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Rectal Cancer Treatment and Response Prediction

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Abstract

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Rectal cancer is one of the most common cancers in Sweden with 2000 new cases annually. Outcomes have improved over recent decades due to better staging, using magnetic resonance imaging (MRI), refined surgical techniques and optimised use of radiotherapy (RT) or chemoradiotherapy (CRT). More recently, total neoadjuvant therapy (TNT), RT/CRT and chemotherapy before surgery, has emerged as a superior treatment for locally advanced rectal cancers (LARC). Rectal cancers are stratified into risk groups for systemic and loco-regional recurrence (LRR), requiring different treatments. Response to neoadjuvant therapy varies considerably between tumours, and despite extensive research, reliable predictors of response remain to be identified. The LARCT-US study treated LARC patients with TNT; 5x5 Gy + 4 CAPOX, an abbreviated RAPIDO-schedule. The aim of this thesis was to explore factors of importance for treatment choice and outcome in rectal cancer patients.

Paper I assessed the neoadjuvant rectal (NAR) score, a short-term surrogate endpoint to compare different regimens in clinical trials. The NAR-score discriminated between different treatments having different cytotoxic effects and applies irrespective of therapy given.

Paper II describes treatment selection over time in an unselected patient cohort from two adjacent Swedish regions. MRI-based risk grouping most strongly influenced treatment choice, with fewer patients receiving RT over time. Variations in MRI-interpretation and a stronger desire to decrease RT may explain regional differences. Accuracy of MRI was poor and requires improvement.

Paper III investigated long-term outcome and recurrence predictors in LARCT-US. The TNT schedule achieved excellent systemic control (25%) and few LRR (6%). The low LRR risk compared with RAPIDO may reflect more adequate distal resection margins practiced at Swedish centres. Besides treatment response, multiple high risk-criteria, tumour deposits, low tumour level and a sub-optimal resection plane were associated with recurrence risk.

Paper IV evaluates quality of life (QoL) and late toxicity following LARCT-US. QoL was comparable to that in the RAPIDO TNT-arm. Major bowel dysfunction was less frequent (45% vs 59%). Grade 3+ late toxicity occurred in 12% at three years and 8% at five years. Overall, the abbreviated TNT schedule achieves favourable oncological outcomes with acceptable QoL and limited late toxicity.

Keywords: Rectal cancer, Neoadjuvant treatment, Radiotherapy, Chemoradiotherapy, Total neoadjuvant therapy, Treatment response, Long-term outcome, Quality of life.

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The wound is the place where the Light enters

To my family

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. **Imam, I.**, Hammarström, K., Sjöblom, T., Glimelius, B. (2021) Neoadjuvant rectal (NAR) score: Value evaluating the efficacy of neoadjuvant therapy and prognostic significance after surgery? *Radiotherapy Oncology*, 157:70-77.

II. **Imam, I.**, Hammarström, K., Glimelius, B. (2023) Determinants of Pre-surgical Treatment in Primary Rectal Cancer: A Population-Based Study. *Cancers (Basel)*, 15(4):1154.

III. **Imam, I.**, Nilsson, PJ., Khan, T., Angenete, E., Glimelius, B. Locoregional and systemic control following total neoadjuvant therapy with short-course radiotherapy for locally advanced rectal cancer – long-term outcomes from the Swedish LARCT-US study. Manuscript. Submitted to *British Journal of Surgery*, October 10, 2025.

IV. **Imam, I.**, Khan, T., Nilsson, PJ., Glimelius, B. Quality of life and late toxicity after total neoadjuvant treatment for locally advanced rectal cancer – LARCT-US. Manuscript. Accepted in *Radiotherapy Oncology,* pending revision October 5, 2025.

Other papers by the PhD candidate not included in this thesis:

Hammarström K, **Imam I**, Korsavidou Hult N, Ekström J, Sjöblom T, Glimelius B. (2019) Determining the use of preoperative (chemo)radiotherapy in primary rectal cancer according to national and international guidelines. *Radiother Oncol.*, 136:106-112.

Osterman E, Hammarström K, **Imam I**, Osterlund E, Sjöblom T, Glimelius B. (2020) Recurrence Risk after Radical Colorectal Cancer Surgery-Less Than before, But How High Is It? *Cancers (Basel)*, 12(11):3308.

Hammarström K, **Imam I**, Mezheyeuski A, Ekström J, Sjöblom T, Glimelius B. (2020) A Comprehensive Evaluation of Associations Between Routinely Collected Staging Information and The Response to (Chemo)Radiotherapy in Rectal Cancer. *Cancers (Basel)*, 13(1):16.

Osterman E, Hammarström K, **Imam I**, Osterlund E, Sjöblom T, Glimelius B. (2021) Completeness and accuracy of the registration of recurrences in the Swedish Colorectal Cancer Registry (SCRCR) and an update of recurrence risk in colon cancer. *Acta Oncol*., 60(7):842-849.

Enblad M, Hammarström K, Folkesson J, **Imam I**, Golubovik M, Glimelius B. (2022) Mucinous rectal cancers: clinical features and prognosis in a population-based cohort. *BJS Open*, 6(2):zrac039.

Karimi M, Osterlund P, Hammarström K, **Imam I**, Frodi J-E, Glimelius B. (2022) Associations between Response to Commonly Used Neo-Adjuvant Schedules in Rectal Cancer and Routinely Collected Clinical and Imaging Parameters. *Cancers (Basel)*, 14(24):6238.

Hammarström K, Nunes L, Mathot L, Mezheyeuski A, Lundin E, Korsavidou Hult N, **Imam I**, Osterlund E, Sjöblom T, Glimelius B. (2024) Clinical and genetic factors associated with tumor response to neoadjuvant (chemo)radiotherapy, survival and recurrence risk in rectal cancer. *Int J Cancer*,155(1):40-53.

Glimelius B, Khan T, Adolfsson K, Angenete E, Berglund Å, Bonde K, Elander N, Fokstuen T, Haux J, **Imam I**, Lagerbäck C, Ljuslinder I, Piwowar A, Zajicova M, Nilsson PJ. (2024) Total neoadjuvant treatment using short-course radiotherapy and four CAPOX cycles in locally advanced rectal cancer with high-risk criteria for recurrence: a Swedish nationwide cohort study (LARCT-US). *EClinicalMedicine*, 5;75:102771.

Contents

Abbreviations

AJCC	American Joint Committee on Cancer
APE	Abdominoperineal Excision
C-index	Harrell's Concordance Index
cCR/pCR	Clinical/Pathological Complete Response/Regression
CEA	Carcinoembryonic Antigen
CI	Confidence Interval
CRC	Colorectal Cancer
CRF	Case Report File
CRM	Circumferential Resection Margin
CRT	Chemoradiotherapy
CT	Computer Tomography
ctDNA	Circulating tumour DNA
cTNM/pTNM	Clinical/Pathological Tumour, Node, Metastasis (staging)
d-/pMMR	Deficient/Proficient Mismatch Repair
DFS	Disease-Free Survival
DM	Distant Metastasis
DRM	Distal Resection Margin
EMVI	Extramural Vascular Invasion
EORTC	European Organisation for Research and Treatment
FIT	Faecal Immunology Test
GHS	Global Health Score
Gy	Gray
HDI	Human Development Index
HR	Hazard Ratio
IQR	Interquartile Range
LAR	Low Anterior Resection
LARC	Locally Advanced Rectal Cancer
LARCT-US	Locally Advanced Rectal Cancer Treatment - Uppsala Style
LARS	Low Anterior Resection Syndrome

LE	Local Excision
LN	Lateral lymph nodes
LRR	Locoregional Recurrence
MDT	Multidisciplinary Team
MRF	Mesorectal Fascia
MRI	Magnetic Resonance Imaging
NAR score	Neoadjuvant Rectal Score
OS	Overall Survival
QoL	Quality of Life
SCRCR	Swedish Colorectal Cancer Registry
scRT	Short-course Radiotherapy
TD	Tumour deposits
TEM	Transanal Endoscopic Microsurgery
TME	Total Mesorectal Excision
TNT	Total Neoadjuvant Therapy
TRG	Tumour Regression Grade
TTR	Time To Recurrence
U-CAN	Uppsala-Umeå comprehensive cancer consortium
UICC	Union for International Cancer Control
W&W	Watch-and-Wait

Introduction

Rectal cancer is one of the most common cancer diagnoses in Sweden and together with colon cancer remains a major cause of cancer-related mortality. Treatment outcome has substantially improved during the past decades due to advances in staging using magnetic resonance imaging, a multidisciplinary approach, improved surgery and the appropriate use of preoperative (neoadjuvant) radiotherapy alone or in combination with chemotherapy. Although, rectal cancers are generally considered to respond poorly to neoadjuvant therapy, the response varies considerably between tumours. A good or even complete response is strongly prognostic, being associated with improved survival and lower risk of recurrence. Much research during the past decade has tried to identify predictors for a very good response to neoadjuvant treatment, however, with limited success. Being able to predict treatment response in rectal cancer patients would greatly improve clinical decision-making, facilitating personalised therapy instead of waiting for post-treatment assessment. The growing interest in organ preservation will, with necessity, increase the use of radiotherapy and chemotherapy also for earlier tumours. To be able to more optimally use neoadjuvant therapy in rectal cancer, several questions must be addressed by a multidisciplinary group of researchers involving oncologists, surgeons, pathologists, radiologists and preclinical scientists. This thesis investigates treatment response in rectal cancer, factors influencing treatment choice and how it has evolved over time, as well as the long-term outcomes of total neoadjuvant therapy and potential predictors associated with its effectiveness. The overall aim was to contribute to more individualised treatment strategies in rectal cancer patients.

Cancer and carcinogenesis

Cancer is one of the leading causes of mortality and morbidity globally, with 18.7 million new cases and 9.7 million deaths in 2022[1]. The incidence continues to increase due to an ageing population and risk factors related to lifestyle, but also due to improved diagnostics and screening programmes[1]. Cancer can be described as a genetic disease caused by acquired mutations over time leading to uncontrolled cell growth and division[2]. Key characteristics of malignant cells, e.g. "the hallmarks of cancer", have been summarised by Hanahan and Weinberg in 2000; such as upholding growth signals, both by activating genes that promote cell growth (oncogenes) and inactivating genes that inhibit unwanted cell growth (suppressors), evading cell death (apoptosis), angiogenesis; the ability to stimulate development of new blood vessels for oxygen and nutrients, and the capacity to invade other tissues and to metastasise, spreading to other sites[3]. More mechanisms have since been added to the model, such as cancer cells' ability to avoid the immune system, promote inflammation, and genome instability and mutation[4,5]. There are genes and pathways that are basic for cell survival irrespective of cancer type, but there are also many known genes and pathways associated with specific tumour types, and are frequently used in the clinical scene to identify, diagnose and classify cancers in patients[6,7].

