stage	Description
Nx	Unknown or unassessable regional lymph nodes
N0	No regional LNM
N1	LNM in 1-3 regional lymph nodes
N2	LNM in ≥4 regional lymph nodes

Table 3. Stages according to T-, N- and M- classification
The 8th edition of the American Joint Committee on Cancer and Union for International Cancer Control

Stage	T-stage	N-stage	M-stage
0	Tis	N0	M0
I	T1-T2	N0	M0
II	T3-T4	N0	M0
III	T1-T4	N1-2	M0
IV	Any T	Any N	M1

The stage-specific 5-year survival for patients diagnosed with colon cancer (CC) in Sweden between 2016 and 2022 was over 90% for stages I and II, approximately 70% for stage III and less than 20% for stage IV.

For patients diagnosed with RC during the same period, the 5-year survival was above 95% for stage I, approximately 85% for stage II, slightly below 70% for stage III and below 20% for stage IV.

In addition to being dependent on stage, CRC survival has been found to be associated with insurance status and ethnicity in the US, albeit the country's high human development index[100]. In fact, privately insured patients were more likely to undergo surgical resection and had higher 5-year survival compared to uninsured patients[28]. Higher CRC incidence, earlier age of onset of CRC and higher CRC mortality have been observed in Black Americans compared to white Americans, with an increasing difference gap along with more advanced stages[101].

Work-up

Biomarkers

Carcinoembryonic antigen, a foetal glycoprotein first isolated in colon carcinoma tissue as early as 1965[102] was found useful as a preoperative CRC marker as well as a postoperative follow-up marker. In fact, elevated blood levels of CEA are correlated to the extent CRC[103, 104]. Importantly, CEA can also be elevated in smokers, males, and the elderly in addition to being normal in a proportion of cases of CRC[105, 106]. CEA is currently used as post-operative follow-up for detection of recurrent disease or during oncologic medical therapy for evaluation of treatment response[41, 106].

CRCs expressing high frequency of microsatellite instability, mainly found in tumours originating from the serrated-polyp pathway and in HNPCC, were also found to exhibit resistance to chemotherapy. Hence, systematic assessment of MSI status is currently recommended by Swedish guidelines[41].

Staging of colon cancer with CT

CT is well accepted as the modality of choice for identifying complications related to CC, such as obstruction, intussusception, perforation or abscess formation requiring emergent treatment, in addition to its accuracy in identifying distant metastases[107, 108].

Upfront surgical resection has been the standard treatment for non-metastatic CC. The emergence of neoadjuvant treatment in the management of locally advanced (stage T3 and above) CC has led to a trending interest for CT-based staging of CC, as witnessed by the FOXTROT[109] or PRODIGE22[110] trials.

CT-based staging of tumoral invasion has been reported with varying accuracy. Hence, accuracy for detecting combined T3-T4 stages has been reported with sensitivity ranging from 74% to 90% and a specificity ranging from 69% to 90%[111-115]. However, including only studies[112] performed using more modern CT with thin slices (≤5 mm) or helical acquisition led to an increase in sensitivity and specificity to 96% and 70%, respectively. A similar trend was observed when including studies using CT with helical acquisition.

Identifying subdivision of T3 stages, which is pertinent considering neoadjuvant treatment, did not improve accuracy of staging[112, 115, 116].

Desmoplastic reaction, inflammation at the tumoral invasion front, exhibits as pericolic fat stranding on CT images, provides an explanation for overstaging of T1-2 CC and the decreased specificity for detecting T3-T4 CC[112].

Trials involving neoadjuvant treatment in locally advanced CC have reported overstaging in 24 to 30% of patients in the control groups[109, 110], which, in that context, translates to overtreatment. Notably, use of MRI has been shown to enhance the accuracy in detecting locally advanced CC[117].

Nodal staging is notoriously challenging due to a lack of consensus regarding criteria for pathologic lymph nodes, often assessed based on size, morphology, heterogeneity, attenuation or clustering[118]. Accuracy of CT-based for detection of nodal invasion is reported with a sensitivity ranging from 41 to 78% and a specificity ranging from 63 to 84%[111-115, 119]. Using thin CT slices (≤5 mm) or helical acquisition did not lead to improved accuracy[112]. Given its disappointing accuracy, CT-based nodal staging was compared with "flipping a coin" in a Dutch study[119]. Moreover, a majority of LNM in CRC measure less than 5 mm[120], making their detection based on size difficult. The well-known challenge of nodal staging within diagnostic radiology has led to the development of a standardised reporting system, NODE-RADS, offering a structured approach in the evaluation of lymph nodes in an oncologic context[121].

The European Society for Gastrointestinal and Abdominal Radiology (ESGAR) recommends CT as a modality for local staging in CC with standard reporting of bowel wall infiltration (identifying T3cd and T4a CC), extramural vein invasion, and retroperitoneal margins for CC located in the ascending or descending colon[122].

Staging of rectal cancer with MRI

MRI has emerged as a pivotal staging modality in RC. The MERCURY trial, taking place in the 2000s, demonstrated the ability of high-resolution MRI to accurately predict the radicality of surgical resection of the rectum[123]. The follow-up study showed later the impact of the predicted circumferential resection margin on both local recurrence and overall survival[124].

Currently, the role of MRI is to risk-stratify patients with RC based on depth of invasion (T-stage), potential nodal invasion (N-stage), predicted circumferential resection margin (CRM), presence of extramural venous invasion, presence of tumour deposits, or sphincter involvement for distal rectal cancer[122].

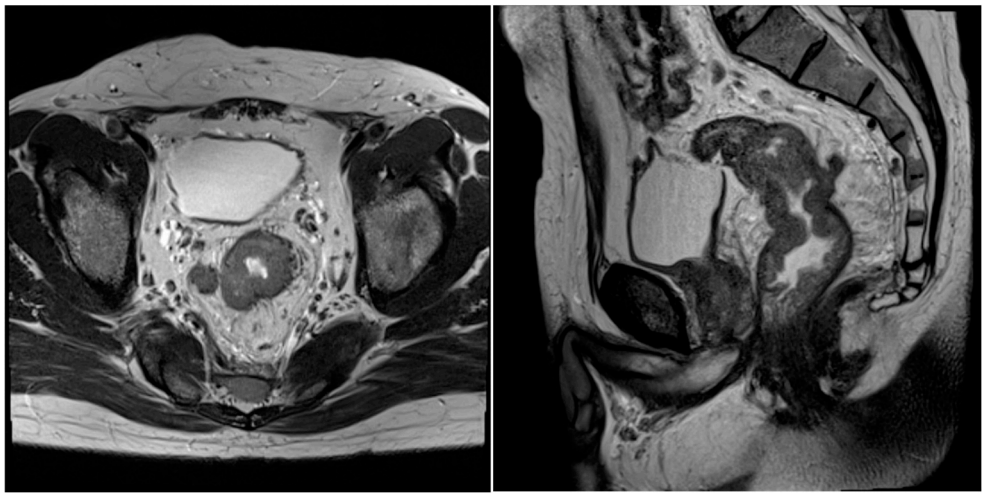

Figure 4. MRI of the rectum.
MRI of the rectum showing a circumferential tumour in the mid rectum with extramural invasion as well as enlarged perirectal lymph nodes. Histopathological assessment confirmed T3 stage. Case courtesy of Ian Bickle, Radiopaedia.org, rID: 32623. Reproduced under Creative Commons CC BY-NC-SA 3.0.

T-stage is a major factor dictating further treatment strategy. Accuracy for discriminating T3-4 from T1-2 RC has been reported with a sensitivity ranging from 58 to 87% and a specificity ranging from 75 to 82%[125-127].

Desmoplastic reaction, previously mentioned in the context of CT-based CC staging, exhibits as spiculations in the mesorectal fat in T2-stage RC and can be challenging to differentiate from T3-stage, explaining the staging overlap between T2 and T3 tumours[128, 129].

N-staging is a major prognostic marker in RC. Similar to CT, MRI-based nodal staging is challenging, with sensitivity ranging from 42 to 77% and specificity ranging from 71 to 87%[119, 126, 127, 130]. ESGAR suggests following size and characteristics (such as round shape, irregular border or heterogenous signal) to assess nodal invasion in RC. Hence, lymph nodes with a short axis ≥9 mm, lymph nodes with a short axis between 5 and 8 mm in combination with two or more morphologically suspicious characteristics, or lymph nodes with a short axis ≤5 mm in combination with 3 morphologically suspicious characteristics[131]. However, these criteria are expressed as “practical guidelines”, acknowledging the known inaccuracies for nodal staging. Efforts have been made over the last decade to harmonise MRI protocols, image interpretation and reporting of RC[128, 131, 132].

Response assessment after neoadjuvant treatment in RC is based on digital rectal examination, endoscopic appearance, and MRI. It is an important aspect of staging since it may change the therapeutic strategy. In fact, investigations regarding

patients exhibiting complete responses following neoadjuvant treatment have led to the development of watch-and-wait programs within trials, as discussed below.

Screening for metastases with Computed Tomography

CT of the thorax, abdomen and pelvis is currently recommended for assessing the presence of distant metastases in CRC[41, 107, 108, 133, 134].

While CT, MRI and contrast-enhanced ultrasound exhibit over 90% sensitivity and positive predictive value for detecting liver lesions larger than 1 cm, the sensitivity and positive predictive value of MRI remain excellent for detecting liver lesions smaller than 1 cm[135].

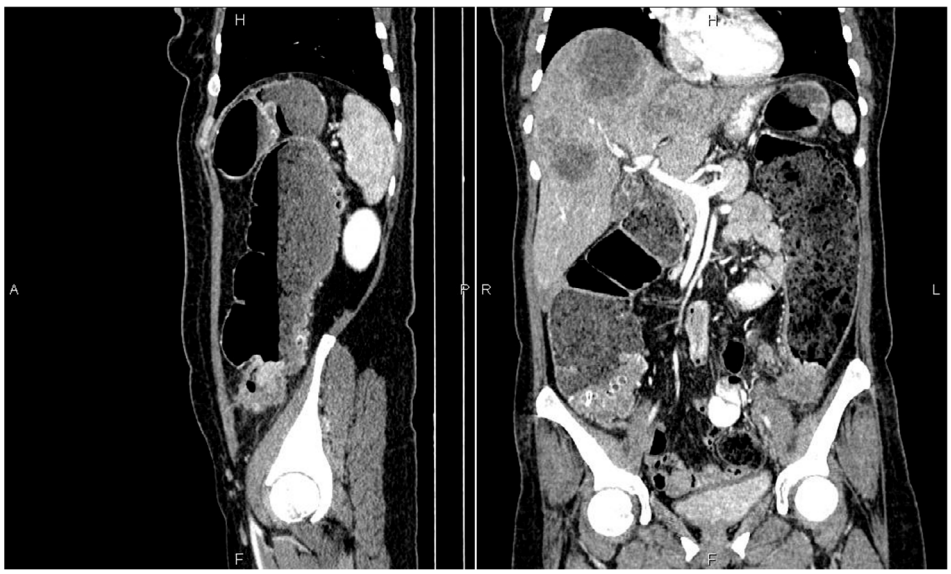

Figure 5. CT of the abdomen with sagittal (left) and coronal (right) reconstructions in a patient with obstructive colon cancer.
Patient with obstructive tumour distal in the descending colon. There is a marked distention of the colon with enlarged adjacent lymph nodes medial to the tumour. The large, non enhancing lesions in the liver are suggestive of metastases. Case courtesy of Mohammad Taghi Niknejad, Radiopaedia.org, rID: 148104. Reproduced under Creative Commons CC BY-NC-SA 3.0.

Moreover, CT has been shown to be equivalent to MRI and PET-CT for detecting peritoneal metastases with 83% sensitivity and 86% specificity, with a high degree of correlation between the CT-based peritoneal carcinoma index and the surgical peritoneal carcinoma index[136].

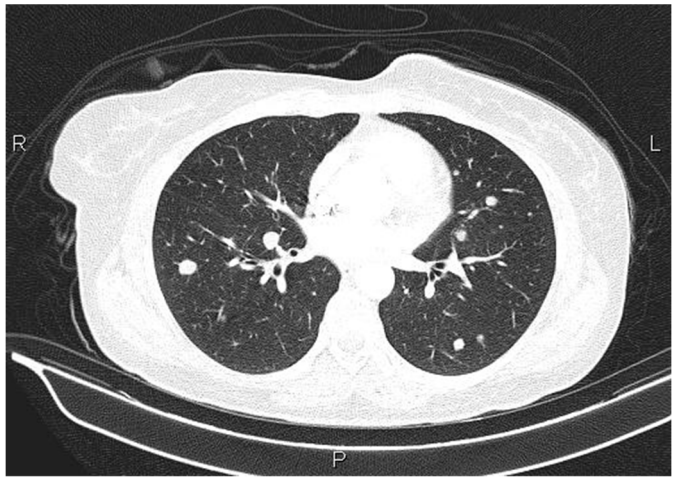

Figure 6. Chest CT in lung window.
Chest CT from the same patient with metastatic colon cancer. Multiple, round lung nodules suggestive of metastatic lesions. Case courtesy of Mohammad Taghi Niknejad, Radiopaedia.org, rID: 148104. Reproduced under Creative Commons CC BY-NC-SA 3.0.

There has been some reluctancy to replace the traditional chest x-ray by CT[137], due to a high frequency of indeterminate, mostly benign, lesions[138, 139] Currently, chest CT is recommended by Swedish Guidelines as metastasis screening modality[41].

Multidisciplinary team conferences

The introduction of colorectal multidisciplinary team conferences (MDT) can be traced back to 1995 in the UK, followed by USA and Europe[140] and currently forms an integral part of cancer care paths. MDTs are generally composed of surgeons, pathologists, radiologists, medical and radiation oncologists, gastroenterologists (depending on the country) and coordinating nurses[140]. MDTs have been shown to enhance preoperative tumour staging, augment the proportion of R0 resection[140, 141], increase the proportion of decisions to operate in metastatic situations as well as the proportion of patients receiving targeted therapy[140]. The introduction of MDTs has been associated with (slight) improvement of oncologic outcomes in CRC[142].

Treatment

Surgical treatment

Elective surgical treatment of CRC depends on the tumour location. For CC, surgical resection will include the colonic segment hosting the tumour as well as the involved mesocolon and its structures (artery, vein, and regional lymph nodes).

Beyond the location of the segmental colonic resection, the extent of lymph node dissection is also subject to some variation. In western routine, lymph node dissection of intermediate lymph nodes "D2" is usually performed as standard treatment[41]. Conversely, the threshold for extending the lymph node dissection to the central nodes ("D3"), also known as a complete mesocolic excision, is lower in eastern countries, such as Japan[143, 144].

Surgical resection techniques for RC have undergone remarkable advances since *Lisfranc*'s perineal approach for rectal amputation in the early 19th century[145]. The surgical technique was revolutionised by *Heald*, in the 1980s, who described the total mesorectal excision (TME)[146, 147]. TME, currently performed today, consists in dissecting the rectum along with the mesorectal fascia (the "holy plane" or "Heald's plane"), which includes the perirectal lymph nodes within the mesorectum. TME contributed to minimising local recurrences while preserving structures involved in genitourinary functions[148, 149].

There are variations of the resection technique, depending on the location of RC. Hence, resection of the rectum can be performed as an anterior resection (with partial mesorectal resection), a TME or an abdominoperineal resection, the latter necessitating a permanent stoma. A proctosigmoidectomy with a terminal colostomy, *Hartmann*'s operation, can be performed as an alternative to a restorative resection in patients deemed at risk for anastomotic leakage. Anecdotally, *Monsieur Hartmann* presented this surgical strategy in 1921 and compared the uneventful post-operative recovery with an appendectomy *à froid* while presenting his technique during a congress[150]. The extent of lymph node dissection in RC surgery is also subject to some variations. Dissection of lateral lymph nodes is routinely performed in Japan for RC located below the peritoneal reflection line[143, 144]. In Sweden, however, lateral lymph node dissection is based on preoperative findings.

Surgery was revolutionised by the first laparoscopic appendectomy performed in 1981 in Germany, not without criticism[151, 152]. After laparoscopic cholecystectomy was reported in 1985[153], minimally invasive surgery was first reported in the more technically challenging field of colorectal surgery by 1991[154]. Laparoscopic CRC surgery was later shown to favour short-term outcomes by decreasing its physiological impact while preserving the long-term oncologic safety[155, 156]. Anecdotally, one study demonstrated increased long-term oncological benefits associated with laparoscopic surgery in CC[157], in line with previous animal studies demonstrating the beneficial impact of minimally invasive surgery on immunological functions[158].

Development of robot-assisted surgery allowed more precise dissection in addition to offering better access in difficult anatomic spaces such as the pelvis, and was proven useful for preserving the quality of resection specimens as well as preserving oncologic outcomes when compared to laparoscopic surgery[159-161].

Neoadjuvant and adjuvant treatments

When considering neoadjuvant chemotherapy in CRC, obtaining MSI status is important for treatment decisions. In fact, high-frequency MSI tumours exhibit weaker treatment response[162], which is why primary surgical resection or neoadjuvant immunotherapy might be recommended instead of "conventional" chemotherapy[41].

Primary treatment of non-metastatic CC consists of upfront surgical (or local) resection. Adjuvant chemotherapy is recommended in high-risk stage II and stage III CC to reduce the risk for recurrence. Neoadjuvant chemotherapy may also be proposed in locally advanced CC as downstaging therapy for borderline resectable CC prior to surgical resection. Radiotherapy has a limited role in CC but can be considered in combination with chemotherapy for downstaging unresectable, locally advanced CC[41].

As previously mentioned, RC is risk-stratified according to MRI findings, constituting the basis for treatment decisions. Upfront surgical (or local) resection is recommended for low-risk RC, while preoperative short-course radiotherapy followed by surgical resection is recommended in intermediate-risk RC. Neoadjuvant radiotherapy combined with chemotherapy is recommended in high-risk RC for downstaging followed by restaging prior to surgical resection[41].

