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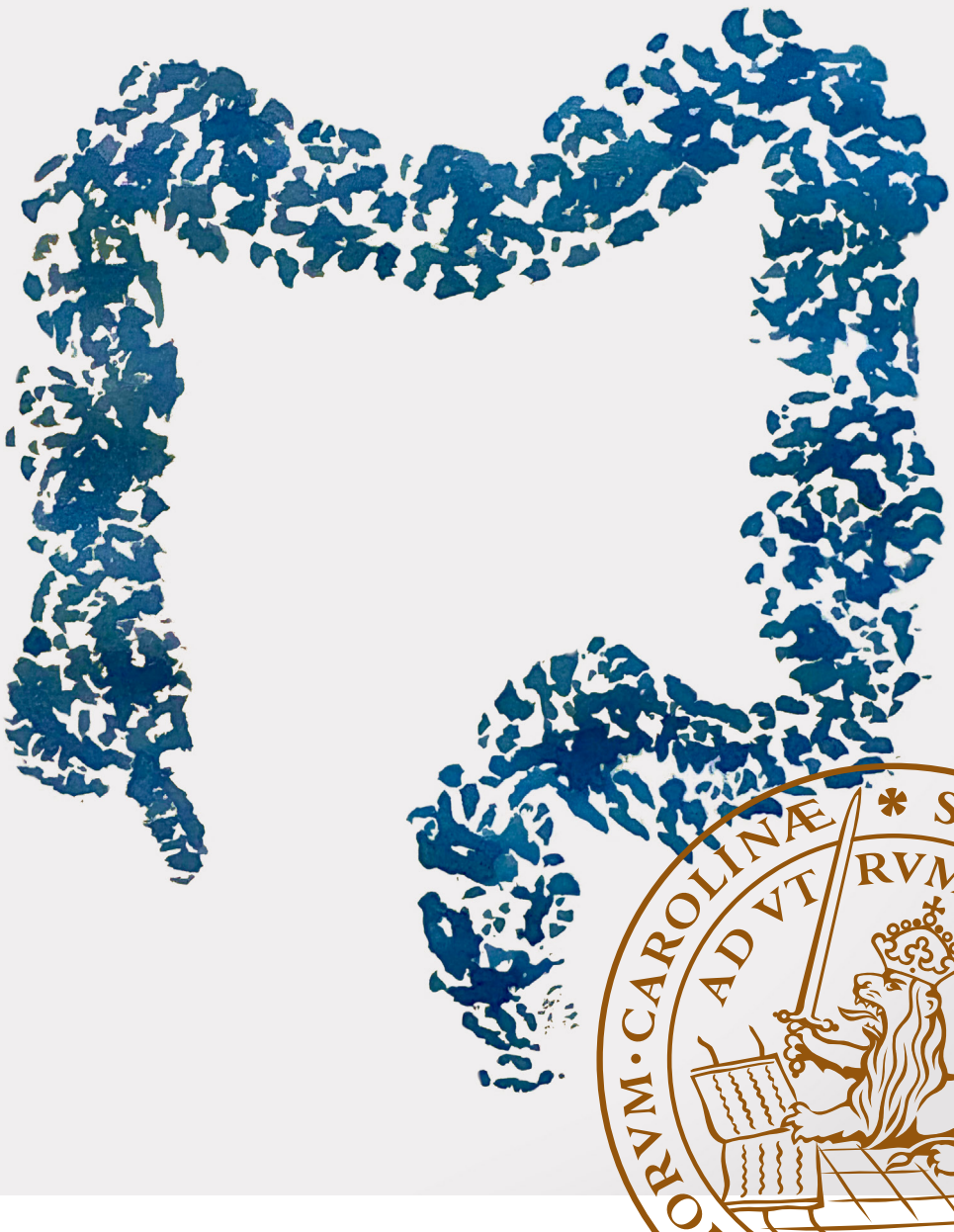

T1 colorectal cancer

Preoperative staging and outcome following surgical and local resection of T1 colorectal cancer

Emelie Nilsson

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 6th of March at 09.00 in KK-aulan, Jan Waldenströms gata 47, Skåne University Hospital, Malmö.

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Abstract

Background: There are two conceptually different surgical treatment options for patients with T1 colorectal cancer (CRC): radical surgical resection and local resection. In addition, adjuvant chemotherapy is recommended in cases with lymph node metastases. However, surgical overtreatment of early CRC is a concern and may be related to limitations in preoperative work-up as well as tumour risk classification. In addition, patients with node-positive T1 CRC disease may be undertreated with respect to adjuvant chemotherapy.

Aims: *Study I:* To assess the accuracy of MRI-based staging in early rectal cancer (RC). *Study II*: Compare recurrence after endoscopic and surgical resection across risk groups in pT1 colon cancer (CC) and identify risk factors for recurrence. *Study III: C*ompare recurrence after transanal endoscopic microsurgery (TEM) and surgical resection across risk groups in pT1 RC. *Study IV*: Investigate the effect of adjuvant chemotherapy on recurrence and survival in pT1 node-positive (T1N+) CRC and identify factors associated with not receiving adjuvant chemotherapy.

Methods: The four studies were retrospective cohort studies based on prospectively collected data derived from the Swedish Colorectal Cancer Registry. *Study I,* patients with RC staged as cT1–2 RC or pT1 (2009–2018), *Study II* patients with pT1 CC (2009– march 2021), *Study III* patients with pT1 RC (2009–2022), *Study IV* pT1 N+ CRC (2009–2022). Neoadjuvant treatment was a general exclusion criterion for all studies.

Results and conclusions: ***Study I.*** MRI plays a pivotal role in the work-up of RC. However, MRI was insufficiently accurate for both T and N staging in early RC, with a risk of both over- and understaging. Based on these findings, MRI should not be used as the sole modality to determine eligibility for local resection. ***Study II.*** Recurrence rates after pT1 CC were low and comparable following endoscopic and surgical resection, even in patients with high-risk tumours. Lymphovascular invasion (LVI) was identified as a strong risk factor for recurrence. Further studies to identify pT1 CC patients with poor prognosis who may benefit from additional treatment are warranted. ***Study III.*** In contrast, local recurrence rates following TEM were significantly higher than those after surgical resection, even in patients with low-risk tumours, calling into question the role of TEM as a curative treatment option. ***Study IV.*** Adjuvant chemotherapy was associated with substantially improved disease-free and overall survival in patients with pT1N+ CRC, highlighting the importance of minimizing unfounded deviations from treatment guidelines.

Key words: Colon, Rectum, Neoplasm, Early diagnosis, Treatment outcome, Risk groups, Risk factors

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To my family

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British Journal of Surgery Open, 2024;8(3)

III. Transanal endoscopic microsurgery is associated with higher recurrence rate in both low- and high-risk T1 rectal cancer compared to surgical resection

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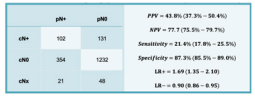
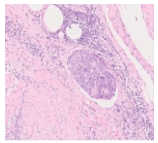
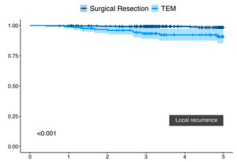
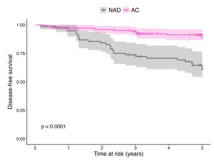
Submitted manuscript

IV. Adjuvant chemotherapy improves disease-free and overall survival in T1 node-positive colorectal cancer

Nilsson E, Mustaniemi J, Rönnow CF, Thorlacius H

Thesis at a glance

	Main aims	Patients	Main results	Teaser	Conclusion
I	Assess accuracy of MRI staging in early rectal cancer	cT1-2 rectal cancer n = 1888 pT1 rectal cancer n = 549	PPV for cT1–T2 was 68%. 70% of patients with pN+ disease were misclassified as cN0. 70% of patients classified as cN+ were actually pN0. When combining cT1–2N0, 41% were incorrectly staged, and 29% of pT1N0 were overstaged.		MRI is insufficient for T and N staging in early rectal cancer and should not be used as the sole modality to determine eligibility for local resection.
II	Compare recurrence rates between endoscopic and surgical resection, across risk groups Identify risk factors for recurrence	pT1 colon cancer n = 1805	Recurrence was comparable after endoscopic and surgical resection (3.7% vs 3.6%), even in high-risk groups (5.4% vs 3.8%, $p = 0.370$) LVI was an independent risk factor for recurrence (HR 3.73, 95% CI 1.76–7.92; p < 0.001)		Recurrence rates are low and does not differ between endoscopic and surgical resection, even in high-risk tumours. LVI is a strong independent risk factor for recurrence.
III	Compare recurrence rates following TEM and surgical resection across risk groups	pT1 rectal cancer n = 859	TEM was associated with a significantly higher local recurrence rate compared with surgery in patients with low-risk tumours (0% vs 8%, $p = 0.016$) and with high-risk tumours (1% vs 8%, $p < 0.001$).		TEM is associated with higher local recurrence rates compared with surgical resection in both low- and high-risk groups.
IV	Investigate the effect of adjuvant chemotherapy on recurrence and survival in pT1N+ colorectal cancer	pT1N+ colorectal cancer n = 222	Adjuvant chemotherapy was associated with a higher 5-year disease-free survival rate (91% vs 63%; HR 0.41, 95% CI 0.18–0.94; $p < 0.0001$).		Adjuvant chemotherapy is associated with increased disease-free and overall survival.

Abbreviations

AC	Adjuvant Chemotherapy
APC	Adenomatous polyposis coli
ASA	American Society of Anaesthesiologists
CC	Colon cancer
CEA	Carcinoembryonic antigen
CI	Confidence interval
CIN	Chromosomal instability
CRC	Colorectal cancer
CRM	Circumferential resection margin
DAG	Directed acyclic graph
DFI	Disease-free interval
DFS	Disease-free survival
EID	Endoscopic intermuscular dissection
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
ESGE	European Society of Gastrointestinal Endoscopy
EPV	Events per variable
EUS	Endoscopic ultrasound
FAP	Familial adenomatous polyposis
FIT	Faecal immunochemical test
FOBT	Faecal occult blood testing
HDI	Human Development Index
HR	Hazard ratio
LNM	Lymph node metastases
LST	Lateral spreading tumours
LVI	Lymphovascular invasion
MAR	Missing at random

MCAR	Missing completely at random
MDC	Multidisciplinary conference
MI	Multiple imputation
MNAR	Missing not at random
MRI	Magnetic resonance imaging
NAD	No additional chemotherapy
NBI	Narrow-band imaging
OS	Overall survival
OR	Odds ratio
PNI	Perineural invasion
PPV	Positive predictive value
RC	Rectal cancer
SCRCR	Swedish Colorectal Cancer Registry
TAE	Transanal excision
TAMIS	Transanal minimally invasive surgery
TEM	Transanal endoscopic microsurgery
TME	Total mesorectal excision
VIF	Variance inflation factor

Background

Colorectal cancer

Epidemiology

In 2022, an estimated 1.9 million new cases of colorectal cancer (CRC) were diagnosed worldwide. CRC ranked third in incidence and was the second most common cause of cancer-related mortality, accounting for approximately 900,000 deaths (1). The highest incidence rates are observed in Europe, Australia/New Zealand, and North America, with substantially higher rates in countries with very high Human Development Index (HDI) compared with those with a low HDI (28.6 vs. 6.4 per 100,000 [ASR[1]]) (1).

In countries undergoing economic development, increasing incidence rates are observed, likely reflecting lifestyle changes, including more sedentary lifestyles and increased consumption of animal-source foods (1). In some very-high-HDI countries, CRC incidence rates are stabilizing or declining (2, 3), a trend that is thought to be attributable to healthier lifestyles and the implementation of screening programmes (2). The median age at diagnosis for CRC is 68 years in women and 65 years in men (4). However, with the increasing incidence of early-onset CRC, the median age at diagnosis is expected to decrease (4, 5).

In Sweden, approximately 8,000 new cases of CRC were diagnosed in 2024, and about 2,700 individuals died from the disease, making CRC the second most common cause of cancer-related death after lung cancer (6). The incidence of colon cancer (CC) is rising in Sweden, while rectal cancer (RC) has remained more stable over time (7). For CC, early-onset cancer (<50 years) demonstrates the greatest increase in incidence. Among late-onset patients, incidence in the left colon appears to be stabilizing or decreasing, whereas right-sided CC is rising across age groups (8). In RC, an increase in incidence is observed among early-onset patients, particularly among men (8, 9), while a decreasing trend is seen in late-onset cases, primarily among those aged 80 years and older (8, 9). Among early-onset cases, rectal and right-sided cancers are most common in men, whereas left-sided cancers are more common in women (8).

[1] Age-standardized rate

Despite the increasing incidence in CC, mortality is decreasing over time for both RC and CC (7). Survival in CRC is strongly associated with the disease stage: patients with stage I disease have a survival exceeding 90%, whereas those with stage IV disease have a survival of approximately 20% (2019–2023) (Figure 1). Given the high survival rates, approximately 60,000 individuals were living with or had previously been diagnosed with CRC in Sweden in 2023 (7).

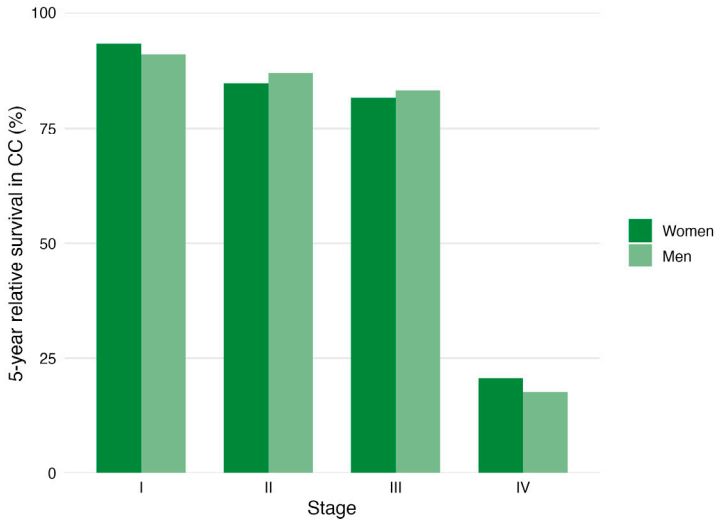


Figure 1. The barchart represents relative 5-year survival in different CC stages in women and men age 20-89 years diagnosed between 2019 and 2023. Similar patterns are observed for RC. Source: Cancerfonden (6).

Risk factors

Several risk factors for CRC have been identified. A family history of CRC, particularly disease in a first-degree relative diagnosed before 60 years of age, or the presence of CRC in multiple non-first-degree relatives, is associated with an increased risk of CRC (10). In addition, children and siblings of patients with colorectal polyps appear to have a higher risk of developing the disease (11).

The two most common hereditary syndromes associated with an increased risk of CRC are familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) (10). CRC secondary to FAP is driven by defects in the adenomatous polyposis coli (APC) gene, whereas HNPCC is caused by alterations in mismatch repair genes (10). Both syndromes have a substantially elevated risk of developing CRC if unrecognized.

Inflammatory bowel disease (IBD) is another condition that has been associated with an increased risk of CRC (10, 12-14), and patients with ulcerative colitis or

Crohn's disease who develop CRC have been reported to have an increased risk of mortality (13, 14).

Furthermore, metabolic conditions such as diabetes mellitus and obesity have been shown to be risk factors for CRC (10, 12). The carcinogenic effects associated with diabetes mellitus may be driven by hyperinsulinemia, which stimulates cell proliferation, as well as elevated insulin-like growth factor-1 (IGF-1), which enhances cell growth and reduces apoptosis. Moreover, chronic inflammation associated with diabetes mellitus has been suggested to play a role (10).

Lifestyle factors, such as a high consumption of red and processed meat, have been demonstrated to increase the risk of CRC (15-17). Furthermore, high body mass index (BMI), particularly in men, appears to increase the risk of CC (17, 18). Alcohol consumption is another established risk factor, with a dose-response relationship, whereby heavy drinking increases the risk by approximately 50%, whereas low consumption (≤1 drink per day) does not appear to increase the risk (17, 19). Current smoking is a modifiable factor that increases the risk of CRC two- to threefold (10). Non-modifiable risk factors comprise increasing age and male sex (10).

Several lifestyle factors protective against CRC have been suggested, such as physical activity, calcium supplementation, dairy products, dietary fibre and whole-grain products (17).

Interestingly, the mucosa-associated microbiota and dysbiosis have been described as important factors in the initiation and progression of CRC (20, 21). Microorganisms such as *pks+ Escherichia coli*, enterotoxigenic *Bacteroides fragilis* and *Fusobacterium nucleatum* have been studied, of which the first two have a clearer association with colorectal carcinogenesis (20).

Carcinogenesis

For CRC to develop, irreversible genetic damage in the epithelial cells of the intestinal mucosa must occur, which in turn predisposes to neoplastic transformation (10). This is followed by clonal cell proliferation, forming precursor lesions that may subsequently progress to cancer through the acquisition of aggressive features. This process generally takes 10–15 years if patients are not affected by certain hereditary conditions (22).

There are different mutation pathways that have been described, of which the chromosomal instability (CIN) pathway is the most common in sporadic CRC, followed by the microsatellite instability (MSI) pathway and serrated (BRAF/CIMP) pathway (10).

The CIN pathway includes mutation of the APC gene, which has a tumour suppressor function and, when lost, promotes activation of Wnt/β-catenin

signalling, resulting in the accumulation of β-catenin (23, 24). Additional alterations include mutations in KRAS, loss of heterozygosity (LOH) of the long arm of chromosome 18 (18q), and loss of the SMAD4 tumour suppressor gene, which in turn affects the TGF-β signalling pathway (23). Both 18q LOH and inactivation of TP53 have been shown to contribute significantly to the CIN phenotype. In addition, mutations in genes such as PIK3CA and the TGF-β receptor are involved in the development of CRC (10).

In the microsatellite instability pathway, mutations occur in mismatch repair (MMR) genes such as MLH1, MSH2, MSH6 and PMS2. This leads to the accumulation of mutations in microsatellite sequences located within DNA coding regions, which ultimately resulting in the development of CRC.

The serrated pathway is characterized by an initiating BRAF mutation and epigenetic silencing of cell cycle-regulatory genes, particularly p16 (CDKN2A), through CpG island hypermethylation (10, 23). In a substantial proportion of cases, methylation of MLH1 occurs, resulting in mismatch repair deficiency and secondary microsatellite instability (10, 23).

In IBD, chronic inflammation acts as a key driver of carcinogenesis. Inflammatory signalling pathways are upregulated, promoting cell proliferation, angiogenesis, and resistance to apoptosis (25). The resulting DNA damage and mutational events typically involve early TP53 mutations, whereas APC mutations occur later or are less frequent than in sporadic CRC (26). Moreover, the gut microbiota appears to play a role in carcinogenesis in these patients, as certain bacterial species suppress inflammation while others promote inflammatory processes that facilitate transformation into dysplasia and, subsequently, carcinoma (25).

Metastasis

CRC can metastasize through two main routes, namely hematogenous and lymphatic spread. The term “metastasis” was first used by the physician Claude Récamier in 1822, when he described the spread of breast cancer to the brain (27).

From the late 19th century until the mid-20th century, the dominant theory describing metastatic spread was based on William S. Halsted’s proposal that cancer cells spread in a stepwise manner, first locally, then regionally via the lymphatic system and ultimately systemically. He also claimed that the hematogenous route was of minor importance (27). In contrast, Bernard Fisher hypothesized that there was no orderly pattern to the dissemination of tumour cells and that LNM were a sign of a host-tumour relationship that enabled distant metastatic disease (27).

LNM is an important prognostic factor, and tumour invasion into lymphatic vessels has been shown to be associated with LNM (28). Until recently, lymphatic invasion has been reported together with venous invasion in histopathological reports

collectively classified as lymphovascular invasion (LVI). However, because these two factors may differ in their prognostic significance, separate reporting has become more common in recent years (28).

In contrast to William S. Halsted's theory, studies demonstrate that tumour cells may disseminate directly through vessels adjacent to the tumour, entering the circulation and subsequently attach at distant sites to form distant metastases (28, 29). The liver is the most common site for distant CRC metastases regardless of LNM, which supports the theory that direct hematogenous spread is an important route in the pathogenesis of distant metastases (28, 30).