Colorectal cancer

Colorectal cancer (CRC) is the third most common cancer worldwide with almost 2.0 million new cases in 2022, and with around 900 000 deaths it makes it the second most common cause of cancer-related death[1]. The incidence of CRC varies globally, but it is increasing. It is more common in countries with a high human development index (HDI)[1,8]. Some known risk factors are a high intake of alcohol, red or processed meat and smoking, but also lack of physical exercise and obesity[9]. However, the largest relative increase in the incidence of CRC is predicted in countries with a low or medium HDI[1,8]. Another well-known risk factor is inflammatory bowel disease, such as ulcerative colitis and Crohn's disease[10,11]. The incidence of CRC increases with age. The median age at diagnosis is about 70 years, but this has dropped in recent years as the incidence increases in the younger population[9,12,13]. This increase is believed to mainly relate to negative changes in diet and physical inactivity. Younger patients, those below 50 years, are more likely to have rectal cancer, while older patients more often have right sided colon cancers. For rectal cancer, male sex is also a risk factor as men have a 31% higher incidence rate compared with women[13].

Rectal cancer

The rectum is in Sweden and many other countries defined as the large bowel up to 15 cm from the anal verge. Rectal cancer makes up about a third of all colorectal cases. There are approximately 2000 rectal cancer cases annually in Sweden and around 800 deaths per year[14,15]. Rectal cancers have a higher risk of clinically symptomatic local recurrences compared with colon cancers mostly due to challenges in surgical removal[16,17]. The introduction of preoperative treatment of the rectal tumour to allow for shrinkage and/or to kill tumour cells not easily removed by the surgery have been a focal point in increasing radical surgery. Improvements in several other fields in the past decades, such as radiology with better imaging of the tumour, better surgical techniques, and more optimal oncological treatment have resulted in major improvements in overall survival (OS) and local recurrence rates. Local recurrence rates in rectal cancer have dropped from 30-40% some decades ago to under 5% at many sites[14]. However, the risk of local recurrence varies greatly depending on the characteristics of the tumours[14]. The search for useful prognostic and predictive factors, both clinical and laboratorial, is ongoing.

Diagnosis

Screening is done with test for blood (haemoglobin) in faeces, in more recent years a faecal immunology test (FIT), with sensitivity 75-80% and specificity 95%. A positive test is followed up by endoscopy. The test is applied in some parts of the world, mostly for individuals over 50 years, and was first introduced in the Stockholm region, Sweden, in 2008[18-20]. The screening programme has now been gradually introduced nationwide from 2021-2022 and includes individuals 60-74 years every other year[19]. Although the screening programme in Sweden is growing, most rectal cancers are discovered in patients presenting with symptoms of visible blood or mucus in faeces, abdominal pain, or changes in bowel habits. Any of the above-mentioned symptoms is indicative for further investigation with firstly, a physical examination with rectoscopy. If the physician, usually the general practitioner in Sweden, identifies a suspect mass, the patient is referred for coloscopy and biopsies are

taken for diagnosis. Secondly, computer tomography (CT) scans of the abdomen and thorax along with magnetic resonance imaging (MRI) of the pelvis are carried out for preoperative staging. Thirdly, a multidisciplinary team (MDT) meeting is held for all newly diagnosed rectal cancers to discuss choice of treatment[14].

Staging and risk classification

The TNM-system (Tumour, Node, Metastasis) is used for tumour staging[21]. It is used by the surgeon and radiologist for clinical staging (cTNM) based on physical investigation, the CT-scans and MRI, and by the pathologist for staging of the surgical specimen (pTNM). This is done to determine how invasive and aggressive the tumour is, as a basis for prognosis for choice of the best treatment strategy for the patient. A summary of the TNM-system based on the 8th edition from AJCC (American Joint Committee on Cancer) (same as UICC, Union for International Cancer Control) can be found in Table 1.

MRI-staging is of key importance for the decision of treatment at MDT conferences. However, as much as the imaging modality has developed technically, there are still difficulties in the interpretation and a risk of over- or underestimating the tumour stage. Differentiation of T1 from T2 and T2 from early T3 tumours is difficult. Direct tumour infiltration which defines T3-stage can be hard to distinguish from fibrosis or peritumoural inflammation of a T2-tumour[22]. Assessment of N-stage is even more problematic. The sensitivity and specificity are only about 75% for nodal staging with MRI[23,24]. This is particularly concerning as pN-positivity is known to be closely related to the risk of local recurrence and distant metastasis[25,26].

On MRI, factors other than TNM-stage are also considered. Extramural vascular invasion (EMVI), the distance to the mesorectal fascia (MRF) and engagement of lymph nodes are all of interest. A tumour is considered EMVI-positive (EMVI+) if vessels beyond the muscularis propria have been infiltrated by tumour cells. EMVI+ is seen only in T3c/d- and T4-tumours and usually means that the tumour is considered locally advanced[22]. MRF+ is defined as a distance ≤1 mm to the fascia on MRI and is also important in predicting outcome in rectal cancer. For pathological analysis, the term circumferential resection margin (CRM) is used to evaluate radicality of the surgery[27]. Lateral lymph nodes (LN) outside the MRF and considered metastasised are denoted LN+ (arbitrarily >10 mm on imaging in several guidelines) and are also related to increased local recurrence risk and worse OS[28]. In recent years, tumour deposits (TD)[29] and if there is metastasis outside of regional lymph nodes (extranodal lymph metastasis) are also investigated on MRI.

Table 1. TNM-system based on the 8th edition by AJCC[14,21]

Primary Tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of a primary tumour
Tis	Carcinoma in situ: invasion of lamina propria
T1	Tumour invades the submucosa
T2	Tumour invades the muscularis propria
T3	Tumour invades the subserosa or into perirectal tissues
3a	Minimal invasion, <1 mm outside the muscularis propria
3b	Small invasion, 1-5 mm outside the muscularis propria
3c	Moderate invasion, 6-15 mm outside the muscularis propria
3d	Extensive invasion, >15 mm outside the muscularis propria
T4	Tumour directly invades other organs or structures and/or perforates visceral peritoneum
4a	Tumour penetrates to the surface of the visceral peritoneum
4b	Tumour directly invades or is adherent to other organs or structures
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
1a	Metastasis in 1 regional lymph node
1b	Metastasis in 2-3 regional lymph nodes
1c	Tumour deposit(s) in the subserosa, mesentery, or non-peritonealised perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
2a	Metastasis in 4-6 regional lymph nodes
2b	Metastasis in 7 or more regional lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
1a	Metastasis confined to 1 organ or site (liver/lungs are the most common organs to be affected)
1b	Metastases in >1 organ/site
1c	Metastasis to the peritoneum with or without organ involvement

Based on the factors investigated on MRI, and tumour level (in Sweden presently measured with rigid rectoscope), the tumours can be grouped into three different risk groups and guide treatment decision. The tumours can be early/"good" that have a low risk of local recurrence, or intermediate/"bad" with a higher risk or locally advanced/"ugly" tumours with risk of non-radical surgery[30]. International and Swedish guidelines have changed over the years based on results in different trials. In Sweden there have been guidelines published in 2008, 2016, 2020 and 2025 respectively. The standard treatments recommended for each risk group have remained basically the same in the past decade, but the risk group criteria have changed (Table 2).

Table 2. Group criteria for risk groups based on difficulty to resect/risk of recurrence according to the different national guidelines from 2008, 2016, 2020 and 2025.

Risk groups	Guidelines			
	2008	2016	2020	2025
"Good"/ Low risk	T1-3aN0	T1-2N0 T3abN0, High/Mid[1] T2-3bN1, High[1] T3cN0-1, High[1]	T1-3abN0-1, High/Mid[1], Low[1] (above ISP) T3cdN0-1, High[1] T4a limited spread T4b easy resection, High[1] N2, High[1] EMVI+, High[1] (above PR)	T1-3abN0-1, High/Mid[1], Low[1] (above ISP) T3cdN0-1, High[1] T4a limited spread T4b easy resection, High[1,3] N2, High[1,3] EMVI+, High[1] (above PR)[3]
"Bad"/ Intermediate risk	T3bc N+ EMVI+ Tumours in ISP	T3abN0, Low[1] T2-3bN1, Mid/Low[1] T3cN0-1, Mid/Low[1] T3d N2 EMVI+	T1-3abN0-1, Low[1] (in ISP) T3cdN0-1, Mid/Low[1] T4a extensive in-volvement T4b easy resection, Mid/Low[1] N2, Mid/Low[1] EMVI+, Mid/Low[1], High (not com-pletely above PR) MRF+ TD or extranodal N+	T1-3ab, Low[1] (in ISP) T3cd, Mid/Low[1] MRF+ TD or extranodal N+
"Ugly"/ High risk	T3d-T4 MRF+	T4 MRF+	T4b difficult resec-tion MRF+ (primary)[2] LN+	T4a extensive in-volvement T4b easy resection, Mid/Low[1] T4b difficult resec-tion N2, Mid/Low[1] EMVI+, High[1] (not completely above PR), Mid/Low[1] MRF+ (primary)[2] LN+

Lymph node positivity, N+; Extramural vascular invasion, EMVI; Intersphincteric plane, ISP; Mesorectal fascia, MRF; Peritoneal reflection, PR; Tumour deposit, TD; Lateral lymph node, LN.

[1]Tumour height from anal verge measured with a rigid rectoscope: Low 0-4 cm, Mid 5-9 cm, and High rectum 10-15 cm.

[2]If MRF+ is caused by growth in or against an easily resectable organ/structure, short-course radiotherapy (scRT) 5x5 Gy can be given (= "intermediate/bad").

[3]Included in the RAPIDO-study, why scRT + chemotherapy can be an option if relatively high risk for distant metastasis. Only chemotherapy (according to the FOxTROT-study for colon cancer) can be considered.