Approximately one fifth[163] of patients with RC receiving neoadjuvant treatment exhibit a pathological complete response at restaging, which has led to questioning the impact of subsequent surgical resection. In fact, withholding subsequent surgical resection in these selected cases has been shown to be non-inferior to resection surgery, resulting in an increased interest for "watch and wait" follow-up strategies, currently under investigation[164]. While watch-and-wait strategy has included patients with locally advanced RC, there is a trending interest to investigate this approach for earlier stages, as witnessed by the ongoing prospective STAR-TREC trial[165].

Morbidity and mortality of treatments

The high prevalence of comorbidities such as type 2 diabetes and cardiovascular diseases among patients diagnosed with CRC has an impact on treatment decisions as well as the morbidity of the treatments themselves and survival[166]. Hence, perioperative major adverse cardiovascular and cerebrovascular events, including cardiovascular-related death, myocardial infarction or stroke, occur in more than 4% of CRC surgeries[167].

According to the 2015 UK National Bowel Cancer Audit[168], all-cause death at 90 days occurred in less than 3% of patients after elective major CRC surgery but increased to more than 15% in an emergent setting. Notably, emergency admissions

for CRC accounted for approximately 20% of the total number of admissions for CRC during the audit period, which, in turn, were linked to an increased post-operative 90-day mortality. Among patients undergoing major surgical resection, 20% were readmitted within 90 days. However, a decreasing trend in perioperative mortality was noted, possibly due to advances in perioperative management[167, 168]. Mortality at 2 years from diagnosis after major CRC surgery was approximately 30% and less than 10% after local resection, while more than half of patients who did not undergo any resection were deceased at 2 years after diagnosis of CRC.

The large spectrum of surgically related complications is dominated by anastomotic leakage, stoma-related complications, wound dehiscence or bowel obstruction, to name a few.

Anastomotic leakage is a dreaded complication occurring in approximately 10% of surgical resections for RC[169] leading to reoperation, prolonged hospital stay, increased cost, as well as increased mortality. Alcohol, smoking, obesity, high ASA score or neoadjuvant chemoradiotherapy were found to be associated with anastomotic leakage[170]. Moreover, anastomotic leakage was associated with increased local recurrence rates[171]. While a permanent stoma is needed after abdomino-perineal resection, up to 40% of patients undergoing anterior resection have a permanent stoma[172]. Stomas are prone to a wide range of complications, such as parastomal herniation, stenosis or prolapse[172] negatively impacting quality of life[173].

Wound dehiscence occurs in up to 3% of patients undergoing open surgical resection for CRC requiring reoperation, leading to increased length of stay and higher mortality[174].

According to a French retrospective study, small bowel obstruction occurred in nearly 20% of patients after CRC surgery. Notably, small bowel obstruction was also associated with increased mortality, with laparoscopic approach associated with decreased incidence of small bowel obstruction in addition to lower long-term mortality[175].

While low anterior resection techniques for RC have contributed to minimising the need for stoma, at least 50%[176] of patients experience low anterior resection syndrome, a constellation of symptoms such as frequency, incontinence, constipation or a sense of uncompleted emptying with a negative impact on quality of life[177]. Moreover, more than half of patients undergoing RC surgery experience urinary or sexual dysfunction, also impacting quality of life[178].

Approximately one third[179] of patients undergoing preoperative radiotherapy for RC exhibit toxicity in the form of radiation enteritis, perineal dermatitis or cystitis. Notably, 20% of patients develop chronic secondary proctitis after pelvic radiotherapy[180].

Chemotherapy-related toxicities affect nearly 50% of patients with CRC[181], in the form of gastrointestinal toxicity, neuropathy, or neutropenia. Most patients experiencing gastrointestinal toxicity will exhibit long-term symptoms. Among patients receiving immunotherapy, 25% will experience side effects such as diarrhoea, colitis, pneumonitis or skin affections such as rashes and pruritus[182].

Hence, the inherent risks of CRC treatments need to be balanced against the oncological benefit, with consideration for the patient's physiologic tolerance.

Histopathological assessment

Histopathological assessment allows to accurately assess the tumour and nodal extension, using the TNM classification. Similar to the diagnosis and work-up, the histopathologic assessment has profound implications on subsequent treatment and follow-up.

Histopathological characteristics of CRC assessed according to Swedish guidelines[41] comprise radicality, resection margins, TME completeness (for rectal resection), depth of invasion of the primary tumour across the bowel wall (T-stage), histologic grade of differentiation, presence of tumour deposits, presence of tumour budding, presence of lymphovascular and perineural invasion, extramural vein invasion, MSI status, molecular analysis such as KRAS, and presence of lymph node metastases. Tumour regression grade is also reported following neoadjuvant treatment.

Adequate assessment of LNM is primordial. A threshold of at least 12 harvested lymph nodes is currently recommended and is a surrogate marker for quality of the surgical resection, based on studies showing increasing survival with increased lymph node harvest[183]. However, whether the survival benefit is related to extensive surgical resection, increased quality of resection specimen or increased histopathological staging accuracy remains elusive[183, 184]. Interestingly, an increased number of harvested lymph nodes has been found to be a favourable consequence of the immunogenic response in CC[185], thereby questioning the utility of extensive lymphadenectomy.

The mucinous CRC subtype is characterised by the presence of extracellular mucin in more than 50% of the tumor[186] and is associated with poorer survival when compared to non-mucinous CRC.

Early colorectal cancer

Local resection has emerged as a feasible treatment alternative for cases of T1 CRC that exhibit a low risk for LNM. Local resection has the advantage of avoiding the physiological burden of surgical resection and its associated complications, in addition to preserving bowel continuity.

The risk of LNM is based on the definitive T-stage, in addition to histopathological characteristics, which requires prior radical resection of the colorectal lesion and is therefore a post-resection diagnosis.

Endoscopic assessment

Different endoscopic visual assessment tools are used to allow proper characterisation of a detected colorectal lesion. The endoscopic assessment will guide further management.

The size of a colorectal lesion is an important marker correlated to the risk of advanced neoplasia[187].Moreover, the morphology of a lesion is also correlated to the risk of neoplasia[188]. The Paris classification[189] categorises superficial mucosal lesions based on their morphology, which is useful to assess endoscopic resectability and resection method, in addition to correlating with the risk of malignancy[188].

Colorectal lesions were traditionally assessed with chromoendoscopy, which consists in applying staining mediums on the mucosal surface. Chromoendoscopy enhances the mucosal architecture and highlights surface polyps, increasing detection of premalignant colorectal lesions[190]. Similar to chromoendoscopy, virtual chromoendoscopy consists in filtering certain wavelengths of light, which sharpens contrast and enhances superficial mucosal structures. Virtual chromoendoscopy has enabled the emergence of classification systems such as Kudo's classification based on pit patterns[191] or NICE criteria based on the vessels and the surface pattern[192] to predict the presence of dysplasia or submucosal invasion[193]. The more recent JNET classification allows a more accurate assessment of depth of invasion[194] based on colour, vessels and surface pattern.

Colorectal lesions considered premalignant should be fully resected *en bloc* rather than biopsied[195]. The SMSA score emerged to assess the level of difficulty of endoscopic resection based on location, morphology, size and access[196]. The SMSA score was later found to be correlated with incomplete endoscopic mucosal resection of large polyps[197] as well as endoscopic resection-related complications[198].

Interestingly, a scoring system was developed to differentiate advanced T1 from T2 CRC, thereby selecting lesions amenable for endoscopic submucosal dissection (ESD) with a 36% sensitivity and 90% specificity[199]. Additionally, magnifying

chromoendoscopy was shown to be more reliable than MRI for assessing deep submucosal invasion in flat lesions in the rectum, thereby limiting overstaging[200].

Hence, advanced endoscopic assessment methods have been developed, allowing to guide further management such as modality of resection, and have therefore had a major impact on the management of colorectal lesions.

Work-up

Forceps biopsies should be avoided

Histopathologic confirmation of CRC is warranted according to current guidelines[41, 133, 134] to establish the diagnosis of CRC as well as determination of MMR status, both of which are relied upon for staging and further management. However, biopsies are only recommended for colorectal lesions not amenable to endoscopic resection[195], otherwise risking iatrogenic epithelial misplacement or pseudo-invasion.

Pseudo-invasion is defined as misplacement of a mucosal component into the submucosal layer or even the muscularis propria after forceps biopsy in both sessile[201, 202] and pedunculated adenoma[203]. Pseudo-invasion can potentially mimic invasive carcinoma and lead to histopathological overstaging. Additionally, pseudo-invasion induces submucosal fibrosis, challenging subsequent endoscopic mucosal resection (EMR) or ESD with longer procedure time, lower *en-bloc* resection rates and lower rates of radicality[195, 204, 205].

Hence, lesions potentially amenable to local resection should undergo *en-bloc* excisional biopsy instead of forceps biopsy with the risk of histopathological overstaging and overtreatment.

Staging of early colon cancer with CT

Differentiation of T1 from T2 stage CC is difficult on CT, if not impossible[206], which is why T1 and T2 stages are often combined as T1-2 to overcome this challenge. Previous investigations have mainly focused on the role of CT in the context of neoadjuvant treatment. However, the accuracy of CT for identifying patients with T1-2N0 CC that could potentially benefit from curative local resection is poorly studied.

Only one previous study with a research question focused on identifying early CC was identified in the literature. Hence, a Danish nationwide study[116], including more than 4500 patients, reported a sensitivity of 75%, a specificity of 73% and a positive predictive value of 44% for identification of T1-T2 CC.

Notably, most patients preoperatively staged cT2 had pT3 tumours at histopathological assessment and patients preoperatively staged cT1 were found to have pT1, pT2 and pT3 stages postoperatively in nearly equal proportions.

By combining T- and N-stages, this study also investigated the accuracy for detecting stage I CC, which was reported to have 63% sensitivity, 80% specificity and a positive predictive value of 42%. Hence, these results suggest that CT-based staging leads to preoperative understaging of CC, with disappointing accuracy for detecting potential candidates for local resection.

Staging of early rectal cancer with MRI

The first MRI of the rectum was reported in the 1980s, followed by investigations correlating MRI findings to relevant anatomic structures[207-209]. Development of high-resolution MRI led to further research allowing discrimination of the bowel wall componments[210]. Considerable research has examined the performance of MRI in selecting candidates for neoadjuvant therapy; however, its role in the staging of early rectal cancer is scarcely investigated within larger cohorts.

A recent nationwide Dutch study[211] including more than 5000 patients diagnosed as cT1-2 RC reported sensitivities and specificities for detecting T1 RC of 45% and 93%, respectively, while the sensitivity and the specificity for detecting T2 RC were 92% and 26%, respectively. A majority of patients with T1 RC were preoperatively staged as cT2, and, conversely, approximately 50% of patients preoperatively staged as cT2 had either T1 or T3 disease. Sensitivity and specificity for detecting nodal invasion were 34% and 83%, respectively. Additionally, among potential candidates for local resection with T1N0 RC, only 30% were accurately staged as cT1N0, while the remaining 70% were overstaged.

Staging of early rectal cancer with EUS

ESGAR recommends endoscopic ultrasonography (EUS) for staging cases of early RC considered for local excision for its ability in distinguishing T1 from T2 RC[131]. Swedish guidelines suggest the possibility of using EUS as a complement to MRI for superficial tumours or for assessment of distal tumours[41]. However, ESGE recommends against the use of EUS or MRI for staging of lesions in the rectum due to the risk of overstaging[212], and suggests that the endoscopic assessment prevails over MRI and/or EUS.

A meta-analysis[213] including 42 studies with more than 5000 patients reported sensitivity and specificity for T1, T2, T3, and T4 stages of 87% and 98%, 81% and 96%, 96% and 91%, 95% and 98%, respectively, thereby recommending EUS as a staging modality for RC. Based on these findings, the authors suggested that EUS could accurately stage RC.

However, a multicentric study[214] including more than 12000 patients reported sensitivities and specificities for T1, T2, T3, T4 stages of 58.2% and 95.9%, 64.1% and 74.1%, 71.2% and 75.6%, 27.2% and 98.5%, respectively, and the authors thereby recommended against the use of EUS for staging RC.

Accuracy of EUS for detecting LNM was reported with a sensitivity ranging from 57 to 73% and a specificity ranging from 76 to 80%[130, 213, 215]

Notably, EUS has the reputation for being operator-dependent. In fact, its accuracy has been associated with operator volume in addition to having questionable interobserver agreement[214, 216]. In fact, there are some concerns regarding potential positive publication bias[217] in studies reporting EUS accuracy. Hence, staging based on ultrasonographic techniques is reported with varying accuracy, and its reliability for selecting candidates for local resection is questionable.

Local resection

Local resection strategies for early CRC were described as early as in the 1950s by *Lockhart-Mummery* and *Duke*[218], paving the way for the concept of "total biopsy" [219]. It was already understood that a certain proportion of patients underwent unnecessary surgical resection, exposing them to significant comorbidities[219]. At that time, local resection in selected cases of early RC was considered as an exception to a standard oncological resection[220]. Notably, "local resection" referred then to the limited extent of the resection and not the surgical approach.

In the 1960s, *Parks* first described transanal mucosectomy (using retractors) for a villous papilloma of the lower rectum[221]. However, the technique was limited to the distal rectum, and access to the proximal rectum was limited by instruments impairing vision. *Mason* described in 1970 a presacral approach for local resection of low rectal lesions, given the high comorbidity and necessity of stoma conferred to APR[222].

During the 1980s, *Buess* developed a device comprising a 40 mm wide introducer with a stereoendoscope and instruments, describing transanal endoscopic microsurgery (TEM)[223, 224]. TEM, still in use today at some centres, allows removal of rectal lesions using everything from mucosal resection to full-thickness resection (the latter below the peritoneal reflection line, in the distal rectum) using pneumorectum for workspace creation. Transanal Minimal Invasive Surgery (TAMIS), described in 2010[225], is based on TEM principles, using a single-incision laparoscopic surgery port. Use of this single incision port allows the use of larger instrument ports (compared to 5 mm instrument ports with TEM) while avoiding the initial costs of the TEM platform.

The above-mentioned resection modalities allowed resection of lesions located in the rectum. Lesions in the colon were amenable thanks to progress in endoscope technology and endoscopic resection techniques, using an approximately 1 cm wide flexible endoscope. EMR, first described in the 1980s[226], allowed removal of mucosal lesions along the proximal and distal gastrointestinal canal. However, EMR was (and still is) limited to mucosal lesions with a size up to 2 cm for *en bloc* one-

piece resection, or alternatively in a piecemeal fashion for lesions larger than 2 cm after thorough endoscopic assessment[195].

To overcome the size limitation for *en-bloc* resection and avoid potentially hazardous piecemeal resections, endoscopic submucosal dissection (ESD) was developed in the late 1990s. Principles of ESD were initially described in 1999 when removing a large flat polyp[227] in the upper gastrointestinal tract and later formalised in the 2000s. By that time, depth of submucosal invasion was believed to be the main risk factor for LNM, thereby contributing to determining the curativity of a local resection. Hence, ESD emerged as an ideal local resection modality which allowed adequate assessment of the depth of submucosal invasion on a resection specimen[228].

Local resection techniques suffer from complications, despite their limited physiological impact. Hence, urethral damage, infection, fistula, bleeding or intrarectal wound dehiscence has been reported in up to 10% of patients undergoing TEM[229]. Faecal incontinence after TEM has been variably reported, with, however, long-term data suggesting a frequency of up to 30%[230]. Compared to surgical resection, TEM (including TAMIS) is safer in terms of morbidity, mortality and need for stoma[231]. Complications after ESD comprise mainly bleeding and perforation[232], occurring in less than 1 and 5% of cases, respectively[233]. Moreover, ESD has been shown to be safer in terms of morbidity and mortality when compared to surgical resection[234].

The literature often classifies failure to achieve *en bloc* resection and R0 resections as complications. High rates of *en bloc* resection, over 90%, with somewhat lower R0 resection rates, over 80%, are achieved using ESD[233], which is comparable to patients undergoing TEM according to larger studies[235-237].

Currently, local resection is considered for patients with cT1-2N0-staged CRC. The definitive diagnosis is confirmed by histologic assessment and is therefore a post-resection diagnosis. Size, morphology, chromoendoscopic appearance and location of a lesion will guide further management according to guidelines. Hence, if submucosal invasion is suspected, *en bloc* resection using ESD is recommended[195]. Interestingly, endoscopic resection of T1 CRC exhibiting low-risk features for LNM has been shown to have recurrence rates as low as 0.8 - 2% at 5 years[238, 239].

For locally resected T1 tumours deemed at low risk for LNM located in the rectum, the local recurrence rate was below 7%, while distant recurrence was slightly above 3%, according to a recent metanalysis including studies with at least 3 years of follow-up[240].

Histopathologic assessment in early CRC

Curativity of local resection of T1 CRC depends on histopathological characteristics, which classify lesions depending on the associated risk for LNM. According to current guidelines[41, 212], T1 CRCs that are locally radically resected, without deep submucosal invasion (Sm2-Sm3), lymphovascular invasion, tumour budding (grade 2-3) and poor tumour differentiation are deemed curative.

T-staging and submucosal invasion

Pedunculated superficial T1 CRCs are reported according to Haggitt's classification[241] categorising the level of invasion in the mucosa (level 0) or in the submucosa in the head of the polyp (level 1), in the neck (level 2), in the stalk (level 3) or in the base of the stalk/bowel wall (level 4), with polyps exhibiting invasion up to level 3 could be considered curative[241].

Depth of submucosal invasion in flat T1 CRC was first reported according to Kudo's classification[242, 243] dividing the submucosa into thirds, with T1sm1, T1sm2 and T1sm3 corresponding to submucosal invasion to the superficial third, the middle third and the deep third. A semi-quantitative classification, based on Kudo's classification, was proposed by Kikuchi, with T1sm1 corresponding to submucosal invasion to 0.2-0.3 mm, T1sm2 corresponding to intermediate invasion and T1sm3 corresponding to submucosal invasion near the muscularis propria, given that the muscularis layer is also resected[243, 244]. A quantitative classification was proposed by Yamamoto[245] with T1sm1, T1sm2, and T1sm3 corresponding to depths of submucosal invasion of up to 0.5 mm, 0.5-1 mm, and beyond 1 mm, respectively.