Other studies challenging the conventional theory by showing that, in most cases, LNM and distant metastases arise from different tumour cell subclones (30), indicating distinct routes of spread. Moreover, dissemination of tumour cells appears to occur early, and sometimes even before a carcinoma is macroscopically detectable (31).

Diagnosis of early CRC

Screening

The aim of CRC screening is to reduce mortality through detection of cancer at earlier stages and by identifying and removing precancerous lesions before they develop into cancer. This have been achieved through screening using various methods (32-38).

As early as 2003, the European Council established recommendations for CRC screening using faecal occult blood testing (FOBT) for individuals aged 50–74 years (39). These recommendations were updated in 2022 (40) due to evidence showing the faecal immunochemical test (FIT) to be more sensitive, while maintaining high specificity for both CRC and the detection of precancerous lesions (41).

In Sweden, pilot studies were introduced before 2010, including programmes in Stockholm and Gotland (40). However, nationwide population-based screening in Sweden was initiated in 2021 using FIT test and is expected to be fully rolled out in 2026. This is well after the recommendations were introduced in 2003, and later than in other very-high-HDI countries (42). Notably, Sweden has decided to deviate from the current European recommendations by initiating screening at 60 years of age, compared with the recommended starting age of 50 years (40). In contrast, given the worrisome increase in early-onset CRC, studies suggest lowering the age of screening initiation to 45 years (43). The screening participation rate in Sweden is currently 66%, that is somewhat higher than in Denmark and Norway but lower than in Finland (40).

The different screening strategies include flexible sigmoidoscopy, colonoscopy and stool-based tests such as FOBT, FIT and the multitarget stool DNA test. If a stool-based test is positive, colonoscopy is recommended to identify or exclude potential precancerous or cancerous lesions. FIT has been shown to be non-inferior to colonoscopy as a screening method regarding CRC-specific mortality in a large-scale randomized controlled trial (RCT) with long-term follow-up (44), with a sensitivity of approximately 75% and a specificity of around 95% for CRC (41, 45).

Screening results in a shift towards earlier cancer stages (I–II) (34-36, 38). In a recent meta-analysis including registries from nine European countries, stage I–II disease was found in 65% of the screened population, which contrasts with 44% in the non-screened (38). In addition, within stage I disease (T1–T2 N0), higher proportion of patients with pT1 tumours have been observed in screened populations compared with non-screened (67% vs 50%) (37). Moreover, local resection as treatment method of CC was more frequently observed in the screened population. Interestingly, a recent study showed no difference in LNM between patients with screening-detected pT1 CRC (12.6%) and non-screening detected pT1 CRC (8.9%) (46).

Standardized follow-up regimens are adhered to after positive FIT, which slightly differ between the Nordic countries (40). Table 1 demonstrate the Swedish follow-up regimen.

Table 1. Recommended follow-up after positive FIT test and subsequent colonoscopy.

If no polyps requiring surveillance or no CRC found after colonoscopy secondary to FIT positive test	FIT in 2 years.
If CRC	Further treatment according to guidelines
Surveillance after positive finding on colonoscopy	
Adenoma ≥10 mm or high grade dysplasia	Colonoscopy in 3 years.
≥ 5 adenomas	
At least one serrated polyp ≥10 mm or dysplasia	
Piecemeal resection of polyp ≥ 20 mm	Colonoscopy 3–6 months
After last surveillance colonoscopy	Return to screening FIT invitation after 5 years

Information retrieved from (47) and (40).

Symptoms

If not included in a screening programme, patients with CRC often seek healthcare due to symptoms such as rectal bleeding, weakness, changes in bowel habits, abdominal pain, or symptoms related to anaemia. However, the disease can remain asymptomatic for a long time, and a proportion of patients have their first healthcare contact in the emergency setting, presenting with cessation of faecal and gas

passage, due to a constricting tumour. For early CRC, emergency symptoms are uncommon, and symptoms such as blood in the stool and anaemia or changes in bowel habits are more likely to prompt patients to seek medical care.

Intestinal wall anatomy and cancer classification

Layers of the large intestinal wall

The wall of the large intestine is composed of several distinct layers. The intestine is lined by the mucosa, which consists of an epithelial lining with cells that exhibit different functions. This epithelium is organized into crypts, where stem cells are typically located (48). Underneath the epithelium lie the lamina propria and the muscularis mucosae which separates the mucosa from the underlying submucosa (49).

The submucosa contains connective tissue, veins and arteries, as well as lymphatic vessels and the submucosal nerve plexus (Meissner's). Underlying this is the muscularis propria, which is composed of an inner circular muscle layer and an outer longitudinal muscle layer, between which lies the myenteric nerve plexus (Auerbach's) (49).

The outermost layer is the serosa, a layer of peritoneum that surrounds parts of the large intestine (49). The serosa covers the large intestine to various extending throughout the length; however, below the peritoneal reflection, intestine lacks a serosal covering.

Figure 2. Illustration of the layers of the large intestinal wall. T1 CRC is defined by invasion into the submucosa.

TNM classification

At present, the 8th edition of the TNM Classification of Malignant Tumours is the standard staging system for CRC and is jointly maintained and updated by the Union for International Cancer Control (UICC) and the American Joint Committee on

Cancer (AJCC). The TNM classification is used for various types of cancer and describes the extent of primary tumour invasion (T), the presence of regional LNM (N), and evidence of distant metastases (M) (Table 2). The least invasive tumour stage, T1, is further subdivided according to the depth of submucosal invasion into Sm1, Sm2, and Sm3 according to the Kikuchi/Kudo classification that is based on the risk for LNM (50, 51). However, accumulating evidence questions the invasion depth as an independent risk factor for LNM (52-54).

CRC is then categorized into an overall cancer stage based on the TNM classification (Table 3). Increasing cancer stage is usually associated with a worse prognosis (Figure 1, page 17). The overall cancer stage is therefore used to guide treatment decisions.

Table 2. Description of TNM staging

pT stage	
	Tumour invasion depth into:
Tx	Unassessable tumour
T1	the submucosa
Sm1	the superficial 1/3 of the submucosa
Sm2	the middle 1/3 of the submucosa
Sm3	the deepest 1/3 of the submucosa
T2	muscularis propria
T3	through muscularis propria, into subserosal fat or pericolic/perirectal tissue
T4	penetrates through the visceral peritoneum and/or grow into adjacent organs and structures
pN stage	
Nx	Nodal status unknown, unassessable regional lymph nodes
N0	No spread of cancer to regional lymph nodes
N1	LNM in 1–3 regional lymph nodes
N2	LMN ≥4 regional lymph nodes
pM stage	
M0	No distant metastases
M1	Distant metastases to other organs/site or peritoneum

TNM stage (55) and Sm- classification according to Kudo (51)/Kikuchi (50).

Table 3. Cancer stages based on pathological TNM categorization.

Stage	Tumour invasion depth	Nodal metastases	Distant metastases
0	Tis	N0	M0
I	T1–T2	N0	M0
II	T3–T4	N0	M0
III	T1–T4	N1–N2	M0
IV	Any T	Any N	M1

Diagnostic work-up and staging in early CRC

Diagnostic work-up

The aim of the diagnostic work-up, including tests and examinations, is to assess patient status and characteristics, confirm the diagnosis through histology, and accurately stage the tumour and potential metastases (56, 57). These results guide the physician's treatment recommendations through weighing risks and benefits.

Treatment decisions are most commonly made within multidisciplinary conferences (MDCs), and if using complete preoperative staging have been shown to increase survival in advanced CRC (58). In some patients with locally resected pT1 CRC, MDC discussion may not always take place prior to resection, however according to Swedish guidelines, MDC is then recommended after the intervention (59).

The work-up for CRC includes a complete colonoscopy to identify and evaluate the lesion, as well as to rule out synchronous lesions. If early CRC is suspected and the tumour is considered suitable for endoscopic resection, direct resection without prior biopsy is recommended to avoid the risk of submucosal fibrosis, which may hamper or preclude local resection (60). However, if deeper invasion is suspected, biopsy is essential to guide further management, and endoscopic tattooing recommended to facilitate perioperatively tumour localisation (60, 61).

Possible distant metastases are primarily evaluated through CT scanning, with the purpose of ruling out synchronous distant metastases in the lungs and abdomen, the liver being the most common site for distant metastases (~ 70%) (29). If liver metastases are suspected, additional imaging with liver-specific contrast-enhanced magnetic resonance imaging (MRI) is primarily recommended, with contrast-enhanced ultrasound (CEUS) as a secondary option (62). Moreover, in RC, MRI is recommended as the first-line modality for local staging, including assessment of tumour invasion depth and the presence of LNM (57, 63)

Blood tests

To evaluate the extent of disease and comorbid conditions, a complete blood count, coagulation parameters, liver and kidney function tests, serum albumin, and carcinoembryonic antigen (CEA) are assessed (56).

An association between elevated preoperative CEA levels and decreased overall and disease-free survival has been observed in older studies, which may partly reflect less effective oncological treatments used historically. Nevertheless, higher preoperative CEA levels are associated with more advanced disease stage (64).

Preoperative CEA for surgically treated patients is primarily used as a reference marker during follow-up to detect recurrence. However, the test is not specific to CRC, and may be elevated in other conditions such as pancreatitis, inflammatory bowel disease, liver cirrhosis, and hypothyroidism, as well as in other malignancies. In addition, higher CEA levels may be observed in smokers, men and older patients (64).

Endoscopic evaluation in early CRC

Endoscopic optical evaluation of a lesion is an important tool in the staging of early CRC and the assessment of the risk of deep submucosal invasion, defined as ≥1000 µm (61, 65, 66). The evaluation of lesion eligibility for local resection are made through assessment of morphological characteristics, including location, size, spontaneous bleeding, ulceration, the non-lifting sign, margin delineation, and classification according to the Paris classification system (65).

The Paris classification categorises lesions based on morphological characteristics, including types 0-Ip or 0-Is, 0-IIa, 0-IIb, 0-IIc, and 0-III lesions (67) (Figure 3).

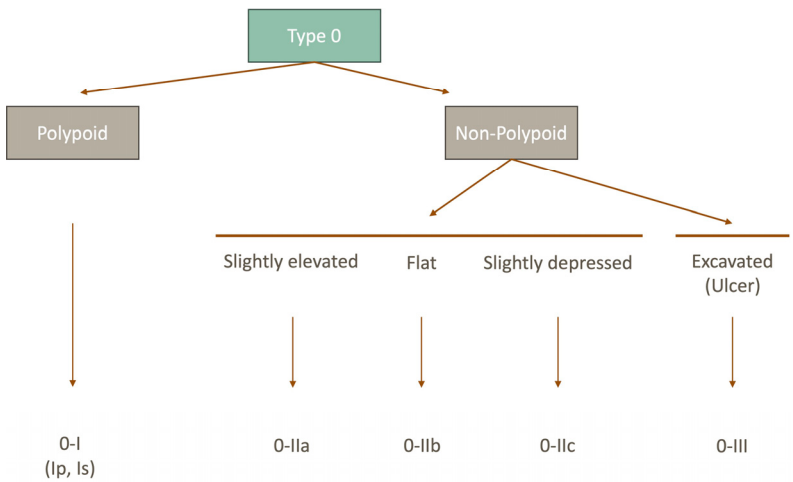


Figure 3. Paris classification of superficial neoplastic leasions, type 0. p, pedunculated; s, sessile. Data source (67)

In addition, advanced imaging techniques, such as narrow-band imaging (NBI), chromoendoscopy, and optical magnification are helpful for assessing surface and vascular patterns of lesions in the large intestine (61). Classification systems such as the Kudo pit pattern classification, the NBI International Colorectal Endoscopic (NICE) classification and the Japanese NBI Expert Team (JNET) classification, are used in clinical practice.

The Kudo pit pattern classification describes how the ”pits”, representing the openings of the colonic crypts, are arranged. The classification system ranges from types I–V, with type I representing normal round pits, and type V characterised by irregular arrangement and size, or loss or decrease of pits with an amorphous structure. Types I–II are considered benign, whereas types III–V indicate dysplasia or malignancy (61).

The NICE and JNET classifications evaluate vascular colour, surface patterns, and predict the most likely histology. A review using the GRADE system strongly recommended NICE type III and Kudo pit pattern type V as predictors of deep submucosal invasion and rated the evidence as high quality (61).

NBI and magnifying chromoendoscopy have been shown to provide higher sensitivity for identifying endoscopic features predictive of pT1 disease and deep submucosal invasion compared with gross morphological assessment alone (68, 69). Lesion size is another important factor that must be taken into consideration when evaluating the depth of invasion.

Lateral spreading tumours (LSTs) are defined as flat or slightly elevated colorectal lesions that, without marked vertical protrusion, reach a lateral diameter ≥ 10 mm (67). LSTs can be classified as granular (LST-G), with either homogeneous or mixed-size nodules, or as non-granular (LST-NG).

LST-G lesions with homogenous nodules are associated with a low risk of submucosal invasion, regardless of size, whereas LST-G lesions with mixed-sized nodules carry a higher risk of submucosal invasion, particularly in lesions exceeding 20 mm. LST-NG lesions are associated with a high risk of submucosal invasion, especially in pseudodepressed subtypes (61, 70).

Preoperative local T staging in early RC using MRI

MRI was gradually implemented as the primary modality for local staging of RC, based on evidence published in the early 2000s demonstrating that MRI could more accurately predict the circumferential resection margin (CRM) than digital examination (71-73). MRI has also been shown to accurately assess the depth of extramural tumour invasion (74), both of which are key characteristics for evaluating locally advanced RC. Based on this information, patients with locally advanced RC may be allocated either to upfront surgical resection or to neoadjuvant therapy, and in cases where the mesorectal fascia is involved, more extensive surgical approaches may be required. In 2012, a European expert panel reached consensus recommending MRI as the first-line modality for primary staging of RC (75). However, if MRI is sufficiently accurate to be used for allocating patients with early RC for local resection is still uncertain.

The accuracy of MRI in discriminating between early T stages within the rectal wall remains a matter of debate. Some studies have suggested good diagnostic accuracy, whereas others have reported difficulties, particularly in distinguishing between T2 and early T3 disease (72, 73, 76). These limitations have been attributed to changes in the peritumoral tissue, such as tumour-induced fibrosis, inflammation, hypervascularity, and desmoplastic reaction, which can be difficult to differentiate from true tumour infiltration (57, 77, 78).

Numerous studies have evaluated the accuracy of MRI, most commonly in small study populations with limited numbers of T1 and T2 tumours (72, 73, 76, 77, 79). While some studies have demonstrated high diagnostic accuracy (77, 79), others have reported less promising results (72, 73, 76).

Large-scale studies evaluating the accuracy of MRI in early RC are sparse. However, Detering et al. conducted a population-based study in 2020 investigating the accuracy of MRI alone and in combination with endoscopic ultrasound (EUS), reporting concerning results (80). The sensitivity of MRI for assessing cT1 disease was 45%, with a specificity of 93%, whereas for cT2 disease the sensitivity was high (92%) but the corresponding specificity was low (26%) (80). Thus, 55% of pT1 tumours were overstaged, precluding these patients from potential local resection. The addition of EUS to MRI reduced the overstaging of pT1 to 31%; however, this came at the cost of a substantial increase in the understaging of pT2 to 28%.

The European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus guidelines (63, 81) recommend EUS as a first-line modality for assessing T1 and T2 rectal tumours, due to the difficulty in differentiating T1 from T2 disease using MRI (75). Some evidence suggests that EUS may perform better than MRI in discriminating between T1 and T2 RC (82, 83). However, even when EUS is added to MRI, diagnostic accuracy is not substantially improved with reported sensitivity and specificity for cT1 disease of 69% and 73% respectively, and for cT2 disease 77% and 61%, respectively (80).

Moreover, the European Society of Gastrointestinal Endoscopy (ESGE) advises against the use of EUS, MRI, or CT for local staging of lesions that are assessed endoscopically as having probable shallow invasion, and for which local resection is recommended. In contrast, when deep invasion is suspected, preoperative staging with imaging is recommended (66).

Nodal staging

As for T staging, the reported accuracy for MRI-assessed N staging has varied in the literature, ranging from 55% to 85% (80, 84, 85) (72, 76, 79). Studies reporting the highest accuracy were generally performed in small cohorts, whereas larger population-based studies demonstrated lower accuracy (80, 84).

As reflected by the wide range of reported accuracy in lymph node staging, there are no reliable criteria to definitively determine whether cancer has spread to the regional lymph nodes.

ESGAR has proposed criteria for identifying regional LNM. Mesorectal lymph nodes are then subgrouped according to size, based on the short-axis diameter, into <5mm, 5–8 mm, and ≥9mm. Suspicious morphological characteristics include a round shape, irregular borders, and heterogeneous signal intensity (60). Notably, lymph node size alone has been shown to be an insufficient marker, as a substantial proportion (45–78%) of LNM measure less than 5 mm (86, 87).

In the 8th edition of TNM classification, tumour deposits have been incorporated and staged as N1c. As tumour deposits and extramural venous invasion (EMVI) are both primarily features of extramural disease, they will not be discussed further.

The challenges of MRI assessment in early RC

Described by Akasu et al., on MRI the submucosa appears as a high-signal-intensity layer, whereas the muscularis propria appears as a low-signal-intensity layer, within which differentiation between the inner and outer muscle layers is difficult (77). Perirectal fat likewise demonstrates high signal intensity. The tumour typically appears as tissue with signal intensity higher than that of muscularis propria but lower than that of the submucosa.

Based on these imaging characteristics, the authors suggested that MRI is generally reliable for T-stage assessment (77). However, other studies report that differentiation between T1 and T2 disease remains difficult, except in selected cases where a thin layer of intact submucosa can be identified between the tumour and the muscularis propria (72, 78).

Furthermore, distinguishing between T2 tumours and minimal T3 invasion is challenging (78). Identification of tumour penetration through the muscularis propria may rely on detecting small interruptions in the muscle layer. However, these findings may be confounded by small vessel penetration without tumour infiltration. In addition, desmoplastic reaction has been reported to account for up to 40% of overstaging from T2 to T3 disease (78).

ESGE categorization of risk groups

Locally resected pT1 CRC are classified according to ESGE guidelines as low-risk or high-risk tumours based on the risk of LNM. Accordingly, patients with high-risk tumours should be recommended completion surgery to remove the bowel segment and associated lymph nodes. However, when these guidelines are strictly

applied, more than 70% of the patients are classified as having high-risk tumours (88). Given that only approximately 10% harbour concomitant LNM (88-92), this indicates a substantial degree of overtreatment. Moreover, recurrence is not explicitly considered in current guidelines, although it would arguably present a more clinically relevant outcome from a patient's perspective.

According to current guidelines, pT1 CRCs with a minimum of one of the following risk factors are classified as high-risk: LVI, high histologic grade, incomplete resection margins (R1/Rx), tumour budding (Bd2–3), and deep submucosal invasion (sm2–3) (66). For a tumour to be classified as low-risk, none of the high-risk features should be present.

The overall recurrence rate in pT1 CRC is low, usually <5% (90, 93); however, increased recurrence rates have been reported in high-risk patients (94).

Risk factors for LNM and recurrence in T1 CRC

Lymph node metastases

The presence of LNM is an established risk factor for recurrence in CRC (90, 93, 95, 96). As described above, approximately 10% of all patients with pT1 CRC are affected by concomitant LNM (88-92). Interestingly, a previous study reported that recurrence rates in CC patients with LNM were 3.6% compared with 1.3% in those without LNM ($p = 0.19$). In contrast, the difference was significant in RC patients, with recurrence rates of 15% versus 1.1%, respectively ($p < 0.0001$) (93).

Risk factors included in the ESGE guidelines

Resection margin

The resection margin is assessed for the presence of cancer cells. Cancer detected at the resection margin is classified as R1, whereas Rx is assigned when the resection margin cannot be assessed reliably and R0 denotes a complete resection with tumour-free margin.

An incomplete resection margin is not considered an independent biological risk factor for LNM, because LNM are present before the resection occurs. However, Lee et al. demonstrated an association between incomplete resection and LNM (91), which may be explained by tumour growth patterns and other inherent pathological features, making complete resection more difficult to achieve.

A positive resection margin is an important risk factor for recurrence following both surgical resection and local resection in early RC (97, 98), with the circumferential

resection margin (CRM) being of particular importance (97). Furthermore, a positive resection margin has been associated with reduced OS and RFS (54).