Treatment of localised rectal cancer

The key treatment for early/"good" non-metastatic tumours is surgery[14]. If the tumour is more advanced, neoadjuvant therapy can be added before surgery, e.g. radiotherapy alone which is the recommendation in Sweden for intermediate/"bad" tumours (short-course radiotherapy, scRT; 5x5 gray (Gy) for one week) or for locally advanced/"ugly" tumours, radiotherapy combined with chemotherapy; chemoradiotherapy (CRT) or, more recently, scRT followed by chemotherapy; total neoadjuvant therapy (TNT) (Table 3)[14,30]. The purpose of preoperative therapy is to lower the risk of local recurrence, and a delay in surgery (in standard practice 6-8 weeks but can be up to 12 weeks) gives the tumour time to shrink to facilitate radical surgery if the tumour is considered difficult to resect upfront. In the case of (near) complete regression of the tumour, an organ preserving strategy or "watch-and-wait" (W&W) can be applied to avoid surgery.

As the risk grouping criteria have been altered over the years, more rectal tumours are presently considered "good" and can be operated directly[31-34]. In the earlier care programmes, the risk groups were mainly based on how difficult the tumour was to resect, but in later years the risk grouping and treatment recommendations are also based on risk of systemic recurrence. The use of adjuvant therapy, i.e. chemotherapy after surgery, in rectal cancer has shown limited benefits in reducing risk of recurrences and is not clinically relevant for most patients[35,36]. It is, however, extensively used and recommended in many guidelines. In Sweden, the use is restrictive based upon the uncertainties. If TNT is given, it is considered that the "adjuvant effect", i.e. to eradicate remaining subclinical disease, has already been reached with the preoperative treatment, hence the name "total neoadjuvant therapy"[37].

Table 3. Recommended treatments according to risk groups in the Swedish guidelines of 2025[14].

Risk groups	Treatment
"Good"	Resection surgery/TEM
"Bad"	Preoperative scRT + Immediate/Delayed surgery
"Ugly"	TNT/scRT + Delayed surgery[1]

Transanal endoscopic microsurgery, TEM; Short course radiotherapy, scRT; Total neoadjuvant treatment, TNT.

[1]In the 2025 national guidelines the previous standard treatment chemoradiotherapy (CRT) for "ugly" tumours has been replaced by total neoadjuvant therapy (TNT) according to the RAPIDO/LARCT-US protocols; 5x5 Gy (scRT) followed by 3-5 months of chemotherapy before surgery. In elderly, frail persons, scRT with delayed surgery is recommended instead of TNT and chemotherapy is then not recommended in the interval to surgery. If the tumour is responding completely to the treatment, surgery may be deferred, and the patient enter a watch-and-wait (W&W) protocol.

Surgery

Immediate surgery for early rectal cancers is the best treatment with low risk of local recurrence. If it is possible to remove the whole tumour endoscopically, local excision (LE) is recommended directly instead of any diagnostic biopsy, mainly for early T1-tumours. An alternative to LE is transanal endoscopic microsurgery (TEM), a local procedure, if the tumour is of low grade or polypoid/not infiltrating beyond the upper third of the submucosa[38].

Total mesorectal excision (TME) is the gold standard for resection surgery in more advanced rectal cancer, where the rectum is resected, including the surrounding fatty tissue that involves blood vessels and lymph nodes. This is increasingly done with either robotic-assistance or with laparoscopic surgery. The goal is to have free margins of the tumour specimen, an "R0"-resection, in all directions[38]. Laterally, or circumferentially, the resection should be outside the MRF to guarantee radicality. If the tumour grows close to the MRF on MRI at staging or close to the CRM after resection, the risk of recurrence is much higher. A 1 mm margin is considered by most to indicate elevated risk, denoted MRF+ or CRM+ before or after surgery, respectively[27,39]. However, a too wide excision distally can lead to sphincter damage and general nerve damage, which causes many issues for the patient. The distal resection margin (DRM) is also important and has been the subject of several investigations[38,40,41]. For most purposes, a DRM in the bowel of 1 cm is considered safe although others have considered even smaller margins as safe[42,43]. Whether pre-treatment modifies this is also much discussed[40].

Sphincter preserving surgery is often the aim to preserve the sphincter function. The anatomy and level of the rectum where the tumour is growing is important when choosing surgical technique. Lower tumours are more difficult to resect as there are important structures surrounding them, such as the inner and outer anal sphincters, and there is less fatty tissue surrounding the rectum. Anterior resection is the standard for high and mid tumours, while abdominoperineal excision (APE) is the standard for low tumours. A low anterior resection (LAR) can be performed if a R0-resection can be achieved. Hartman's procedure can be a curative option if there are comorbidities, the patient has poor sphincter function, or other risk factors[14].

If an anterior resection is performed, a temporary loop ileostomy is often constructed to lower the risks of anastomosis leakage and help with faster healing. The stoma is then removed, in recent time if no complications have occurred, 8-12 days later, but usually it is kept for 6-8 weeks or longer[14]. However, the stoma comes with its own complications, especially ileostomy, where high stoma output can lead to dehydration, electrolyte disturbances and even kidney failure[38].

Neoadjuvant therapy

Preoperative radiotherapy has an established role in the treatment of rectal cancer. However, the recommendations and its use vary considerably, internationally and in some countries also nationally[44-47], probably reflecting different values ascribed to the radiation-induced negative effects[48]. There has been an endeavour to reduce the use of radiation while maintaining high local control rates[49-51], but it has been partly counterbalanced by the ambition to preserve the organ. In Sweden today, treatment with scRT alone preoperatively is recommended when the risk of local recurrence is ≥6-8% if only surgery is performed[14]. Studies have shown that the addition of radiotherapy lowers the relative risk by 50-70%, irrespective of type of surgery[52,53].

scRT has been developed in Sweden, but the more conventional hyperfractionated strategy, 1.8-2 Gy up to 45-50.4 Gy for 5-6 weeks, is still the reference treatment in many other countries[54-57]. The combination with concomitant chemotherapy, CRT, improves local control in locally advanced rectal cancer (LARC; cT3-4 and/or N+)[58-60]. In recent years, randomised studies; RAPIDO, STELLAR, UNICANCER-PRODIGE 23, have compared TNT to CRT[61-63]. The TNT protocols vary but consist mainly of scRT followed by chemotherapy, or CRT preceded, or followed, by chemotherapy. All intended oncological treatment is given prior to surgery, although when the TNT protocol has included CRT, additional chemotherapy has also frequently been given after surgery. The incidence of patients that respond with complete remission (no tumour can be detected during palpation, at endoscopy and radiologically, cCR, or pathologically, where no tumour cells can be seen in the surgical specimen, pCR) increases with TNT compared to CRT alone. The aim of TNT, i.e. to provide chemotherapy before the surgery, has been to more effectively kill micrometastatic tumour deposits than adjuvant chemotherapy. The trials have shown that the risk of distant metastasis has decreased but the risk of locoregional recurrence (even increased in RAPIDO) and overall survival does not seem to be affected.

Acute toxicity of radiotherapy, caused by inflammation of the rectum and surrounding tissue, can lead to abdominal pain, diarrhoea, cramping, urinary and/or rectal urgency and bleeding. Nausea and fatigue are common symptoms of both radio- and chemotherapy. The main concern with chemotherapy is haematological toxicity, but it also effects the gastrointestinal mucosa, resulting in diarrhoea and ulcers. Platinum based regimens may induce peripheral neuropathy with tingling, numbness, and cold sensitivity commonly in fingers and toes. Severe toxicity can impair fine motoric skills and balance. Hand-foot syndrome is common when capecitabine is used. Since both

radiotherapy and chemotherapy come with side effects and challenges, scRT alone is recommended to elderly and fragile patients even if they have a LARC.

Organ preservation

An organ preserving strategy, W&W, can be applied in patients that have an excellent response to the neoadjuvant treatment and achieve cCR. Rectal tumours take time to disappear and the longest time for this is not known[64,65]. For practical purposes, many have recommended a 12-week interval from the end of the radiotherapy. If the tumour is near a cCR, more time can be required for the tumour to disappear but frequently a local procedure is then applied. The patients are then monitored closely through the W&W programme, instead of undergoing resection of the rectum. In these patients, the effect of the neoadjuvant treatment is then determinant for local control, while in patients undergoing TME, local control is achieved by the surgery itself. Hence, the necessity for active surveillance. The W&W programme, at specialised centres in Sweden, monitor the patients with MRI screening and clinical examination every three months during the first two years and then every six months up to five years. So far, the results have been promising, with few patients that have local regrowth that is unsalvageable[66,67] and with low rates of locoregional and systemic recurrence. Most cases of local regrowth occur within the first year. As the use of TNT increases, more patients with LARC achieves a cCR and can enter the W&W programme. The chances of good treatment response are even greater for less advanced tumours both after scRT and CRT[68].

Treatment response and prognosis

Carcinoembryonic antigen (CEA) is related to tumour response and prognosis in rectal cancer. A low CEA is associated with a better chance of a good response to RT/CRT[68-71]. Advanced T- and N-stage and tumour size are also associated with treatment response[70-73]. Many of the studies exploring different predictive factors are small and even if larger, the findings are not consistent. For example, tumour length as a measure of size, reported by us and seen in LARCT-US/AdmL[73,74], did not correlate with a measure of tumour regression in a British study[75].

In rectal cancer, pCR is associated with excellent disease-free survival (DFS) and OS, and low rates of recurrence of both local and distant metastasis[76-78]. Several studies have shown that around 10-15% of patients treated with CRT achieve pCR and that TNT increases the rate of pCR, varying from

15-30%[61-63,79]. cCR is strongly correlated to pCR. Many investigations to find biomarkers in blood related to cCR and pCR are ongoing[80].

NAR-score

The neoadjuvant rectal (NAR) score has been developed as a surrogate endpoint for rectal cancer trials comparing different treatments in clinical trials for rectal cancer[81] and has been validated in several studies[82-85]. It can be used to more easily evaluate treatment response and predict OS and DFS in early stages of a trial instead of having to wait many years for the ultimate endpoint OS. The formula for calculating the score includes clinical- and pathological T-stage (cT, pT) to incorporate tumour response, and then also pathological N-stage (pN), which is an important factor for outcome. The score can have 24 different values from 0 to 100, where a low score means good response, and a high score means poor response (Figure 1). Consequently, a low (<8) or intermediate (8-16) score means better outcome and a high score (>16) indicates poor OS and higher risk of local recurrence. However, van der Valk et al dismissed the NAR-score as single pathological parameters (pT, pN) have similar concordance[86].