Importantly, while depth of submucosal invasion has previously been shown to correlate to LNM [246-249], more recent publications have not been able to demonstrate its impact on LNM[250-255] with findings suggestive of a possible confounding effect in adjusted analysis[251]. Interestingly, lymphatics are more developed in the superficial third of the submucosa compared to the deep submucosa[256], which contrasts findings of increased risk for LNM with depth of submucosal invasion. Moreover, lateral extent of mucosal and submucosal invasion and not (only) depth of submucosal invasion has been suggested to be associated with LNM, according to some authors[257, 258]. In this context, it is interesting to note that updated ESGE guidelines state that if deep submucosal invasion is the only high-risk feature presented in a resected T1 RC, intensified surveillance can be recommended instead of subsequent surgery[212].

Tumour differentiation grade

The differentiation grade of tumour cells is based on the morphological appearance of tumour cells at histopathological assessment, such as the shape, size and general structure of the glands[259]. In fact, poorly differentiated tumour cells are associated with the presence of LNM in T1 CRC[247] in addition to being associated with poor

survival in CRC[249]. However, lack of a standardised classification system and a high degree of subjectivity yielded low levels of interobserver agreement [260, 261] which, combined with tumour heterogeneity[262], led to the simplification and standardisation of differentiation grade. Currently, differentiation grade is dichotomised into "well/moderate" and "poor"[243, 263].

Tumour budding

Tumour budding (TB) was initially described as cancer cell clusters located at the tumoral invasion front[264] but was later standardised as a single cancer cell or cluster of up to 4 cancer cells[265]. TB represents a combined process of dedifferentiation and migration of cancer cells into surrounding stroma[266, 267], implying the epithelial-mesenchymal transition (EMT) mechanism. EMT allows polarised epithelial cells to exhibit mesenchymal cell phenotypes by interaction with the basal membrane, acquiring properties such as migratory capacity or apoptosis resistance[267, 268]. TB is stratified on a 3-item scale depending on the number of buds[265]. Tumour budding is associated with LVI as well as LNM in T1 CRC and recurrence in early CRC [264, 267, 269, 270].

Lymphovascular invasion

Lymphovascular invasion (LVI) is defined as the presence of cancer cells in lymphatic or vascular structures[271] and is associated with poor histologic grade at the invasion front[272], tumour budding, LNM[264] as well as recurrence[273]. Significant rates of interobserver variability regarding assessment of LVI have been reported[251, 274, 275] with, according to a Dutch study, an impact on proportions of subsequent surgery in patients with locally resected early CRC. However, no impact on oncological outcome could be observed[275] in that study. Hence, higher rates of LVI due to interobserver variability led to overstaging with subsequent overtreatment of T1 CRC.

Perineural invasion

Perineural invasion (PNI), initially described in aggressive head and neck malignancies[276], is characterised by the presence of tumoral cells in the nerves or along their sheaths, involving at least 33% of the circumference[277]. The presence of PNI is associated with increasing tumoral stage, moderate and poor tumour differentiation grade and poor survival[277].

Radicality

Radicality of resection defines whether all the tumoral tissue is resected and surrounded by adequate margins of healthy tissue. Radicality can be assessed macroscopically by endoscopic or direct vision, while microscopic radicality is assessed at histopathology.

Locally resected high-risk T1 CRC

Locally resected T1 CRC exhibiting at least one high-risk feature is considered at high risk for LNM. In these cases, subsequent surgical resection is recommended, allowing lymph nodes to be analysed and potential indications for adjuvant therapy to be explored.

In this context, it is important to note that current guidelines classify approximately 70% of all T1 CRC[239, 278] as high-risk lesions, implying subsequent surgery to be recommended for these. However, the true incidence of LNM is reported to range from 10% to 18%[248, 279, 280] and adherence to guidelines will result in a substantial risk for overtreating patients with surgery. In addition, risk factors of recurrence following endoscopic resection are not as extensively studied as risk factors of LNM and are not necessarily the same. Nevertheless, previous studies have reported that the risk of recurrence following endoscopic resection of low-risk T1 CRC was 2%[238, 239]. Indeed, the risk of recurrence following endoscopic resection of high-risk lesions has been reported to be higher, with a large variety in the literature ranging from 6 to 20%[238, 239, 281]. On the other hand, a recent study investigating risk factors of recurrence following endoscopic resection found rectal tumour location to be the only significant risk factor of recurrence[239], illustrating that current risk stratification is suboptimal.

Moreover, a recent meta-analysis investigating recurrence following endoscopic resection of early RC found equal risk of recurrence in high-risk tumours following subsequent surgery and adjuvant therapy. Notably, the risk of recurrence was increased for high-risk patients receiving no additional treatment in that study[240].

Furthermore, a previous meta-analysis has shown that primary resection of T1 RC using TEM/TAMIS had higher recurrence rates compared to primary resection using endoscopic techniques, regardless of the risk of LNM[282]. Additionally, the method used for primary local resection in early rectal cancer affects the outcomes of subsequent surgical resections. In fact, full-thickness bowel resection performed during TEM or transanal surgery has been associated with longer subsequent operation times, increased rates of incomplete TME, increased rates of reoperation, increased rates of stoma, and increased rates of abdominoperineal resection[283-285]. However, these worse outcomes associated with completion surgery have not been demonstrated with endoscopic resection as the primary local resection modality[286, 287]. This difference is explained by full-thickness resection breaching the deep embryological planes surrounding the rectum, which results in perirectal fibrosis, further challenging surgical resection along the dissection planes. Regarding T1 CC, prior endoscopic resection does not impair subsequent resection surgery[287].

The ongoing randomised TESAR trial intends to compare completion TME against adjuvant chemoradiotherapy after non-curative local resection for early-stage RC, deemed at high risk for LNM[288]. This trial will permit to properly investigate the oncologic impact of adjuvant treatment as a complement to local resection.

Hence, current risk assessment, striving to identify the minority of patients with T1 CRC that actually have LNM, is insecure and results in overtreatment with surgery. The risk of recurrence following endoscopic resection is elusive, and the modality of local resection has an impact on subsequent surgical resection. Finally, local resection combined with adjuvant (chemo)radiotherapy has the potential to yield the same oncological outcome as completing surgical resection while preserving bowel continuity and avoiding potential morbidity and mortality.

Health economical aspects

Measuring health

The utility value of a state of health can be measured using questionnaires such as the EQ-5D or the SF-6D, which are self-completed questionnaires. These were developed in the 1990s, covering up different aspects of health such as mobility, self-care, usual activities, pain/discomfort and anxiety/depression, mental health and vitality[289]. These questionnaires can be used to evaluate the health status in the general population of a country[290] (so-called "value set") but also in a specific patient group[291] using condition-specific questionnaires to increase the sensitivity of the measure.

Measuring costs

Costs related to healthcare or health intervention can be divided into three components comprising direct, indirect and intangible costs[292], the latter being used in insurance compensation after adverse life events.

Direct costs are costs directly related to a health intervention which can be divided into direct medical costs and direct non-medical costs. Direct medical costs include costs related to visiting a healthcare provider, for work-up or follow-up examinations, for both drug and non-drug treatments (including surgery for the latter) and inpatient care. Direct medical costs can be further grouped as costs related to the disease of interest or related to comorbidities (possibly related to the disease of interest)[292]. Direct non-medical costs include transportation costs but may also represent costs for alternative and complementary medicine[292].

Indirect costs relate to loss of productivity measured by absenteeism. From a societal perspective, productivity can also be defined as the production of goods or services, involvement in volunteer work or even household duties[292].

Health economical evaluation

Cost-minimisation analysis compares costs of health interventions with a comparable effect, with the less expensive alternative being the most cost-effective [293]. Notably, this method is only suitable for comparing health interventions with similar outcomes or effects[294].

Cost-benefit analysis measures costs and benefits in monetary terms, with net benefit representing gain of welfare by society[295] allowing comparison of health care interventions in terms of net benefit.

Cost-effectiveness analysis compares healthcare interventions with different effectiveness and different costs using the Incremental Cost-Effectiveness Ratio (ICER). The ICER is calculated by dividing the incremental/differential costs of the intervention by the differential effectiveness of the intervention in question, with the effectiveness being measured in terms of number of lives saved, prevented complications or cured diseases. Interpretation of cost-effectiveness analyses is limited by the challenges of identifying an appropriate outcome as well as the lack of a proper definition of cost-effectiveness[294].

Cost-utility analysis is a specific application of cost-effectiveness analysis using ICER, where the incremental costs of a healthcare intervention are divided by the incremental QALY, obtaining the incremental costs for a gained year of perfect state of health. Cost-utility analysis therefore allows to incorporate costs, survival and quality of life into one single measure. There are different thresholds for ICER depending on the disease severity and countries[294]. As an example, the willingness-to-pay applied in practice in Sweden ranges from 250 000 SEK per QALY for low-severity disease up to 1 000 000 SEK per QALY for high-severity diseases[296].

In Sweden, "Tandvårds- och läkemedelsförmånsverket" uses cost-minimisation analysis and cost-utility analysis as principal methods for evaluating healthcare interventions[297].

Health economic data collection

Health economic evaluation can be either model-based or trial-based. Model-based economic evaluations rely on a mathematical model synthesising health and/or economic data from different sources such as clinical trials, observational studies, or surveys. The output of the mathematical model is usually expressed as an estimate of cost per QALY or a measure of value for money, conditioned by the model assumptions, including sensitivity analyses[298, 299].

Piggyback or trial-based economic evaluations are performed along a trial such as phase 3 drug trials[298]. However, economic evaluation is often not the primary outcome of the trial, and the design might therefore not be completely suitable for economic evaluation[300].

Costs of CRC

In 2018, the total annual cost for CC in Sweden reached well over 260 million EUR (MEUR) and 150 MEUR for RC. Direct costs for CRC were 190 MEUR with 22 MEUR for cancer drugs. Indirect costs related to morbidity and mortality combined for CRC accounted for 183 MEUR[301]. From a wider perspective, CRC represented 12% of total costs related to cancer in Sweden in 2016.

From a patient's perspective, CRC diagnosis and following treatment leads to a 25 to 30% transient loss of taxable income the year following diagnosis[302], according to a study evaluating indirect costs of stage I-III CRC in Sweden. Notably, a significant work loss persisted 5 years after diagnosis, albeit with no severe impact on disposable income, suggesting a mitigating effect on loss of income by the Swedish welfare system.

Comparisons of costs between surgical resection modalities have previously been reported in the litterature[303-305]. Reported costs of surgical care per patient with CRC varied between 1 149 USD and 34 606 USD, while costs related to chemotherapy ranged from 1 883 USD to 18 021 USD, according to a recent systematic review with worldwide coverage[306]. Hence, the substantial variability in costs across countries makes comparisons from an international perspective challenging.

Early CRC can mainly be managed by either local or surgical resection. The need for subsequent surgical treatment after initial local treatment depends on the risk for LNM, which further impacts the costs of treatment. The costs related to follow-up might also impact total costs. Cost comparison of treatment in early CRC accounting for the potential need for treating lymph nodes is lacking, in addition to being challenging.

The challenges of allocating patients for organ-sparing treatment

The proportion of patients diagnosed with early CRC is expected to increase with implementation and enhancement of screening programmes[52, 53]. Local resection is currently a well-established treatment modality for selected cases of T1-stage CRC, exhibiting low risk for LNM. When feasible, local resection is a preferable approach given the morbidity, the mortality, and the risk for permanent stoma associated with surgical resection.

Increased awareness has been drawn over the high proportion of patients with early CRC overtreated with surgical resection[168], when local resection is a potential curative alternative. The accuracy of currently available staging modalities in early CRC is, to some extent, poorly investigated, and its clinical impact remains uncertain. Further investigating the accuracy and the clinical impact of current staging modalities will permit optimising the role of local resection in the management of patients with early CRC.

While LNM is only present in approximately 10%[248, 279, 280] of patients undergoing resection for T1 CRC, more than 60%[239, 278] of T1 lesions are considered at high risk for LNM, according to current guidelines. Subsequent surgical resection is recommended for these high-risk lesions, treating potential LNM and preventing recurrent disease. However, there is significant discrepancy between the lesions considered at high risk for LNM and the observed prevalence of LNM, suggesting that most of these lesions are overtreated with surgical resection. Moreover, the risk of LNM and recurrence should be weighed against the risk associated with surgical resection. Optimising criteria for lesions at high risk for LNM as well as recurrence will allow limiting overtreatment in this patient group.

Costs associated with local and surgical treatment modalities for CRC have been previously established. However, the impact of subsequent surgery following local resection on costs needs to be considered. The potential need for subsequent surgery makes cost comparison challenging in early CRC. Addressing this aspect will allow to clarify the roles of available treatment alternatives from a health-economical perspective.

Aims

The overall aims of the present thesis are to optimize work-up and management of patients with early CRC. The findings of this thesis will assist clinicians involved in the management of these patients to further clarify the role of current staging methods.

Paper I

To investigate the accuracy and clinical impact of CT-based T-staging, N-staging and TN-staging accuracies in early CC with combined cT1-2 stages.

Paper II

To investigate the accuracy and clinical impact of MRI-based T-staging, N-staging and TN-staging accuracies in early RC with combined cT1-2 stages.

Paper III

To compare costs associated with local and surgical treatments of T1 RC in addition to compare costs according to a model-based hypothetical cost scenario accounting for the need for potential subsequent surgical resection after primary local resection.

Paper IV

To investigate impact of tumour location in early R on LNM and recurrence, among other risk-factors.

Material and methods

The Swedish Colorectal Cancer Registry

The Swedish Colorectal Cancer Registry (SCRCR) is a prospectively maintained Swedish national quality registry on all cases of colorectal cancer, initiated in 1995. The aims of the SCRCR are to monitor adherence to national objectives set for diagnosing and treating patients with CRC, to serve as a basis for improvements in the management of patients with CRC, to identify and promote equal treatment of CRC throughout regions and hospitals in Sweden, as well as to serve for research purposes[307]. The SCRCR has been proven reliable in terms of coverage and accuracy[308, 309].

Data

The registry contains data such as age at CRC diagnosis, patient sex (defined according to the biological sex of the patient), body mass index, patient status according to the American Society of Anaesthesiologists classification, preoperative staging data, data on neoadjuvant treatment, operative and perioperative information, postoperative data such as complications, histopathological staging, potential adjuvant treatment and up to 5-year follow-up data. Additionally, the SCRCR collects data such as date of diagnosis, date of operation, date of last follow-up, data regarding recurrence and recurrence characteristics, as well as mortality during follow-up.

Staging

All patients diagnosed with CRC undergo CT of the thorax and the abdomen for metastases screening and for loco-regional staging in patients with CC, according to Swedish guidelines[41] while patients with RC undergo locoregional staging with MRI. All radiology exams undergo a second read by a gastrointestinal radiologist during MDT. Preoperative TNM stages reported in the SCRCR are defined during MDT discussions, based on radiological assessment. Histopathological TNM stages, in addition to other histopathological characteristics, are reported according to Swedish guidelines[310].

Preoperative clinical cT1 and cT2 stages are combined as cT1-2 in the SCRCR. N-stage is reported as N0, N1 or N2 and was dichotomised in Paper I-IV as N0 and N+ (comprising N1 or N2).

Population

Paper I

In paper I, all patients with non-synchronous and non-metachronous CC, preoperatively staged cT1-2, diagnosed between 2009 and 2018 and who underwent a surgical resection, were retrieved from the SCRCR. The following exclusion criteria were applied: emergency operation; undetermined histopathological stages (pTx and pNx); neoadjuvant chemo/radiotherapy; time from diagnosis to surgery exceeding 1 year; unspecified tumour location within the colon; missing values on the aforementioned criteria, age, sex and lack of CT examination. The patients remaining after exclusion constituted the study cohort for analyses on patients with preoperatively staged cT1-2CC.

All patients with non-synchronous and non-metachronous CC, histopathologically staged pT1, diagnosed between 2009 and 2018 and who underwent a surgical resection, were retrieved from the SCRCR. The following exclusion criteria were applied: emergency operation; undetermined histopathological stages (pNx); neoadjuvant chemo/radiotherapy; time from diagnosis to surgery exceeding 1 year; unspecified tumour location within the colon; missing values on the aforementioned criteria, age, sex and lack of CT examination. The patients remaining after exclusion constituted the study cohort for analyses on patients with histopathologically staged pT1 CC.

Paper II

All patients with non-synchronous and non-metachronous RC, preoperatively staged cT1-2, diagnosed between 2009 and 2018, with no undetermined histopathological T-stage pTx, were retrieved from the SCRCR. The following exclusion criteria were applied: endoscopic resection; neoadjuvant chemo/radiotherapy; emergency operation; time from diagnosis to surgery exceeding 1 year; undetermined histopathological N-stage (pNx); missing values on the aforementioned criteria, age, sex and MRI examination. The patients remaining after exclusion constituted the study cohort for analyses on patients with preoperatively staged cT1-2 RC.

All patients with non-synchronous and non-metachronous RC, histopathologically staged pT1, diagnosed between 2009 and 2018, were retrieved from the SCRCR. The following exclusion criteria were applied: endoscopic resection; neoadjuvant chemo/radiotherapy; emergency operation; time from diagnosis to surgery exceeding 1 year; undetermined histopathological N-stage (pNx); missing values on the aforementioned criteria, age, sex and MRI examination. The patients remaining after exclusion constituted the study cohort for analyses on histopathologically staged pT1 patients.

Paper III

All patients with histopathologically staged pT1 RC undergoing ESD, TEM, open resection, laparoscopic resection, or robotic resection between 2011 and 2017 in Skåne County were identified in the SCRCR. The following exclusion criteria were applied: patients with synchronous colorectal lesions; patients with hereditary forms of CRC; chemo/radiation therapy; postoperative mortality; and patients residing outside Skåne County. The patients remaining after exclusion constituted the study cohort used for determination of treatment costs.