Histologic grade

Histologic grade is divided into high and low grade according to the Vienna and WHO classification (99, 100). Grading is based on assessment of gland formation, cellular atypia, and architectural disorder. Well- and moderately differentiated tumours are defined as low grade, whereas poorly differentiated and undifferentiated tumours are classified as high grade.

High histologic grade has been shown to be a risk factor for LNM in some studies (54, 88, 90, 101) but not in others (52). The prognostic significance of high histologic grade remains uncertain, as studies assessing relapse-free survival report conflicting results (54, 89). Nevertheless, high histologic grade has been reported as an independent risk factor for recurrence after pT1 CRC in at least one study (93).

Lymphovascular invasion

LVI is defined as tumour growth observed within lymphatic and/or venous vessels (102, 103). Both vascular and lymphatic invasion have been shown to be independent risk factors for LNM in pT1 CRC (52, 54, 88-90, 93, 104).

Several studies have reported venous invasion as a risk factor for recurrence (90, 105-107). However, whether LVI as an entity is associated with recurrence in pT1 CRC remains uncertain (54). It is plausible that lymphatic invasion more frequently leads to lymph node metastases (LNM), whereas venous invasion more often result in direct dissemination into the systemic circulation and subsequent distant recurreces (108).

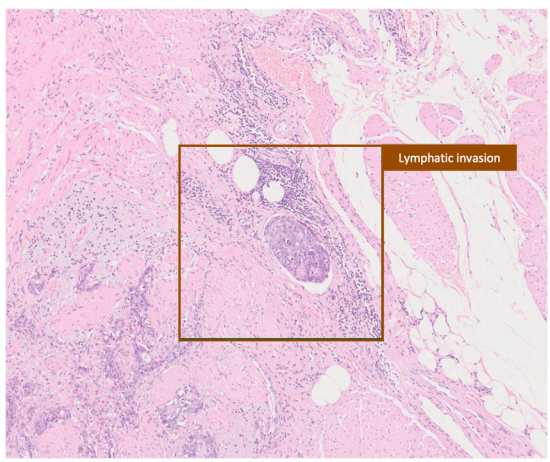


Figure 4. Picture shows tumour growth into lymphatic vessel. Image by Dr Almorched, pathology department SUS, Malmö.

Submucosal invasion

A three-tier system is used to classify the depth of submucosal invasion and was introduced by Kudo et al. and Kikuchi et al. in the early 1990s (50, 51) to risk-stratify early sessile pT1 CRC. Sm1 represents tumour invasion into the superficial one-third of the submucosa, Sm2 invasion into the middle one-third, and Sm3 represents invasion into the deep one-third.

Earlier meta-analyses have found deep submucosal invasion to be associated with an increased risk of LNM (88, 109). However, accumulating evidence suggests that deep submucosal invasion alone is not an independent risk factor when adjusted for other highly influential pathological features (52-54). When deep submucosal invasion is present in the absence of other high-risk features, the reported incidence of LNM is as low as 2.5% (110).

Furthermore, deep submucosal invasion does not appear to increase the risk of recurrence in pT1 CRC (54, 107, 111, 112).

Figure 5. Illustration of pT1 invasion depth according to Kikuchi-classification Sm1 (left), Sm2 (middle) and Sm3 (right).

Tumour budding

According to the International Tumour Budding Consensus Conference (ITBCC) in 2016 (113), tumour budding is defined as a single cancer cell or a cluster of up to four cells. Tumour budding has been shown to be an independent risk factor for LNM in pT1 CRC (53, 91, 114, 115). Moreover, in stage II CRC, tumour budding is a predictor of survival and should be considered in treatment decision-making for CRC (113).

Tumour budding is divided into three categories: 0–4 buds (Bd1, low), 5–9 buds (Bd2, intermediate), and ≥ 10 buds (Bd3, high). Both Bd2 and Bd3 are associated with an increased risk of LNM in pT1 CRC (113), which is why both are included in the ESGE high-risk classification (66).

Interestingly, one study evaluating this classification found that splitting Bd1 into Bd0 (no budding) and a revised Bd1 (1–4 buds) further improved the prediction of associations with other unfavourable factors, such as TNM stage, tumour grade, lymphatic invasion, venous invasion, and perineural invasion (PNI). In that study,

36% of pT1 tumours were classified as Bd0, 42% as Bd1, and Bd 2 and Bd 3 each accounted for 11%.

Studies evaluating the association between high-grade tumour budding and recurrence in early CRC are sparse, however, one study identified high-grade tumour budding as an independent risk factor for recurrence in pT1 CRC (106).

Other potential risk factors for LNM and recurrence in pT1 CRC

Mucinous tumour

Mucinous adenocarcinoma is identified as a tumour composed of more than 50% extracellular mucin pools which contain malignant cells (102). Mucinous histology has been identified as an independent risk factor for LNM in pT1 CRC (52, 116). However, in early CRC, mucinous histology does not appear to independently influence recurrence rates (117) nor survival (118).

Tumour location

Various LNM rates have been reported in the right colon, left colon and rectum, with lower rates proximally and progressively higher rates distally (119, 120). Okabe et al. described LNM occurrence of 3% in right-sided CC, 8% in left-sided CC and 15% in the RC; however, location was not an independent risk factor after adjustments for other influential risk factors (120). Studies evaluating whether rectal tumour location is associated with LNM have shown conflicting results (121, 122). However, there is growing evidence suggesting rectal location to be independently associated with recurrence in pT1 cancer (106, 111, 123).

Tumour Size

Whether tumour size influences the occurrence of concomitant LNM in pT1 CRC remains debated. Several studies, including meta-analyses, have not identified tumour size as an independent risk factor for LNM when other established risk factors are accounted for (54, 109, 121, 124). However, one study reported tumour size > 4.5 cm to be an independent risk factor for LNM in CC but not in rectosigmoid cancer or RC (125). Another study demonstrated that tumour size ≥ 1cm was independently associated with LNM in patients younger than 45 years (126).

Findings regarding the association between tumour size and recurrence risk in T1 CRC are likewise conflicting. (54, 109, 127-129).

Perineural invasion

PNI is defined as the presence of tumour cells within one of the three layers of a nerve (epineurium, perineurium and endoneurium), or when tumour cells surround more than one third of the nerve circumference (102).

PNI has been shown to be associated with LNM in pT1 CRC (52, 130). In meta-analyses of CRC across various stages, PNI has also been associated with increased local recurrence, as well as decreased DFS, cancer-specific survival and OS (131, 132).

Clinical factors

Biological sex has not been identified as an independent risk factor for LNM in pT1 CRC (52, 54, 101). However, female sex may be protective with respect to OS and RFS in patients with pT1 CRC (54). Moreover, proximal CC is more common among women (133), which may be relevant when interpreting sex-related differences. Age at diagnosis <60 years has been demonstrated to be a risk factor for LNM (52), whereas increasing age has been associated with poorer RFS (54).

Surgical resection

The conventional treatment of T1 CRC is surgical resection. The resection includes the affected bowel segment together with the associated mesocolon or mesorectum. The mesocolon and mesorectum are composed of adipose and connective tissue containing nerves, blood vessels, lymphatic vessels and lymph nodes.

To reduce the risk of recurrence and to enable accurate pathological staging, it is important that the lymphovascular drainage of the tumour is completely removed. Adequately performed surgery allows for proper lymph node evaluation and accurate tumour staging. To achieve proper pathological staging a lymph node yield of 12 or above have been standard. However, a recent study demonstrates that a cut-off of 9 is enough, and that a low lymph node yield is primarily a sign of a tumour biology. Thus, higher yield was associated with elevated immune response and better survival in both node-negative and node-positive patients (134).

For RC located in the mid- and low rectum, total mesorectal excision (TME) is the gold standard surgical approach. The method was introduced by Professor Heald in the 1980s, who demonstrated substantially reduced local recurrence rates when dissection was performed in “the holy plane”, corresponding to the embryological planes, while preserving the integrity of the mesorectal fascia and mesorectum (135-137).

For proximal RC, studies have shown that partial mesorectal excision (PME) is a safe treatment option, associated with fewer surgical complications, including lower rates of anastomotic leakage, while achieving similar OS, DFS, and local recurrence rates compared with TME (138, 139). The most common surgical procedures for RC include anterior resection, abdominoperineal resection (APR) and Hartmann’s procedure (140).

Anterior resection is most commonly applied for RC located in the mid and proximal rectum and in some cases of distal RC. The resection is performed at a

distance from the pelvic floor and an anastomosis between the rectal remnant and colon is allowing restoration of bowel continuity (141).

First described by Ernest Miles in 1908, APR is a method for treating very low RC. The procedure includes en bloc removal of the internal and external anal sphincters, the anal canal, and the entire rectum with associated mesorectum resulting in a permanent colostomy (142).

The Hartmann procedure was first described in 1921 by Henri Hartmann, when he presented his work at the 30th Congress of the French Surgical Association. He described two patients in whom he performed sigmoid resection with closure of the rectal remnant and formation of a permanent colostomy, due to obstructing carcinoma of the sigmoid colon (143). The procedure is still used today, both to treat sigmoid and upper RC as well as in other selected conditions.

The three most common surgeries for CC are right hemicolectomy, sigmoid colon resection and left hemicolectomy (144). To determine the appropriate type of resection, accurate localisation of the tumour is crucial; therefore, preoperative endoscopic tattooing is often performed to enable intraoperative localisation, even in minimally invasive surgery. Similar to the principles of TME, the vessels draining the tumour in CC are identified and divided close to their origin, and the associated mesocolon containing lymph nodes is removed en bloc together with the bowel segment.

Morbidity and Complications

Even minimally invasive surgery imposes a significant physiological burden on the body, and optimal physiological conditions are crucial for postoperative healing. However, the risk of complications following surgical resection remains substantial, even under optimal circumstances and is considered higher after RC surgery than after CC resection, particularly with respect to anastomotic leakage and infectious complications (145-147). Notably, anastomotic leakage has been associated with a high rate (up to 65%) of permanent stoma formation after anterior resection (148). Other complications accompanied surgical resection of CRC are ileus, sexual and urinary dysfunction, bowel dysfunction, and hernias (149-155), which negatively impact quality of life (156-158). Importantly, surgical resection is also associated with perioperative mortality (146, 154, 159, 160).

I addition, as described above, APR is an extensive surgical procedure, associated with permanent stoma formation due to removal of the sphincter complex. This results in substantial morbidity, both from the permanent stoma itself and from stoma-related complications.

Local resection

Local resection of pT1 CRC has increased with advances in endoscopic resection techniques and the aim of reducing morbidity associated with radical surgical resection. If the tumour is assessed as histopathological low risk, including complete resection (R0) and no evidence on preoperative work-up of LNM or distant metastases (cN0M0), local resection is often considered curative. However, when high-risk features for LNM are present, including deep submucosal invasion, LVI, high histologic grade, and tumour budding (Bd2–3) or incomplete resection, completion surgery is usually recommended (66).

For lesions located in the rectum, both transanal local excision techniques and endoscopic techniques are available, whereas only endoscopic techniques are used for colonic lesions.

Already in the 1970s, Parks and Stuart described a transanal excision (TAE) technique (161). Since then, several transanal and endoscopic techniques have been developed, including transanal endoscopic microsurgery (TEM), transanal minimally invasive surgery (TAMIS), and endoscopic resection techniques such as snare polypectomy, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and endoscopic intermuscular dissection (EID) (66, 162). These techniques have different advantages and limitations, which are described below.

Compared to surgical resection, local resection is associated with significantly lower intraoperative blood loss, shorter operative time and hospital stay, as well as fewer postoperative complications (153, 154, 159, 160, 163). In low-risk patients, OS and DFS appear comparable between local and surgical resection (54, 164-166). Importantly, when local recurrence occurs, quality of life reduction and the substantial associated mortality, reaching up to 40% have been observed (167-170), therefore initial high quality resections are essential.

Transanal local resection

Transanal excision

TAE was initially intended for the removal of villous tumours (161). The use of an anal retractor enabled direct visualisation of the lesion, and partial-thickness excision was initially performed. Subsequently, full-thickness resections were introduced to improve oncological radicality, as the indication for the technique extended to include resection of T1 RC (65, 171).

The method is limited by restricted visualisation of the surgical field and was therefore mainly applicable to low rectal lesions. Compared with later-introduced TEM and TAMIS, TAE has been associated with higher rates of fragmented

specimens, and lower rates of complete (R0) resection, and higher local recurrence rates (171-174).

Transanal endoscopic microsurgery

In the 1980s, Professor Gehard Buess developed the TEM technique including the specialized instruments needed (175). It was taken into clinical use in 1983 and became a successful alternative to the conventional TAE.

The technique is based on a dedicated endosurgical unit consisting of a rigid rectoscope, and a stereoscopic optical system, that is stabilised by fixation to the operation table and general anaesthesia is typically use (175, 176). TEM is feasible up to 25 cm from anal verge (176) and closure of the rectal wall defect is routinely preformed when the lesion is located proximal to the peritoneal reflection, whereas defects distal to the reflection may be left unclosed.

When comparing TEM with surgical resection, studies have shown lower perioperative mortality, fewer postoperative complications, shorter operative time, reduced intraoperative blood loss, and shorter hospital stay (159, 160, 163, 176, 177). Disadvantages of TEM include the high cost of the specialised equipment and a long learning curve (176).

A recent meta-analysis demonstrated an overall complication rate of 11%, which is lower than that associated with surgical resection (178). Types of complications after TEM include temporary anal incontinence, bleeding, suture dehiscence, infection, pain, stricture, and fistulas (178). Moreover, completion surgery due to high-risk features has been shown to result in recurrence rates comparable to those observed in low-risk pT1 RC treated with TEM alone (179).

Notably, higher local recurrence rates following TEM compared with surgical resection have been reported (159, 160, 163, 177). Moreover, when TME is performed after initial full-thickness local resection, a meta-analysis (including TEM and TAE) has demonstrated higher overall morbidity, increased reintervention rates and a higher risk of incomplete mesorectal excision compared with primary TME (180).

A possible explanation for incomplete mesorectal excision is that prior local resection may cause defects in the mesorectal fascia (181), thereby complicating the subsequent TME due to disruption of surgical dissection planes (182). In addition, higher rates of APR have been reported following surgical resection preceded by TEM, particularly if the TME is performed early after initial intervention (183, 184). This may be explained by fibrotic scarring in the resection area, which hampers dissection towards the pelvic floor and thereby limits the feasibility of low colorectal and coloanal anastomoses (183).

No significant reduction in long-term outcomes, including recurrence and overall survival (OS) has been reported when TEM was performed prior to TME (182, 184). However, these studies are limited by small sample sizes. One study reported

disease-free survival to be adversely affected in cases with inferior TME specimen quality, even though not directly related to TEM (184).

Transanal minimally invasive surgery

TAMIS was first described by Atallah et al. in 2009 (185). The technique was defined by the authors as a hybrid between TEM and single-incision laparoscopic surgery. Instead of a rigid endosurgical unit with a rectoscope fixed to the operating table, the port applied in the rectum is made of thermoplastic elastomer (185).

This port, together with the use of conventional laparoscopic instruments, results in substantially lower costs compared with the highly specialised instruments required for TEM. Another difference compared to TEM is the narrower diameter (3 cm) of the rectoscope, which may be less traumatic to the anal canal (185).

A recent meta-analysis reported similar rates of positive resection margins after TAMIS compared to rigid platforms (TEM and transanal endoscopic operation), as well as comparable rates of specimen fragmentation (186). The short-term complications and readmission rates were lower following TAMIS; however, no difference was observed in major complication rates (Clavien-Dindo ≥IIIb) (186).

Interestingly, TAMIS and ESD are currently being compared in the TRIASSIC study, where local recurrence is the primary endpoint, and secondary outcomes include cost comparison, complication rates, and patient-reported burden (187).

Endoscopic resection

Polypectomy and endoscopic mucosal resection

Conventional polypectomy and EMR are frequently used for lesions considered benign based on the macroscopic assessment. These two techniques both use a snare as the main cutting instrument, which may be cold or hot (60). The EMR procedure involves injection of a solution to create a submucosal cushion, which lifts the lesion from muscularis propria. The lift usually improves the access to the lesion and reduces the risk of cutting deeper than intended, which could otherwise result in perforation.

The specimen from EMR may include parts of the submucosa, and very superficial pT1 CRC may be removed. In CRC, en bloc resection is crucial to reduce the risk of recurrence, because piecemeal resection have substantially higher recurrence rates, also in adenomas (66). The EMR technique is limited by the size of the lesion, and when lesions exceed 20 mm, en bloc resection is difficult to achieve.

Endoscopic submucosal dissection

When superficial submucosal invasiveness is suspected in non-pedunculated lesions, ESD is the technique of choice (66). The technique was developed in Japan

in the late 1990s, initially for gastric lesions, and was later applied to colorectal lesions (188). ESD provides more precise dissection of the submucosa and there is typically no size limit (189). The three basic steps of the ESD procedure include elevation of the lesion from muscularis propria through fluid injection into the submucosal layer, circumferential marking and mucosal incision around the lesion using dedicated ESD knives, and submucosal dissection beneath the lesion with concomitant haemostasis (70, 189, 190).

The ESGE 2023 guidelines describe several refinements of the conventional ESD technique, including underwater ESD, tunnelling, and pocket-creation method, which have been associated with improved resection outcomes. For example, the pocket-creation method has been reported to improve both R0 resection rates from 78% to 93.5% and en bloc resection rates from 93% to 99.8% (189). Notably, when ESD is performed on deeply invasive T1 tumours (sm2–3 or ≥1000μm), the R0 resection rates have been reported to decrease substantially (from 97% to 65%), even though en bloc rates remain feasible (191).

Compared with EMR, ESD procedure are associated with longer duration and higher risk of perforation (70), however considerably improved precision using ESD leads to higher R0 and en bloc resection rates, which have been proven crucial in reducing cancer recurrence. Of note, the procedure has a considerably long learning curve and to gain the optimal results the procedure should be performed by experienced endoscopists (190).

Reported complications include post-procedural bleeding, perforation, post-ESD electrocoagulation syndrome, and stricture formation. Post-ESD electrocoagulation syndrome is characterized by localized peritoneal inflammation, presenting with abdominal tenderness and fever or laboratory-confirmed inflammation (elevated C-reactive protein and leukocytosis) in the absence of delayed perforation (192, 193). Post interventional bleeding rates are similar to or lower than those observed after EMR (~3–4%), likely due to prophylactic coagulation of large vessels during ESD (189). Perforation during the ESD procedure is considered the most serious complication. Most perforations are detected during the procedure and closed with endoscopic clips; therefore, rescue surgery is rarely required (189). Delayed perforations occur infrequently. However, in such cases, or when immediate closure of a defect with intraperitoneal location is not possible, emergency surgery is most often required (189). Stricture formation is rare after ESD treatment of CRC; however, the risk increases when ≥90 % of the luminal circumference is resected (194). Such strictures can usually be managed with endoscopic balloon dilation (189).

In complete resections of pT1 CRC with low-risk features, local recurrence rates have been reported to be low, ranging from 0.7% to 1.2%, while high-risk tumours are associated with increased recurrence rates (7.0%–10%) (94, 167). Importantly, in cases of completion surgery after endoscopically resected high-risk pT1 cancers surgical resection has been shown to be safe (195), with no differences in operative

time or postoperative complications, including anastomotic leakage and ileus (124), and no differences in long-term outcomes, including recurrence, RFS, disease specific survival or OS compared with primary surgery (124, 166, 191, 196).

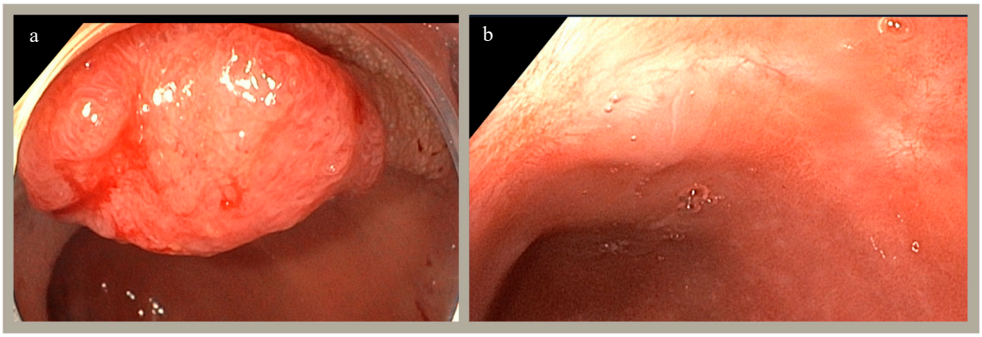


Figure 6a) pT1 RC located 10 cm from anal verge. Histopathology showing Sm2, LVI negative, PNI negative, Bd 2, later radically resected with ESD **(b)** Follow-up pictures 6 months post-ESD, showing no recurrent disease. Published with approval from endoscopy unit SUS Malmö.