(cT-pT)	pN0	pN1	pN2
4	0	2.6	10
3	0.9	6.7	18
2	3.7	13	27
1	8.4	20	38
0	15	30	50
-1	23	42	65
-2	34	55	82
-3	46	70	100

Figure 1. Possible NAR-scores based on value of pN, pT and cT. NAR-score groups: Low <8, Intermediate 8-16, High >16.

NAR-score formula: $NAR = \frac{[5\,\boldsymbol{pN} - 3(\boldsymbol{cT} - \boldsymbol{pT}) + 12]^2}{9.61}$

Patient related outcome

As treatment of rectal cancer evolves and the outcome improves, particularly with lower rates of local recurrences, patients live longer and must live with the negative effects of surgical and oncological treatments that can impair quality of life (QoL), and this has become a growing aspect to investigate. QoL in rectal cancer patients has been evaluated in several studies with the European Organisation for Research and Treatment of Cancer (EORTC) questionnaires QLQ-C30[87] and QLQ-CR29[88], the latter being developed specifically for colorectal cancer patients. The questionnaires consist of single items of symptoms and functioning scales. After transformation, scores range from 0 to 100. Lower scores mean fewer symptoms, while for functioning scores a high score indicates better function.

The desire to avoid a permanent stoma after surgery is strong in many patients. In some cases, it is possible to avoid a stoma altogether or at least that it is temporary, which is the aim of a LAR approach. However, often the functional outcome is poor, and many patients end up with dysfunction of the bowel, or low anterior resection syndrome (LARS)[89]. This entails issues with frequent bowel movements, urgency and incontinence. The LARS-score ranges from 0 to 42 points and can be divided into no LARS (0-20 points), minor LARS (21-29 points), and major LARS (30-42 points)[89]. Up to 50% of patients undergoing LAR develop LARS[38]. This has also been an underlying reason for the growing aspiration for organ preservation and avoidance of surgery altogether. Other late surgical complications are issues with the stoma (if the patient has one), anastomotic complications, intestinal obstruction or ileus and urinary dysfunction.

Long-term urogenital issues are also a common late complication of radiotherapy. Another concern is negative effects on the skeleton in the pelvic area, which can cause insufficiency fractures. The combination of radiation and surgery increases the risk of developing a hernia or abscesses. In patients treated with radiotherapy, late effects can occur after several years. The major concern for chemotherapy, especially if it is platinum based, such as oxaliplatin which is widely used, is permanent neuropathy. The Swedish prospective LARCT-US (locally advanced rectal cancer treatment - Uppsala style) study used an abbreviated TNT-schedule of the RAPIDO-trial with fewer cycles of chemotherapy (oxaliplatin with capecitabine, CAPOX, or 5-fluorouracil, FOLFOX) which showed lower rates of neurotoxicity with similar response to treatment and without compromising the rate of locoregional recurrence (LRR) at the three-year follow-up[74].

The Swedish Colorectal Cancer Registry

Rectal cancers have been registered in a quality register in Sweden since 1995, and from 2007, colon cancer is also included creating the Swedish Colorectal Cancer Registry (SCRCR)[90]. The nationwide coverage of the register is estimated up to 99% of all CRC. The comprehensiveness for rectal cancer is 98.8% and the overall validity 90%[91]. Weekly updates on survival are done using the National Death Registry. The SCRCR contains detailed information on diagnosis, characteristics of the tumour, from radiology and endoscopy, and pathological if operated, treatment and follow-up. The registration of five-year recurrence rate has also been estimated to be high[92]. Personal identification numbers are used for linkage to other registries and enable quality control to medical records.

Present Investigations

Aims

The aim of this thesis was to explore factors of importance for treatment choice and outcomes of treatment in non-metastatic rectal cancer patients. The specific aims of each paper were as follows:

I. To further explore the value of the NAR-score in a nation-wide cohort of rectal cancer patients, to investigate whether it applies to longer waiting times to surgery and if it applies in patients treated with other treatments than that for which the score had originally been developed.

II. To describe treatment choices according to detailed MRI characteristics in an unselected population-based rectal cancer patient cohort and to understand selection mechanisms for different treatments and changes over time. A secondary aim was to investigate the accuracy of MRI in tumour staging in clinical routine.

III. To assess long-term outcomes of the LARCT-US study, a real-life cohort of rectal cancer patients with risk criteria for recurrence treated with an abbreviated RAPIDO TNT-schedule, to improve understanding of the increased locoregional recurrence risk reported in RAPIDO and to explore who benefits most from TNT.

IV. To assess QoL and late toxicity in the patients participating in the prospective LARCT-US phase II study.

Study designs

Paper I was a retrospective national cohort study, while **paper II** was a prospective population-based cohort study. **Papers III-IV** are follow-up studies of the prospective national observational cohort study, LARCT-US. The inclusion period, number of patients and study designs are presented in Table 4.

Table 4. Study cohorts of paper I-IV.

Study	Period	Patients	Design
I	2007-2015	10 246	Retrospective national cohort study
II	2010-2020	1 150	Prospective population-based cohort study
III-IV	2016-2020	437	Prospective national observational cohort study

Patients and methods

For **paper I**, data was retrieved for 11 726 surgically operated patients diagnosed with non-metastasised rectal cancer between 2007 and 2015 from the SCRCR. Patients that had sufficient information to calculate NAR-score (n=10 246) were categorised primarily into groups based on what neoadjuvant therapy they received. The treatment groups are presented in Table 5. A total of 273 patients were excluded as they did not fit into any of the treatment groups or did not complete treatment.

Table 5. Treatment groups in paper I.

Treatment group	Specifics on treatment	No. of patients
Primary surgery	No neoadjuvant therapy	3850
scRT+immediate surgery	5x5 Gy for 1 week, surgery <21 days after start of therapy	3286
Long-course RT	25x2 Gy for 5 weeks	124
(C)RT+chemotherapy	Systemic chemotherapy before/after RT/CRT	382
scRT + delayed surgery	21–120 days between start of therapy and surgery	1032
CRT + delayed surgery	25–28x1.8–2 Gy to about 50 Gy for 5–5½ weeks with a fluoropyrimidine	1299

Short-course radiotherapy, scRT; Gray, Gy; radiotherapy, RT; chemoradiotherapy; CRT.
‘‘scRT + delayed surgery” and ‘‘CRT + delayed surgery” patients were further divided into two groups according to time to surgery, (3)6–8 weeks vs. 8–17 weeks.

In **Paper II**, 1150 patients without synchronous metastases, from two adjacent Swedish regions (Uppsala n=542, Dalarna n=608) were analysed. All patients living in Uppsala and Dalarna regions in Sweden and diagnosed with rectal cancer between 2010 and 2020 were identified from the SCRCR and a biobank

initiative, Uppsala-Umeå Comprehensive Cancer Consortium (U-CAN), initiated in June 2010[93]. Clinical information containing staging, treatment and follow-up was obtained from the SCRCR. Missing information was collected from the clinical records including the MDT reports, and from re-evaluations of images and pathological slides, as described[68]. Risk grouping was made using the "good–bad–ugly" concept (Table 2) according to the 2008, 2016 and 2020 guidelines.

In **papers III** and **IV** patients were from the LARCT-US study. Following completed inclusion of the RAPIDO trial in June 2016, all Swedish centres from five of six healthcare regions began treating LARC patients fulfilling the inclusion criteria in RAPIDO (≥1 risk criterion on MRI: cT4, cN2, MRF+, EMVI+ or LN+) with a modified schedule (scRT + 4 CAPOX/6 FOLFOX) until release of the results of the RAPIDO trial in June 2020. Patients were treated either according to a phase II protocol with written patient consent, or according to the same protocol in routine care (ad modum LARCT-US, AdmL). In total, 273 patients were included in LARCT-US and 189 patients in AdmL. Of these, 437 patients were curatively treated with either radical surgery (n=375) or W&W (n=62) and were included in the analyses. Information on follow-up for **paper III** was retrieved from SCRCR and from case report forms (CRFs) from LARCT-US, and the same for information on late toxicity for **paper IV**.

For **paper IV**, QoL-data were retrieved from questionnaires sent out to 188 patients of which 144 patients responded and were still recurrence-free at the time of completion of the questionnaire (data collection was delayed due to the COVID-19 pandemic, extending follow-up up to five years) and could be included in the analyses. Late toxicity could be analysed for 260 patients at three years and 214 patients at five years follow-up.

Statistical methods

For group comparisons of categorical variables, Pearson's Chi2-test was used. Kruskal–Wallis's test, Mann-Whitney U test and Median test were used for continuous variables. OS and time to recurrence (TTR) were illustrated with the Kaplan-Meier method and compared by log-rank test. Univariable and multivariable analyses of Cox regression were done in **papers I** and **III**.

In **paper I**, the Cox regression analyses were done in accordance with the Dutch NAR study[86] for all patients that received CRT to calculate hazard ratios (HR) for NAR-score and for cT, pT and pN used when calculating NAR-score. The Harrell's concordance index (C-index) was calculated for the NAR-score model, for pT and pN, separately (''pathologic model") and the two pathological factors in combination with cT (''combined model"), to

evaluate the concordance between the observed and the predicted outcome. All models were adjusted for age and gender. The Akaike information criterion was used to evaluate the goodness of fit of the model.

In **paper II**, logistic regression analyses were performed of associations between patient characteristics, Uppsala and Dalarna regions, year of diagnosis, tumour level and MRI characteristics defining risk group and selection to preoperative therapy (RT or CRT/scRT+CT). Univariable logistic regression was used to identify predictors of receiving preoperative treatment. Variables likely to be associated with receiving preoperative treatment were included in a multivariable logistic regression based on a statistical significance of *p*-value <0.10. Cohen's kappa was used to evaluate the correlation between clinical and pathological T- and N-stage.

In **paper III**, the univariable Cox regression analyses were presented in forest plots, with HR and corresponding 95% confidence intervals (CI). The Firth's penalized Cox regression[94] was applied when subgroups had no or very few events. Variables with a p-value <0.10 in univariable analyses were considered for inclusion in the multivariable models; however, if risk of reduced model interpretability was present, some variables were not included. Some variables were also excluded due to high collinearity. The CI for binomial proportions were calculated using either the exact Clopper–Pearson method for smaller samples (n<30) or when event counts were low (≤2), as it ensures nominal coverage even in such constrained scenarios. The Wilson score method was used for larger sample sizes with more events. For OS and TTR, median values and interquartile ranges (IQR) were reported. The reporting followed the Strengthening the reporting of observational studies in epidemiology statement (STROBE).