All patients with histopathologically staged pT1 RC, treated either by local resection or surgical resection between 2009 and 2018, were retrieved from the SCRCR. The following exclusion criteria were applied: neoadjuvant chemo/radiotherapy; synchronous cancers; pedunculated lesions; missing data on depth of submucosal invasion, lymphovascular invasion or histologic grade. Tumour budding is not registered in the SCRCR and could not be included in current analyses. The patients remaining after exclusion constituted the patient cohort for application of the hypothetical cost scenario, using previously determined costs on the cohort of patients from Skåne County.

Paper IV

All patients with non-synchronous and non-metachronous histopathologically staged pT1 and pT2 RC, diagnosed between 2009 and 2021, were retrieved from the SCRCR. The following exclusion criteria were applied: local resection; emergency surgery; inconsistent surgical technique; undetermined histopathological N-stage (pNx); chemo/radiotherapy; undetermined tumour location; missing values on aforementioned criteria. The patients remaining after exclusion constituted the first patient cohort for analyses on risk factors for lymph node metastasis.

Additional exclusion criteria were applied as follows to the previous patient cohort: presence of distant metastases at diagnosis or unknown distant metastases status at diagnosis, death within one year of follow-up after surgical resection and patients lost to follow-up. The patients remaining after exclusion constituted the second patient cohort for analyses on risk factors for recurrence.

Methods

Staging accuracy, Paper I-II

The aim of Paper I and Paper II was to retrospectively investigate the accuracy of locoregional staging with CT and MRI in CC and RC, respectively, by comparing preoperative clinical cT- and cN-stages with histopathological pT- and pN-stages in patients with preoperatively staged cT1-2 CC and RC as well as histopathologically staged T1 CC or RC.

T-stage accuracy was evaluated by positive predictive value (corresponding to the accuracy) in patients preoperatively staged cT1-2.

N-stage accuracy was evaluated by overall accuracy, sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for detection of LNM.

In paper I, the potential impact of age at diagnosis, sex, time to surgery, year of surgery and tumour location on T-stage and N-stage accuracies was evaluated in patients with preoperatively staged cT1-2 CC. Tumour location was dichotomised as right-sided and left-sided colon cancer. Tumours located from the caecum to the transverse colon were classed as right-sided tumours while left-sided tumour included tumours located from the splenic flexure to the sigmoid colon.

In paper II, the potential impact of age at diagnosis, sex, time to surgery, year of surgery, use of EUS and hospital volume on T-stage and N-stage accuracies was evaluated in patients with preoperatively staged cT1-2 RC. Time to surgery was defined as the time between the date of diagnosis and the date of surgical resection, measured in days. Median volume per treating hospital during the study period was used as a threshold for determining high-volume centres, with high-volume centres treating more than 30 patients preoperatively staged cT1-2 RC and low-volume centres treating less than 30 patients.

Information regarding length and weight was missing in a significant proportion of patient which limited the use of BMI as a factor in logistic regression analyses.

Statistics

Univariate and multivariate logistic regression analyses were used to investigate the potential impact of age at diagnosis, sex, and year of surgical operation in addition to tumour location within the colon for patients with CC as well as use of EUS and centre volume for patients with RC.

Python was used for exploratory data analysis and data selection. R Studio (R core team 2020, R foundation for statistical computing, Vienna, Austria) was used for statistical analyses. Continuous data is presented as median and range. *p*-values <0.05 were deemed significant.

Cost analysis and hypothetical cost scenarios, Paper III

Cost analysis

The patient cohort from Skåne County was used to determine total direct costs of different resection alternatives for histopathologically staged pT1 RC.

Direct costs comprised costs related to the procedure and costs related to 1-year follow-up. Procedural costs included all costs during hospitalisation for the procedure until discharge, including procedure-related costs, radiology, hospital fees, and ancillary services. Costs during follow-up were defined for all events occurring from discharge to 1-year follow-up and included subsequent surgical resection for patients undergoing initial non-curative local resection, conversion of diverting ileostomies, visits at the outpatient colorectal surgery clinic, stoma care, endoscopic examinations, radiology, emergency visits, and hospital stays.

The Regional Price and Reimbursement List (year 2017) for the Southern Healthcare Region was used to establish costs. The costs of open resection, laparoscopic resection and robotic resection were not included in the Regional Price and Reimbursement List and were determined by the surgical department economist based on data from 2017. An additional cost of 25% was added in cases of conversion from laparoscopic or robotic to open resection.

Patients remained in their initial procedure group, even in case of conversion to open resection or when undergoing subsequent surgery resection after initial local resection (ESD or TEM), thereby analysing costs in an "intention-to-treat" fashion.

Indirect costs were not determined since the median age of the patients was above the age of retirement.

All costs were converted from Swedish kronor (SEK) to euros (EUR) at the 2017 conversion rate defined by Riksbanken (1 EUR = 9.63 SEK).

Hypothetical cost scenarios

The setup of the hypothetical cost scenarios consisted of either primary local resection (ESD, TEM) on all patients with pT1 RC followed by completion surgical resection in all cases at high risk for LNM, or primary surgical resection (open resection, laparoscopic resection, robot-assisted resection) on all patients with pT1 RC.

Lesions considered at low risk for LNM were defined as T1 RC with superficial submucosal invasion (Sm1), low-grade histology, and absence of LVI, according to ESGE's 2015 guidelines[311], prevailing at the time of the study. Currently, ESGE's updated guidelines from 2022 nuance the impact of deep submucosal invasion in T1 RC, stating that if the single high-risk feature for a T1 RC is submucosal invasion deeper than Sm1, chemoradiotherapy or surveillance might be preferred over surgical resection[212].

Median total costs derived from the Skåne County cohort were applied to the hypothetical cost scenarios, assuming that the Skåne County cohort was representative of the national cohort of patients with pT1 RC, that subsequent surgery was performed in all cases of high-risk T1 RC following local resection and that all local resections were microscopically radical and performed *en bloc*. The cost of subsequent surgery was defined as the median cost of the two less expensive surgical resection alternatives.

Total 1-year costs were defined for each scenario: upfront ESD followed by subsequent surgical resection in all high-risk cases, upfront TEM followed by subsequent surgical resection in all high-risk cases, open resection as primary treatment, laparoscopic resection as primary treatment and robotic resection as primary treatment.

Statistics

Wilcoxon rank-sum (Mann-Withney U) test was used to perform pairwise comparison of costs of treatments in the cohort of patients used for determining costs of treatment. Differences in operating room time and hospitalisation rate were compared using Kruskal-Wallis test.

Statistical analyses were performed with STATA statistical software (release 14.2, College Station, Texas, United States).

Oncological impact of tumour location, Paper IV

Tumour location

Tumour location was defined as the distance from the distal tumour border and the anal verge, measured preoperatively by rigid rectoscopy and reported in centimetres. Tumour location was categorised as distal, mid and proximal for tumours located between 0 and <5 cm, between 5 cm and <10 cm and between 10 cm and 15 cm, respectively.

Impact of height on LNM

The impact of tumour location on LNM was investigated along with the following factors: age at diagnosis, sex, histopathological T-stage, presence of LVI, presence of PNI, mucinous subtype and histologic grade.

Impact of height on recurrence

The impact of tumour location on recurrence was investigated along with the following factors: age at diagnosis, sex, histopathological T-stage, histopathological N-stage, lateral resection margin, presence of LVI, presence of PNI, mucinous subtype and histologic grade.

Lateral resection margin, reported in millimetres, corresponds to the minimum distance between the tumour and the lateral resection plane and was dichotomised at a threshold value of ≤1 mm[134] prior to analyses.

Recurrence comprised both local and/or distant recurrence. Recurrence-free interval (RFI) was defined as the time between the date of surgical resection and the date of detected recurrence. The follow-up period was set to 6 years to account for late 5-year routine follow-up.

Missing values

The proportion of complete cases reached 89.6% in the patient cohort for analyses on LNM. In the patient cohort for analyses on recurrence, 73.3% of patients had complete data.

A multiple imputation technique, Multiple Imputation by Chained Equation (MICE)[312], was used to handle missing values. The MICE technique imputes missing values by iteratively filling missing values using predictive models in multiple datasets.

Prior to analyses on LNM, missing values on LVI, PNI, mucinous subtype, histologic grade were imputed using MICE with 10 imputed datasets and 20 iterations.

The proportion of complete cases was 73.3% in the patient cohort for analyses on recurrence. Missing values on dichotomized lateral resection margin, LVI, PNI, mucinous subtype, and histologic grade were imputed using MICE with 5 imputed datasets and 20 iterations.

Sensitivity analyses were performed by comparing results obtained on the imputed dataset with analyses performed on complete data (list-wise deletion).

Statistics

Categorical and continuous variables reported as baseline characteristics were compared using the Chi-square test (or Fisher's exact test) and the Kruskal-Wallis rank-sum test, respectively.

The impact of tumour location on LNM, among other abovementioned factors, was evaluated with univariate and multivariate logistic regression in each imputed dataset (10). The results from each dataset were combined, yielding pooled results.

The impact of tumour location on recurrence, adjusted for other abovementioned factors, was evaluated with univariate and multivariate Cox regression in each imputed dataset (5). The results from each dataset were combined, yielding pooled results. RFI was used as a time variable in Cox regression analysis. Patients were right-censored at the most recent date of follow-up or death. Proportional hazards

were assumed based on Kaplan-Meier plots, log-log plots and the Schoenfeld residuals test.

Statistical analyses were performed using R (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org.) with the package MICE[312].

Ethical considerations

All studies in the present thesis received approval by the Regional Ethical Review Board, Lund University: 2017/546 (Paper I, Paper II and Paper III) and 2020-06676 (Paper IV).

All studies in the present thesis were conducted in accordance with the Declaration of Helsinki.

All data retrieved from the SCRCR was coded, and patient anonymity was guaranteed.

Results

Paper I

Patients preoperatively staged with cT1-2 colon cancer

A total of 5694 patients with surgically resected CC, preoperatively staged cT1-2, were identified in the SCRCR and screened for eligibility. After applying exclusion criteria, 4849 patients remained for analysis (Figure 7).

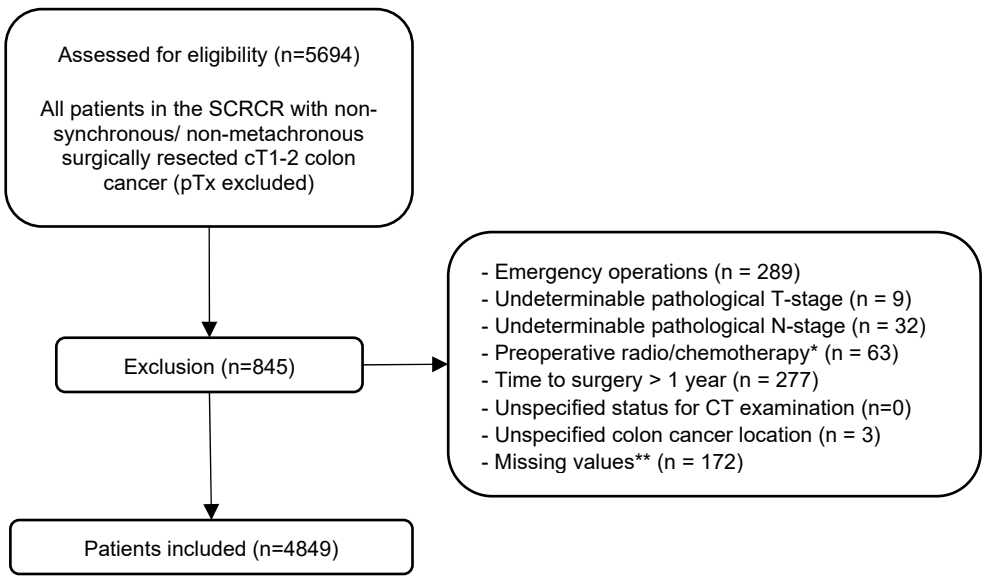

Figure 7. Overview of patients with preoperatively staged cT1-2 CC
* Includes exclusion of pT0 cases (n=8) persistent after exclusion of pre-operative radio- or chemotherapy (n=55)
** Missing values for age, sex, cN stage, pT stage, pN stage, emergent vs elective operation, pre-operative radio- or chemotherapy, diagnosis date, operation date, status for CT examination and status for cancer location in colon

Table 4. Baseline characteristics of patients with preoperatively staged cT1-2 CC.

Cases preoperatively staged cT1-2 by CT	4849
Sex	
- Male	2416 (49.8%)
- Female	2433 (50.2%)
Age at diagnosis[a]	74 (22-97)
Time to surgery[b]	35 (1-328)
Tumour location	
- Right-sided	3030 (62.5%)
- Left-sided	1819 (37.5%)
Treating centers	57
Histopathological T-stage	
- pT1	624 (12.9%)
- pT2	1327 (27.4%)
- pT3	2445 (50.4%)
- pT4	453 (9.3%)
Histopathological N-stage	
- pN0	3375 (69.6%)
- pN+	1474 (30.4%)
Treating centres	57

[a]: in years; [b]T: in days;

The median age was 74 (22-97) years, and 50.2% were women. The median time from diagnosis to surgery was 35 days, and 4607 (95%) patients were operated on within 90 days. Among included patients, 3030 (62.5%), had right-sided tumour. Pathologically verified LNM was present in 1474 (30.4%) patients. Baseline characteristics are presented in
Table 4.

Accuracy of T-stage is presented in
Table 4. T-stage was accurate in 1951 (40.3%) of the 4849 patients in the cT1-2 cohort, with 624 (12.9%) tumours staged pT1 and 1327 (27.4%) tumours staged pT2. Accuracy, corresponding to the positive predictive value, was 40.2%. Conversely, 2445 (50.4%) and 453 (9.3%) patients histopathologically staged as pT3 and pT4, respectively, were understaged as cT1-2 preoperatively.

Results from uni- and multivariate logistic regression on T-stage accuracy are presented in Table 5. Left-sided tumour was a significant factor associated with accurate T-staging in both uni- and multivariate analysis, while lower age was associated with T-staging accuracy in univariate analysis.

Table 5. Factors potentially influencing T-stage accuracy in patients with preopertively staged cT1-2 CC.

	Univariate			Multivariate		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Age at diagnosis[a]	0.99	0.99-1.00	<0.05	1.00	0.99-1.00	0.3
Sex						
- Male	1	Ref	Ref	1	Ref	Ref
- Female	1.04	0.92-1.17	0.5	1.09	0.97-1.23	0.1
Year of surgery						
- 2009	Ref			Ref		
- 2010	0.84	0.60-1.16	0.3	0.85	0.61-1.17	0.3
- 2011	1.06	0.77-1.47	0.7	1.06	0.76-1.46	0.7
- 2012	0.99	0.73-1.34	0.9	1.01	0.74-1.37	0.9
- 2013	1.06	0.79-1.43	0.7	1.06	0.78-1.43	0.7
- 2014	1.09	0.82-1.46	0.6	1.12	0.84-1.50	0.4
- 2015	1.18	0.89-1.56	0.2	1.21	0.91-1.60	0.2
- 2016	1.06	0.81-1.40	0.7	1.09	0.83-1.43	0.5
- 2017	1.03	0.79-1.35	0.8	1.06	0.81-1.39	0.7
- 2018	1.19	0.92-1.56	0.2	1.23	0.94-1.60	0.1
Location						
- Right-sided	1	Ref	Ref	1	Ref	Ref
- Left-sided	1.37	1.22-1.54	<0.001	1.38	1.22-1.55	<0.001

OR: Odds ratio; CI: 95% confidence interval; [a]: OR per increasing year of age;

Table 6. N-stage accuracy in patients with preoperatively staged cT1-2 CC.

Preoperative stage by CT	**Histopathological stage**		**Total**
	pN0	**pN+**	
cN0	2898	1062	3960
cN+	403	368	771
cNx	74	44	118
Total	3375	1474	4849

Accuracy of N-staging is presented in Table 6. LNM was detected in 1474 (30.4%) patients. The nodal stage was accurate in 2898 (59.8%) out of 3960 patients preoperatively staged cN0 and 368 (47.7%) patients out of 771 patients staged cN+. Among 3960 patients preoperatively staged cN0, 1062 (26.8%) patients had LNM, thus understaged. Overstaging occurred in 403 (52.3%) out of 771 patients preoperatively staged cN+ and found to have no LNM at histopathological assessment. Among 118 patients with undetermined preoperative N-stage (cNx), 74 (62.7%) had no LNM (pN0) by final histopathology.

Overall N-staging accuracy was 67%. The sensitivity and specificity for detecting LNM were 26% and 88%, respectively. The positive predictive value and the negative predictive value for detection of LNM were 48% and 73%, respectively. The positive likelihood ratio and negative likelihood ratio for detecting LNM were 2.1 and 0.85, respectively.

Results from uni- and multivariate logistic regression on N-stage accuracy are presented in Table 7. Increasing age at diagnosis was found to be associated with increasing N-stage accuracy in both uni- and multivariate analyses, while right-sided tumour location was found to increase N-stage accuracy in univariate but not in multivariate analyses.

Table 7. Factors potentially influencing N-stage accuracy in patients with preopertively staged cT1-2 CC.