Endoscopic intermuscular dissection

ESD provides a high proportion of negative resection margins in pT1sm1 tumours. However, when deeper invasion is present, R0 resection rates decrease (162). To overcome this limitation, EID was developed. The procedure is similar to ESD; however, the dissection is extended into the intermuscular space. A lifting solution may be injected between the muscle layers of the muscularis propria to facilitate easier dissection. Selective partial myotomy of the inner circular muscle layer of the muscularis propria is performed with the aim of achieving en bloc resection (162, 197).

Promising results have been reported, including high rates of en bloc resections (96–98%) and R0 resections rates of approximately 90% in T1 RC with deep submucosal invasion (sm2–3) (162, 197). Adverse events have been reported in a minority of patients, including perianal pain, transient incontinence, inflammatory response, delayed bleeding, and rectal stenosis managed with dilatation (162, 197).

Adjuvant Chemotherapy (AC)

Charles Heidelberger and associates developed the antimetabolite 5-fluorouracil (5-FU), which was patented in 1957 (198). Initially it was used for disseminated and advanced CRC (199, 200). During the 1940s and 1950s, the five-year survival for stage III CRC was approximately 15–30%, increasing to 45–60% over the subsequent two decades (201). In 1990, Moertel et al. published a pivotal trial

demonstrating that adjuvant chemotherapy (AC) using fluorouracil and levamisole significantly reduced mortality by 33% and recurrence by 41% in stage III disease (202). This finding revolutionized the treatment of CRC. Subsequently, several large studies were conducted, and 5-FU in combination with leucovorin became the standard AC (95, 203, 204). In 2004, the MOSAIC trial was published, reporting further improvements in prognosis, with increased disease-free survival achieved by the addition of oxaliplatin to 5-FU/leucovorin (205).

The current standard AC consists of either FOLFOX (Leucovorin, 5-FU, oxaliplatin) or CAPOX (capecitabine, oxaliplatin). Until 2020, when the IDEA collaboration non-inferiority study was published, six months of treatment was considered standard (206). The trials were initiated due to treatment-related side effects, with the hypothesis that shorter treatment durations would reduce toxicity.

Non-inferiority of three months of treatment was not demonstrated for FOLFOX but was generally achieved for CAPOX. However, the absolute reduction in OS was small (0.4%), while significant reductions in neurotoxicity were observed, along with decreased rates of hand-foot syndrome, mucositis, nausea, fatigue, and diarrhoea (206, 207). In older patients, no additional benefit from oxaliplatin has been observed; however, increased toxicity has been reported. Therefore, fluoropyrimidine monotherapy is more commonly used (208-211).

To determine whether three or six months of FOLFOX should be administered, several risk factors are taken into consideration including, examination of fewer than 12 lymph nodes, a ratio of metastatic to examined lymph nodes ≥0.33, high histologic grade, lymphatic and venous invasion, EMVI, PNI, tumour perforation, emergency surgery, positive CRM, R1-resection, tumour budding and elevated preoperative CEA levels (212).

Patients with pT1N1–2 CRC (T1N+) are classified as stage III and, according to guidelines, should be recommended AC. However, in the pivotal trials on which these guidelines are based, pT1 patients were either underrepresented (202) or absent (205). To date, two observational cohort studies have investigated the effect of AC on survival in pT1N+ disease (213, 214), but no studies have evaluated its impact on recurrence. In addition, deviations from AC treatment guidelines have been reported in patients with pT1N+, and older age has been identified as a factor associated with avoidance of AC (213). Whether other factors predict deviation from guideline-recommended treatment remains unclear.

“Listen to the patients, they are telling you the diagnosis”

Knowledge gaps and research questions

Studies on MRI accuracy have primarily focused on patients with advanced RC to guide neoadjuvant treatment allocation. However, studies evaluating the accuracy of MRI in early RC are sparse.

Is MRI sufficiently accurate to guide patient selection for local resection in early RC?

Risk stratification of locally resected pT1 tumours is based on the risk of concomitant LNM rather than recurrence. Studies investigating recurrence risk after surgical and local resection across risk groups are sparse. In addition, CRC is often grouped as one entity in studies on early CRC. However, accumulating evidence indicates that rectal location is a risk factor for recurrence in pT1 CRC.

Do recurrence rates differ across risk groups when comparing surgical resection with different local resection techniques?

In the trials on which current guidelines for AC are based, T1 CRC is underrepresented. Few cohort studies have focused on cancer-specific survival or OS after AC, and none have evaluated recurrence per se. In addition, studies indicate that patients with T1 cancer may be undertreated; however, the factors predicting avoidance of AC remain unclear.

Does AC affect recurrence and survival in patients with pT1 CRC? How common are deviations from treatment guidelines, and what factors influence treatment choice?

Aims

The overall aim of this thesis was to contribute to the knowledge on preoperative evaluation and prognosis following different treatment strategies in patients with T1 CRC, as a step toward more personalized care for this specific patient group.

Study I

To assess the accuracy of MRI for T and N staging in early RC.

Study II

To compare recurrence rates after endoscopic and surgical resection across risk groups and identify risk factors for recurrence in T1 CC.

Study III

To compare recurrence rates between transanal endoscopic microsurgery and surgical resection across risk groups in T1 RC.

Study IV

To investigate the effect of AC on recurrence and survival in T1 node-positive CRC as well as identify factors associated with not receiving AC.

Material and methods

The Swedish colorectal cancer registry

The Swedish Colorectal Cancer Registry (SCRCR) was used as the data source for all four studies included in this thesis. The registry was launched in 1995, initially covering RC patients, and was later expanded to include CC patients in 2007 (215, 216). SCRCR is a nationwide registry, for which annual reports demonstrate high coverage during the study period, exceeding 96% for CC and 97% for RC, with coverage in most years ranging between 98% and 99% (210). The registry has been evaluated and shown to have high validity for the variables used in the studies included in this thesis, with a completeness of approximately 99% (215-219).

The registry is extensive and includes variables related to preoperative investigations, surgical treatment, oncological treatment, patient and tumour characteristics, as well as follow-up data at 1, 3, and 5 years. During the study period, follow-up routinely comprised clinical examination, measurement of CEA, and imaging of the thorax and abdomen at all follow-up visits, with an additional colonoscopy at the 3-year follow-up (220). Locally resected patients are followed with colonoscopy at shorter intervals, depending on the tumour risk profile (59). The overarching aim of the registry is to improve treatment quality and survival outcomes in patients with CRC (210, 221).

Study design and ethical considerations

The four studies included in this thesis are registry-based observational cohort studies. *Studies II–IV* include recurrence data, and *Study IV* also includes survival data, based on prospectively collected follow-up information.

The studies were designed and conducted in accordance with the Declaration of Helsinki. *Study I* was approved prior to initiation by the regional ethical review board at Lund University (2017/546). Approval for *Study II–IV* was granted by the Swedish Ethical Review Authority: *Study II* (2020–06676) and *Study III* and *IV* (2023–01159–01). Data retrieved from the SCRCR were de-identified, and the study populations were sufficiently large to ensure individual anonymity. Prior to registration in the SCRCR, patients are informed about the purpose and function of the registry and are given the opportunity to opt out at any time (222).

Table 4. Overview of patients and outcomes in the four studies included in the thesis.

S	Time period	Type of cancer	Study population	Primary aims	Outcome
I	2009–2018	cT1-T2 RC	1888 patients	MRI accuracy T and N stage	Sensitivity Specificity PPV NPV LR– LR+
I	2009–2018	pT1 RC	549 patients	Same as above	Sensitivity Specificity LR– LR+
II	2009–2021	pT1 CC non-pedunculated	1805 patients	Recurrence after endoscopic vs surgical resection	Recurrence in high and low-risk group Overall DFI Risk factors for recurrence
III	2009–2022	pT1 RC	859 patients	Recurrence after TEM vs surgical resection	Recurrence in high and low-risk group Overall DFI
IV	2009–2022	pT1N+ CRC	222 patients	Recurrence and survival after AC vs NAD	DFS OS DFI Determinants of NAD

AC; adjuvant chemotherapy, CC; colon cancer, CRC; colorectal cancer, DFI; disease-free intervall, DFS; disease-free survival, NAD; no additional chemotherapy, NPV; negative predicitve value, OS; overall survival, RC; rectal cancer, PPV; positive predictive values, S; Study

Study populations

Study I included two partially overlapping cohorts comprising patients diagnosed with RC between 2009 and 2018 who underwent surgical resection and had undergone a preoperative MRI examination.

The first cohort included all patients with non-synchronous and non-metachronous RC who were preoperatively staged as cT1–T2 on MRI. The second cohort included all patients with pathologically confirmed pT1 RC. Exclusion criteria included the absence of preoperative MRI examination, neoadjuvant treatment (radiotherapy and/or chemotherapy), emergency resection, an interval greater than 1 year between MRI assessment and surgery, and missing information on T or N stage, including pNx.

Study II included non-synchronous pT1 CC patients diagnosed between January 2009 and March 2021 who underwent surgical intervention. Exclusion criteria included neoadjuvant treatment, metastatic disease at preoperative evaluation, appendiceal neoplasms, pedunculated tumours, inconsistencies between tumour location and resection method, and missing data for the aforementioned variables. Patients who were awaiting follow-up or were lost to follow-up were also excluded.

Study III included patients with non-synchronous pT1 RC diagnosed between January 2009 and December 2022 who underwent surgical intervention. Exclusion criteria included neoadjuvant treatment, distant metastases at preoperative evaluation, non-adenocarcinoma histology, endoscopic resection, unspecified local excision, inconsistencies between tumour location and resection method, and missing data for the aforementioned variables. In addition, patients who died within one year, had incomplete one-year follow-up (defined as follow-up <10 months postoperatively), or were awaiting or lost to follow-up were excluded.

Study IV included patients with pT1N+ CRC diagnosed between January 2009 and December 2022. Exclusion criteria included neoadjuvant treatment, distant metastases at preoperative evaluation, local resection or total colectomy, death within 30 days, missing data for the aforementioned variables, and patients who were awaiting or lost to follow-up.

Definitions of risk groups, risk factors and outcomes

Risk groups

Risk groups used in *Studies II and III* were defined according to the ESGE criteria for elevated risk of LNM in T1 CRC, including high histologic grade, deep submucosal invasion (Sm2–3), LVI, incomplete resection margins (R1/Rx) and tumour budding (Bd2–3) (66). Because information on tumour budding was not available in the SCRCR during the study period, LNM risk stratification was based on the remaining four factors. Low risk was defined as absence of all risk factors, whereas high risk was defined as presence of at least one risk factor.

High-risk features

High histologic grade

Deep submucosal invasion (Sm2–3)

Lymphovascular invasion

Incomplete resection margin (R1/Rx)

Table 5. Definitions of factors based on information in SCRCR, and definitions of time-to-event outcomes.

Variable	Label	Definition
Histologic grade	Low grade	High or medium differentiation. Glandular formation ≥ 50%
	High grade	Poorly or undifferentiated. Glandular formation of < 50%
Lymphovascular invasion	LVI	Tumour growth into lymphatic or venous vessels
Perineural invasion	PNI	Tumour growth into a nerve or in contact with more than 1/3 of the circumference of a nerve.
Mucinous tumour		Tumour consisting of at least 50% extracellular mucin containing malignant epithelium
Submucosal invasion	1	into the superficial 1/3 of the submucosa
	2	into the middle to 1/3 of the submucosa
	3	into the deepest 1/3 of the submucosa
Tumour stage	1	Tumour invasion into the submucosa
	2	Invasion into muscularis propria
	3	Invasion into subserosal fat or pericolic/perirectal tissue
	4	Invasion through the serosa and/or into adjacent organs
Nodal stage	N0	No spread of tumour to lymph nodes
	N+	Metastases to lymph nodes refers to tumour engagement of > 0.2mm. N+ is a pooled variable used in *Study IV* representing N1–N2.
	N1	1–3 LNM
	N2	4 or more LNM
	Nx	Regional lymph nodes not assessable
Resection margin	R0	Resection margin free of tumour cells
	R1	Tumour cells present at the resection margin
	Rx	Resection margin not assessable
Local recurrence		Recurrence in the anastomosis or adjacent tissue close to the location of the primary tumour and recurrence in corresponding mesocolic lymph nodes.
Distant recurrence		Distant recurrence diagnosed either histopathologically or radiologically verified
Disease-free survival	DFS	Event: Recurrence or death Time: surgical date → recurrence or death date Censored: at last follow-up
Overall survival	OS	Event: Death Time: surgical date → death date Censored: at last follow-up
Disease-free interval	DFI	Event: Recurrence Time: surgical date → recurrence date Censored: at last follow-up or death

Potential confounding factors and adjustments

In *Study I–II*, multivariable analyses were performed, and adjustments were made within these models. *Study I* investigated factors associated with the accuracy of T and N staging. The examined variables were selected based on clinical reasoning and included age at diagnosis, sex, time to surgery, year of surgery, use of additional EUS, and treatment centre volume.

In *Study II*, risk factors for recurrence in T1 CC were evaluated with type of resection as the primary variable of interest. Additional covariates included sex, histologic grade, LVI, mucinous histology, depth of submucosal invasion and tumour location.

In *Study III*, disease-free interval (DFI) was evaluated using an adjusted Cox proportional hazards regression model. Potential confounders included sex, age at diagnosis, American Society of Anaesthesiologists (ASA) class, LVI, PNI, mucinous subtype, depth of submucosal invasion, and resection margin status. ASA class was dichotomized into I–II and III–IV and resection margin into R0 vs R1/Rx. In the risk-group analyses, the clinical factors were used for adjustment.

In *Study IV*, the association of AC with disease-free survival (DFS), OS, and DFI was evaluated using adjusted analyses. Due to the small study population and low event frequency, a minimal adjustment set informed by a directed acyclic graph (DAG) was applied. The minimal sufficient adjustment set included sex, age at diagnosis, ASA class (dichotomized), reoperation, tumour location (colon/rectum), N stage (N1/N2), and year of surgery. Year of surgery was dichotomized according to the implementation of Enhanced Recovery After Colorectal Surgery (ERACS) in Sweden, with 2009–2013 representing pre/early implementation and 2014–2022 representing late implementation/consolidation (223-226).

Statistical analyses

In *Study I*, the R programming language and RStudio (R Core Team, 2020, R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses. In *Studies II–IV*, IBM SPSS versions 28.0 and 29.0 (SPSS Inc., Chicago, IL, USA) were used, and in addition, the R programming language and RStudio (version 4.4.2; R Core Team, 2024) were used in *Studies III and IV* (227, 228).

A p-value <0.05 was considered statistically significant, and 95% confidence intervals (CI) were used throughout all studies.

Descriptive statistics

Statistical methods used for qualitative descriptive analyses included Pearson's chi-square test, or Fisher's exact test when appropriate. The Freeman–Halton extension was applied for categorical variables with more than two levels. For comparison of continuous variables, the Mann–Whitney U test was used due to non-normal distributions.

MRI accuracy

In *Study I*, tumour stage accuracy in the cT1–2 cohort was assessed using the positive predictive value (PPV). Due to the lack of information on T3 and T4 stages, overall accuracy based on the standard formula could not be calculated. Nodal staging was evaluated using accuracy, sensitivity, specificity, PPV, and negative predictive value (NPV), together with positive and negative likelihood ratios (LR+, LR–) (Table 6).

Table 6. Description of formulas related to evaluation of accuracy.

	pN+	pN0
cN+	a	b
cN0	c	d
cNx	e	f

$$\boldsymbol{PPV = \frac{a}{a+b}}$$

$$\boldsymbol{NPV = \frac{d}{c+d}}$$

$$\boldsymbol{Sensitivity = \frac{a}{a+c+e}}$$

$$\boldsymbol{Specificity = \frac{d}{b+d+f}}$$

PPV, positive predictive value; NPV, negative predictive value; p, pathological stage; c, clinical stage as assessed by MRI in this thesis.

$$Accuracy = \text{sensitivity} * \text{prevalence} + \text{specificity} * (1 - \text{prevalence})$$

$$LR+ = \frac{Sensitivity}{1 - Specificity}$$

$$LR- = \frac{1 - Sensitivity}{Specificity}$$

Logistic regression

Univariable and multivariable logistic regression models were applied in *Studies I, III and IV*. The logistic regression analyses were performed to evaluate factors associated with MRI accuracy in *Study I*, to conduct risk-group analyses in *Study III,* and to assess predictors of no additional chemotherapy (NAD) in *Study IV*. The

assumptions underlying the logistic regression model were considered to be met for *Study I and IV*, including a binary outcome, independent observations, no indication of multicollinearity, and a sufficient number of events per variable (EPV). In S*tudy III*, the sufficient EPV was not considered met among patients with local recurrence in the low-risk group; therefore, further logistic regression analyses were not performed for this subgroup.

Survival analysis

Survival analyses were performed in *Studies II–IV*. In *Study II*, Kaplan–Meier analyses with accompanying number-at-risk tables were used to compare recurrence following endoscopic versus surgical resection. Three- and five-year DFI estimates were derived from the survival tables. Kaplan–Meier curves were visually assessed and compared using log-rank tests to evaluate differences in DFI in the overall cohort, as well as stratified by low- and high-risk groups. Cox proportional hazards regression was used to evaluate overall recurrence after endoscopic and surgical resection, with additional risk factors included in univariable and multivariable models.

In *Study III*, Kaplan–Meier analyses were applied to evaluate DFI according to surgical approach (TEM versus surgical resection) and the log-rank test was used to assess statistical differences. Cox proportional hazards regression analyses were performed in both unadjusted and adjusted models.

In *Study IV*, 5-year DFS, OS, and DFI were estimated for patients receiving AC and NAD respectively, using Kaplan–Meier analyses. Log-rank tests were used for statistical comparisons. In addition, unadjusted and adjusted Cox proportional hazards regression models were applied to evaluate the association between AC and DFS, as well as AC and OS. The minimal sufficient adjustment set was identified using a DAG (Figure 7). For DFI, due to the low number of recurrence events, bivariate adjusted models were used instead of multivariable models.

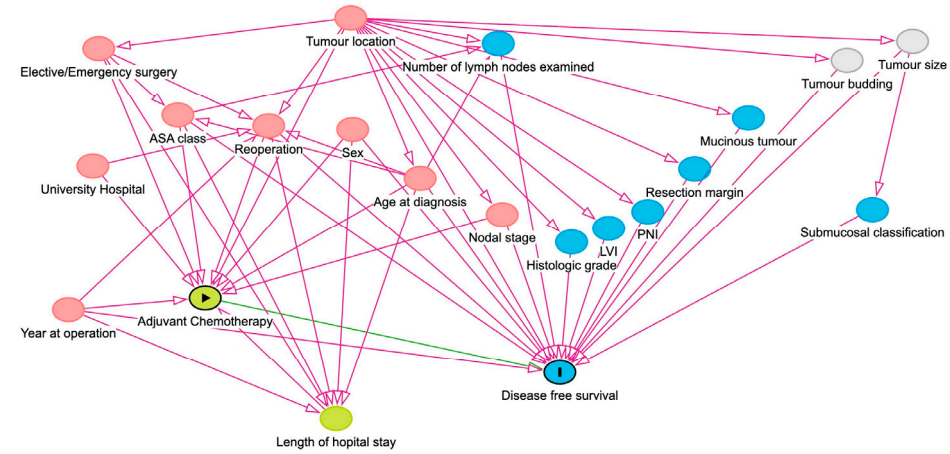


Figure 7. DAG showing the selection process of potential confounding factors in *Study IV*.