In **paper IV**, QoL-scores were analysed and interpreted according to the EORTC guidelines[95]. Welch's test was used to compare QoL-scores in patients with or without grade 3+ late toxicity. To be able to compare with the RAPIDO data[96], the same set of analyses were done (besides correcting for a mistake in the RAPIDO report).

P-values <0.05 were considered statistically significant. The statistical analyses were performed in the programs IBM SPSS version 25.0 and in R version 3.6.1 for **paper I**, SPSS version 27.0 and R version 4.1.3 for **paper II**, R version 4.4.1 for **paper III** and R version 4.4.3 for **paper IV**.

Ethical considerations

The Ethics Committee in Uppsala, Sweden (Dnr 2017/235) and the research ethics committee at Uppsala University (Dnr 2011/092, 2015/419 and 2018/490) approved studies of **papers I-II**.

For **papers III-IV**, the research ethics committee at Uppsala University approved the LARCT-US protocol (Dnr 2016/305). The treatment protocol was classified as a reference treatment by the Swedish Medical Products Agency and did not require a separate approval. An additional approval permitted for retrospective collection of data from SCRCR (Dnr 2016/305/9). Since SCRCR contained limited data compared to the LARCT-US CRFs, supplementary information from treating hospitals was authorised. All patients provided informed consent prior to treatment. The study was registered at clincialtrials.gov (NCT03729687).

Results

Baseline characteristics of the patient cohorts are presented in Table 6.

Table 6. Baseline characteristics of patient cohorts.

Characteristics	Paper I (n=9 973)	Paper II (n=1 150)	Paper III-IV (n=437)
Age, median (range)	69 (23-96)	71 (26-96)	64 (24-81)
Sex, male	5 993 (60)	671 (58)	256 (59)
cT-stage			
T1-2	2 867 (29)	324 (28)	-
T3	5 473 (55)	566 (49)	199 (46)[1]
T4	1 733 (17)	221 (19)	238 (54)
cN-stage			
N0	4 566 (46)	453 (39)	41 (9)
N+	4 768 (48)	655 (57)	396 (91)
MRF+	228 (10)[2]	188 (33)[2]	335 (77)
EMVI+	-	281 (24)	231 (53)
Tumour level			
Low 0-4 cm	2 172 (22)	269 (23)	129 (30)
Mid 5-9 cm	3 558 (36)	410 (36)	159 (36)
High 10-15 cm	4 155 (42)	468 (41)	149 (34)

Mesorectal fascia, MRF; Extramural vascular invasion, EMVI. Values are presented as n (%), unless otherwise specified.

[1]12 cT2N+ tumours were included in LARCT-US/AdmL

[2]MRF+ only presented for cT3 tumours.

In **paper I**, mean NAR-score differed statistically significantly (p<0.0001) between different treatments. The highest proportion of pCR was seen in the group receiving (C)RT + chemotherapy (11.5%, 95%CI[8.6–14.9]) and had the lowest mean NAR-score of 16.3, while CRT + delayed surgery had 17.7. There were significant differences (p<0.05) in OS and TTR of patients with a low NAR-score (<8) compared to those with a high score (>16) for both CRT- and scRT. CRT-patients + delayed surgery 6-8 weeks had the strongest correlation (Figure 2); the patient group for which the score was developed. Longer delay to surgery after receiving CRT gave similar NAR-scores compared to a delay of 6–8 weeks. The discrimination between NAR-score groups and survival was also seen for patients with primary surgery and scRT + immediate surgery. C-index for the NAR-score model (0.623) was not superior to when only pathological T- and N-stage was used (0.646).

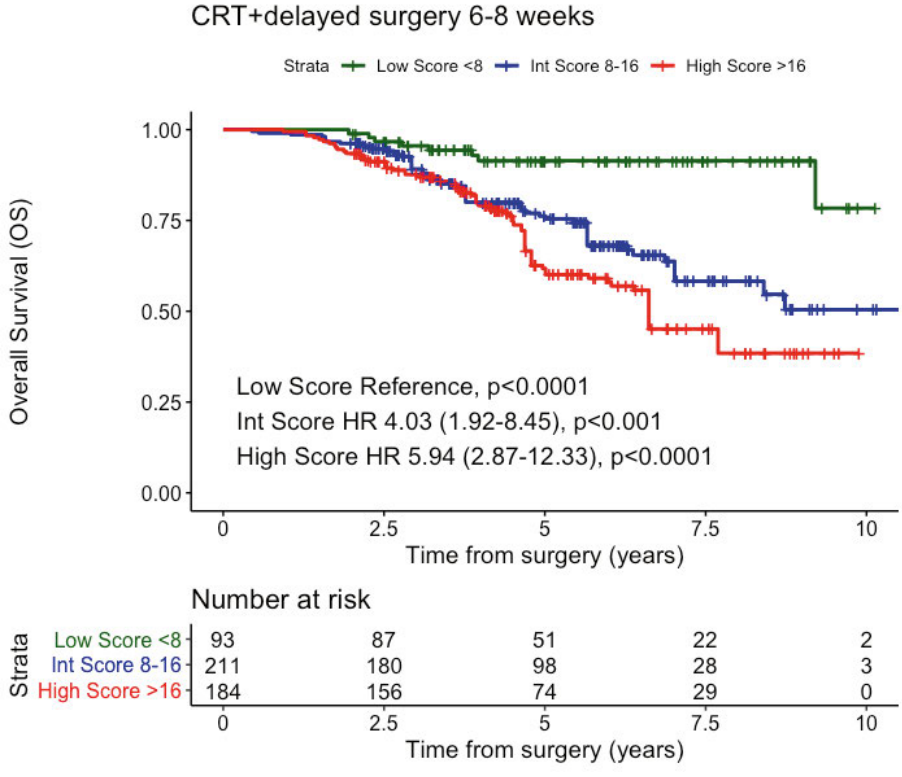

Figure 2. Overall survival (OS) in NAR-score groups of patients treated with CRT with delay to surgery 6-8 weeks, for which the score was originally developed.

In **paper II**, patients from Dalarna were older, had less advanced tumours and were pre-treated less often (52% vs 63%, p<0.001) compared with Uppsala patients. All MRI-characteristics (T-/N-stage, MRF, EMVI) and tumour level

were important for treatment choice, and independent associations were seen, but not for age and sex. Age, however, influenced whether chemotherapy was added or not. Since the risk grouping was modified over the years to diminish the proportion pre-treated, fewer patients were irradiated over time. Figure 3 shows how all tumours would be categorised according to the different guidelines. The correlation between clinical and pathological T-stage was fair/moderate (accuracy 59%, K=0.37, p<0.001) and poor for N-stage (accuracy 54%, K=0.16, p<0.001). Risk grouping based on MRI-characteristics influenced treatment choice the most. Adherence to the guidelines was high but some variability was seen. For "ugly" tumours, about 7% did not receive any pre-treatment, while more "bad" tumours were treated with CRT/scRT+CT in the period 2015-2018, and even more so in 2019-2020.

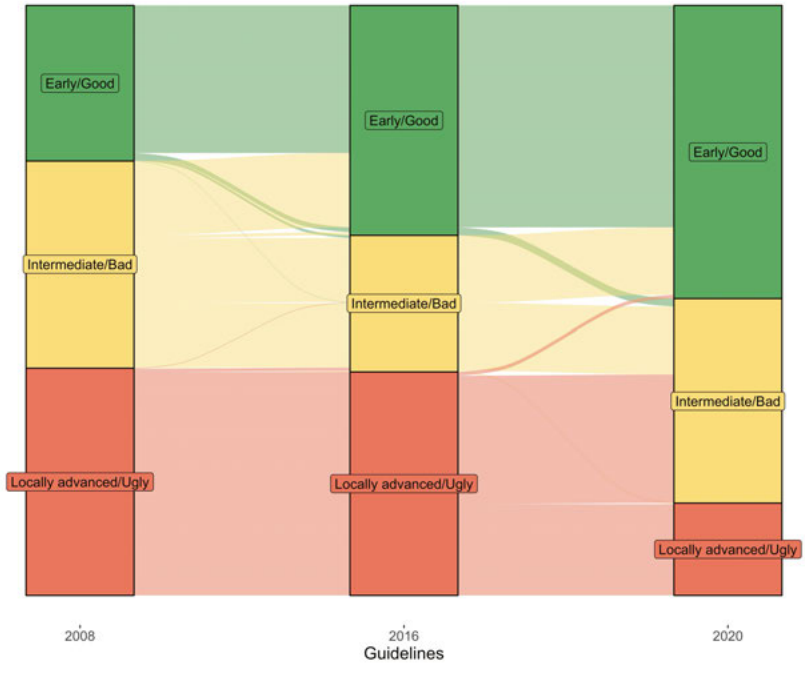

Figure 3. Alluvial diagram of the distribution of risk groups after re-classification of all tumours with available information (n=1038) according to the different guidelines (2008, 2016 and 2020).

In **paper III**, after minimum five-year follow-up, 117 (27%) patients in LARCT-US/AdmL had recurred, of which 26 (6%, 95%CI 3.7-8.2) were LRR and 108 (25%, 95%CI 20.7-28.7) were DM. The median TTR from the start of RT was 1.4 years (IQR 1.0-2.1, range 0.4-5.8 years, Figure 4). Patients with a CR (n=109, 25%; sustained cCR ≥1 year n=48, pCR n=61) showed excellent outcome with no LRR and few DM (13%). Of the W&W-patients, local

regrowth was detected in 21 patients (14 within one year and later in seven). R0 surgery was performed in these patients, and no LRR has occurred. Overall, DM has occurred in eight (13%) W&W patients after median time of 1.8 years (IQR 1.2-2.1). The five-year OS was 85% (95%CI 82.1-88.7). Patients with CR had a significantly better OS compared with non-CR. Site of DM was most commonly pulmonary followed by liver and then peritoneal and extra-regional lymph nodes. Site of LRR was only registered for LARCT-US patients (n=15/26) and regional lymph nodes were most common. Of the 151 patients in LARCT-US that had an anterior resection or a Hartmann's procedure, only three (2%) had an anastomotic recurrence. The response to treatment (CR) had the strongest association with recurrence. Low tumour level (<5 cm) was associated with LRR. In primarily operated patients, the multivariable analyses showed that TD and tumour regression grade (TRG) 0 and 1 were associated with DM, while suboptimal resection plane was associated with both DM and LRR. A low NAR-score was significant for both LRR and DM in the univariate analyses. The DRM was ≤10 mm in 8% after a sphincter-saving procedure. The risks of LRR and DM were slightly higher if ≤10 mm compared with DRM >10 mm (6% vs 4% for LRR and 31% vs 27% for DM). Compliance to the treatment (follow through ≥75%) was 88% in LARCT-US patients.