	Univariate			Multivariate		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Age at diagnosis[a]	1.02	1.01-1.02	<0.001	1.02	1.01-1.02	<0.001
Sex						
- Male	1	Ref	Ref	1	Ref	Ref
- Female	1.04	0.92-1.17	0.6	1.01	0.89-1.14	0.9
Year of surgery						
- 2009	1	Ref	Ref	1	Ref	Ref
- 2010	0.97	0.69-1.35	0.9	0.95	0.68-1.33	0.8
- 2011	0.91	0.65-1.28	0.6	0.91	0.65-1.28	0.6
- 2012	0.89	0.65-1.22	0.5	0.86	0.63-1.18	0.4
- 2013	0.94	0.69-1.28	0.7	0.93	0.68-1.27	0.6
- 2014	0.98	0.72-1.32	0.9	0.94	0.70-1.28	0.7
- 2015	1.09	0.81-1.47	0.6	1.06	0.79-1.43	0.7
- 2016	1.09	0.75-1.32	0.9	0.97	0.72-1.28	0.8
- 2017	1.02	0.77-1.35	0.9	0.98	0.74-1.30	0.9
- 2018	0.95	0.72-1.25	0.7	0.92	0.70-1.21	0.6
Location						
- Right-sided	1	Ref	Ref	1	Ref	Ref
- Left-sided	0.87	0.77-0.98	0.022	0.93	0.82-1.06	0.3

OR: Odds ratio; CI: confidence interval; [a]:OR per increasing year of age;

Patients with histopathologically staged pT1 colon cancer

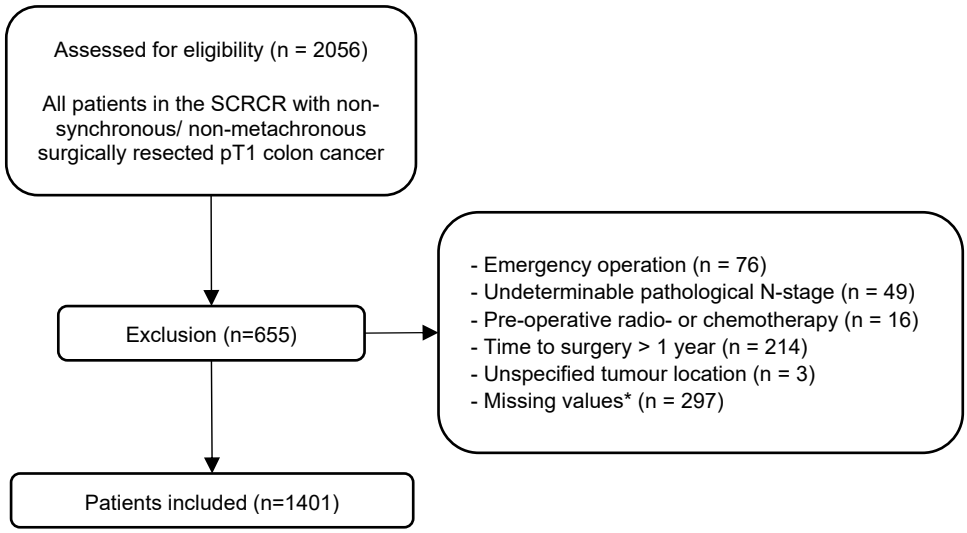

Figure 8. Overview of patients with histopathologically staged pT1 CC.
* Missing values for age, sex, cT stage, cN stage, pN stage, emergent versus elective operation, pre-operative radio- or chemotherapy, diagnosis date, operation date, status for CT examination and location of cancer within the colon.

Table 8. Baseline characteristics of patients with histopathologically staged pT1 CC.

Cases histopathologically staged pT1	1401
Sex	
- Male	721 (51.5%)
- Female	680 (48.5%)
Age at diagnosis[a]	72 (20-96)
Time to surgery[b]	44 (1-316)
Tumour location	
- Right-sided	661 (47.2%)
- Left-sided	740 (52.8%)
Preoperative T-stage by CT	
- cT1-2	624 (44.5%)
- cT3	139 (9.9%)
- cT4	15 (1.1%)
- cTx	623 (44.5%)
Pathological N-stage	
- pN0	1244 (88.8%)
- pN+	157 (11.2%)

[a]: in years; [b]: in days;

A total of 2056 patients with histopathologically staged pT1 CC were retrieved from the SCRCR and screened for eligibility. After application of exclusion criteria, 1401 patients remained for analysis (Figure 8). The median age was 72 years, and 49% were women. The median time from diagnosis to surgery was 44 days. Tumours were right-sided in 661 (47.2%) patients. LNM was histopathologically confirmed in 157 (11.2%) of patients. Baseline characteristics are reported in Table 8.

Among 1401 patients with histopathologically staged pT1 CC, 624 (44.5%) were accurately preoperatively staged as cT1-2 while 139 (9.9%) and 11 (1,1%) patients were overstaged as cT3 and cT4, respectively (Table 8). Preoperative T-stage was indeterminate (cTx) in 623 (44.5%) patients.

Table 9. N-staging accuracy patients with histopathologically staged pT1 CC.

Preoperative stage by CT	Histopathological stage		Total
	pN0	pN+	
cN0	1018	105	1123
cN+	80	29	109
cNx	146	23	169
Total	1244	157	1401

Accuracy of N-staging is presented in Table 9. Among 157 (11.2%) patients with histopathologically detected LNM, 105 (66.9%) were preoperatively understaged as cN0, 23 (14.6%) patients had preoperatively indeterminate N-stage (cNx), and the remaining 29 (18.5%) patients were accurately staged as cN+. Among patients preoperatively staged cN+, 80 (73.4%) patients had no LNM at histopathological assessment and were thus overstaged. Overall N-staging accuracy was 74.7%. Sensitivity and specificity for detecting LNM were 22% and 93%, respectively. The positive predictive value and negative predictive value for detection of LNM were 27% and 91%, respectively. The positive likelihood ratio and negative likelihood ratio for detecting LNM were 2.97 and 0.91, respectively.

Combined T- and N-stage accuracy

Among 3960 patients who were preoperatively staged with AJCC stage I CC (cT1-2N0), 1480 (37.4%) patients were accurately staged at pT1N0 or pT2N0 at histopathological assessment. The remaining 2480 (62.6%) patients had more advanced disease at histopathological assessment (>pT2 and/or pN+) and were thus preoperatively understaged.

Among 1244 patients with histopathologically staged pT1N0 CC, 512 (41.2%) were accurately preoperatively cT1-2N0, and the remaining 732 (58.8%) patients were thus overstaged.

Paper II

Patients preoperatively staged cT1-2 rectal cancer

A total of 2295 patients with preoperatively staged cT1-2 RC in the SCRCR were screened for eligibility. After applying exclusion criteria, 1888 patients remained for analyses (Figure 9).

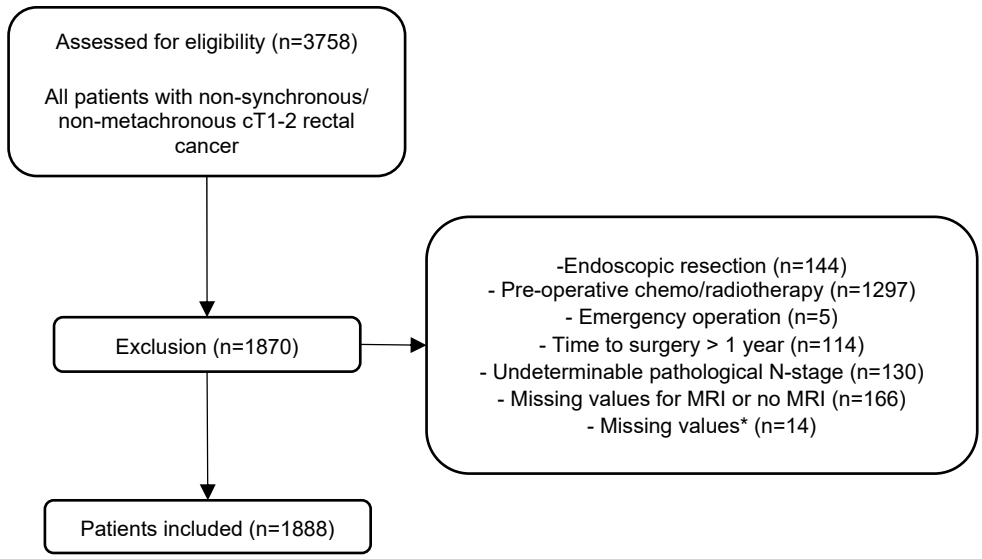

Figure 9. Overview of patient with preoperatively staged cT1-2 staged RC.
*Missing values for age, sex, cN-stage, pN-stage, emergent versus elective operation, preoperative chemo-/radiotherapy, diagnosis or operation date.

Baseline characteristics are reported in Table 10. The median age was 71 (25-95) years old, and 1079 (57.2%) were male. Median time to surgery was 47 days. Among the 52 centres treating patients, 26 were defined as low-volume centres (<30 cases) and 26 were defined as high-volume centres, the latter caring for 1608 (85.2%) patients in the present cohort. EUS was combined with MRI in 54 (2.9%) patients. The median time from diagnosis to surgery was 44 days.

Table 10. Baseline characteristics of the patients with preoperatively staged cT1-2 RC.

Cases preoperatively staged cT1-2 by MRI	1888
Sex	
- Male	1079 (57.2%)
- Female	809 (42.8%)
Age at diagnosis[a]	71 (25-95)
Time to surgery[b]	47 (1-362)
Treating centres	52
- Low volume centers (n=26)	280 (14.8%)
- High volume centers (n=26)	1608 (85.2%)
EUS use	54 (2.86%)
Surgical approach	
- Anterior resection	1228 (65.0%)
- Abdominoperineal resection	368 (19.5%)
- Hartman's procedure	222 (11.8%)
- Other	70 (3.7%)
Histopathological T-stage	
- pT1	426 (22.5%)
- pT2	855 (45.3%)
- pT3	566 (30.0%)
- pT4	41 (2.2%)
Histopathological N-stage	
- pN0	1411 (74.7%)
- pN+	477 (25.2%)

[a]: in years; [b]: in days; EUS : endoscopic ultrasound;

T-stage accuracy is reported in Table 10. Among 1888 patients with preoperatively staged cT1-2 RC, 1281 (67.8%) patients were pT1 or pT2 stage at histopathological assessment and thus, accurately staged, while overstaging occurred in 566 (30.0%) patients who had pT3-staged RC at histopathological assessment and 41 (2.2%) patients who had pT4-staged RC. Positive predictive value for detection of combined T1-T2 stage was 67.8%, corresponding to accuracy. Combining EUS with MRI increased the accuracy of detecting T1-T2 stage to 85.2% (46 out of 54 patients), compared to 67.3% (1235 out of 1834 patients) with MRI alone.

Uni- and multivariate regression analyses on T-stage accuracy are presented in Table 11. Low age, females, increasing time to surgery, EUS and diagnosis year 2016 were found to be associated with increased T-stage accuracy in both uni- and multivariate analysis.

Table 11. Factors potentially influencing T-stage accuracy in patients preoperatively staged cT1-2 RC.

	Univariate			Multivariate		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Age at diagnosis[a]	0.99	0.98-1.00	<0.01	0.99	0.98-1.0	<0.01
Sex						
- Male	1	Ref.		1	Ref.	
- Female	1.41	1.16-1.72	< 0.001	1.47	1.20-1.80	<0.001
Time to surgery[b]	1.00	1.00-1.01	< 0.05	1.00	1.00-1.01	<0.01
Year of surgery						
- 2009	1	Ref.		1	Ref.	
- 2010	0.93	0.59-1.48	0.77	0.93	0.58-1.48	0.74
- 2011	0.70	0.45-1.10	0.12	0.68	0.43-1.06	0.09
- 2012	0.81	0.52-1.26	0.35	0.79	0.50-1.22	0.29
- 2013	1.33	0.85-2.09	0.21	1.33	0.84-2.11	0.22
- 2014	1.07	0.69-1.67	0.76	1.10	0.71-1.75	0.65
- 2015	1.20	0.77-1.85	0.42	1.19	0.77-1.89	0.42
- 2016	2.02	1.27-3.25	<0.01	2.18	1.39-3.60	<0.001
- 2017	1.06	0.69-1.61	0.79	1.12	0.74-1.74	0.55
- 2018	1.03	0.67-1.57	0.89	1.07	0.70-1.66	0.71
EUS use						
- No	1	Ref.		1	Ref.	
- Yes	2.79	1.38-6.42	<0.01	2.82	1.41-6.75	<0.01
Center volume						
- Low volume	1	Ref.		1	Ref.	
- High volume	0.91	0.69-1.19	0.49	0.80	0.60-1.05	0.11

OR: Odds ratio; CI: confidence interval; [a]: OR per increasing year of age; [b]: OR per increasing days;

N-stages are reported in Table 12. Histopathologically confirmed LNM was present in 477 (25.3%) out of 1888 patients. Overall accuracy for nodal staging was 71%. Sensitivity and specificity for detecting LNM were 21% and 87%, respectively. The positive predictive value and negative predictive value for detection of LNM were 44% and 78%, respectively. The positive likelihood ratio and negative likelihood ratio for detecting LNM were 1.69 and 0.90, respectively. Among 233 patients preoperatively staged cN+, 131 (56.2%) patients had no LNM at histopathological assessment and were thus overstaged. Conversely, among 477 patients who had LNM confirmed by histopathology, 354 (74.2%) patients were preoperatively understaged as cN0.

Table 12. N-stage accuracy in patients preoperatively staged cT1-2.

Clinical stage by MR	Histopathological stage		Total
	pN0	pN+	
cN0	1232	354	1586
cN+	131	103	233
cNx	48	21	69
Total	1411	477	1888

Table 13. Factors potentially influencing N-stage accuracy in patients preoperatively staged cT1-2.

	Univariate			Multivariate		
	OR	CI	*p*-value	OR	CI	*p*-value
Age at diagnosis	1.00	0.99-1.01	0.77	1.00	0.99-1.01	0.73
Sex						
- Male	1	Ref.		1	Ref.	
- Female	1.16	0.95-1.42	0.14	1.18	0.96-1.44	0.12
Time to surgery	0.99	0.997-1.002	0.67	1.00	0.997-1.003	0.96
Year of surgery						
- 2009	1	Ref.		1	Ref.	
- 2010	0.58	0.36-0.92	<0.05	0.58	0.36-0.93	<0.05
- 2011	0.60	0.37-0.95	<0.05	0.60	0.37-0.96	<0.05
- 2012	0.65	0.41-1.02	0.07	0.65	0.41-1.03	0.07
- 2013	0.92	0.57-1.47	0.73	0.93	0.58-1.49	0.77
- 2014	1.00	0.62-1.61	0.98	1.02	0.63-1.64	0.95
- 2015	0.77	0.49-1.22	0.27	0.78	0.49-1.23	0.28
- 2016	1.28	0.79-2.07	0.31	1.32	0.81-2.13	0.26
- 2017	0.96	0.61-1.50	0.86	0.99	0.63-1.55	0.96
- 2018	0.92	0.58-1.44	0.72	0.93	0.59-1.46	0.76
EUS use						
- No	1	Ref.		1	Ref.	
- Yes	1.19	0.66-2.29	0.58	1.35	0.74-2.62	0.35
Center volume						
- Low volume	1	Ref.		1	Ref.	
- High volume	1.00	0.75-1.31	0.98	0.92	0.69-1.22	0.58

OR: Odds ratio; CI: confidence interval; [a]: OR per increasing year of age; [b]: OR per increasing days;

Uni- and multivariate regression analyses on N-stage accuracy are presented in Table 13. RC diagnoses made in the years 2010 and 2011 were associated with inaccurate N-staging in both uni- and multivariate regression analyses. N-stage accuracy for cases diagnosed in the years 2010 and 2011 was 68% compared to 72% (range 62%-78%) for the remaining years (2009, 2012-2018). Neither age at diagnosis, sex, time to surgery nor use of EUS impacted N-staging accuracy.

Patients with histopathologically staged pT1 rectal cancer

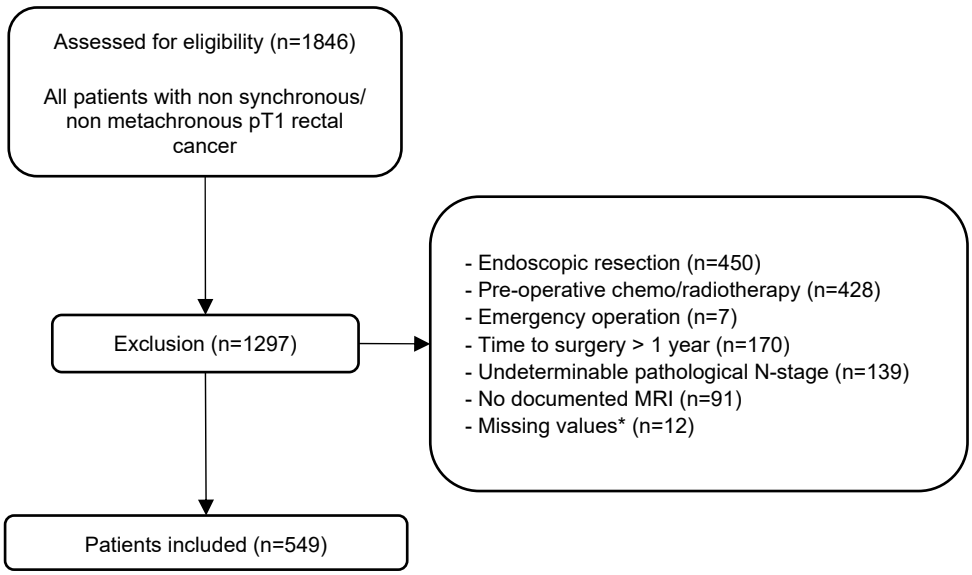

Figure 10. Overview of patients with histopathological staged pT1 rectal cancer.
*: Missing value for age, sex, cN-stage, pN-stage, emergent versus elective operation, preoperative chemo-/radiotherapy, diagnosis or operation date.

Among 1846 patients staged pT1 RC in the SCRCR screened for eligibility, 1297 met the exclusion criteria, and the 549 remaining cases with pT1 were included for analyses (Figure 10).