Handling of missing data

In *Studies II–IV*, missing data were handled using multiple imputation (MI). In *Study II*, MI was performed in IBM SPSS Statistics version 28 using the Mersenne Twister random number generator, with 20 imputations performed. Prior to imputation, patterns of missingness were visually assessed. The completed MI models were subsequently evaluated through inspection of post-imputation iteration tables.

In *Studies III and IV*, multiple imputation by chained equations (MICE) was performed in R. Pre-imputation analyses were conducted to evaluate patterns of missingness, correlations between variables, and the plausibility of the missing-at-random (MAR) assumption. All variables included in the hypothesis-testing analyses were also included in the imputation models. In addition, the Nelson–Aalen estimator was incorporated in accordance with recommendations for MI in time-to-event analyses (229). The maximum number of iterations was set to 100, and 50 imputations were generated.

Model diagnostics included inspection of caterpillar plots to assess convergence and density plots to evaluate the distributions of imputed versus observed values for each variable. Alternative MI models were constructed as sensitivity analyses to assess the robustness of the primary imputation model.

In all studies using MI, sensitivity analyses based on complete-case analyses were performed and are reported separately as supplementary tables accompanying each study.

Evaluation of statistical analysis and diagnostics

In *Study II*, the proportional hazards assumption was assessed visually using Kaplan–Meier curves and log–log survival plots for all variables included in the multivariable model.

In Studies III and IV, the proportional hazards assumption was evaluated using a combination of visual inspection of Kaplan–Meier curves, log–log survival plots, as well as formal testing with Schoenfeld residuals (individual, global, and pooled tests).

The study population in *Study IV* was relatively small (n = 222 patients) with 42 DFS events and 38 OS events. Therefore, a DAG was used to identify a minimal sufficient adjustment set. Seven potential confounders were identified, and additional analyses were performed to evaluate model robustness. Model stability was assessed using EPV, the global shrinkage factor (S), and a ridge-penalized Cox regression model. Diagnostics of the multivariable logistic regression model investigating factors predictive of NAD in *Study IV* included evaluation of multicollinearity using variance inflation factor (VIF), inspection of residual plots, and Hosmer–Lemeshow goodness-of-fit test.

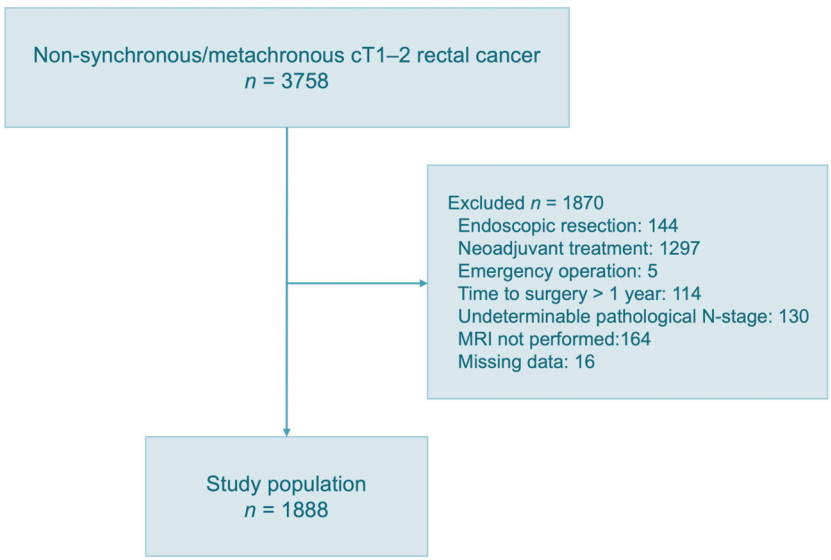
Main findings

Study I

Study cohorts

Patients who undergone surgical resection and were classified as cT1–2 during preoperative evaluation were identified in the SCRCR (2009–2018) and constituted the primary cohort. The secondary cohort consisted of patients with pT1 RC, during the same time period. Patient selection is presented in Figure 8a and b, respectively.

a)



b)

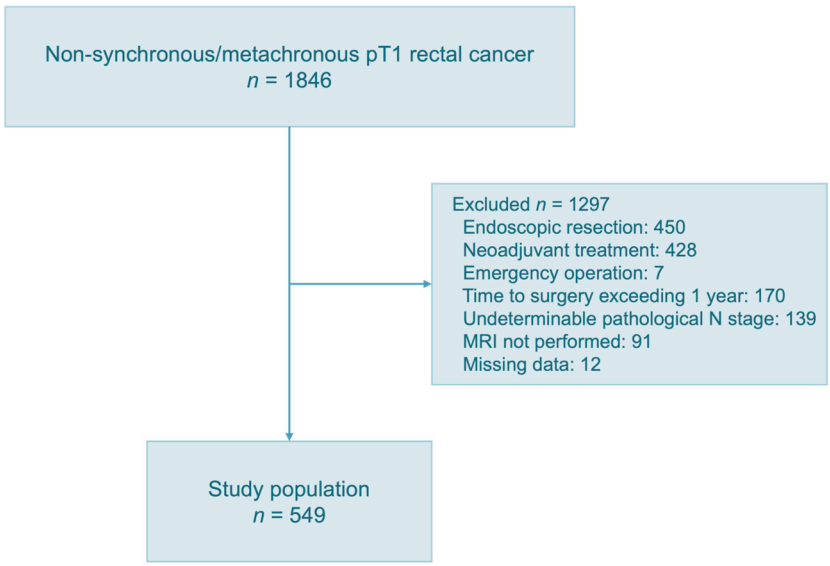


Figure 8a–b. Flowcharts illustrating patient selection for the first **(a)** and second **(b)** cohorts in *Study I*.

T and N stage accuracy in the cT1-2 cohort

In the cT1–2 cohort, MRI demonstrated a PPV of 67.8% for T-staging. Among the 1888 patients, 30% (n = 566) had pathological T3 disease and 2.2% (n = 41) pathological T4 disease. Diagnostic accuracy measures for lymph node staging are presented in Table 7. MRI incorrectly staged 74% (n = 354) of pN+ as cN0 and 56% (n =131) of tumours staged as cN+ did not have metastases in the pathological evaluation.

Table 7. The cT1–2 cohort showing nodal categorization according to pathological and clinical (MRI) evaluation. The **overall accuracy** for detection of LNM was **70.7%** (95% CI, 68.5–72.7).

	pN+	**pN0**
cN+	102	131
cN0	354	1232
cNx	21	48

$$\boldsymbol{PPV = 43.8\%\ (37.3 - 50.4)}$$
$$\boldsymbol{NPV = 77.7\%\ (75.5 - 79.7)}$$
$$\boldsymbol{Sensitivity = 21.4\%\ (17.8 - 25.5)}$$
$$\boldsymbol{Specificity = 87.3\%\ (85.5 - 89.0)}$$
$$\boldsymbol{LR+ = 1.69\ (1.35 - 2.10)}$$
$$\boldsymbol{LR- = 0.90\ (0.86 - 0.95)}$$

A total of 1,888 patients were included in the analysis. PPV, positive predictive value; NPV, negative predicitve value; LR+, positive likelihood ratio; LR–, negative likelihood ratio; p, pathological stage; c, clinical stage. A 95% CI i presenten parentheses.

Accuracy in the pT1 cohort

Of the 549 patients with pT1 RC, 123 (22.4%) were assigned a tumour stage different from cT1–2. The most common misclassification was as cT3 (n = 67), followed by cTx (n = 53) and cT4 (n = 3). Out of 63 patients with pN+ disease, MRI incorrectly classified 70% (n = 44) as cN0. Conversely, 70% (38/56) of the tumours classified as cN+ were pN0.

Patients eligible for local resection (cT1-2 N0)

Patients who, according to MRI, would be considered eligible for local resection (i.e., cT1–2 N0) numbered 1586. Of these, 41% (n = 653) were understaged. In the pT1 cohort, 29% (142/486) of pT1N0 were overstaged as either cN+ or cT3–4.

Factor associated with enhanced accuracy of MRI

Factors potentially affecting the accuracy of MRI in early RC was examined in a multivariable model (Table 8). Age at diagnosis, time to surgery, female sex, EUS use and the year 2016 were associated with MRI accuracy.

Table 8. Factors examined for association with increased accuracy of MRI cT1–2 staging.

		Univariable			Multivariable		
Variable		OR	95% CI	p-value	OR	95% CI	p-value
Age at diagnosis	Years	0.986	0.977–0.995	< 0.01	**0.986**	**0.977–0.995**	**<0.01**
Time to surgery	Days	1.003	1.000–1.006	< 0.05	**1.004**	**1.001–1.008**	**<0.01**
Sex	Male	1.00	Ref.		1.00	Ref	
	Female	1.41	1.16–1.72	< 0.001	**1.47**	**1.20–1.80**	**<0.001**
Year of surgery	2009	1.00	Ref.		1.00	Ref	
	2010	0.93	0.59–1.48	0.77	0.92	0.58–1.48	0.74
	2011	0.70	0.45–1.10	0.12	0.67	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	0.68–1.67	0.76	1.11	0.71–1.75	0.65
	2015	1.20	0.77–1.86	0.42	1.20	0.77–1.89	0.42
	2016	2.02	1.27–3.25	< 0.01	**2.23**	**1.39–3.60**	**< 0.001**
	2017	1.06	0.69–1.61	0.79	1.14	0.74–1.75	0.55
	2018	1.03	0.67–1.57	0.89	1.08	0.70–1.66	0.71
EUS use	No	1.00	Ref		1.00	Ref	
	Yes	2.79	1.38–6.42	< 0.01	**2.90**	**1.41–6.75**	**< 0.01**
Center volume	Low	1.00	Ref		1.00	Ref	
	High	0.91	0.69–1.19	0.49	0.80	0.60–1.05	0.11

High-volume centers: > 30 (median) cT1–2 cases per center.
Odds ration (OR) > 1: indicates increased accuracy.

Study II

Study cohort and patient characteristics

A total of 3586 patients with non-synchronous pT1 CC who had undergone either surgical or endoscopic resection were identified in the SCRCR (2009 – Mar 2021). After exclusions, 1805 patients remained (Figure 9), of whom 1317 had undergone surgical resection and 488 endoscopic resections. Local recurrence was more frequently observed after endoscopic resection than after surgical resection (1.6% vs. 0.5%), while distant recurrence rates were similar between the groups (3.1% and 3.1%). A larger portion of patients in the endoscopic group was categorised as indeterminate (46% vs. 12%). The surgical group had a higher proportion of patients with high-risk features compared to the endoscopic group (64% vs. 30%), while the proportion of patients classified as low-risk was similar between the groups. Moreover, among surgically resected patients, LNM was observed in 11.7% (n = 154), and 7.4% (n = 97) received AC. Tumour location also differed between the treatment groups: endoscopic resection was predominantly performed in the left colon (90%), whereas surgically resected patients showed a more even distribution between left (51%) and right colon.

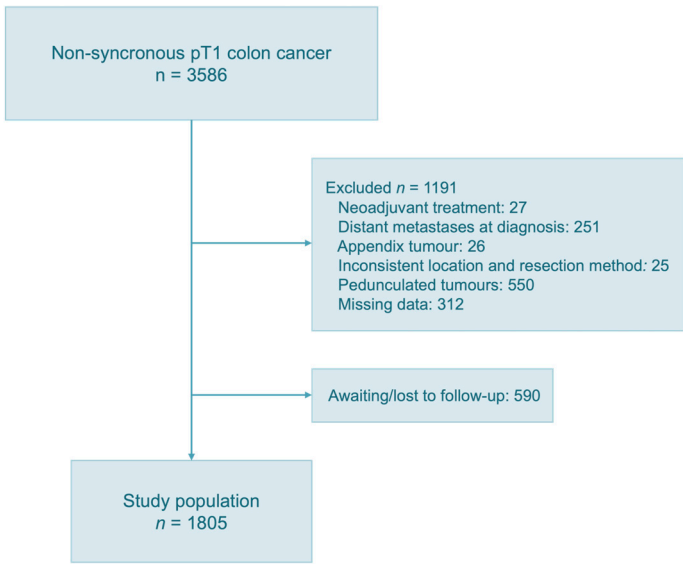


Figure 9. Flow chart illustrating patients selection in *Study II*.

Overall recurrence

Recurrence occurred in 3.6% of patients who underwent surgical resection and in 3.7% of those who underwent endoscopic resection. The 5-year DFI was 96.2% in the surgical group and 95.6% in the endoscopic group (Figure 10). No significant difference in DFI was observed in the adjusted Cox proportional hazard regression model (Hazard ratio (HR) 1.03, 95% CI 0.56–1.91; $p = 0.920$).

Figure 10. Kaplan–Meier curve with corresponding number-at-risk table showing recurrence over time among surgically and endoscopically resected patients. The *p*-value was derived from the log-rank test.

Recurrence across groups

No significant difference in recurrence rates was observed between surgical and endoscopic resection across risk groups (Table 9, Figure 11).

Table 9. Recurrence rates after surgical versus endoscopic resection, stratified by risk groups.

Risk group	Type of resection	Total *n*	Recurrence % (*n*)	p-value
Low-risk				
	Surgical	329	3.6 (12)	0.373
	Endoscopic	118	1.7 (2)	
High-risk				
	Surgical	836	3.8 (32)	0.370
	Endoscopic	148	5.4 (8)	
Indeterminate-risk				
	Surgical	152	2.6 (4)	0.768
	Endoscopic	222	3.6 (8)	

Low-risk: low grade, absence of LVI, Sm1 and R0-resected tumours.
High-risk: at least one of high grade, LVI, Sm > 1 or R1/Rx resection.
Indeterminate-risk: low-risk classification precluded due to missing data.

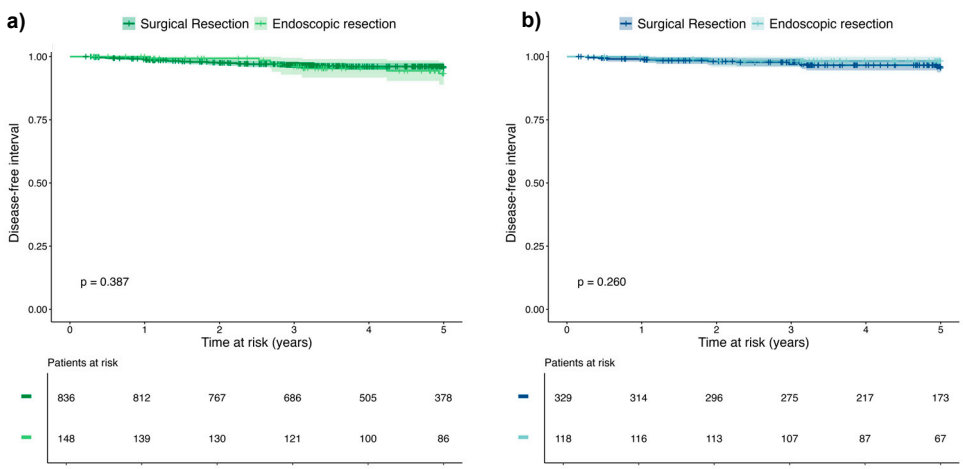


Figure 11a–b. Kaplan–Meier curves with corresponding number-at-risk tables, showing recurrence over time among surgically and endoscopically resected patients stratified by risk groups with **(a)** the low-risk group and **(b)** the high-risk group.

Risk factors for recurrence

In patients with tumours where LVI was present the recurrence rate was 10% compared to 3% if absent. For Sm1 recurrence occurred in 3.7%, in Sm2 3.8%, and Sm3 3.2%. High histologic grade was accompanied by 7.0 % recurrence whereas low grade patients experienced recurrence in 3.7% of cases. Patients with incomplete resection margin (R1/Rx) had recurrence in 5.3% of the cases and R0 in 3.6%. Moreover, if PNI was present 16.7% had recurrence compared to 3.3% if absent. In multivariable analysis, LVI was the only independent risk factor for recurrence in pT1 CC, whereas high histologic grade and deep submucosal invasion depth were not (Table 10).

Table 10. Multivariable Cox proportional hazards regression analysis of potential risk factors for recurrence.

Variable		Incidence*	HR	95% CI	p-value
Type of resection	Surgical	86	1.00	Ref.	
	Endoscopic	83	1.03	0.56–1.91	0.920
Sex	Male	75	1.00	Ref.	
	Female	95	1.26	0.77–2.07	0.352
Age at diagnosis	Years	-	1.00	0.98–1.03	0.762
Histologic grade	Low grade	84	1.00	Ref.	
	High grade	172	**1.37**	**0.59–3.15**	**0.464**
LVI	No	66	1.00	Ref.	
	Yes	251	**3.73**	**1.76–7.92**	**<0.001**
Mucinous tumour	No	82	1.00	Ref.	
	Yes	158	1.75	0.74–4.15	0.201
Submucosal invasion	Sm1	85	1.00	Ref.	
	Sm2	88	**1.06**	**0.56–2.04**	**0.853**
	Sm3	75	**0.89**	**0.46–1.71**	**0.721**
Tumour location	Right colon	87	1.00	Ref.	
	Left colon	83	1.07	0.62–1.85	0.802

*Number of recurrence per 10 000/years at risk.

Study III

Study cohort and patient characteristics

Information on surgically treated pT1 RC patients diagnosed between 2009 and 2022 was retrieved from the SCRCR. After exclusions, 859 patients constituted the final study population (Figure 12), of whom 631 underwent surgical resection and 228 were treated with TEM. Compared with patients undergoing surgical resection, those treated with TEM more frequently had low histologic grade, superficial submucosal invasion (Sm1) and R1/Rx resections. In addition, patients in the TEM group were older and more often classified as ASA III.

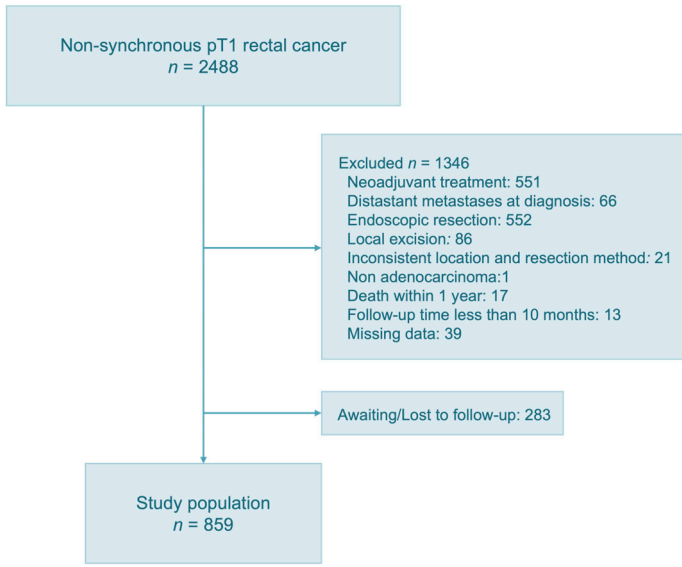


Figure 12. Flow chart illustrating patient selection in *Study III*.

Recurrence after surgical resection and TEM

Overall recurrence occurred in 11.0% (25/228) of patients treated with TEM and in 4.9% (31/631) of those treated with surgical resection. Local recurrence was more frequently observed after TEM than after surgical resection (7.5% vs 1.0%), whereas rates of distant recurrences were similar between the groups (4.4% vs 4.3%). Five-year DFI was 88% (95% CI, 83–93) after TEM and differed significantly from 95% (95% CI, 93–97) after surgical resection (Figure 13). The difference was confirmed in adjusted analyses (HR 2.83, 95% CI: 1.56–5.13; p = 0.001).