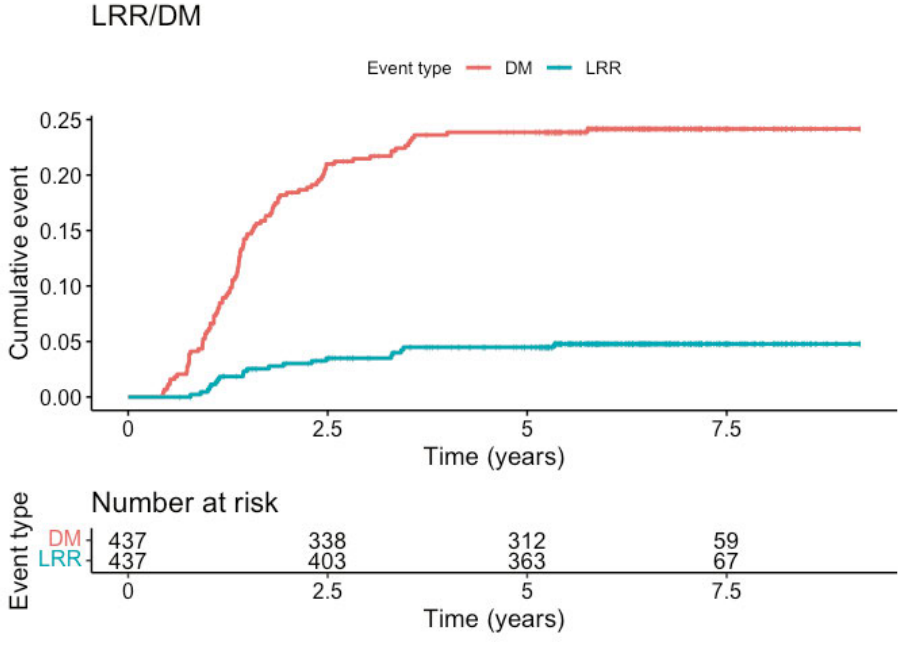

Figure 4. Occurrence of distant metastasis (DM) and locoregional recurrence (LRR) in LARCT-US/AdmL patients.

In **paper IV**, QoL analyses showed that patients in LARCT-US had mean global health score (GHS) 73.3 (99%CI 68-78) and for the functioning (physical, role, emotional, cognitive, social) scales, the mean scores were around 86 (83-90) (Figure 5). Flatulence was the most common symptom with mean score 35.2 (99%CI 29-41, Figure 6) and there was no significant difference between patients with and without a stoma (mean score 34.7 vs 35.8). Urinary frequency (28.1, 99%CI 23-33), fatigue (21.1, 99%CI 16-26), bloating (20.7, 99%CI 15-27), insomnia (18.3, 99%CI 12-24) and diarrhoea (16.2, 99%CI 11-22) were also common symptoms. The incidence of LARS could be investigated in 53 stoma-free patients operated with LAR. Forty-two patients (79%) had LARS of which 25 patients (47%) had major LARS. Additionally, 22 W&W-patients that were recurrence-free had also responded to the LARS-questionnaire, of whom 18 (81%) had LARS and 10 (45%) major LARS. At three-year follow-up, 33 patients (12%) had grade 3+ late toxicity. Stoma and hernia complications (both 3%) were the most common toxicities. At the five-year follow-up, 16 patients (8%) had grade 3+ late toxicity. Amongst them, reoperation related to ileus (2%) was most common. Of the patients included in the QoL-analysis 27 (19%) had grade 3+ late toxicity at three-year follow-up. Patients with late toxicity had worse mean scores with statistical significance for fatigue, dysuria, financial difficulties, global health score (GHS), role functioning and social functioning.

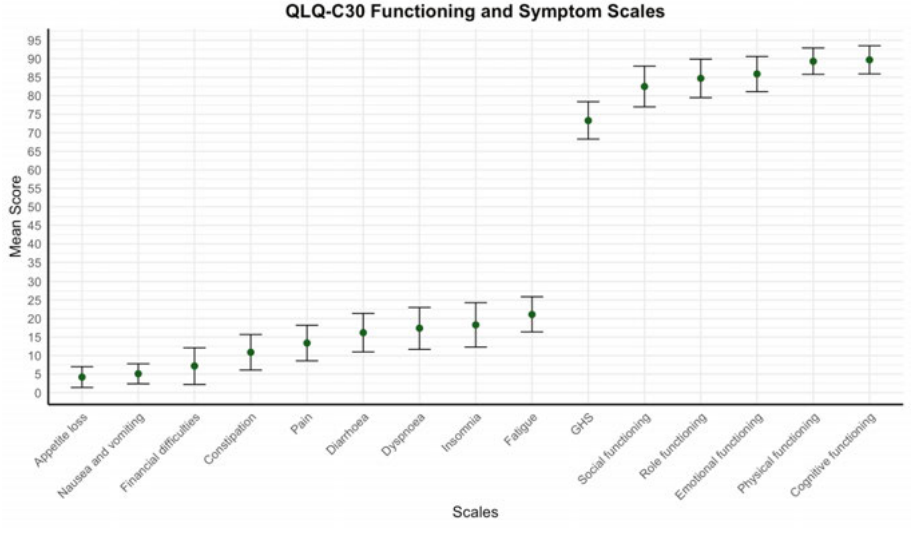

Figure 5. EORTC QLQ-C30 Functioning and Symptom Scales, mean and 99% confidence intervals, at three-year follow-up for LARCT-US patients. Global Health Score, GHS.

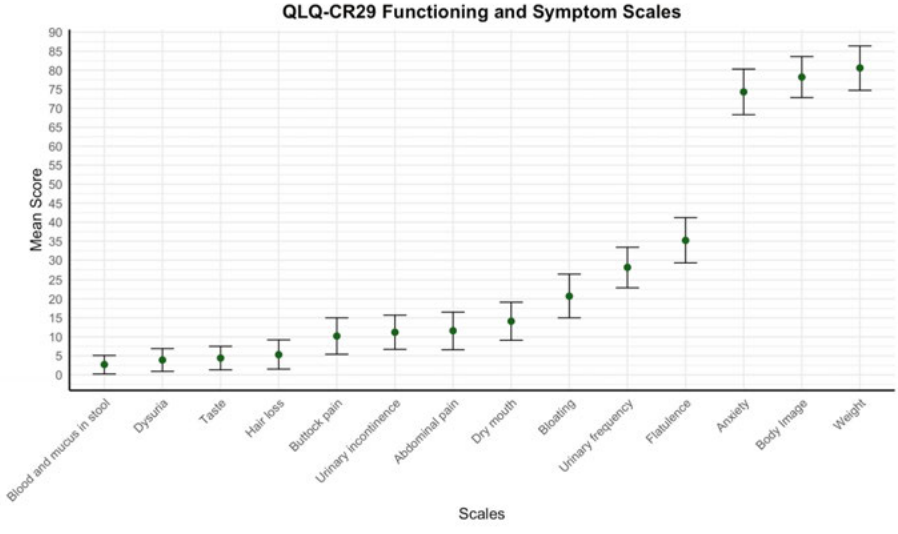

Figure 6. EORTC QLQ-CR29 Functioning and Symptom Scales, mean and 99% confidence intervals, at three-year follow-up for LARCT-US patients.

Discussion

In **paper I**, the NAR-score was able to discriminate between two different treatments that have different cell killing effect, which was the primary aim of developing the NAR-score. The score is robust in that it appears to work irrespective of therapy given. Since patients with a low NAR-score had significantly better outcome compared with those with a high score, it appears as if it is of value as a surrogate marker in the evaluation of different schedules. The difference between groups was more apparent if neoadjuvant treatment with delay to surgery was applied, reflecting the importance of downstaging/downsizing. The strongest association was seen in patients that had CRT (the treatment the score was designed for) or (C)RT + chemotherapy (which can be considered comparable to TNT, and the RAPIDO-trial was ongoing at the end of this study period). The less clear distinction of low/high NAR-score in scRT + delayed surgery could be explained by the treatment being preferred for older and frail patients, with a median age 10 years higher compared with CRT. Patients with longer delay to surgery did not have lower mean NAR-score or better survival, which is somewhat contra intuitive as it is believed that longer wait to surgery should permit for more tumour regression and thus lower NAR-score[97,98]. In the Stockholm III trial, longer delay to surgery >8 weeks did not result in more tumour regression[34], indicating that tumours that do respond well to neoadjuvant treatment and have a positive effect on

outcome will most likely respond within the first two months from start of therapy. Nor have any of the few prospective randomised trials comparing different intervals after the same CRT found any difference[99,100]. When the NAR-score was calculated for the two groups that were not treated prior to surgery for downstaging/downsizing, i.e. primary surgery or scRT + immediate surgery, approximately half of the patients still had a NAR-score of ≤16 (Low or Intermediate score) indicating the uncertainty in clinical staging with MRI. The uncertainty of MRI for early-stage rectal tumours and N-stage is well-known[23,24]. In SCRCR, cT1 and cT2 are not registered separately, consequently they were all considered as cT2 when calculating the NAR-score. However, since the NAR-score is heavily influenced by the N-status (Figure 1), the uncertainty of MRI explains the discrepancy seen in patients with immediate surgery better than the cT-staging being "overestimated". The NAR-score thus contains prognostic information but no more than what can be achieved from pT- and pN-stage combined, i.e., the UICC stage. In this latter aspect, the study confirms the results of the Dutch study that dismissed the score, but the NAR-score can still be of clinical value for the purpose for which it was developed.