Table 14. Baseline characteristics of patients with histopathologically staged pT1 rectal cancer

Cases histopathologically staged T1	549
Sex	
- Male	302 (55.0%)
- Female	247 (45.0%)
Age at diagnosis[a]	69 (31-94)
Time to surgery[b]	52 (1-362)
Surgical approach	
- Anterior resection	352 (64.1%)
- APR	103 (18.8%)
- Hartman's procedure	46 (8.4%)
- Other	48 (8.7%)
Preoperative T-stage by MRI	
- cT1-2	426 (77.6%)
- cT3	67 (12.2%)
- cT4	3 (0.5%)
- cTx	53 (9.7%)
Pathological N-stage	
- pN0	486 (88.5%)
- pN+	63 (11.5%)

[a]: in years; [b]: in days;

Baseline characteristics are reported in Table 14. The median age was 69 (31-94) years, and 302 (55.0%) were male. Median time to surgery was 52 (1-362) days.

T-stages are reported in Table 14. Among 549 patients with histopathologically staged pT1 RC, 123 (22.4%) patients were preoperatively overstaged as cT3 and cT4, of whom 53 (9.7%) patients had preoperatively indeterminate tumour stage cTx.

N-stages are reported in Table 15. Among 63 (11.5%) patients with histopathologically verified LNM, 44 (70%) patients were preoperatively staged as cN0 and thus, understaged. Conversely, among 56 (10.2%) patients preoperatively staged cN+, 38 (68%) patients had no LNM according to histopathology and were overstaged. Among 23 patients with preoperative indeterminate nodal status, staged cNx, 22 out of 23 did not have LNM at histopathological assessment. Overall accuracy for nodal staging was 81.1%. The sensitivity and specificity for detection of LNM were 29% and 88%, respectively. The positive predictive value and negative predictive value for detection of LNM were 32% and 91%, respectively. The positive likelihood ratio and negative likelihood ratio for detection of nodal invasion were 2.35 and 0.81, respectively.

Table 15. N-stage accuracy in patients with histopathologically staged pT1 RC.

Clinical stage by MRI	Histopathological stage		Total
	pN0	pN+	
cN0	427	44	471
cN+	38	18	56
cNx	21	1	22
Total	486	63	22

Combined T- and N-stage accuracy

Among 1586 patients preoperatively staged with stage I RC (cT1-2N0), 933 (58.8%) patients had histopathologically verified pT1N0 or pT2N0 RC and were accurately staged, while 653 (41.2%) patients had a higher histopathological stage and were understaged.

Conversely, among 486 patients with histopathologically verified pT1N0 RC, 142 (29.2%) were preoperatively staged cT3-4 and/or cN+ and were thus overstaged.

Paper III

Cost analysis

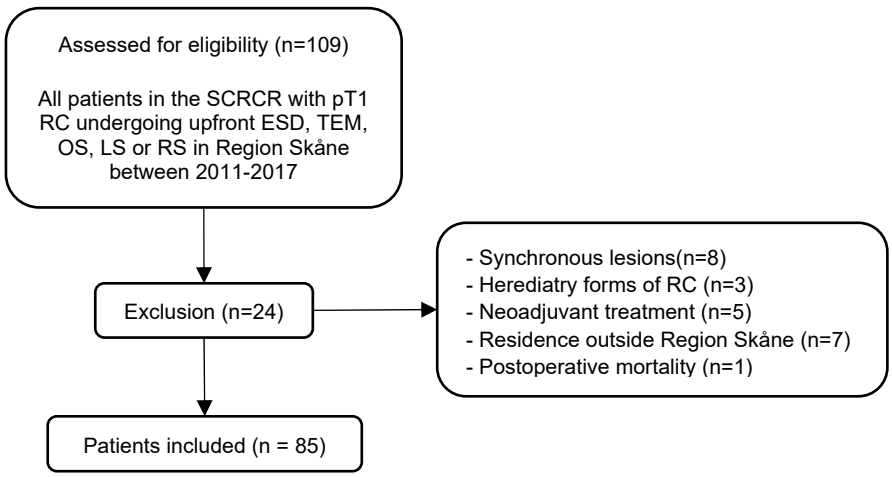

Figure 11. Overview of patients treated for histopathological staged pT1 rectal cancer in Skåne County.

A total of 109 patients with pT1 RC were identified from the SCRCR. After application of exclusion criteria, 85 patients remained for determination of costs of treatment (Figure 11).

Characteristics of patients among the different treatment groups are reported in Table 16. Among the 85 patients included, 16 patients were treated with ESD, 17 patients with TEM, 35 patients underwent open resections, 9 patients underwent laparoscopic resection and 8 patients underwent robotic resection.

Among included patients, 47 (55%) were males and the median age was 69 (38-89) years. Body mass index (BMI) was highest in the laparoscopic resection group and lowest in the robotic resection group; median Charlson comorbidity index (CCI) was 5 in all the treatment groups; median length of hospital stay was highest in the open resection group and none in the ESD group. The shortest median operating room time was recorded in the TEM group and the longest in the RR group. Differences in procedure time were statistically significant (p-value <0.05) but not between TEM and ESD. Length of hospital stay differed also significantly (p-value <0.001) between groups.

Conversion to open resection occurred in 3 patients in both the laparoscopic and robotic resection groups. Among 52 patients who underwent surgical resection, 12

patients had a permanent colostomy, while 32 patients out of 33 patients had a diverting ileostomy reversal within one year of follow-up.

Tumour size, not available in surgical resection groups, was 4 (3-7) cm in the ESD group and 5 (4-10) cm in the TEM group. All tumours were resected *en bloc* and were R0. Among 16 patients in the ESD group, 11 patients exhibited high-risk features for LNM, and 3 patients underwent subsequent surgical resection (1 open resection and 2 robotic resections) due to patient preference, comorbidities or high age. In the TEM group, 2 out of 6 patients with tumours exhibiting high-risk features for LNM underwent subsequent surgical resection (2 robotic resections).

Table 16. Characteristics of patients in the 5 treatment groups.

	ESD	TEM	OR	LR	RR	Total
Total	16	17	35	9	8	85
Age[a]	64 (44-89)	70 (62-79)	68 (38-86)	72 (59-80)	69 (60-76)	69 (38-89)
Male	9 (56%)	9 (53%)	19 (54%)	7 (78%)	3 (38%)	47 (55%)
BMI[a]	25.5 (17-34)	28 (22-33)	26 (16-36.5)	27 (23-31)	25 (22-30)	26 (16-36.5)
CCI[a]	5 (2-7)	5 (4-9)	5 (2-11)	5 (4-8)	5 (4-6)	5 (2-11)
Procedure time[a]	83 (18-594)	65 (25-234)	264 (152-398)	359 (245-554)	465 (341-692)	241 (18-692)
Hospitalisation[a]	0 (0-3)	2 (0-15)	10 (6-24)	7 (5-28)	9 (6-28)	7 (0-28)
Conversion	/	/	/	3	3	6
High-risk T1	11	17	/	/	/	28
Subsequent surgery	3	2	/	/	/	5
Permanent colostomy	/	/	10	0	2	12
Diversion ileostomy	/		20	7	6	33
Ileostomy reversal	/	/		32		32

[a]: presented as median and (range); CCI: Charlson comorbidity index; ESD; endoscopic submucosal dissection, TEM; transanal endoscopic microsurgery; OR; open resection, LR; laparoscopic resection, RR; robotic resection;

Complications across treatment groups are reported in Table 17. A total of 28 complications occurred in 21 patients, with 23 of those complications classed as Clavien-Dindo I or II and amenable to medical treatment.

Perforation occurred in 3 patients in the local resection groups; one case required closure with clips in the ESD group, while the two other complications, one in the ESD group and one in the TEM group, required clips or suturing in addition to antibiotics and prolonged observation.

Table 17. Post-procedural and post-operative complications across the five treatment groups, according to the Clavien-Dindo classification.

Procedures		**ESD**	**TEM**	**OR**	**LR**	**RR**	**Total**
		16	17	35	9	8	**85**
Complications	**Clavien-Dindo**						
Perioperative perforation[a]	I	1					1
Perioperative perforation[b]	II	1	1				2
Perioperative anastomotic leak	II			2			2
Postoperative infection[c]	II			5	2		7
Bowel paralysis	II		1	3	2	1	7
Acute renal failure	II			1			1
Atrial fibrillation	II				1		1
High stoma output	II					1	1
Postoperative anastomotic leak	IIIa				1		1
Pelvic Abscess	IIIa			1			1
Subcutaneous wound rupture	IIIb			1			1
Perforation of the small intestines	IVa				1		1
Acute renal failure (dialysis)	IVa			1			1
Clavien-Dindo	**I**	1	-	-	-	-	1
	II	1	2	11	5	2	22
	III	-	-	2	1	-	3
	IV	-	-	1	1	-	2
Total		2	2	14	6	2	**28**

[a] Closed with clip, no other treatment, [b] Closed with clip (ESD) or suturing (TEM), prolonged observation and antibiotics. [c] Comprising; 2 cases of pneumonia, 2 cases of sepsis, 1 case of clostridium difficile colitis;
ESD; endoscopic submucosal dissection; TEM; transanal endoscopic microsurgery; OR; open resection, LR; laparoscopic resection, RR; robotic resection

Among complications, 5 were classed as Clavien-Dindo III or IV and required intervention or surgery as treatment. Two patients in the surgical resection groups required emergency surgery, one for incisional dehiscence in the open resection group and one for perforation of the small bowel in the laparoscopic resection group, with both patients requiring admission to the ICU. In the open resection group, one patient developed postoperative ileus, pneumonia, and dialysis-requiring acute renal failure, leading to ICU admission.

Table 18. Costs according to the five treatment groups.

		n	Costs[a]	IQR[b]	Total costs[a]	IQR[b]
ESD	Procedure	16	2 650	2 650-4 770	5 165	2 906-28 190
	Follow-up		1 979	170-25 539		
TEM	Procedure	17	12 736	11 280-19 242	14 871	13 162-40 323
	Follow-up		1 987	426-27 587		
OR	Procedure	35	14.236	12 234-31 944	21 453	13 421-37 732
	Follow-up		5 912	687-18 615		
LR	Procedure	9	13 831	10 636-28 602	22 488	12 062-36 237
	Follow-up		6 351	426-13 237		
RR	Procedure	8	21 125	17 861-31 064	26 562	22 407-38 438
	Follow-up		6 541	1 599-13 644		
All procedures	Procedure	85	13 235	2 650-31 944	19 807	2 906-40 323
	Follow-up		3 493	170-27 587		

[a]: expressed as median costs; [b]: interquartile range; Costs in euros (€);
ESD: endoscopic submucosal dissection, TEM; transanal endoscopic microsurgery; OR: open resection; LR; laparoscopic resection; RR; robotic resection;

The median procedure costs, median follow-up costs, and the median total costs are presented in Table 18. Table 19 reports pairwise comparison of costs between treatment groups. ESD was found to have significantly lower procedural and total costs compared to all other groups. TEM was also significantly associated with lower procedural and total costs compared to open resection and robotic resection, but not regarding the procedural costs of laparoscopic resection. Procedural costs and total costs of open resection were significantly lower than robotic resection.

Table 19. Pairwise comparison of procedural and total 1-year costs.

		Median procedural costs	Median total 1-year costs
ESD versus:	**TEM**	p <0.001	p=0.001
	OR	p<0.001	p<0.001
	LR	p<0.001	p=0.003
	RR	p<0.001	p=0.002
TEM versus:	**OR**	p=0.008	p=0.001
	LR	p=0.722	p=0.033
	RR	p<0.001	p <0.001
OR versus:	**LR**	p=0.630	p=0.873
	RR	p<0.001	p=0.010
LR versus:	**RR**	p=0.070	p=0.070

p: p-value determined using Mann-Withney U-test; ESD; endoscopic submucosal dissection, TEM; transanal endoscopic microsurgery, OR; open resection, LR; laparoscopic resection, RR; robotic resection;

Hypothetical cost scenarios

A total of 1787 patients with locally and surgically resected histopathologically staged T1 RC were identified in the SCRCR. After application of exclusion criteria, 779 patients remained for analyses (Figure 12).

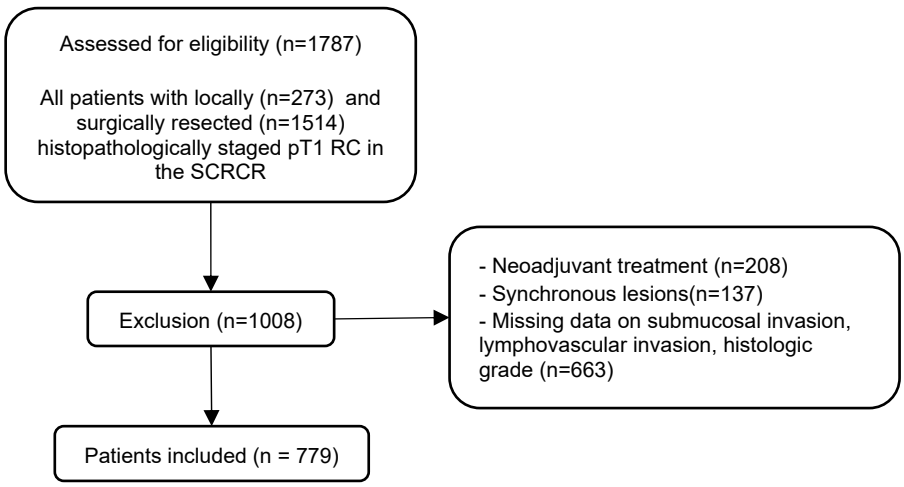

Figure 12. Overview of patients treated for histopathological staged pT1 rectal cancer in Sweden.

Table 20. Baseline characteristics of the pT1 national study cohort.

Total	779
Sex	
- Male	449 (57.6%)
- Female	330 (42.4.0%)
Age at diagnosis	70 (31-96)
Overall high-risk T1[a]	531 (68.2%)
Local resection	90 (11.6%)
- High-risk T1[a]	35 (39%)
Surgical resection	689 (88.4%)
- High-risk T1[a]	496 (72.0%)
- LNM	84 (12.2%)

[a]Defined as presence of deep submucosal invasion (Sm>1) and/or lymphvascular invasion and/or high histologic grade;

Baseline characteristics of patients are presented in Table 20. Among included patients, 449 (57.6%) out of 779 were male and the median age was 70 (31-96) years. Local resection was performed in 90 (11.6%) patients, while 689 (88.4%) patients underwent surgical resection.

Overall, 531 (68.2%) patients had histopathologically staged pT1 RC exhibiting features with high risk for LNM. Among 90 patients primarily treated with local resection, 35 (39%) patients had high-risk lesions, while 496 (72.0%) patients out of 689 patients treated with surgical resection had high-risk lesions. Among 689 patients undergoing surgical resection, 84 (12.2%) patients had LNM at histopathological assessment.

The estimated total 1-year costs per patient according to hypothetical cost scenarios are presented in Table 21. Costs of open resection, laparoscopic resection and robotic resection were equivalent to those previously defined. Costs of primary local resection using ESD or TEM included procedural costs of ESD or TEM, costs of subsequent surgery and 1-year follow-up in 68% of high-risk cases.

According to hypothetical cost scenarios accounting for subsequent surgery in 68% of cases primarily treated with local resection, the total 1-year cost was lowest for ESD with €18 168 per patient, while primary local resection by TEM was the most expensive alternative with €28 319 per patient, even compared to upfront surgical resection.

Table 21. Costs according to hypothetical cost scenarios based on different index procedures on all T1 RC.

Index procedure	Per patient 1-year cost
ESD	18 168 €
TEM	28 319 €
OR	21 724 €
LR	22 772 €
RR	26 896 €

ESD; endoscopic submucosal dissection; TEM; transanal endoscopic microsurgery; OR; open resection, LR; laparoscopic resection, RR; robotic resection

Paper IV

A total of 6744 patients surgically resected for histopathologically staged pT1 and pT2 RC were identified in the SCRCR. After applying exclusion criteria, 2424 patients remained for analyses on LNM (Figure 13).

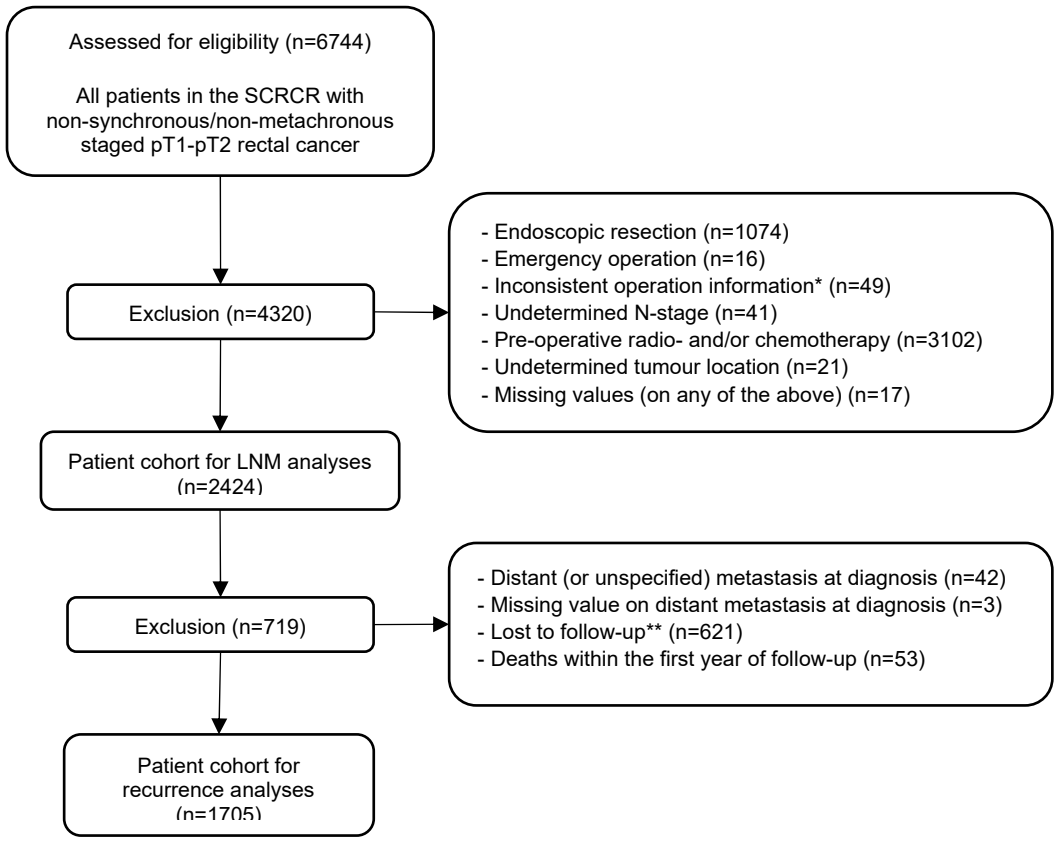

Figure 13. Overview of the study populations for analyses on LNM and recurrence.
* Right hemicolectomy (n=2), Left hemicolectomy (n=3), Unspecified colectomy (n=22), Laparotomy without resection (n=1), Other procedures (n=21)
** Missing value for recurrence or death (n=618), missing follow-up or recurrence date (n=3)

Baseline characteristics are presented in Table 22. The median age at diagnosis was 71 (64-78) years; 1361 (56.1%) patients were males, and 736 (30.4%) patients had histopathologically staged T1 RC. The majority of tumours were located in the mid rectum (46.6%), followed by the proximal rectum (38.8%). Patients with proximal RC had a younger age at diagnosis compared to distal RC (p-value <0.05). Sex and proportion of T1 versus T2 stages were similar across tumour locations. There was

an increased prevalence of LVI, PNI, histologic grade and mucinous subtype in distally located tumours, but only PNI (p-value <0.05) and mucinous subtype (p-value <0.001) were found to be significantly increased.