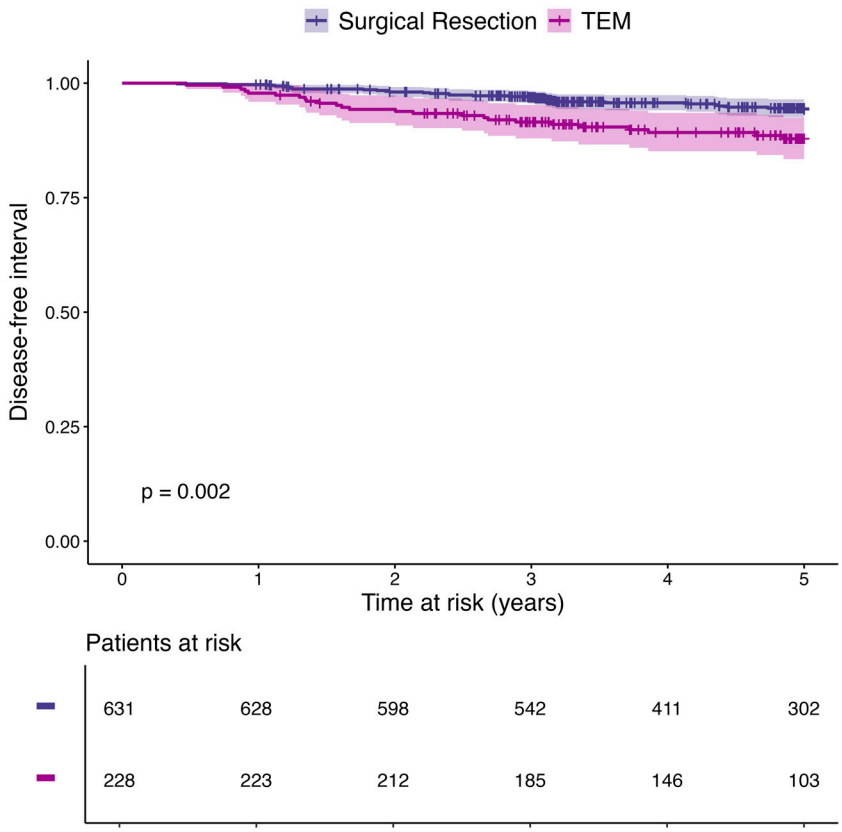


Figure 13. Kaplan–Meier curve with corresponding number-at-risk table showing recurrence over time in surgically resected and TEM-treated patients. The *p*-value was derived from the log-rank test.

Recurrences in risk groups

As shown in Table 11, patients undergoing TEM had higher local recurrence rates both in low- and high-risk groups compared to patients treated with surgical resection. No differences were observed between the groups with respect to distant recurrences. In addition, Kaplan–Meier curves with corresponding number-at-risk tables demonstrated similar findings (Figure 14).

When comparing low-risk and high-risk patients within the TEM group, no significant differences were observed in either overall recurrence rates (11.1% vs 11.8%) or local recurrence rates (8.3% vs 7.9%).

Table 11. Recurrence rates after surgical resection versus TEM, stratified by risk group and recurrence location.

Risk group	Type of resection	Total *n*	Recurrence % (*n*)	*p*-value
Overall recurrence				
Low-risk	Surgical resection	103	1.9 (2)	0.039
	TEM	36	11.1 (4)	
High-risk	Surgical resection	400	6.5 (26)	0.052
	TEM	127	11.8 (15)	
Indeterminate-risk	Surgical	128	2.3 (3)	0.063
	TEM	65	9.2 (6)	
Local recurrence				
Low-risk	Surgical resection	103	**0**	**0.016**
	TEM	36	**8.3 (3)**	
High-risk	Surgical resection	400	**1.3 (5)**	**<0.001**
	TEM	127	**7.9 (10)**	
Indeterminate-risk	Surgical resection	128	0.8 (1)	0.045
	TEM	65	6.2 (4)	
Distant recurrence				
Low-risk	Surgical resection	103	1.9 (2)	0.572
	TEM	36	5.6 (2)	
High-risk	Surgical resection	400	5.8 (23)	0.427
	TEM	127	3.9 (5)	
Indeterminate-risk	Surgical resection	128	1.6 (2)	0.337
	TEM	65	4.6 (3)	

Low-risk: low grade, absence of LVI, Sm1 and R0-resected tumours.
High-risk: at least one of high grade, LVI, Sm > 1 or R1/Rx.
Indeterminate-risk: low-risk classification precluded due to missing data.
In five patients recurrence occurred as both local and distant. These patients were therefore included in both in the local and distant recurrence group.

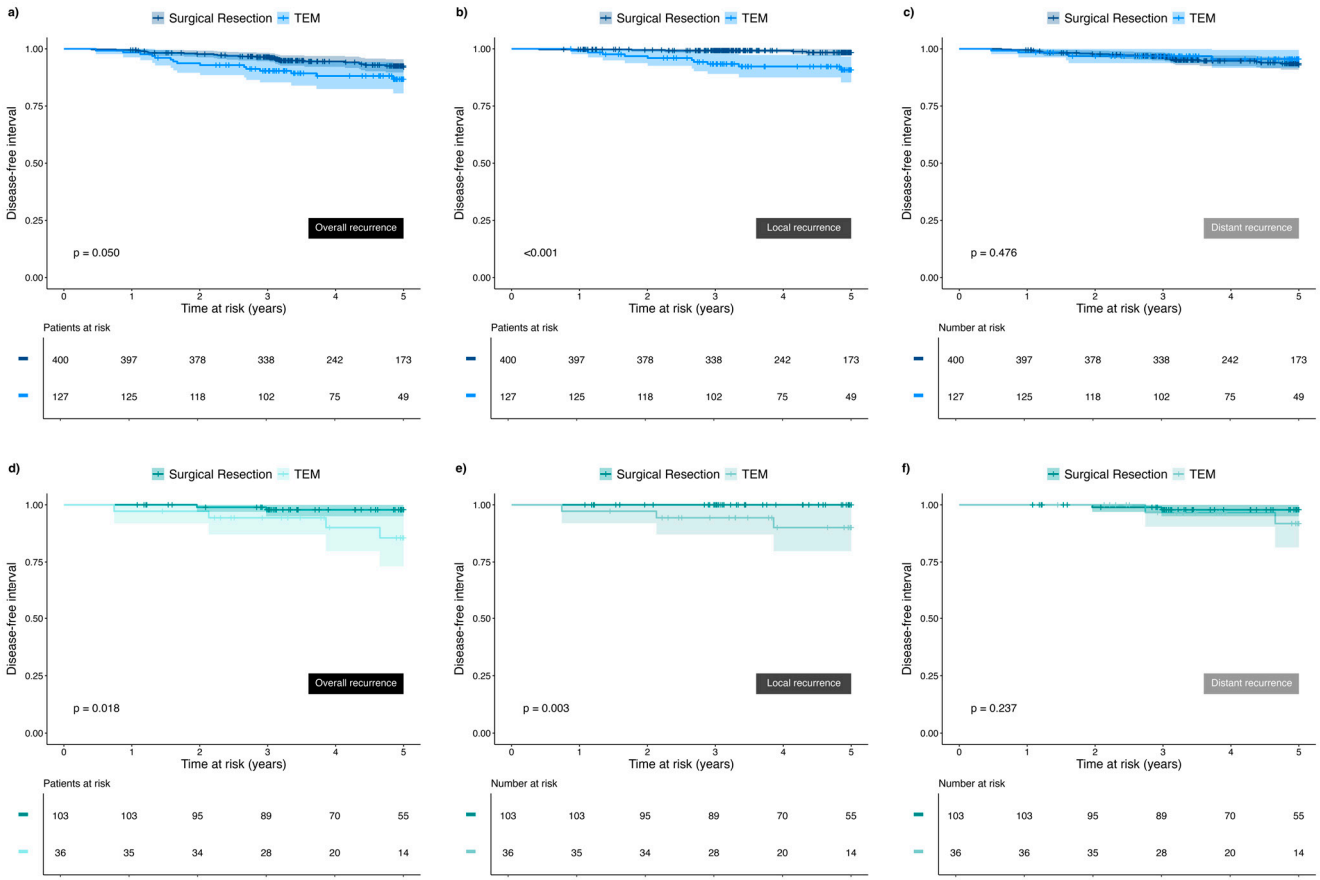


Figure 14a–f. Kaplan–Meier curves with corresponding number-at-risk tables showing recurrence after surgical resection versus TEM, stratified by risk group and recurrence location. Dark blue **(a–c)** represents the high-risk group and turquoise **(d–f)** the low-risk group. *P*-values were derived from the log-rank test.

Study IV

Study cohort and patient characteristics

Figure 15 illustrates the patient selection process with data derived from the SCRCR between 2009 and 2022. Of the 222 surgically treated pT1N+ CRC patients, 66% (n = 146) received AC. Patients treated with AC were younger, more frequently classified as ASA I–II, less likely to have undergone a reoperation, had a shorter length of hospital stay, and less often had tumours presenting with PNI or mucinous histology.

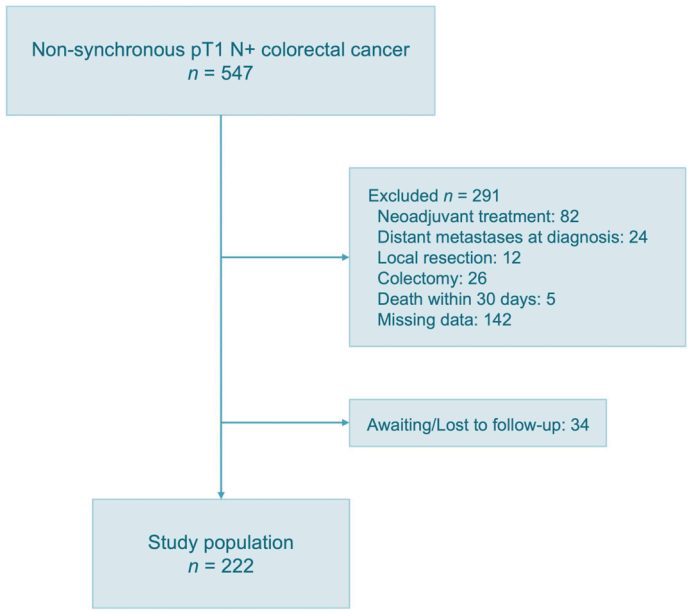


Figure 15. Flow chart illustrating patient selection in *Study IV*.

Recurrence and survival

The proportion of patients who received AC and experienced either recurrence or death was 9.6% (14/146), compared with 36.8% (28/76) among patients receiving NAD. DFS, OS, and DFI with corresponding number-at-risk tables and HRs are illustrated in Figure 16 a-c.

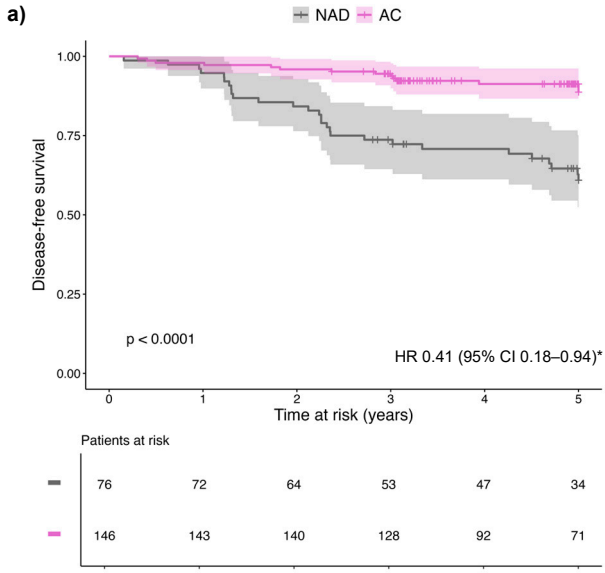


Figure 16a. Kaplan–Meier curve showing the effect of AC on **DFS**. The *p*-value was derived from the log-rank test. The HR estimate was adjusted for sex, age at diagnosis, ASA class, reoperation, tumour location, N stage, and year of surgery. An HR < 1 indicates a benefit of AC. The corresponding number-at-risk table is shown below the graph. Five-year DFS was 91% (95% CI 87–96) in patients receiving AC and 63% (95% CI 52–75) in those receiving NAD. * indicates statistical significance in adjusted analysis.

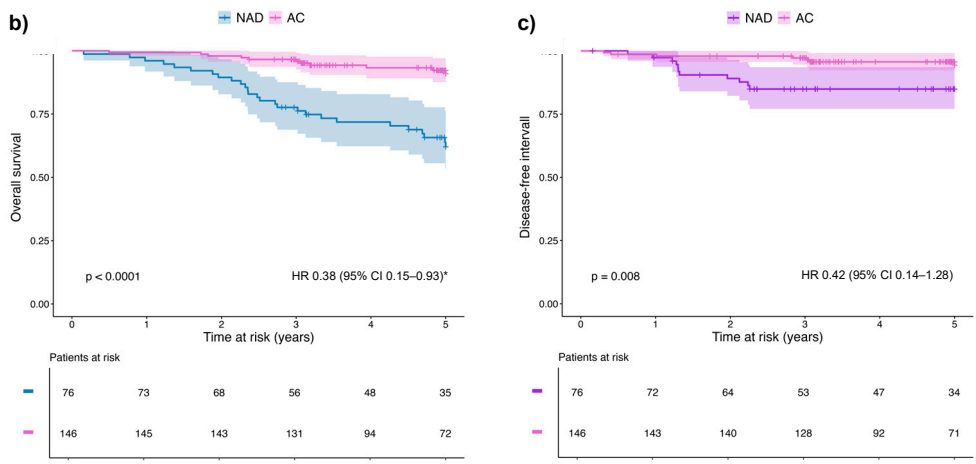


Figure 16b–c. Kaplan–Meier curves showing the effect of AC on **(b) OS** and **(c) DFI**. *P*-values were derived from the log-rank test; HR < 1 indicates a benefit of AC and corresponding number-at-risk tables are shown below the graphs. **(b)** Five-year **OS** was 92% (95% CI 88–97) versus 64% (95% CI 54–76) for AC and NAD. The HR estimate was adjusted for sex, age at diagnosis, ASA class, reoperation, tumour location, N stage, and year of surgery. **(c)** Five-year **DFI** 96% (95% CI 92–99) versus 85% (95% CI 77–94) for AC versus NAD, respectively. HR estimate was adjusted for the most influential confounder, i.e. age at diagnosis. * indicates statistical significance in adjusted analysis.

Factors associated with NAD

Table 12 illustrates that age at diagnosis, year of surgery, reoperation and length of hospital stay were independently associated with NAD in patients with pT1N+ CRC. ASA class III–IV was significantly associated with NAD in univariate analysis, but not in multivariable analysis.

Table 12. Univariable and multivariable logistic regression analyses showing associations between clinical and pathological factors and NAD.

		Univariable			Multivariable		
Variable		OR	95% CI	p-value	OR	95% CI	p-value
Sex	Male	1.00	Ref.		1.00	Ref.	
	Female	1.14	0.66–1.99	0.640	1.07	0.51–2.27	0.851
Age at diagnosis	Years	1.13	1.08–1.17	<0.0001	**1.13**	**1.08–1.18**	**<0.0001**
ASA	I–II	1.00	Ref.		1.00	Ref.	
	III–IV	3.12	1.60–6.10	<0.001	**2.29**	**0.98–5.37**	**0.058**
Year of surgery	2009–2013	1.00	Ref.		1.00	Ref.	
	2014–2022	0.34	1.19–0.60	<0.001	**0.39**	**0.18–0.81**	**0.013**
Reoperation	No	1.00	Ref.		1.00	Ref.	
	Yes	5.82	1.99–17.02	0.001	**5.42**	**1.13–26.05**	**0.036**
University hospital	No	1.00	Ref.		1.00	Ref.	
	Yes	0.79	0.41–1.52	0.481	0.72	0.30–1.72	0.454
LOS	(days)	1.15	1.08–1.23	<0.0001	**1.08**	**1.00–1.18**	**0.048**
Tumour location	Colon	1.00	Ref.		1.00	Ref.	
	Rectum	0.86	0.45–1.59	0.624	1.01	0.43–2.37	0.978
Resection margin	R0	1.00	Ref.		1.00	Ref.	
	R1/Rx	1.07	0.25–4.60	0.923	1.28	0.20–8.27	0.794
N stage	N1	1.00	Ref.		1.00		
	N2	1.11	0.44–2.77	0.825	0.82	0.25–2.71	0.748

$p < 0.05$ was considered significant. **OR > 1: association with NAD.**

Oh it's healing……..

The Cardigans, 2003

Discussion

Methodological consideration and overall limitations

The design of all four studies included in this thesis was observational, with data retrieved from the SCRCR, a nation-wide registry that has been validated on multiple occasions and show to have a high degree of completeness (215-219).

Population-based cancer registries provide a unique opportunity to study rare diseases and uncommon clinical events. Given that all studies in this thesis focus on pT1 CRC, which represents the rarest T stage and is associated with the lowest recurrence rate, nationwide coverage enables investigation of recurrence patterns and long-term outcomes at a scale that would be difficult to achieve in a prospective randomized setting. Considering the aim of *Study IV*, a prospective randomized trial would not be ethically justifiable, given the existing evidence supporting the superiority of AC compared with NAD in stage III disease overall, further underscoring the value of registry-based design.

The registry provides prospectively collected follow-up data and baseline characteristics of the patients, which has enabled investigation of recurrence and adjustment for baseline characteristics, thereby improving the reliability of the estimates. A recent validation study by Arnarson et al. (2024) demonstrated agreement of overall recurrence registration of 95.7%, with a Cohen´s kappa coefficient of 0.86, indicating excellent agreement. In contrast, agreement was moderate when assessing location of first identified recurrence, local or distant (219). Moderate agreement was also observed for the recorded dates for local and distant recurrence; however, the correlation was strong (r = 0.9). As time to recurrence was used in *Study II– IV*, these findings are of importance and needs to be considered. Nevertheless, because follow-up was analysed over years rather than months or weeks, it is unlikely that minor discrepancies in recurrence dating substantially affected the findings of this thesis. Moreover, 98% of patients were registered in the SCRCR within one year of diagnosis (219). Although, the timeliness of follow-up data registration was not a specifically evaluated in the latest validation study, it is plausible that registrations may have been affected by the COVID-19 pandemic.

Confounders

To examine associations between treatment and outcome, simple univariate models may be used. However, to establish an independent association, potential confounding must be considered. Without appropriate adjustment, confounding factors may distort the association between exposure and outcome. Confounding can mask or attenuate a true association, exaggerate an effect or even generate a spurious association. The selecting of valid confounders therefore requires both methodological stringency and research field specific knowledge. Moreover, the inclusion of important confounding variables must be balanced against the risk of overadjustment, which may increase variance and obscure a true association.

Because recurrence is rare in T1 CRC, careful consideration of the number of confounders and model stability has been central throughout this thesis. Confounder selection was guided by both clinical reasoning and statistical considerations. Exemplified by *Study IV*, where limited number of events necessitated a parsimonious modelling strategy; therefore, a DAG was used to identify a minimal sufficient adjustment set. Owing to the low number of events (~ 40), specific model diagnostics were applied to evaluate model stability. The models were considered stable despite low EPV ratios. Nevertheless, unmeasured confounding can never be fully excluded, and some degree of residual bias may persist even after adjustment. Figure 17 illustrates the definition of a confounding factor using a DAG (230).

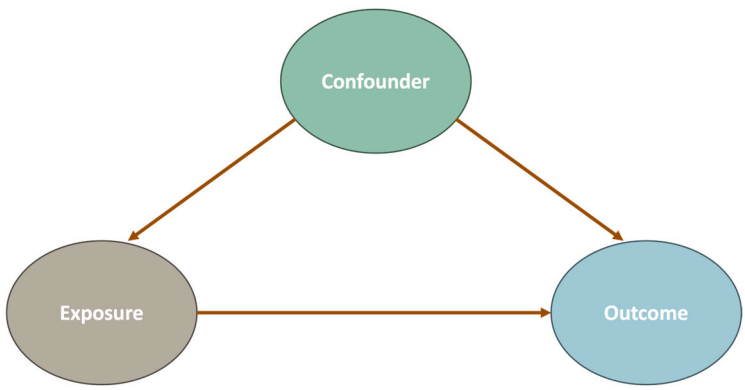


Figure 17. Directed acyclic graph illustrating a confounding relationship, in which a confounder is a cause of both the exposure and the outcome.

Missingness and multiple imputation

Studies based on registry data are frequently challenged by missingness in one or several variables, which was most evident in *Studies II and III* of this thesis. When missingness is spread throughout covariates, complete-case analyses may lead to exclusion of a substantial proportion of the dataset, potentially introducing bias into

the estimates. Historically, complete-case analysis was considered the most transparent approach to handling missing data. However, perspectives on missing data handling in medical research have evolved, based on methodological studies examining missingness mechanisms and associated biases.