In **paper II**, risk grouping based on MRI-characteristics influenced treatment choice the most. Age influenced the choice of neoadjuvant treatment, while sex was not important in contrast to other studies[101,102]. Since the risk grouping was modified over the 11-year period, at least partly to diminish the proportion pre-treated, fewer patients were irradiated with time. Adherence to the guidelines was overall high, and most patients were treated according to the "good-bad-ugly" concept, but some variability due to age and inclusion in ongoing clinical trials (RAPIDO, LARCT-US) was seen, explaining why some "ugly" tumours only had scRT or no pre-treatment and why more "bad" tumours had CRT/scRT+CT in later years. Other patient-related factors, such as co-morbidities, previous radiation and personal wishes could also explain deviations from treatment recommendations. Differences in MR-interpretation, in addition to a stronger desire to decrease irradiation, may explain less advanced tumours in Dalarna, and possibly that fewer patients were pre-treated there. Moreover, the absence of an RT department in the Dalarna region required the patients to be referred to Uppsala University Hospital. These patients thus had to travel at least 60 km to the irradiation facility. This together with Dalarna having an older population compared with other Swedish regions inevitably influenced their proneness to avoid pre-treatment in these patients or the patients opting out from it. This shows that despite the efforts of Swedish health care to provide similar care to all citizens there are still differences that are difficult to overcome. Further, the incidence of rectal

cancer is increasing in younger patients and with more advanced tumours, which could also contribute to the difference in the two regions. The accuracy of MRI needs improvement, especially for N-staging. This also supports the findings from **paper I** where half of the patients with immediate surgery had a low/intermediate NAR-score despite no time for downstaging. The overall accuracy of the MRI-evaluation is probably better for more advanced tumours, but since our aim was to describe what determines treatment in clinical routine, no independent review of the MR-images was performed.

Paper III shows that the LARCT-US schedule, consisting of scRT followed by four cycles of CAPOX (or six cycles of FOLFOX) results in a decreased risk of DM, such as that which was seen for the TNT-arm of RAPIDO compared to the previous standard CRT with optional adjuvant chemotherapy. LRR was seen in 11% of the patients in the TNT-arm of RAPIDO compared with 6% in the CRT-arm. The risk of LRR in LARCT-US was comparable to that of the CRT-arm, despite more advanced tumours in LARCT-US. The high rate in RAPIDO has been the subject of detailed investigation and a too narrow surgical DRM after a sphincter-preserving approach at a few hospitals in the Netherlands, could be a possible explanation[103]. The rate of sphincter-preserving surgery among the Swedish RAPIDO-patients was lower. In LARCT-US, the rate of sphincter-preserving surgery was similar to that of the Swedish RAPIDO-patients and few narrow DRMs were observed. Thus, indicating that surgeons should bear in mind that there may be tumour cells present distal of the tumour that are non-detectable on MRI, despite significant tumour shrinkage after TNT. If organ preservation is a primary aim, four cycles appear sufficient and do not seem worse regarding the risks of DM. However, six cycles may be superior if the risk of DM is high, as in LARC with many high-risk criteria and if the patient can tolerate full doses. However, if there is little to no tumour response at the evaluation after three or four cycles, there is probably minimal gain in continuing with two-three more cycles. Compliance to the abbreviated schedule used in the Swedish LARCT-US/AdmL population was worse compared to the longer schedule in the RAPIDO trial[104]. This shows that TNT is not well tolerated by all LARC-patients in routine care, often older patients and with more advanced tumours, requiring irradiation to large volumes and in the end extended surgery.

In **Paper IV**, the QoL and late toxicity analyses for LARCT-US/AdmL showed similar results to that of the experimental arm in RAPIDO. An improvement in neurotoxicity with two (or three) fewer cycles of chemotherapy has already been shown[74] and **paper III** showed that local control was better. No other major differences were seen in QoL. Discrepancy in the TNT-arm of RAPIDO for mean score of flatulence when comparing patients with or

without stoma, which could not be found in LARCT-US, may be a chance finding. The fewer number of cycles of chemotherapy should in theory perhaps also result in fewer patients having late effects, however, this may have been counteracted by more advanced tumours and older patients being included in LARCT-US/AdmL compared with the randomised RAPIDO-trial. Nor did the STELLAR trial, providing a similar TNT-schedule of scRT followed by 4 cycles of CAPOX, find any differences in QoL when comparing with CRT. With longer follow-up time of six years, QoL was overall higher compared with RAPIDO and LARCT-US[105]. The prevalence of major LARS was lower in LARCT-US compared with RAPIDO (47% vs 59%), while total LARS was similar (78-79%). This can be explained by the more prevalent sphincter-preserving surgery in RAPIDO[61,74]. A direct comparison of late toxicity between LARCT-US and RAPIDO was not possible as different toxicities were recorded, as mainly postoperative complications were recorded in LARCT-US/AdmL. The Polish II study compared TNT, comprising of scRT + 3 FOLFOX4, with CRT and found no differences in late toxicity at seven-years follow-up[106]. They recorded mainly post-operative complications, and the rates were similar to those of LARCT-US/AdmL. Altogether, these comparisons reveal that QoL and late toxicity after TNT are not fundamentally different from those after RT alone or different CRT regimens. In summary, the LARCT-US schedule does not appear to compromise overall QoL or increase late toxicity compared with other sometimes less intense neoadjuvant treatments. This is reassuring and suggests that concerns of late toxicity should not limit the use of this TNT schedule.

Papers III and **IV** thus show that i) the lower risk of DM seen in RAPIDO for TNT compared with CRT is upheld over time with the abbreviated schedule of LARCT-US, ii) the increased risk of LRR seen in RAPIDO was not apparent for LARCT-US, suggesting that the choice of surgical approach is more important than the intensity or length of the oncological treatment, and iii) the LARCT-US schedule does not affect QoL negatively compared with the RAPIDO schedule, but rather the fewer number of cycles of chemotherapy decrease neurotoxicity. The best treatment strategy is for LARC patients is still not determined, nevertheless, as long-term results of several randomised studies have now been presented[63,107-109], TNT is rapidly becoming the new standard over CRT, with more patients achieving pCR and cCR, allowing for a W&W-strategy in more patients. TNT has shown a lowering of the risks of DM but does not seem to improve risk of LRR or OS. Further, which TNT-schedule that is the best is also still an ongoing discussion. In the UNICANCER-PRODIGE 23 trial, TNT comprised of a triple-regimen of mFOLFIRINOX followed by CRT and then adjuvant therapy[62]. The study

showed similar rates of pCR as in RAPIDO, as well as a significantly prolonged DFS, lower DM-risk and possibly improved OS. Compliance was high, over 90%, in the PRODIGE-23 study[109]. As LARCT-US/AdmL better represents a real-life situation and compliance was worse compared to both PRODIGE-23 and RAPIDO, it raises the question as to whether many patients in routine care would be able to tolerate the more intense and longer TNT of the PRODIGE-23 trial. As treating physicians, we must consider risks and benefits of every treatment. Even if a triple-regimen + CRT (+ adjuvant therapy) seems better at controlling systemic disease, there was no improvement in local control. As the results presented in **papers III-IV** have shown, LARCT-US appears to be a good TNT-option. However, as discussed, if organ preservation is the goal, the shorter schedule appears to be as good, but the slightly longer RAPIDO-schedule could probably be better for systemic control, if the patient can tolerate more treatment. Correspondingly, the PRODIGE-schedule could be considered for younger patients with high-risk tumours. In PRODIGE-23, QoL was assessed every six months up to two-years, showing clear improvement over time[110]. At the two-year follow-up, QoL was overall similar (for some items slightly better) compared with RAPIDO at three years. It can be assumed that there was further improvement at three years for the PRODIGE-23 patients, thus better than what was seen in both RAPIDO and LARCT-US. However, again, difference in median age between the studies should be taken into account. Finally, these data and those of the RAPIDO trial suggest that baseline information on the original tumour should be considered when the surgical approach after TNT is determined in non-completely responding tumours to uphold appropriate local control.

Strengths and limitations

An advantage in all articles is the use of the SCRCR. Clinicians, mainly surgeons and oncologists, report all cases and data can be entered throughout the entire treatment course. Unavoidably, some variables are missing or inaccurately documented. The U-CAN ethical permission allows for the supplementation of relevant variables from the clinical records. A separate ethical approval allows the same supplementation of all missing/correction of variables in SCRCR, even those where registration has stopped, for CRC patients living in the Uppsala region (and the Dalarna region for rectal cancer patients) at the time of diagnosis since 2010. Thanks to this, missing values and errors have been minimised, and the number of variables registered, quite extensive. Corrections in SCRCR are not always possible but mistakes are corrected in the research files. At the same time, Sweden has exceptionally high-quality registry reporting with high coverage[91,92]. For **paper I**, this allowed for a large-

scale national study. Our cohort represents the entire Swedish population with a large sample size, over 10 000 patients. While heterogeneity is typically a disadvantage in registry studies, in this context it provides an opportunity to examine differences between treatment groups and timing to surgery making the results more generalisable. For **paper II**, comparisons of the information from the SCRCR were made with the medical records, allowing for correction of wrongly documented data. With our large, unselected population-based cohort, this resulted in close to 100% coverage.

The main limitations of **paper I** are its retrospective design and that it is a registry study. A prospective study would provide better control of the study populations. For **paper II**, it would have been valuable to additionally evaluate TD and LN on MRI, which has recently been advocated as important in the clinical staging[29] and is today often included in the radiology report at the MDT conference. Both have been incorporated in the latest guidelines. In addition, other factors not included in the guidelines, such as mucinous tumour, are also reported by radiologists and may have influenced the treatment decision[111,112]. The heterogeneity of the cohort and its subdivision into several groups limited the number of patients in some subgroups. This was particularly evident when comparing across time periods, with the most recent one (2019–2020) being only two years and hence half the number of patients compared with the two earlier periods. Furthermore, no independent review of the MRI images was performed as the aim was to describe what determines treatment in routine clinical practice by "specially trained teams".

For **papers III-IV**, LARCT-US had a prospective study design, however the data for AdmL was register-based and comes with its limitations, as discussed above. A slightly higher incidence of late toxicity in LARCT-US patients compared with AdmL may reflect more complete registration within a clinical study. QoL data were available only for a subset of patients, but the response rate was high (83%), exceeding most comparable trials (40-70%)[105,110,113-116], including RAPIDO (79%)[96]. Data collection was delayed during the COVID-19 pandemic, extending follow-up up to five years, but this was not believed to influence the results. Inter-trial comparisons are challenging. LARCT-US was deliberately designed like RAPIDO, with the same inclusion and exclusion criteria, to make comparisons possible. Inclusion began immediately after closure of RAPIDO, with the same teams in Sweden handling recruitment of patients to both trials (about 40% of the RAPIDO-patients were from Sweden) and CRFs were identical. Still, key differences exist. LARCT-US/AdmL is a prospective study whereas RAPIDO was a randomised trial. Patients' responses to QoL questionnaires may vary across regions/countries even if the same validated questionnaires are used. Despite

this, the large number of patients and the population-based nature of the cohort reflect a real-life situation, better than the randomised trials. Further advantages of this study are a uniform homogeneous treatment, the use of validated instruments and complete follow-up. The thorough registration of outcome data in the SCRCR makes comparisons with the RAPIDO trial possible.