Table 22. Baseline characteristics of patients with histopathologically staged pT1-pT2 rectal cancer, with regard to tumour location and lymph node metastasis.

	Tumour location			Total
	Distal	Mid	Proximal	
Included patients	363 (15.0%)	1 121 (46.2%)	940 (38.8%)	2 424
Age at diagnosis	73 (65-79)	71 (63-78)	70 (63-77)	71 (64-78)
Sex				
- Female	160 (44.1%)	475 (42.4%)	428 (45.5%)	1 063 (43.9%)
- Male	203 (55.9%)	646 (57.6%)	512 (54.5%)	1 361 (56.1%)
T stage				
- pT1	103 (28.4%)	356 (31.8%)	277 (29.5%)	736 (30.4%)
- pT2	260 (71.6%)	765 (68.2%)	663 (70.5%)	1 688 (69.6%)
LVI				
- Absent	284 (78.2%)	920 (82.1%)	790 (84.0%)	1 994 (82.3%)
- Present	66 (18.2%)	160 (14.3%)	123 (13.1%)	349 (14.4%)
- Missing	13 (3.6%)	41 (3.7%)	27 (2.9%)	81 (3.3%)
PNI				
- Absent	315 (86.8%)	1031 (92.0%)	869 (92.4%)	2 215 (91.4%)
- Present	24 (6.6%)	38 (3.4%)	28 (3.0%)	90 (3.7%)
- Missing	24 (6.6%)	52 (4.6%)	43 (4.6%)	119 (4.9%)
MUC				
- Absent	314 (86.5%)	1017 (90.7%)	862 (9.2%)	2 193 (90.5%)
- Present	36 (9.9%)	57 (5.1%)	45 (4.8%)	138 (5.7%)
- Missing	13 (3.6%)	47 (4.2%)	33 (3.5%)	93 (3.8%)
HGR				
- Low-grade	316 (87.1%)	988 (88.1%)	843 (89.7%)	2 147 (88.6%)
- High-grade	34 (9.4%)	90 (8.0%)	64 (6.8%)	188 (7.8%)
- Missing	13 (3.6%)	43 (3.8%)	33 (3.5%)	89 (3.7%)
LNM	66 (18.2%)	194 (17.3%)	203 (21.6%)	463 (19.1%)
Harvested LN	16 (12-22)	17 (13-23)	17 (13-24)	17 (13-23)
- Missing	5 (1.4%)	13 (1.6%)	4 (0.4%)	22 (0.9%)

[a] Expressed as median and interquartile range; LVI: lymphovascular invasion; PNI: Perineural invasion; MUC: mucinous subtype; HGR: Histologic grade; LNM: lymph node metastasis; LN: lymph nodes;

Impact of tumour location on LNM

LNM was found in 463 (19.1%) patients, with higher rates in proximal (21.6%) compared to distal (18.2%) and mid (17.3%) locations (Table 22). Overall, the median number of lymph nodes yielded at surgery was 17.

Proximal tumour location was associated with LNM in pooled multivariate logistic regression analyses (OR 1.504, CI 1.079-2.097, *p*-value <0.05) but not in univariate analyses. Among potential confounders, LVI, PNI, T2 stage, high histologic grade and decreasing age at diagnosis were all significantly associated with LNM in both pooled uni- and multivariate logistic regression analyses, while mucinous subtype was associated with LNM in pooled univariate analyses but not in pooled multivariate analyses (Table 23).

Table 23. Pooled uni- and multivariate logistic regression for potential impact of tumour location on lymph node metastases, including potential confounders.

	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Tumour location						
- Distal	1	Ref	Ref	1	Ref	Ref
- Mid	0.942	0.692-1.282	0.703	1.090	0.783-1.516	0.610
- Proximal	1.239	0.910-1.688	0.173	1.504	1.079-2.097	<0.05
Age at diagnosis[a]	0.990	0.981-0.999	<0.05	0.988	0.978-0.997	<0.05
Sex						
- Female	1	Ref	Ref	1	Ref	Ref
- Male	1.153	0.939-1.416	0.175	1.109	0.892-1.378	0.352
T-stage						
- pT1	1	Ref	Ref	1	Ref	Ref
- pT2	1.941	1.517-2.483	<0.001	1.835	1.418-2.374	<0.001
LVI						
- Absent	1	Ref	Ref	1	Ref	Ref
- Present	4.713	3.694-6.013	<0.001	4.132	3.200-5.336	<0.001
PNI						
- Absent	1	Ref	Ref	1	Ref	Ref
- Present	3.870	2.529-5.922	<0.001	2.246	1.389-3.632	<0.001
MUC						
- Absent	1	Ref	Ref	1	Ref	Ref
- Present	1.614	1.092-2.386	<0.05	1.291	0.836-1.994	0.250
HGR						
- Low-grade	1	Ref	Ref	1	Ref	Ref
- High-grade	2.117	1.529-2.931	<0.001	1.515	1.046-2.194	<0.05

OR: Odds Ratio; CI: confidence interval; [a]: OR per increasing year of age at diagnosis; LVI: lymphovascular invasion; PNI: perineural invasion; MUC: mucinous subtype; HGR: Histologic grade;

A total of 252 (10.4%) patients had missing data, and 2172 had complete data. Rates of LNM were comparable with the dataset with complete cases (*p*-value 0.09). ORs and significance were similar in uni- and multivariate logistic regression analyses performed in patients with complete data except for proximal location (OR 1.36, CI 0.97-1.93, *p*-value 0.08) and high histologic grade (OR 1.45, CI 0.98-2.10, *p*-value 0.06) that were not significant in multivariate analyses.

Impact of tumour location on recurrence

After further application of exclusion criteria on the patient cohort for LNM analyses, 1705 patients remained for recurrence analyses (Figure 13).

Adjuvant therapy was proposed in 31 (12.7%), 90 (11.9%) and 100 (14.2%) patients with distal, mid and proximal located tumours, respectively (Table 24). Lateral resection margin was significantly lower for patients with distal tumours (*p*-value <0.05). Recurrence was detected in 130 (7.6%) patients during a median follow-up of 60 months, with 28 (11.4%), 63 (8.3%) and 39 (5.6%) recurrences detected in patients with distal, mid and proximal tumours, respectively. The 5-year DFI was 92% for the whole cohort and 86%, 91% and 94% for patients with distal, mid and proximal tumours, respectively.

Distal (HR 2.051, CI 1.248-3.371, *p*-value <0.05) and mid (HR 1.592, CI 1.061-2.388, *p*-value <0.05) tumour locations were both significantly associated with recurrence in pooled uni- and multivariate analyses (Figure 14, Table 25, Table 26). Other factors independently associated with recurrence were LNM (HR 2.127, CI 1.447-3.127, *p*-value <0.001), histopathological T2-stage (1.908, CI 1.201-3.031, *p*-value <0.05) and LVI (1.815, CI 1.178-2.798, *p*-value <0.05), while mucinous subtype and high histologic grade were only associated with recurrence in pooled univariate analyses.

Table 24. Baseline characteristics of patients with histopathologically staged pT1-pT2 rectal cancer, with regard to tumour location and recurrence.

	Tumour location			Total
	Distal	Mid	Proximal	
Included patients	245 (14.4%)	758 (44.4%)	702 (41.2%)	1 705
Age[a]	72 (64-79)	71 (63-78)	69 (63-76)	70 (63-77)
Sex				
- Female	114 (46.5%)	327 (43.1%)	339 (48.3%)	780 (45.7%)
- Male	131 (53.5%)	431 (56.9%)	363 (51.7%)	925 (54.3%)
T stage				
- pT1	73 (29.8%)	245 (32.3%)	218 (31.1%)	536 (31.4%)
- pT2	172 (71.2%)	513 (67.7%)	484 (68.9%)	1 169 (68.6%)
N stage				
- pN0	202 (82.4%)	629 (83.0%)	562 (80.1%)	1 393 (81.7%)
- pN+	43 (17.6%)	129 (17.0%)	140 (19.9%)	312 (18.3%)
Lateral margin (mm) [a]	8 (4-13)	12 (7-19)	16 (10-25)	13 (8-20)
- Missing	36 (14.7%)	81 (10.6%)	99 (14.1%)	216 (12.7%)
Distal margin (mm) [a]	35 (20-46)	24 (15-40)	40 (25-55)	30 (20-50)
- Missing	53 (21.6%)	99 (13.1%)	91 (13.0%)	243 (14.3%)
LVI				
- Absent	195 (79.6%)	624 (82.3%)	596 (84.9%)	1 415 (83.0%)
- Present	39 (15.9%)	102 (13.5%)	83 (11.8%)	224 (13.1%)
- Missing	11 (4.5%)	32 (4.2%)	23 (3.3%)	66 (3.9%)
PNI				
- Absent	212 (86.5%)	694 (91.6%)	646 (92.0%)	1 552 (91.0%)
- Present	12 (4.9%)	20 (2.6%)	19 (2.7%)	51 (3.0%)
- Missing	21 (8.6%)	44 (5.8%)	37 (5.3%)	102 (6.0%)
MUC				
- Absent	213 (86.9%)	679 (89.6%)	645 (91.9%)	1 537 (90.2%)
- Present	23 (9.4%)	43 (5.7%)	33 (4.7%)	99 (5.8%)
- Missing	9 (3.7%)	36 (4.7%)	24 (3.4%)	69 (4.0%)
Histologic grade				
- Low-grade	209 (85.3%)	665 (87.7%)	622 (88.6%)	1 496 (87.7%)
- High-grade	26 (10.6%)	61 (8.0%)	51 (7.3%)	138 (8.1%)
- Missing	10 (4.1%)	32 (4.2%)	29 (4.1%)	71 (4.2%)
Adjuvant therapy				
- No	212 (86.5%)	661 (87.2%)	596 (84.9%)	1469 (86.2%)
- Yes	31 (12.7%)	90 (11.9%)	100 (14.2%)	221 (12.9%)
- Missing	2 (0.8%)	7 (0.9%)	6 (0.8%)	15 (0.9%)
Recurrence	**28 (11.4%)**	**63 (8.3%)**	**39 (5.6%)**	**130 (7.6%)**

a Expressed as median and interquartile range; LVI : lymphovascular invasion; PNI: Perineural invasion; MUC: Mucinous subtype;

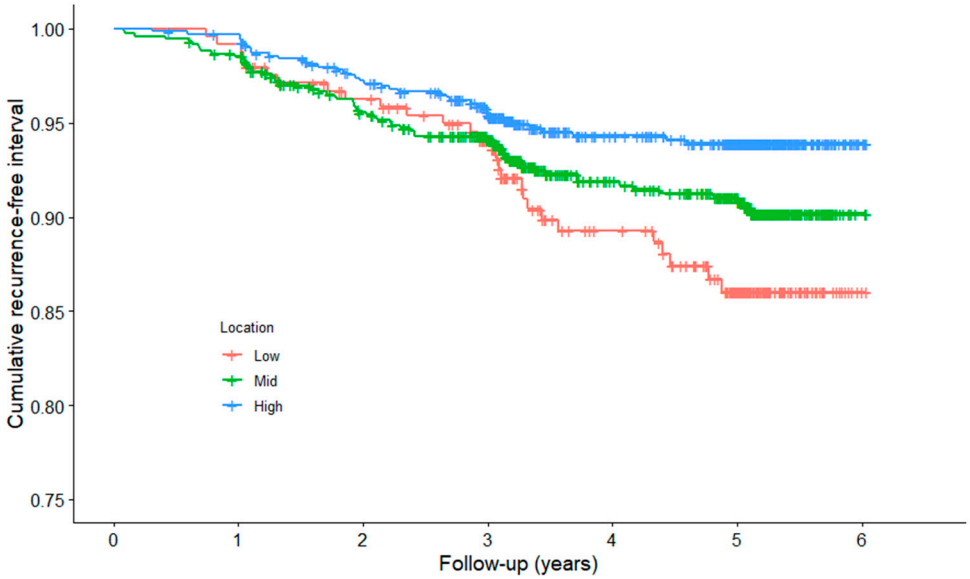

Figure 14. Kaplan-Meier curve for recurrence according to tumour location.
The Y-axis is scaled between 0.75 and 1.00. Distal: between 0 and <5cm from the anal verge; mid: between 5 and <10 cm; proximal: between 10 and 15 cm;

Table 25. Risk table for Kaplan-Meier curve in Figure 14.

	Number of patients at risk						
Tumour location							
- Distal[a]	245	243	225	199	148	101	2
- Proximal[b]	758	744	692	627	445	373	11
- Proximal[c]	702	698	662	605	451	374	16
Follow-up time[d]	0	1	2	3	4	5	6

[a]: between 0 and <5 cm from the anal verge; [b]: between 5 and <10 cm [c]: between 10 and 15 cm; [d]: in years

Missing data was found in 455 (26.7%) out of 1705 patients; rates of recurrence did not differ between cases with missing data and complete cases (*p*-value=0.15). HRs and significance were similar between analyses on complete cases and imputed datasets, with the exception of the mid-rectal tumour location (HR 1.53, CI 0.99-2.36, *p*-value 0.06) that did not reach significance on complete case analysis. On the other hand, positive lateral resection margin (≤1 mm) was associated with recurrence on univariate analysis on complete data.

Table 26. Pooled uni- and multivariate Cox regression for potential impact of tumour location on recurrence, including potential confounders.

	Recurrence rate[a]	Univariate Analysis			Multivariate analysis		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Tumour location							
- Proximal	127	1	Ref	Ref	1	Ref	Ref
- Mid	199	1.554	1.038-2.326	<0.05	1.592	1.061-2.388	<0.05
- Distal	273	2.145	1.313-3.501	<0.05	2.051	1.248-3.371	<0.05
Age at diagnosis[b]		1.002	0.986-1.018	0.800	0.998	0.983-1.014	0.837
Sex							
- Female	142	1	Ref	Ref	1	Ref	Ref
- Male	211	1.481	1.034-2.123	<0.05	1.467	1.020-2.111	<0.05
T stage							
- T1	99	1	Ref	Ref	1	Ref	Ref
- T2	217	2.189	1.389-3.449	<0.001	1.908	1.201-3.031	<0.05
N stage							
- N0	137	1	Ref	Ref	1	Ref	Ref
- N+	378	2.751	1.920-3.942	<0.001	2.127	1.447-3.127	<0.001
Lateral margin							
- > 1 mm	176	1	Ref	Ref	1	Ref	Ref
- ≤ 1 mm	384	2.482	0.908-6.781	0.076	1.927	0.683-5.437	0.213
LVI							
- Absent	149	1	Ref	Ref	1	Ref	Ref
- Present	394	2.607	1.757-3.866	<0.001	1.815	1.178-2.795	<0.05
PNI							
- Absent	170	1	Ref	Ref	1	Ref	Ref
- Present	498	2.740	1.401-5.355	<0.05	1.521	0.753-3.074	0.240
MUC							
- Absent	171	1	Ref	Ref	1	Ref	Ref
- Present	321	1.823	1.021-3.256	<0.05	1.351	0.718-2.542	0.348
HGR							
- Low-grade	170	1	Ref	Ref	1	Ref	Ref
- High-grade	285	1.630	0.942-2.820	0.080	1.060	0.584-1.924	0.847

[a]: per 10 000 pat-years, based on complete data; [b]: HR per increasing year of age at diagnosis; HR: Hazard ratio; CI: confidence interval; LVI: Lymphovascular invasion; PNI: Perineural invasion; MUC: Mucinous subtype; HGR: Histologic grade;

Discussion

Staging (in)accuracy

Organ-sparing local resection is a beneficial treatment alternative in terms of morbidity and mortality and is curative in selected cases of T1 CRC. Selection of candidates eligible for local resection is partially based on pretherapeutic CT- and MR-based staging. Hence, assessing their respective accuracies is highly relevant for understanding their impact on patient selection.

Understaging occurred in more than 50% of patients with CC staged cT1-2 by CT while occurring in more than 30% for patients with RC staged cT1-2. Conversely, while some degree of preoperative overstaging occurred in patients with pT1 CRC, a substantial proportion of patients had indefinite preoperative T-stage. Moreover, a high degree of overlap between T1 and T3 was noted in patients with RC staged by MRI.

While accuracy for nodal staging reached 70% in Paper I and Paper II, the sensitivity for detecting nodal invasion did not exceed 30%, which is in the lower span of previously reported sensitivies[119, 211]. Most patients with pathologically verified nodal invasion were preoperatively inaccurately staged cN0 and thereby understaged. Conversely, most patients preoperatively staged cN+ by CT or MRI did not exhibit lymph node invasion at histopathological assessment and were thus overstaged. Expressed differently, current staging modalities are problematic for patients with LNM as well as for patients with presumed LNM.