The literature suggests that complete-case analysis and MI perform similarly under a missing-completely-at-random (MCAR) mechanism (231). In contrast, under the the missing-at-random (MAR) assumption, which is more common in medical research, MI generally introduces less bias and yield smaller average errors and show better 95% coverage probabilities than complete-case analyses (231). MI was introduced by Rubin et al. in 1987, with an accessible overview published in 1988 (232) describing a robust imputation framework that has since been further developed and refined. This work has resulted in several published practical guidelines, aimed at improving accessibility and application within the research community (229, 233-235). Alongside technical advances and software development, MI has become a widely available and used tool. Appropriate use of MI requires careful pre-imputational assessments as well as explicit consideration of underlying assumptions prior to model specification.

MI was applied in *Studies II– IV*. Pre-imputational discussion and assessment were conducted to identify factors predictive of missingness. Considering MCAR is exceedingly rare in clinical settings, this was not assumed. To assess plausibility of missing-not-at-random (MNAR) mechanisms, missingness pattern matrices were examined, revealing no evidence suggestive of MNAR, such as clustering of missingness by outcome, or systematic horizontal or vertical patterns indicating missingness within specific subgroups. Nevertheless, MNAR can never be fully excluded; therefore, caution was exercised throughout the imputation processes and sensitivity analyses of the MI model was performed.

Identification of observed variables that predict missingness is essential for the MAR assumption to be plausible. In *Study III*, three auxiliary variables and several covariates already planned for inclusion in the primary analyses were identified as predictors of missingness. In contrast, in *Study IV* only one auxiliary variable was identified; however, five variables already planned for inclusion in analyses addressing the study aims were predictive of missingness, which was considered satisfactory.

In addition, the pre-imputation assessment included evaluation of factors associated with observed values in variables affected by missingness. As proposed in the literature, all variables planned for primary analyses, including outcome, time-to-event variables and the Nelson–Aalen estimate (229, 235) were included in the imputation models to reduce bias in *Studies III and IV*. These analyses were performed in R.

In *Study II*, IBM SPSS was used, which limited the inclusion of the Nelson–Aalen estimate and restricted the extent of diagnostic evaluation. Nevertheless, visual

diagnostics of imputed datasets could be performed in *Study II*, whereas MI models in *Study III and IV* were evaluated more comprehensively. When comparing results from the multivariable imputed Cox proportional hazards regression model in *Study II* with sensitivity complete-case analyses, indications of reduced bias and increased statistical power were observed, supporting the validity of the MI model.

Model evaluation and diagnostics

Most statistical models are based on specific assumptions. For Cox proportional hazards regression, the assumption of proportional hazards is central. Throughout this thesis (*Studies II-IV*), proportionality was assessed visually using Kaplan–Meier curves and log–log plots, and, in the latter two studies, complemented by tests based on Schoenfeld residuals.

Visual assessment provides an opportunity to detect violations of proportionality and to explore their magnitude and timing; however, interpretation may vary between observers. In contrast, the Schoenfeld residual test is objective, detects whether the effects of covariates change over time and offers a formal statistical evaluation with an associated *p*-value (236). As these methods have complementary strengths, the use of both is preferred.

Although *Study II* relied solely on visual assessment, this was considered appropriate as no borderline or ambiguous indications of non-proportionality were observed.

Violations of the proportional hazards assumption were observed on a few occasions throughout this thesis. In *Study II*, violations were identified for PNI and resection margin; in *Study III*, for histologic grade; and in *Study IV*, for tumour location, exclusively in the DFI-model. As these variables were included as covariates for confounding adjustment and were not primary variables of interest, and as the violations were mainly driven by sparse events within specific subgroups, exclusion of these covariates was considered an appropriate approach to avoid model instability and misspecification.

In *Study IV*, the DFS model had an EPV of 5.25 and $S \approx 0.82$, while the OS model had an EPV of 4.75 and $S \approx 0.84$. Although the EPVs were borderline, the shrinkage factors indicated an acceptable risk of overfitting. In ridge-penalized Cox regression, effect estimates and 95% CIs were similar to those in the primary models, suggesting a low risk of overfitting.

For the logistic regression model examining factors associated with NAD, ten randomly selected imputed datasets were evaluated for multicollinearity and model fit. VIFs were all below 1.32, indicating a low risk of multicollinearity. Inspection of residual plots revealed a few outliers; however, Hosmer-Lemeshow goodness-of-

fit tests yielded *p*-values ranging from 0.21 to 0.56, indicating no evidence of poor model fit.

Study specific limitations and considerations

The studies included in this thesis have limitations that should be considered when interpreting the results. Limitations of *Study I* includes T-stage accuracy described using the PPV rather than a full accuracy measure, as data derived from the SCRCR were limited to cT1–2 and pT1 cases. However, as previous studies report PPVs as an accuracy metric, comparisons with existing literature were still feasible. Moreover, by excluding patients undergoing local resection, a bias negatively impacting the T-stage accuracy may potentially have been introduced. Potential overstaging of benign lesions could not be examined, as the SCRCR registers only malignant lesions. In addition, the lack of information on MRI protocols and equipment, factors that could potentially affect the results, constitutes another limitation.

An overarching limitation of *Studies II and III* was the lack of information on tumour size and tumour budding. Tumour budding is included in the ESGE guidelines for the classification into high- and low-risk T1 CRC (66), as it has been shown to be an independent predictor of LNM (113). Tumour budding has been associated with other unfavourable tumour features like histologic grade, lymphatic, venous and perineural invasion, suggesting the impact of the findings in this thesis is modest. However, one study has found Bd2/3 to be associated with recurrence in pT1CRC after adjustment of venous invasion and tumour location, why selection bias cannot be discarded. A potential bias may have masked true high-risk cases as low-risk. Whether size independently affect recurrence risk is not settled (54, 109, 127-129). However, tumour size may predict local recurrence in T1 RC following TEM (129) and is also used as a factor allocating patients to different treatment strategies depending on technical limitations in TEM technique.

In the context of *Study III*, a likely scenario is that larger tumours were present among patients undergoing surgical resection compared with those treated with TEM (129), which may have introduced selection bias, if larger tumour size was independently associated with recurrence. If such a bias was present, the true difference in recurrence between TEM and surgical resection would likely be even greater than suggested by the present findings, had tumour size been adjusted for.

In contrast, in *Study II*, potentially smaller tumours in the endoscopically treated group may have introduced selection bias between endoscopic and surgical resection, thereby masking a true difference in recurrence rates. However, as tumour size does not appear to be a strong independent risk factor for recurrence in early CRC according to prior literature, the impact of such a bias is considered minor. Moreover, ASA class could not be considered because of missing information,

primarily in the endoscopic group. As ASA class may influence treatment choice, selection bias cannot be ruled out. However, a large impact of ASA on recurrence is less probable. Finally, a high proportion of indeterminate assessments was observed in the endoscopic group, which may reflect specimen quality and potential piecemeal resections. Information on en bloc/piecemeal resections is not recorded in the SCRCR and constitutes a limitation. Piecemeal resections may have contributed to higher recurrence rates in the endoscopic group, compared with those that might have been observed if only en bloc resections had been performed.

The main limitation of *Study IV* was the rarity of the specific cancer stage T1N+ and the low number of recurrence events. Information on AC type and duration was not available, which may have influenced the outcomes.

Baseline characteristics differed between AC and NAD groups as anticipated when drawing the study design. The primary analytic plan was to use propensity score matching to compare the groups. However, the study population demonstrated insufficient covariate overlap to allow reliable proper propensity score modelling. Consequently, a Cox proportional hazards regression model with a minimally sufficient adjustment set, was applied.

Propensity score matching is based on a score derived from variables associated with the exposure (treatment) (237). The literature describes that careful evaluation of overlap is crucial to avoid introducing bias into the effect estimates (238) and that traditional regression methods perform comparably to propensity score approaches (238, 239). Furthermore, propensity score methods do not appear to reduce residual confounding compared with conventional regression adjustments (237).

Taken together, propensity score methods may be useful in specific circumstances and should be chosen based on the characteristics of the study population. Based on the considerations above, conventional regression methods were considered the most appropriate analytic approach for *Study IV*.

Main findings of this thesis

The main findings of this thesis include insufficient accuracy of preoperative MRI for both T and N staging in early RC. Moreover, no differences in recurrence rates were observed between endoscopic and surgical resection for pT1 CC in either low- or high-risk groups, whereas LVI was identified as a strong independent risk factor for recurrence. In pT1 RC, TEM was associated with higher local recurrence rates compared with surgical resection in both low- and high-risk groups. Finally, AC was associated with improved DFS and OS in pT1N+ CRC, and older age at diagnosis, reoperation, and longer hospital stay were independently associated with NAD.

The findings presented address clinically important aspects of pT1 CRC and contribute to ongoing efforts to provide individualized care for patients with early CRC. The relevance of studying this patient group is increasing globally as screening programs expand. In Sweden, CRC screening was introduced relatively recently and is currently being implemented. Consequently, the anticipated stage shift has not yet been fully observed, with an increased proportion of patients diagnosed with pT1 CRC is still expected.

MRI staging accuracy of early rectal cancer

Preoperative staging using MRI is standard practice and has historically been used primarily to allocate patients with advanced CRC to neoadjuvant treatment (72, 73, 240). *Study I* aimed to investigate whether MRI was sufficiently accurate for identifying patients with early RC who are suitable for local resection. Local resection is an attractive treatment option, as it is associated with fewer complications, lower morbidity, and lower perioperative mortality compared with surgical resection (149-153, 241). However, this benefit needs to be weighed against the risk of leaving concomitant LNM, which may be followed by worse long-term prognosis.

The accuracy of T stage assessment in the main cT1–2 cohort was reflected by a PPV of 68%. In the existing literature, studies report PPV estimates that vary widely, ranging from 20% to 67% for cT1 and from 38% to 59% for cT2 disease (72, 73, 76). The PPV of *Study I* lays in the upper range, however, was expected to perform better compared with the existing findings due to categorization of cT1 and cT2 as a single category. The observed variation in reported PPV estimates in the literature may, at least in part, be explained by the small study sizes.

In *Study I*, more than 30% of patients who were preoperatively classified as cT1-T2 were found to have more advanced pathological T stage, consistent with findings by Detering et al. (80). Understaging may partly be attributed to invasion extended minimally beyond the muscularis propria, which could be difficult to discriminate on MRI. Potential clinical consequences of understagning may include aborted local treatment attempts that prolongs time to definitive treatment and in some cases incomplete local resections, potentially leading to a worse prognosis.

Overstaging of pT1 tumours as cT3 or cT4 was observed in 13% of patients, in line with previous reports (80). Consequently, overstaging of tumour invasion depth may incorrectly exclude patients with pT1 RC from treatment with local resection. Tumour growth patterns, such as invasion close to the deep border of the muscularis propria, as well as reactive changes in connective tissue surrounding the primary tumour including hypervascularity, inflammatory cell aggregates, desmoplastic reactions and malignant fibrosis, may complicate image interpretation and discriminating T2 from T3, and contribute to overstaging (57, 77, 78). In addition,

the MRI imaging plane is crucial for accurate T staging, as tumour delineation must be adequately represented to ensure correct interpretation (77).

Interestingly, approximately 10% of tumours in the pT1 cohort were inaccurately staged as cTx. If cTx classification primarily reflects difficulties in discriminating benign lesions from early RC (pT1–T2), this category could potentially assist in allocating patients to initial local resection. However, if cTx is applied mainly due to challenges in distinguishing between cT2 and cT3 disease, it would not be useful for this purpose. This distinction may be of relevance for future studies.

The addition of EUS to MRI was one of the factors associated with improved T-stage accuracy in this study, confirming findings from a previous study (80). However, the use of EUS was limited, and broader conclusions cannot be drawn. Female sex was another factor that appeared to have a small to moderate (OR 1.47) effect on T-stage accuracy. To our knowledge, this has not been reported previously (57, 242).

Accurate N-stage assessment is considered essential for the safe allocation of patients to local resection (243), as erroneous classification may result in undetected concomitant LNM. Notably in *Study I*, nearly 75% (354/477) of patients with pN+ disease were incorrectly classified as cN0, and more than half of patients classified as cN+ (131/233) did not have LNM. These findings correspond to an overall accuracy of 70%, which lies within the wide range previously reported in the literature (55–84%) (76, 79, 80, 85, 244).

Variability in reported accuracy may reflect variations in reader experience. However, in this study, centre volume of MRI examinations did not affect N-stage accuracy. Moreover, the criteria used to identify LNM on MRI are not optimal and producing guidelines remain challenging (63, 75). Current assessment relies on lymph node size, in combination with morphological features such as irregular borders, round shape (increased short-axis diameter) and heterogeneous signal intensity (63, 245). Achieving an acceptable balance between sensitivity and specificity appears difficult (245), and previous studies have shown that a substantial proportion of LNM measure less than 5 mm, further complicating assessment (86, 87).

Finally, for patients to be allocated to local resection, MRI evaluation should indicate cT1–2N0 disease. Notably, only 59% of patients classified as cT1–2N0 were correctly staged, and 29% of patients with pT1N0 disease were overstaged as either cT3–4 or cN+, thereby hampering allocation to local resection and potentially excluding a large proportion of patients from this less invasive treatment.

Local compared to surgical resection and risk factors for recurrence

Recurrence rates after local and surgical resection across risk-groups were the primary outcomes of *Studies II and III*. The two studies investigated CC and RC separately, as research has suggested that recurrence rates differ according to tumour location (colon/rectum) (111, 127, 246). The main finding of *Study II* was an overall low recurrence rate in T1 CC, with no difference in recurrence rates between surgical and endoscopic resection, even across risk-groups. Although, LVI was identified as a strong independent risk factor for recurrence. In contrast, *Study III* demonstrated that TEM was associated with significantly higher local recurrence rates, even among low-risk patients.

Local resection in pT1 CRC represents an alternative to standard surgical resection. It has been associated with fewer complications, shorter hospital stays, and lower costs for endoscopic local resection technique (149-153, 241, 247-249). Moreover, local resection may be a suitable option for older or comorbid patients with increased surgical risk. However, these advantages must be weighed against the risk of recurrent disease.

To the best of our knowledge, *Study II* was the first study to exclusively investigate recurrence rates after endoscopic and surgical resection in T1 CC across risk groups defined according to current guidelines. Overall, the recurrence rates in both the surgical and endoscopic groups were low (3.6% vs 3.7%), in line with earlier studies (166, 250).

Interestingly, when applying ESGE criteria based on LNM risk, recurrence rates remained low even in the high-risk group, with no statistically significant difference in recurrence rates between surgical and endoscopic resection (3.8% vs 5.4%). This represents an important and novel finding. As relatively few studies have reported outcomes separately for CC and RC, comparisons with existing literature are limited. Nevertheless, Ikematsu et al. reported low recurrence rates in both endoscopically and surgically resected high-risk CC patients (1.4% vs 1.9%) (123), consistent with the findings of *Study II*, although those recurrence rates were somewhat lower in comparison. When CRC is investigated as a single entity, high-risk T1 disease typically demonstrates higher recurrence rates following endoscopic compared with surgical resection (105, 107, 251, 252). The findings from *Study II* therefore suggest that pT1 CC may exhibit a recurrence pattern different from that of pT1 RC.

LVI is an established risk factor for concurrent LNM and is included in the ESGE risk classification (243). In *Study II*, LVI was identified as a strong independent risk factor for recurrence (HR 3.73, 95% CI 1.76–7.92) in line with prior studies (105, 246, 253). Notably, recurrence occurred in 10% of cases when LVI was present, compared with 3% if absent.

In contrast, submucosal invasion, another factor included in the ESGE risk categories, was not identified as a risk factor for recurrence in pT1 CC, in line with earlier studies (54, 107, 111, 112). Notably, recurrence rates were nearly identical across Sm1–Sm3 categories. Although depth of submucosal invasion has traditionally been central to risk stratification in pT1 CRC, evidence questioning its independent prognostic value for LNM is growing (52, 53), supporting the findings of *Study II*. As a consequence of these prior studies, the updated ESGE guidelines for RC, suggests that when deep submucosal invasion is the only risk factor present, subsequent surgery is not strongly recommended, and surveillance and/or CRT may be preferred (66).

PNI is a potential risk factor for recurrence, rarely present in pT1 CRC. In this thesis, PNI was observed in 0.2 % of the CC patients in *Study II*, in 2 % of the RC patients in *Study III* and in 8% of the patients with pT1N+ CRC in *Study IV*. Although direct statistical comparison between the studies is not feasible, PNI appears less common in CC than in RC, and most frequent in the presence of LNM. Due to violation of the proportional hazards' assumption based on the rare occurrence, PNI was not included in the risk factor analyses in *Study II*. Notably, recurrence occurred in nearly 17% of cases when PNI was present, compared with 3% when PNI was absent. PNI has previously been associated with reduced survival and increased recurrence rates in CRC across T stages (131, 132, 254-256). Furthermore, one of these studies reported that PNI was associated with reduced recurrence-free survival despite neoadjuvant oncological treatment, reinforcing its role as a marker of poor prognosis (256).

In *Study III*, local recurrence was observed significantly more often following TEM compared with surgical resection, consistent with prior reports (159, 160, 163, 177). When stratified by risk group, local recurrence rates remained significantly higher after TEM than after surgery in both high-risk patients (7.9% vs. 1%) and, notably, also in the low-risk group (8.3% vs. 0%). To the best of our knowledge, this is the first study to compare local recurrence between TEM and surgical resection while accounting for ESGE-defined risk groups.

Furthermore, local recurrence rates following TEM are strikingly similar in low- and high-risk groups, and no statistically significant difference between patients was observed. These findings are of particular importance, as current guidelines recommend subsequent surgery for high-risk patients, whereas low-risk patients are generally considered cured after TEM. Studies investigating TEM separately have reported conflicting results regarding recurrence rates in high and low-risk groups. One study reported similar recurrence rates across risk groups (129), whereas others have demonstrated differences in recurrence rates (179, 257, 258). In addition, a wide range of local recurrence rates has been reported among patients with low-risk tumours (4.3–30%) (129, 179, 257, 258), which may reflect limited statistical power and variability in the criteria used to identify risk groups, making comparisons difficult.

In total, almost one fifth of the resections were considered incomplete after TEM in *Study III*. This rate is consistent with previous reports and is a well-recognized limitation of TEM (171, 173, 257, 259, 260). Notably, even low-risk patients (R0 resections only) experienced considerably higher local recurrence rates, suggesting that additional mechanisms beyond margin status contribute to local failure.

Potential explanations may relate to the TEM-specific technique, in which full-thickness rectal wall resections are frequently performed. One possible explanation is the displacement of free tumour cells during the TEM procedure, with subsequent reimplantation into adjacent tissues. In the case of full-thickness resections, this may involve pelvic tissues, thereby increasing the risk of local recurrence. Undetected concomitant LNM may also contribute to local recurrence, although this explanation is less likely in the low-risk group.

Supporting the findings of *Study III*, a recent study by Wetterholm et al. reported local recurrence rates as high as 32% following TEM for pT2 RC (261), reinforcing the association between TEM and elevated local recurrence rates in early RC. In cases of local recurrence, salvage surgery is often achieved with R0 resection (195). However, patients who experience local recurrence after RC have been shown to have reduced quality of life and decreased survival (168-170), which is important to consider when recommending treatment to this patients group.

Overall recurrence was more common after TEM than after surgical resection (11% vs 5%) with a HR of 2.8, indicating a substantial increase in recurrence risk. This finding is supported by meta-analyses (159, 163). In contrast, no difference in distant recurrence rates was observed between TEM and surgical resection, consistent with earlier reports (159, 163, 177).

Adjuvant chemotherapy in pT1N+ colorectal cancer

T1N+ CRC represents a small proportion of all stage III CRC cases and is underrepresented in the clinical trials that provide evidence for current treatment guidelines (202, 205, 262). In *Study IV*, only 66% of patients with pT1N+ disease received AC, a proportion that falls within the range previously reported for T1–T2N+ CRC (53% –71%) (213, 263). In contrast, treatment rates among unselected stage III CRC populations (T1–4N+) appear to be approximately 10 percentage points higher than those observed in the present study (264, 265).