Concluding remarks and future perspectives

Prediction of outcome, factors impacting treatment choice in rectal cancer and the outcome of TNT have been the focus of the articles presented. The importance of pCR for outcome has been shown in **papers I** and **III**, while **paper II** showed that the desire for organ preservation and increasing chance for tumour downsizing and to achieving cCR have affected guidelines and treatment choices over the years. Although information on LARS was available for W&W-patients, **Paper IV** did not investigate if there were any differences in QoL for patients with CR compared with non-CR, however this would of course be of interest.

There is a desire to further improve the detection of patients responding well to neoadjuvant treatment. By finding the "good or poor responders" it would facilitate treatment choice and many patients that do not benefit from the treatment could then avoid the adverse effects. This has however been hampered by a lack of prospectively collected tumour material, especially before treatment/at baseline. There are few collections with more than one hundred cases and sufficient material of high quality. Further, there are still few studies that have found markers of clinical relevance that can identify "good or poor responders".

Material collected from the RAPIDO-trial together with material from U-CAN has resulted in a large collection of tumour material and blood enabling the exploration of the relevance of prognostic and predictive markers in a better way than previously. Better knowledge of response predictors can modify treatment for many patients and e.g., also allow the initiation of RT or CRT/TNT in patients with early tumours otherwise operated directly. Analyses for metabolomics have already been done, with some promising results. Analyses of proteomics have started, and results will be available soon. There is also the potential to analyse circulating tumour DNA (ctDNA), a more novel and promising technique that has been explored in several studies[117].

The fields of metabolomics and proteomics have been expanding in recent years as techniques for the testing of metabolites and proteins in blood samples have been evolving. There are still few studies that focus on finding potential markers for treatment response in rectal cancer within these fields. Consequently, the findings of future projects mentioned will hopefully be of great

value and contribute to the field. The hope is to find biomarkers in blood that can have clinical value and, in the future, can potentially be used in the clinic as a standard practice and could be added to the treatment guidelines.

The NAR-score can be used as a surrogate endpoint, but we have shown that is does not have more information than pT- and pN-stage alone. The score has already been analysed on the national material (**Paper I**), and on our own material (Uppsala and Dalarna region) together with another slightly larger population cohort (Stockholm region)[70]. The NAR-score was also investigated in **paper III** and showed an association to both LRR and DM in a prospective study, further proving the practical use of the score.

Paper II is based on a population-based cohort from two different regions in Sweden (Uppsala- and Dalarna region) and has now been compiled to include 1800 rectal cancer (M0) patients from 2010-2022. What has not yet been investigated in this cohort and would be of interest is to evaluate the results; how the strategies that have been applied over the years have impacted the risk for local recurrence, distant metastases, and survival. It would also be of interest to investigate resource access and if there have been differences in the regions. We have already shown that rectal cancer patients are slightly less radiated today than only some years ago. Less radiation could mean more relapses, but at the same time less expenses for healthcare and fewer adverse side-effects for the patients. This investigation is now ongoing and another set of patients from the Gävleborg region is included to create an even larger cohort.

TNT as used in **papers III+IV** represents an improvement over the previous reference treatment CRT with postoperative adjuvant chemotherapy in that fewer distant metastases were observed. It also results in more cCRs with the obvious advantage of less patients requiring major surgery. The treatment is however more intense, at least if adjuvant chemotherapy, the least evidence-based component, is part of the treatment. Over-treatment of groups of patients may, thus, have become more pronounced, and selection of the optimal patients is crucial. The TNT schedule used in LARCT-US will most likely not be a final solution since it only marginally, albeit clinically significantly, decreases the risk of DM. The weakest component is still the treatment for the disseminated systemic disease. Tripple combination chemotherapy, as e.g. used in PRODIGE-23 may be more effective but issues of patient tolerability will then be more important. Many LARCT-US patients did not tolerate the less intense doublet regimen used. Also, the radiation schedule and how it is delivered can be improved. At present, a nationwide randomised study (PRORECT, clincialtrials.gov NCT04525989) compares photons with protons in these patients. Hopefully there will be a toxicity benefit related to how the radiotherapy is delivered.

Another emerging treatment option, already established in many other cancer types, is immunotherapy. In Sweden, it is recommended as first-line treatment in patients with metastatic colorectal cancer and a deficient mismatch repair system (dMMR) – a biomarker known to predict good response to immunotherapy. Immunotherapy for localised rectal cancer is not yet approved by the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA)[14]. As the field is rapidly changing, the Swedish guidelines recommend that all non-metastatic dMMR cases should be discussed in MDTs at university hospitals[14]. The prevalence of dMMR is said to be present in 5-10% of rectal cancer patients[14]. However, in the population-based Uppsala/Dalarna study, only 2% were dMMR[73]. Several studies are currently investigating the use of immunotherapy alone or combined with TNT for LARC, and the results are promising, with up to 100% cCR in dMMR patients[118] and higher rates of cCR in patients with a proficient MMR (pMMR) if combined with TNT[119,120]. Severe adverse effects appear comparable to, or slightly more frequent than seen with CRT/TNT, although results vary across studies[119,120]. The high costs of immunotherapy is also an important consideration. Larger randomised studies are necessary to evaluate the short and long-term effects and outcomes of immunotherapy in non-metastatic rectal cancer, supporting further individualisation of treatment.

Populärvetenskaplig sammanfattning

Ändtarmscancer är en av de vanligaste cancerformerna i Sverige med 2000 nya fall årligen. Prognosen har förbättrats markant under de senaste decennierna tack vare bättre stadieindelning med magnetisk resonanstomografi (MRT), förfinade kirurgiska tekniker och optimerad onkologisk behandling. Ändtarmscancer delas in i riskgrupper utifrån risken för återfall, vilket kräver olika behandlingsstrategier. Standard idag är att operera direkt om tumören är liten och det anses lätt att kunna få bort hela tumören. Vid mer avancerad sjukdom eller när tumören behöver krympa för att underlätta kirurgi, ges preoperativ (neoadjuvant) behandling. Detta kan bestå, antingen bara av strålbehandling, eller strålbehandling i kombination med kemoterapi (radiokemoterapi). På senare tid har total neoadjuvant behandling (TNT), oftast då strålning följt av kemoterapi, framstått som en överlägsen behandling för lokalt avancerad rektalcancer (LARC).

Behandlingssvar varierar avsevärt mellan tumörer. Vissa kan svara så pass bra på neoadjuvant behandling att hela tumören försvinner. Detta har medfört en önskan till att undvika kirurgi, organbevarande strategi, och att man följer patienten kliniskt med endoskopisk undersökning (att titta upp i tarmen) och röntgen. Trots omfattande forskning återstår det att identifiera tillförlitliga markörer för god respons. TNT leder till att fler patienter får komplett regress av tumören jämfört med den tidigare standarden med radiokemoterapi. LARCT-US studien behandlade LARC-patienter i nästan hela Sverige med TNT. Detta var ett något förkortat behandlingsprotokoll baserat på en annan internationell randomiserad studie (RAPIDO) som jämförde TNT mot radiokemoterapi. I RAPIDO-studien sågs färre fall av fjärrmetastaser (systemiska återfall), men däremot en viss ökning av lokala återfall (11% vs 6%). Syftet med denna avhandling var att identifiera faktorer som påverkar valet av neoadjuvant behandling och att undersöka effekterna av behandling hos rektalcancerpatienter.

Delarbete I utvärderade ”neoadjuvant rectal (NAR) score”, som utvecklades för att kunna förutsäga prognos och kunna jämföra olika behandlingar i kliniska prövningar. NAR-score kunde skilja mellan två olika behandlingar som har olika celldödande effekter och verkar fungera oavsett given behandling.

Delarbete II ger en beskrivning av behandlingsval över tid i en oselekterad patientkohort från två angränsande svenska regioner (Uppsala och Dalarna). MRT-baserad riskgruppering påverkade behandlingsvalet mest, med färre patienter som fick strålbehandling över tid och ändringar i vårdprogrammet för ändtarmscancer har följt detta. Variationer i MR-tolkning och en starkare önskan att minska på strålning i Dalarna kan förklara regionala skillnader. Överenskommenselen mellan kliniskt (MRT) och patologiskt tumörstadium var bristfällig, särskilt för lymfkörtelstadieindelning, och kräver förbättring.

I delarbete III undersöktes resultaten efter längre uppföljning och vad som kan förutsäga återfall i LARCT-US. Det förkortade TNT-schemat uppnådde utmärkt systemisk kontroll (25%) och få lokala återfall (6%). Den låga risken för lokalrecidiv jämfört med i RAPIDO kan återspegla att man vid svenska sjukhus opererade med mer adekvata marginaler runt tumören och därmed minskade risken för kvarvarande tumörceller utanför operationsområdet. Flera tumörrelaterade faktorer som bedöms på MRT och behandlingsrespons var associerade med återfallsrisk.

Delarbete IV utvärderar livskvalitet (QoL) och senbiverkningar efter LARCT-US. QoL var jämförbar med TNT-armen i RAPIDO. Allvarlig tarmdysfunktion var mindre frekvent i LARCT-US (45% vs 59%). Allvarliga senbiverkningar förekom hos 12% vid tre års uppföljning och hos 8% vid fem år. Sammantaget uppnår det förkortade TNT-schemat gynnsamma onkologiska resultat med acceptabel QoL och få med svåra senbiverkningar.

Sammanfattningsvis var fokus för de delarbeten som presenterats prediktion av utfall och faktorer som påverkar behandlingsval vid ändtarmscancer, samt utfallet av TNT. Betydelsen av behandlingssvar för utfall har påvisats i delarbete I och III, medan delarbete II visade att strävan om att strålbehandla färre individer har ökat över tid och påverkat riktlinjer och behandlingsval genom åren. Däremot märktes inte strävan mot att inte behöva operera så många patienter i den studien, men den omfattar inte de senaste åren då denna önskan ökat som mest. TNT är nu i Sverige standardbehandling för LARC, men fortsatta studier behövs för att hitta behandlingsstrategier som minskar risken för återfall ytterligare i dessa patienter och som ger färre biverkningar, både akuta och sena.

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