Combining T- and N-staging together revealed significant understaging occurring in patients with presumably cT1-2N0 disease as well as significant overstaging in patients with histopathologically proven localised pT1N0 disease.

Left-sided CC was found to be associated with enhanced T-stage accuracy (OR 1.38), possibly explained by a predominance of polyps with flat morphology for the right colon and thereby more difficult to discriminate from the surrounding bowel wall. On the other hand, right-sided CC location was associated with enhanced N-stage accuracy in unadjusted analyses (OR 0.87), a finding for which no rational explanation could be found.

Use of EUS in combination with MRI was found to increase T-stage accuracy in RC, consistent with previous findings[211]. However, the increase was marginal and

based on a small number of patients undergoing EUS in complement to MRI, which limits conclusions regarding its use.

Underestimating the T-stage preoperatively might lead to the patient being referred for local resection which, in turn, will be found impossible or result in a more advanced tumoral stage/non-radical resection at histopathological assessment, warranting a subsequent curative resection surgery. While local resection strategies share a more limited physiological impact as compared to invasive surgical treatment, the choice of local resection modality might significantly impact the outcome of subsequent surgical resection, especially for early RC. As previously mentioned, local resection modalities breaching the bowel wall, such as TEM, has been shown to impede subsequent surgical resection[283-285]. Hence, inaccurate allocation to local resection based on underestimated preoperative T-stage does not impair further treatment in the setting of early CRC, conditioned by the primary local resection method.

Conversely, overestimating T-stage in the setting of early CRC warrants a surgical resection, potentially in combination with some form of neoadjuvant treatment, in lieu of local treatment. This overestimation will lead to unnecessary overtreatment and confer an unnecessary increased treatment-related risk. Notably, overtreatment will go undetectable in cases subjected to neoadjuvant treatment.

Sharing similar consequences with inaccurate T-stage, inaccurate N-staging in early CRC has more subtle implications in the setting of a hypothetical curative local resection as the sole treatment. The large proportion of patients with undetected nodal invasion witnessed in our results might potentially lead to residual disease and possible disease progress in the absence of curative surgical resection. Reciprocally, according to present findings, most patients with preoperatively presumed LNM will have no lymph node metastasis at pathological examination.

CT and MRI play an important role in planning the surgical strategy. However, our findings question their current use for nodal staging in T1 CRC, especially since microscopic nodal metastases go undetected in addition to the lack of validated radiological criteria for lymph node invasion in CC and, to a certain extent, in RC. In fact, most metastatic lymph nodes in CRC measure less than 5 mm[120], which questions current radiological criteria for nodal invasion[131].

Regarding methodology, performing analyses using a measure of agreement (such as Cohen's kappa coefficient) was considered, especially since it is used in some previous publications and could facilitate comparison with these. However, a measure of agreement is more appropriate in validating assessment tools, for example. T- and N-stages assessed by histopathology were considered as a "gold standard" reference. Given the research question we intended to address, opting for diagnostic test measures was an obvious choice allowing to report findings in a practical and tangible way for clinicians.

Exclusion of patients with missing information regarding histopathological nodal status (thereby excluding patients who underwent local resection) decreased the number of patients contributing to the analysis of T-stage accuracy. Moreover, patients treated with local resection might potentially have benefitted from accurate pretreatment T-staging (in the absence of evidence of lymph node metastasis on CT or MRI). Hence, excluding this group could potentially introduce a selection bias and negatively impact T-staging accuracies found in the present work.

Benign polyps were not included in present analyses, and potential staging overlap between benign polyps and early CRC could not be further investigated.

Body mass index was intended to be used as a marker for intra-abdominal fat, hypothesising a potential beneficial effect of increasing body mass index on T- and/or N-stage accuracy. However, body mass index was not available for a significant proportion of included patients and could therefore not be included in analyses. Notably, data on length and weight was unavailable for a certain proportion of patients, which limited its use a factor potentially impacting accuracy.

Other limitations include lack of specifications regarding the manufacturer and model of CT or MRI used and examination protocols in use, in addition to criteria used for assessing nodal status on CT and MRI. This is an important aspect that might potentially impede reproducibility or generalisation of present findings.

The design of the present studies, retrospective, constitutes another limiting factor. Notably, a previous study investigated the validity of the registered T- and N-stages in the SCRCR for CC by comparing them with electronic health records and found staging discordance in approximately 20% of cases, underlining a lack of clarity in the radiology report[313].

Major strengths of present studies reside in the high number of included patients in addition to the use of prospectively collected "real-world" data from the SCRCR, reflecting staging accuracies of CT and MRI in true clinical settings. Moreover, results in the present study are comparable with previous findings.

The proportion of patients presenting with early CRC is expected to increase with wide implementation of screening programmes. CT and MRI performed in the context of work-up yielded unreliable preoperative staging data in patients with early CRC, with a risk of both undertreatment and overtreatment. Further development regarding endoscopic tumoral staging as well as alternative predictors of nodal invasion should be pursued to optimise management of patients with early CRC.

Costs of resection of early rectal cancer

An aging population combined with technical and medical progress continuously inflates costs related to healthcare[314], which justifies regular health economic evaluations.

Various local and surgical approaches are available for T1 RC. As previously mentioned, locally resected T1 RC is considered curative in the absence of risk factors for LNM. In cases with high risk for LNM, subsequent surgical resection is warranted, which impacts the total cost of treatment. Hence, comparing costs related to different available treatment alternatives in T1 RC is challenged by the potential need for subsequent surgical resection.

As previously reported, current radiological modalities do not permit accurate selection of candidates for potential curative local resection. Local resection could potentially overcome this limitation and provide an accurate T-stage with, however, the need for subsequent surgery in patients with high-risk T1 RC or more advanced T-stage. We intended, therefore, to compare costs of different treatment alternatives, accounting for the need for potential subsequent surgery.

Present findings revealed ESD as significantly less expensive compared to TEM, open resection, laparoscopic resection and robotic resection groups in terms of both median procedural and median total costs. TEM was only found to be less expensive compared to open and robotic resection but not laparoscopic resection, in terms of procedural and total costs. Moreover, open resection was found to be less expensive than robotic resection.

Hypothetical cost scenarios consisted in adding procedural costs of subsequent surgery to the total costs of local resection in cases of T1 RC exhibiting high-risk features for LNM. According to the hypothetical cost scenarios, the total costs of upfront local resection using ESD, in addition to subsequent surgical resection in high-risk cases, were noticeably lower compared to the alternative of using TEM as upfront local resection modality. Furthermore, an upfront resection strategy based on TEM was a more expensive alternative compared to open, laparoscopic or robotic resection.

The study was limited by focusing on direct costs, justified by the age of included patients being over the age of retirement. However, indirect costs of CRC in Sweden account for more than 40% of total costs, according to a recent report on costs of cancer[301]. However, a lower impact of local resection alternatives on indirect costs might be expected, given the limited impact of local resection methods on morbidity and mortality.

Another limitation regards the generalisability of current findings. In fact, costs of CRC treatment have been reported with a significant span, which might challenge direct comparison of costs from an international perspective.

Oncologic impact of distal early rectal cancer

The decision to perform organ-sparing local resection treatment in T1 CRC is based on the risk of leaving potential LNM untreated. A majority of T1 CRCs are considered at high risk of LNM according to current guidelines, contrasting with the lower prevalence of LNM in T1 CRC undergoing surgical resection and thus, overtreated. Further research efforts are needed to optimise stratification of the risk of LNM and limit the unnecessary surgical resection.

Distal RC requires multimodal treatment, even in earlier stages when located in the vicinity of the sphincter plane. In the context of potentially locally resectable early rectal cancer, the oncologic impact of tumour location within the rectum is poorly investigated, and the limited available literature is conflicting. Moreover, while many efforts have focused on the risk factors for LNM, the risk factors for recurrence are still elusive.

Incidence of LNM was highest for proximally located tumours while being similar for mid-located and distally located tumours. Proximal location was only found to be significantly associated with increased incidence of LNM in adjusted analyses with, however, a limited effect size (OR 1.504). Among independent predictors of LNM, LVI was found to have the strongest effect size (OR 4.132), followed by PNI (OR 2.246), T-stage (OR 1.835), high histologic grade (OR 1.515) and younger age (0.988 per increasing year of age). In this context, while lymph node harvest for distally located tumours was comparable to other tumour locations, the potential impact of lateral lymph nodes in relation to the differences in LNM has to be considered. Thus, the tapered morphology of the rectum and its surrounding mesorectum containing lymph nodes, in addition to the location-dependent lymphatic drainage of the rectum (via inferior mesenteric vein branches in the proximal rectum and via the internal iliac vein in the distal rectum), raises questions regarding the role of the lateral lymph nodes in the present findings. Hence, lateral lymph nodes are not routinely harvested during surgical resection for RC in Sweden, and it is possible that LNM were not identified among distal tumours in the present study.

Conversely, distal tumour location (HR 2.051) followed by mid location (1.592) was found to be an independent predictor of tumour recurrence. In adjusted analyses, the strongest independent factor associated with recurrence was the presence of LNM (HR 2.127), closely followed by distal tumour location, T-stage (OR 1.908), LVI (OR 1.815), and male sex (OR 1.467).

Findings in the present study shed light on the significant impact of tumour location on recurrence in early RC, with an effect size comparable to T2 vs T1 stage or presence vs absence of LNM. Knowledge of this aspect has implications for the clinical management and follow-up of early RC, suggesting a cautious approach to managing distally located tumours. Notably, the present study does not compare

local against surgical resection on the risk of recurrence. Nevertheless, one could speculate that distal tumours are referred for local resection to a higher extent and subsequent surgery performed to a lower extent, given that these tumours are generally treated with abdominoperineal resection with permanent stoma. Therefore, comparing local and surgical resection might be misleading if tumour location is not taken into consideration. However, it is possible that the increased recurrences found in distally located tumours could be a consequence of untreated lateral lymph nodes. Extrapolating the present findings to local resection suggests that adjuvant treatment might play an important role in combination with local resection for distally located early RC.

The present findings are strengthened by the large number of included patients as well as its methodology, mitigating the impact of missing data, in addition to rely on prospectively collected, high-coverage, registry data. The present research question is poorly addressed in the literature and present findings strongly contribute to filling the knowledge gap.

Although use of multiple imputation strengthens the present study by allowing an increase in the number of patients available for analyses, some degree of uncertainty cannot be ruled out and might constitute some form of limitation. However, sensitivity analyses on complete datasets allowed to attenuate the uncertainty.

Excluding patients who received neoadjuvant treatment, radiation therapy or chemoradiation therapy led to the exclusion of patients with early RC at the level of the sphincter plane, since Swedish guidelines recommend neoadjuvant radiotherapy for this group of patients. Hence, present findings should be carefully interpreted for this specific patient group.

Neither adjuvant chemotherapy nor surgical resection methods were included in the analyses (particularly regarding recurrence) since the number of factors included in the analyses was limited by the total number of recurrences, with the risk of compromising statistical power. Hence, their impact could not be properly evaluated. However, the proportion of patients referred for adjuvant chemotherapy was similar with regard to tumour location. Moreover, including surgical resection modality could potentially introduce some degree of collinearity in the regression analyses, given its high dependency on tumour location.

Tumour budding as well as tumour size are not present in the SCRCR and their oncologic impact with regards to tumour location could not be evaluated.

Conclusion

Based on the included papers in this thesis, the conclusions are:

- Staging of early CRC, performed with CT for CC and MRI for RC is inadequate, with a high risk of both over- and understaging T-stage and unreliable N-staging. Based on our findings, these modalities should be interpreted with caution and not alone dictate eligibility for local resection, which requires a multimodal approach by experienced clinicians.
- The cost of ESD for the treatment of T1 RC was significantly lower compared to surgical resection and TEM. In fact, even when hypothetically all T1 RC underwent ESD, followed by subsequent surgery in all high-risk cases, ESD still had the lowest total cost. Based on our findings, initiating treatment of suspected T1 RC with ESD is defendable from a health-economic standpoint in addition to limiting overtreatment by yielding accurate tumour stage.
- Risk of recurrence in early RC was found to be significantly associated with tumour location and increased gradually in mid and distal compared to proximal tumours. Notably, the risk of recurrence in distal compared to proximal tumours was twice as high. Our findings exemplify the need for a higher awareness on increased risk of poor oncologic outcome in mid and especially distal early RC, which might imply a more intense follow-up.

Future perspectives

Past preclinical, clinical, and technical research efforts combined with dedication have given current patients diagnosed with early CRC the possibility to avoid the burden of surgical resection. These research efforts need to be pursued, as the challenges are still many.

Risk-based approach. Currently, pathologic examination is the only currently available accurate T-staging modality for early CRC, which can be made with the help of local resection without impairing potential subsequent surgical resection. However, in the absence of accurate methods for assessing lymph nodes, further efforts should be pursued to enhance stratification of risk of LNM but also risk of recurrence in early CRC. Thus, to ensure a better correspondence between risk factors and true presence of LNM will allow most patients currently considered at high risk for LNM today to avoid completion surgery tomorrow.

Developing cancer immunology. There is increasing knowledge regarding the intricate relationship between the immune system and cancer, with research showing the impact of the manifestation of the immune system in CRC. Under certain circumstances, some authors have suggested a protective role of adjacent lymph nodes in CRC, questioning the impact of lymphadenectomy[315]. Hence, including the immunogenic response in the risk stratification of early CRC might potentially contribute to limit overtreatment.

Adjuvant therapy. Combining radiotherapy and/or chemotherapy with local resection, as previously and currently investigated, thereby broadening the treatment arsenal, in conjunction with a robust and well-discriminating risk-stratification might contribute to avoiding overtreatment.

Prevention. Last, but certainly not least, prevention should be a priority in a modern healthcare setting. Adherence to screening should be strategically addressed, using an adapted information campaign but also by developing an adequate screening modality. Moreover, improvement of alimentary habits, limitation of sedentarism and promotion of a healthy lifestyle should be our priority for younger generations.

Popular science summary

Kolorektalcancer (tjock- och ändtarmscancer) är en av de vanligast förekommande cancerformerna i världen och vanlig förekommande tumörsjukdom i befolkningen som drabbar cirka 6000 patienter varje årligen i Sverige. Historiskt sett har behandlingen varit kirurgisk resektion, där tarmsegmentet innefattandes tumören, samt tillhörande tarmkäx innehållande dränerande lymfkörtlar, tas bort. Senaste decennierna har behandlingen blivit långt mer komplex och kan idag innefatta bl.a. strål- och eller cellgiftsbehandling innan eller efter kirurgi. Därtill har utvecklingen av endoskopiska tekniker medfört att tidiga cancrar, som ej växer ner i muskellagret i tarmen, kan tas bort med lokal resektion.

Vinsterna för patienterna att genomgå lokal resektion i stället för kirurgi är stora och innefattar minskad samsjuklighet, dödlighet och risk för stomi. Att kunna identifiera dessa patienter vid utredning är därför mycket viktigt men dåligt studerat i litteraturen. Vid utredning av misstänkt kolorektalcancer görs rutinmässigt skiktröntgen (CT) för koloncancer (tjocktarmscancer) och magnetkamera-undersökning (MR) för rektalcancer (ändtarmscancer), för att bedöma tumörens växtdjup samt för att utreda om det finns spridning till lymfkörtlarna. Det är dåligt studerat hur träffsäkra dessa undersökningar är vid tidig kolorektalcancer, således vid fall där lokal resektion kan övervägas.

Vidare är lokal resektion begränsad av att man ej tar med dränerade lymfkörtlar. För närvarande uppskattas risken för spridning till lymfkörtlarna genom analys av vissa riskfaktorer i tumören som tagits bort. Dessvärre är nuvarande riskbedömning osäker och resulterar i att majoriteten av patienter med tidig kolorektalcancer klassificeras att ha högrisk för lymfkörtelspridnign, trots att endast ca 10% av denna patientgrupp faktiskt har spridning till lymfkörtlarna. Detta resulterar således till att patienter opereras i onödan.

I denna avhandling har preoperativ utredning med CT och MR undersökts vid tidig kolorektalcancer. Vi fann att tillförlitligheten av dessa röntgenundersökningar är låg beträffande tumörens växtdjup och utredning gällande spridning till lymfkörtlar. Baserat på våra fynd bör dessa undersökningar ej vara avgörande i om en patient skall bedömas för lokal resektion eller ej.

Vidare har en studie utförts som jämför kostnaderna för behandling av tidig rektalcancer med lokala resektionsmetoder, endoskopisk submukös dissektion (ESD) samt transanal endoskopisk mikrokirurgi (TEM) och olika kirurgiska

resektionsmetoder. Vi fann att ESD var det klart minst kostsamma alternativet för att behandla denna patientgrupp. En hypotetisk kostberäkning utfördes baserad på att samtliga patienter med tidig rektalcancer genomgick ESD eller TEM som första behandling, följt av kirurgi i de fall det fanns riskfaktorer i tumören, vilket innefattar mer än 60% av patienterna. Trots att vi la till kostnaden för efterföljande kirurgi var det minst kostsamma alternativet att inleda behandlingen med ESD.

Slutligen har betydelsen av tumörlokalisation i ändtarmen på risk för canceråterfall studerats vid tidig rektalcancer. Vi fann att tumörens lokalisation hade signifikant betydelse på risk för återfall. Risken för återfall ökade gradvis ju närmre analkanalen tumören satt och var dubblerad när vi jämförde låga med höga tumörer. Denna studie belyser vikten av att ta hänsyn till tumörlokalisation vid hantering av patienter med tidig rektalcancer.

Sammantaget ger denna avhandling värdefull information gällande utredning, riskbedömning och kostnadsaspekter vid behandling av patienter med tidig kolorektalcancer. I detta sammanhang är det väl värt att nämna att denna patientgrupp bedöms öka succesivt närmsta decennierna pga. införandet av kolorektalcancer screening i Sverige.

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