As studies focusing specifically on pT1N+ cancer are rare, this is, to the best of our knowledge, the first population-based registry study to compare DFS between patients treated with AC and those receiving NAD. Patients with NAD experienced recurrence or died almost four times more often than patients treated with AC (36.8% vs. 9.6%). After adjustment for potential confounders, AC remained associated with significantly improved DFS (HR 0.41). In contrast, a recent study examining relapse-free survival in unselected stage III CRC (pT1–T4) reported no

significant difference between AC and NAD in early CRC subgroup analyses (263), contrasting with the findings in *Study IV*. However, in that study, pT1 and pT2 tumours were analysed as a single group (pT1–T2), with additional stratification by N stage (N1–N2), which may have reduced the statistical power to detect a true difference. Moreover, the combination of T stages precludes direct comparison with the findings of *Study IV*.

In line with two previous studies on pT1N+ CC (213, 214), Study *IV* demonstrated improved OS following AC.

Literature specifically addressing recurrence in relation to AC in pT1N+ CRC is limited. In the present study, the 5-year DFI was higher among patients treated with AC compared to those receiving NAD, with recurrence rates of 5 % and 15%, respectively. However, after adjustment for age at diagnosis, the strongest confounder, the difference between the AC and NAD groups was no longer statistically significant. Notably, the HR remained low (0.42), suggesting that a clinically relevant difference cannot be excluded and warrants further investigation in larger studies.

Deviation from guideline recommendations for AC treatment in node-positive CRC does occur, and some patients decline the offered treatment (264, 266). In *Study IV*, older age at diagnosis was independently associated with NAD, in line with previous findings in pT1N+ CRC (213, 214). Notably, ASA class was not identified as an independent predictor of NAD, although it showed borderline significance in multivariable analyses. This finding is consistent with an earlier study in which NAD was not dependent on comorbidity level, as assessed using the Charlson Comorbidity Index (213). In contrast, studies investigating unselected stage III populations have reported contrasting results (267, 268), suggesting that the impact of comorbidity on NAD may vary with T stage.

The anticipated higher risk of toxicity in the elderly and comorbid patients, particularly with combined regimens including oxaliplatin (208, 269, 270), may be an explanation for reduced use of AC treatment in this patient group. Studies investigating combination therapy in older patients have not been able to demonstrate a clear survival benefit (209); therefore single-agent therapy is more often preferred because of its more favourable toxicity profile (211, 271, 272).

Wildes et al. evaluated the combined effect of age and comorbidity in stage III disease using a composite score and found that higher scores were associated with avoidance of chemotherapy (including both neoadjuvant and adjuvant treatment). Notably, even patients with the highest age/comorbidity scores demonstrated significant survival benefit from chemotherapy (273). Finally, one earlier study reported that non-completion of AC was associated with older age, but not with comorbidity or the patients functional status (Eastern Cooperative Oncology Group score) (274), constituting an interesting finding for understanding the mechanisms underlying treatment recommendations and shared decision-making.

Furthermore, patients in the present cohort who underwent reoperation had fivefold higher odds of NAD. Although prior studies specifically addressing this association are scarce, this finding was not clinically unexpected. Postoperative complications requiring surgical intervention are typically significant and may reduce the likelihood of sufficient recovery in time for initiation of AC. Similarly, delayed recovery, reflected by a longer duration of hospital stay, was independently associated with NAD. Longer hospital stay may result from surgical complications, but also medical conditions such as cardiac or pulmonary diseases. Although direct evidence is limited on avoidance of AC, delayed initiation of AC in CRC overall has been associated with both postoperative complications and extended hospital stay (275, 276). Interestingly, treatment delays observed were more frequent in pT1N+ patients (29%) compared with pT2–T4N+ (3–17%)(276). The same factors contributing to delayed initiation of AC may also contribute to NAD altogether.

Conclusions

- MRI alone is insufficient to reliably identify patients suitable for local resection, owing to substantial limitations in accuracy for both T and N staging in early RC. Improved preoperative staging is therefore essential to allocate patients with pT1 CRC to the most appropriate treatment. Advances in imaging techniques and clinical expertise in early CRC are crucial to achieving this goal.

- Recurrence rates after pT1 CC are low and comparable following endoscopic and surgical resection, not only among patients with low-risk tumours but also among those with high-risk tumours. LVI is a strong independent risk factor for recurrence. As current guideline-based risk stratification fails to identify patients with poor prognosis, future studies should focus on improving the identification of patients most likely to benefit from completion surgery.

- Local recurrence rates following TEM are significantly higher than those after surgical resection in patients with both low- and high-risk tumours. These findings call into question the use of TEM with curative intent in pT1 RC. Accordingly, alternative local resection techniques should be considered.

- AC substantially improves disease-free and overall survival in patients with pT1N+ CRC. Age at diagnosis, reoperation, and longer hospital stay are important factors associated with not receiving AC. These findings underscore the importance of avoiding unjustified deviations from current treatment recommendations for AC in patients with pT1N+ CRC.

Future perspectives

With full-scale implementation of CRC screening in Sweden, the number of patients diagnosed with pT1 disease is expected to increase.

There are two major concerns that need to be addressed in future research.

First, current preoperative assessment remains insufficient. Neither endoscopic assessment, MRI, nor EUS appears accurate enough to reliably stage early CRC, thereby complicating patient selection for local resection in a clinical setting. Improved precision in discriminating T stage and identifying LNM is essential to enhance the quality of care for patients with early CRC. While advances in MRI technology may improve spatial resolution, research efforts across multiple fields are required to identify optimal strategies for pre-interventional evaluation. One potentially promising approach is contrast-enhanced magneto-motive ultrasound (CE-MMUS) using nanoparticles. Preclinical studies have demonstrated encouraging results in mapping lymphatic drainage and detecting lymph nodes by providing additional information on perfusion, delineation, and tissue characteristics such as lymph node stiffness (277).

Second, current ESGE guideline categorization, which provides clinical guidance on which patients are in need of completion surgery after local resection, is based solely on the risk of concomitant LNM. This approach excludes the potential early risk of hematogenous spread leading to distant recurrence and may lead to surgical overtreatment. As demonstrated in this thesis, recurrence rates are relatively low in both low- and high-risk pT1 CC. However, LVI is a strong risk factor for recurrence but does not fully explain the observed recurrence risk by itself. Thus, there is an urgent need to identify patients at increased risk of recurrence who would benefit from completion surgery or adjuvant treatment, as distinct from those at low risk of recurrence, in order to reduce overtreatment.

Several promising research directions for improving recurrence prediction exist. For recurrence to occur, tumour cells must either remain at the surgical site, leading to local recurrence, and/or have disseminated via lymphatic channels or the bloodstream, potentially resulting in distant recurrence. Studies investigating circulating tumour DNA (ctDNA) for the detection of minimal residual disease are promising. This so-called “liquid biopsy” may serve as a biomarker to identify patients who would benefit from adjuvant treatment (278). Several ongoing clinical trials, primarily involving stage II and III disease, are evaluating treatment

escalation in stage III patients with elevated ctDNA levels and omission of AC in stage II patients when ctDNA is absent (278). There is potential for ctDNA to serve as a predictive marker for recurrence in stage I disease, in which selected patients may benefit from AC despite the absence of LNM. Further research is warranted.

From a histopathological perspective, LVI was identified as an independent risk factor for recurrence in this thesis. However, histopathological features such as LVI, PNI, and tumour budding are less frequently observed in pT1 CRC than in more advanced T stages. Pathological assessment of locally resected pT1 CRC is not always performed or reported using standardized reporting templates, in contrast to surgically resected specimens, for which structured reporting is mandatory. When risk factors are not explicitly required to be reported as absent, a potential expectation bias may be introduced, which could lead to underestimation of adverse histopathological features. The implementation of standardized reporting templates may therefore improve staging accuracy and risk stratification. Furthermore, the assessment of histopathological risk factors may be underreported in pT1 CRC due to the inherent difficulty in identifying small lymphatic and venous vessels, as well as nerves. Earlier depth-of-invasion models inferred greater lymphatic relevance of the deeper submucosa based on the observed associations between deeper invasion and higher LNM risk (50). However, this inference has since been challenged by several studies (52-54). By contrast, lymphatic-specific immunohistochemical staining (D2-40) has demonstrated a significantly higher density of lymphatic vessels in the superficial submucosa compared with the deeper two-thirds (279). The literature further indicates that the detection rate of lymphatic invasion in early CRC increases substantially when immunohistochemical staining is used in addition to conventional hematoxylin and eosin (H&E) staining, with reported rates of approximately 23% compared with 8% in H&E staining alone (280). Similarly, S-100 and elastin staining have been shown to significantly improve detection rates of PNI and vascular invasion, respectively (281-283). Improved detection of clinically relevant histopathological risk factors in pT1 CRC may enhance the identification of patients who may benefit from subsequent surgery.

A parallel area of interest includes recurrence as a consequence of early dissemination of tumour cells, which may result in either LNM or distant recurrence. Studies suggest that metastatic properties may be acquired early during tumour development, and in some cases even before the tumour becomes macroscopically detectable (31). Hu et al. proposed that tumours may be “born bad”, indicating that aggressive biological behaviour can be established at an early tumour stage. In addition, evidence suggests that LNM and distant metastases arise from independent tumour cell subclones in the majority of cases (30). Such genetic information could potentially be assessed for risk stratification in future clinical settings.

Furthermore, the inflammatory response appears to play an important role in tumour biology and prognosis. In surgically resected patients treated according to established surgical principles, a low lymph node yield is an indicator of worse

prognosis. However, low lymph node yield has recently been shown to depend primarily on tumour biology and a diminished host immune response, rather than on a more radical surgical approach (134). Studies investigating prognostic protein markers in stage II CRC have identified immune-related proteins, including FOXP3 (a regulator of tumour-associated antigens expressed in regulatory T cells), prostaglandin-endoperoxide synthase 2 (the gene encoding COX-2), and chemokine receptor 3 (a regulator of leukocyte trafficking), as potential markers of invasive behaviour and prognostic significance (101, 284). Interestingly, a recent study by Martling et al. demonstrated that acetylsalicylic acid significantly reduced recurrence in CRC patients with alterations in the PI3K pathway genes (285). Moreover, tumour protein expression patterns reflecting metastatic potential, such as E-cadherin, CD44, vimentin, and epithelial cell adhesion molecule (EpCAM), may play an increasingly important role in future clinical cancer diagnostics, thereby complementing conventional histopathological assessment (101, 284).

Finally, local recurrence of pT1 CRC following ESD with complete resection is reported to be low (94, 167). Technical refinements in conventional ESD aimed at increasing R0 and en bloc resection rates have now been followed by the relatively new technique EID. As the resection is carried out between the muscle layers in the muscularis propria, EID may even further improve complete resection rates of pT1 tumours, particularly when invasion has reached the deepest layer of the submucosa, with the potential to cure even more patients using local resection.

In parallel with advancements in endoscopic therapy, organ-preserving strategies are being explored in early RC using radiotherapy-based approaches. A large ongoing trial, STAR-TREC, is investigating organ-preserving strategies in early RC using long-course chemoradiotherapy or short-course radiotherapy, followed by a response-adapted approach. This includes a watch-and-wait strategy in patients achieving a complete clinical response and selective local excision using TEM in cases of incomplete response (286, 287). Furthermore, the addition of oncological treatment after local resection of high-risk T1 RC may become a more commonly used treatment option, as studies comparing completion TME with adjuvant chemoradiotherapy after local resection have demonstrated similar recurrence rates (288).

Most patients with pT1 CRC have an excellent prognosis. However, some are at an elevated risk of recurrence. In this context, the aim of future research should be to deliver effective, individualized treatment to each pT1 CRC patient while minimizing morbidity and enhancing quality of life.

Populärvetenskaplig sammanfattning

Tarmcancer är den tredje vanligaste cancerformen globalt och delas in i tjock- och ändtarmscancer. Varje år insjuknar cirka 1,9 miljoner individer och omkring 900 000 avlider till följd av sjukdomen. Överlevnaden är starkt kopplad till i vilket stadium cancersjukdomen upptäcks. Femårsöverlevnaden överstiger 90 % när tumören fortfarande är belägen i tarmväggen och inte har vuxit igenom muskellagren, men sjunker till omkring 20 % när cancersjukdomen har spridit sig till andra organ.

I Sverige diagnostiseras årligen cirka 8 000 personer med tarmcancer och omkring 2 700 avlider i sjukdomen. År 2023 levde cirka 60 000 individer i Sverige med tarmcancer eller som tidigare hade insjuknat och behandlats för sjukdomen, vilket speglar den relativt höga överlevnaden. Förekomsten av tarmcancer ökar dessutom framför allt bland unga individer. Orsaken till denna utveckling är ännu inte klarlagd.

Eftersom avancerade stadier av tarmcancer är associerade med sämre prognos har screening för tjock- och ändtarmscancer successivt införts i Sverige med start från det år individen fyller 60 år. Denna åtgärd förväntas leda till att cancer upptäcks tidigare samt att möjliggöra avlägsnande av slemhinneförändringar (polyper) som annars skulle kunna utvecklas till cancer.

Standardbehandlingen av tarmcancer är operation vilket innebär avlägsnande av det tarmsegment där tumören är belägen, samt tillhörande tarmkäx innehållande lymfkörtlar. Med tekniska framsteg har metoder för lokalt avlägsnande av tumören utvecklats. Detta är en mer skonsam behandling där tumören avlägsnas inifrån tarmen, till exempel med hjälp av koloskopi, vilket innebär att tarmen inte behöver delas och återkopplas utan att tarmens längd kan bevaras.

Operation är förenad med komplikationer och betydande sjuklighet, inklusive risk för permanent stomi. Dessa risker föreligger i mindre utsträckning vid lokalt borttagande av tumören. Däremot föreligger då i stället en risk för att eventuellt cancersjuka lymfkörtlar kvarlämnas, vilket i förlängningen kan leda till canceråterfall.

För att lokal behandling ska vara möjlig krävs att cancerutredningen påvisar en tumör med ytligt engagemang av tarmväggen och utan tecken till spridning till lymfkörtlar.

Det övergripande syftet med avhandlingen var att på sikt optimera behandlingen för patienter med tidig tarmcancer. De specifika målen var att undersöka om den utredning som genomförs innan operation är specifik nog för att identifiera vilka patienter som kan behandlas med lokalt avlägsnande av tumören, samt att identifiera riskfaktorer för återfall och undersöka återfallsrisk och överlevnad efter operation, lokalt avlägsnande av tumör och onkologisk behandling.

Magnetresonanstomografi (MR) är standardmetod för stadieindelning av ändtarmscancer. Undersökningen har hög precision vid utvärdering av avancerade tumörer som kan vara i behov av onkologisk behandling före operation, men däremot är kunskapen begränsad avseende metodens tillförlitlighet vid bedömning av tidig tarmcancer. **Arbete I** visar att tillförlitligheten hos MR vid tidig tarmcancer är låg både när det gäller bedömning av tumörens invasionsdjup i tarmväggen och förekomst av lymfkörtelspridning. Mot bakgrund av dessa fynd bör MR-utlåtanden inte ensamt ligga till grund för behandlingsstrategin hos patienter med tidig tarmcancer.

I **arbete II** utvärderades risken för återfall efter endoskopisk behandling (lokalt avlägsnande via koloskopi) av tidig tjocktarmscancer jämfört med operation, utifrån tumörens riskgruppstillhörighet. Enligt gällande riktlinjer bör patienter med hög risk för lymfkörtelspridning rekommenderas kompletterande operation. Problemet är att majoriteten av patienterna klassificeras som högriskpatienter, medan endast cirka 10 % faktiskt har spridning till lymfkörtlarna. Denna riskkategorisering leder således till överbehandling av patienter med tidig tjocktarmscancer. Dessutom tar gällande riktlinjer inte hänsyn till risken för återfall, vilket är av central betydelse ur ett patientperspektiv.

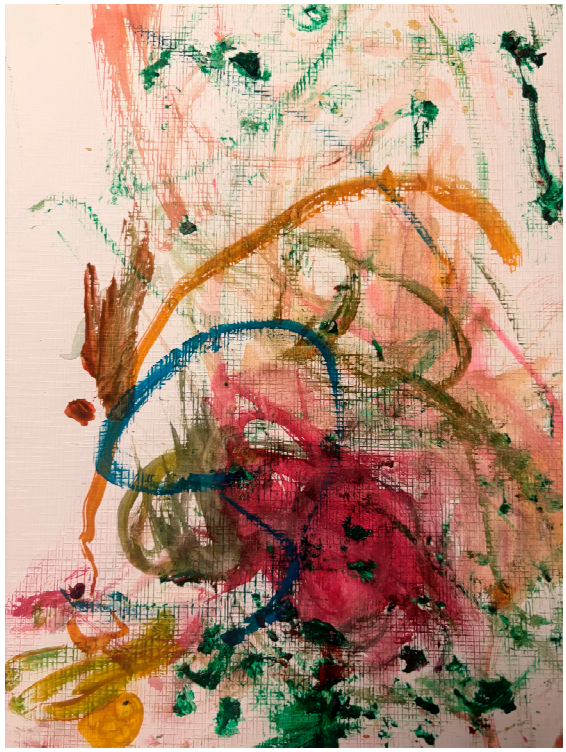
I arbete II visades att återfallsrisken generellt var låg och ingen skillnad kunde påvisas mellan behandlingsmetoderna, inte heller vid analys av de olika riskgrupperna. Förekomst av tumörväxt i lymf- eller blodkärl identifierades som en stark riskfaktor för återfall. Sammantaget talar resultaten för att endoskopisk behandling av tjocktarmscancer är i de flesta fall ett lämpligt alternativ för patienter med tidig tjocktarmscancer. Samtidigt finns det faktorer som medför en ökad risk för återfall. Framtida studier behöver således identifiera vilka patienter som faktiskt löper ökad risk för återfall och kan vara betjänta av kompletterande behandling.

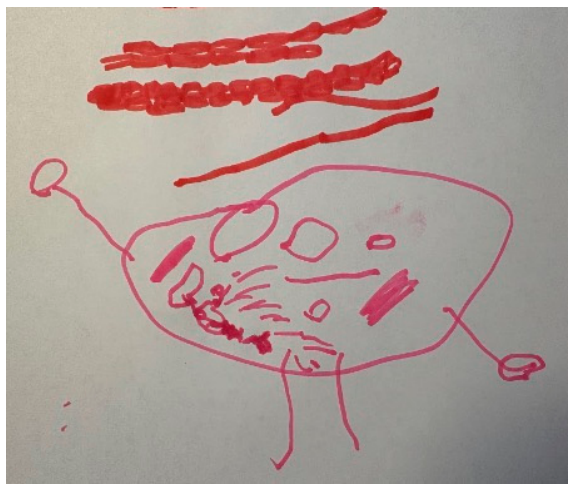
Transanal endoskopisk mikrokirurgi (TEM) är en av de första metoderna som utvecklades för att ta bort tumörer lokalt i ändtarmen. Resultat från **arbete III** visar att återfallsrisken var förhöjd hos den patientgrupp som behandlades med TEM jämfört med operation. Detta gällde även när risken var låg för lymfkörtelspridning. Sammantaget talar dessa fynd starkt emot att TEM bör användas som behandlingsalternativ i botande syfte vid tidig ändtarmscancer. Vid indikation för lokalt avlägsnande av tumören bör andra etablerade tekniker övervägas.

I de fall där en patient genomgår operation för tidig tarmcancer och lymfkörtelspridning bekräftas vid mikroskopisk undersökning, bör

kemoterapibehandling (cellgifter) rekommenderas i enlighet med nationella riktlinjer. I de studier som ligger till grund för dessa riktlinjer är patienter med ytlig tumörinvasion underrepresenterade. Det finns dessutom indikationer på att behandlingsriktlinjerna inte alltid följs i denna patientgrupp. **Arbete IV** visade att både sjukdomsfri- och total överlevnad förbättrades av behandling med kemoterapi som gavs efter operationen. Ålder vid insjuknande, reoperation och vårdtid var viktiga faktorer som påverkade behandlingsbeslut. Mot bakgrund av den tydligt förbättrade prognosen understryker resultaten vikten av att undvika ogrundade avsteg från gällande behandlingsriktlinjer.

Sammanfattningsvis bidrar detta avhandlingsarbete med värdefull kunskap om utredning, riskfaktorer för återfall, återfallsrisk i relation till operation och lokalt avlägsnande av tumör samt prognostisk betydelse av tilläggsbehandling med kemoterapi vid tidig tjock- och ändtarmscancer.





Interpretations of “tarmen”. The upper illustration was created by Luca Nilsson, and the lower illustration by Giulia Nilsson.

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