Tailored treatment for colon and rectal cancer

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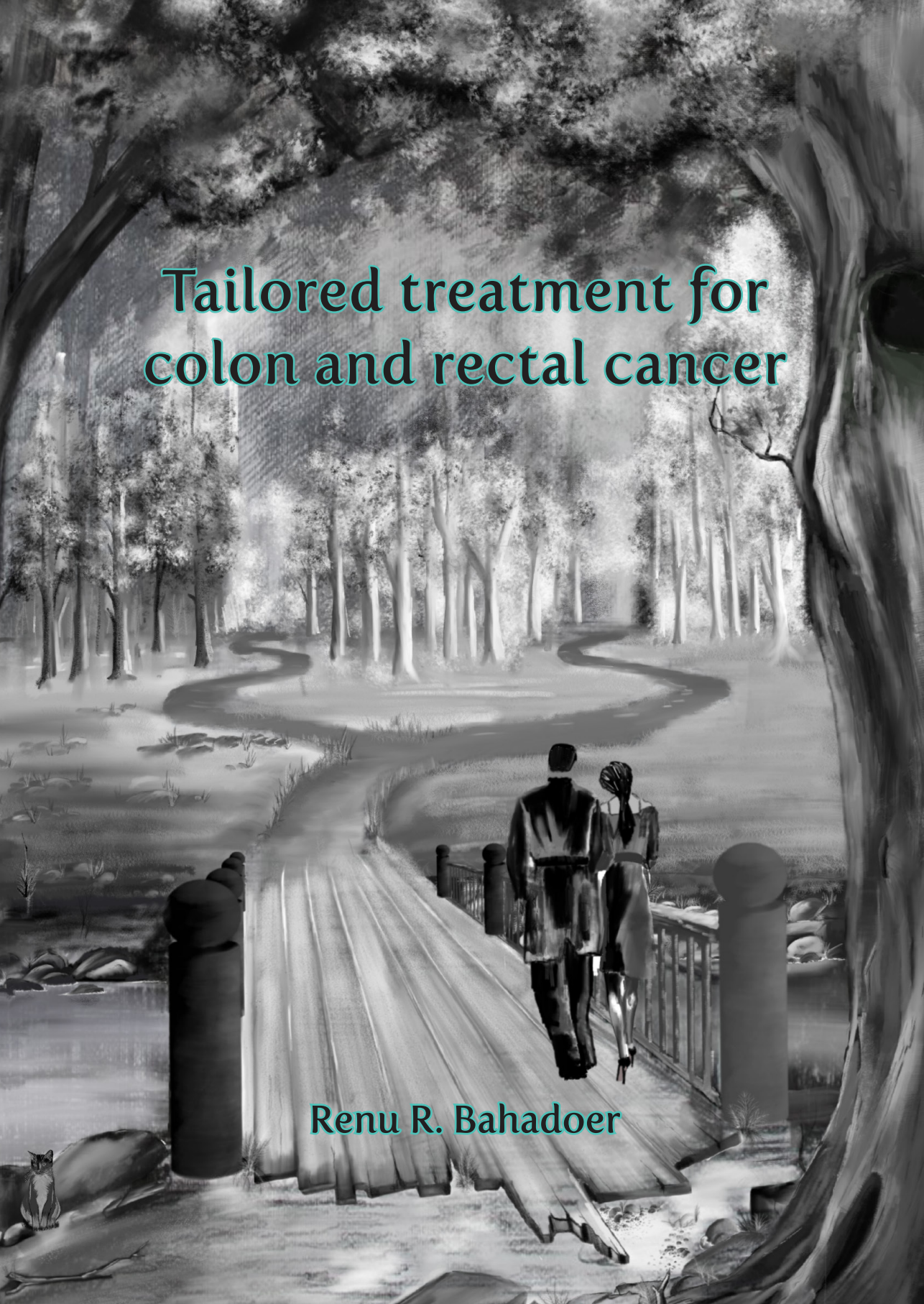

Renu R. Bahadoer

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Cover: original drawing by Ajmal Farid

The cover represents the treatment path that patients follow in modern-day medicine. There is no longer 'one right' treatment. Nowadays there are various treatment options, when possible based on the patients preferences - a tailored treatment.

If you leaf through the book you will also see that the people on the cover continue their path.

The cover also presents my own journey the past few years. I am very proud of the end result (my dissertation) but also grateful for the journey and for everything I have learnt along the way.

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Tailored treatment for colon and rectal cancer

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“It always seems impossible until it’s done.” - Nelson Mandela

CONTENTS

INTRODUCTION


1

General introduction and thesis outline

Epidemiology

Colorectal cancer is the third most common cancer in men and the second most commonly occurring cancer in women. It comes second in terms of mortality. In 2020 there were worldwide approximately 1.1 million and 732,000 new cases of colon and rectal cancer, respectively. Leading to 577,000 deaths of patients with colon cancer and 339,000 deaths of patients with rectal cancer.[1] In 2020, in the Netherlands, 8,100 patients were diagnosed with colon cancer and 3,100 patients with rectal cancer. The incidence increased over time with a peak in 2014 after the introduction of colorectal screening [2], and a decrease in 2020, most likely due to the COVID-19 pandemic [3] (figure 1).

However, improvements in diagnostics and treatment increased overall survival over the years, with the greatest gains for rectal cancer (figure 2).

Colon and rectal cancer are often referred to as colorectal cancer together. However, the colon and rectum have a different embryological origin, anatomy and function. As a consequence the multimodal treatment of colon and rectal cancer is different.[4-6] Moreover, environmental

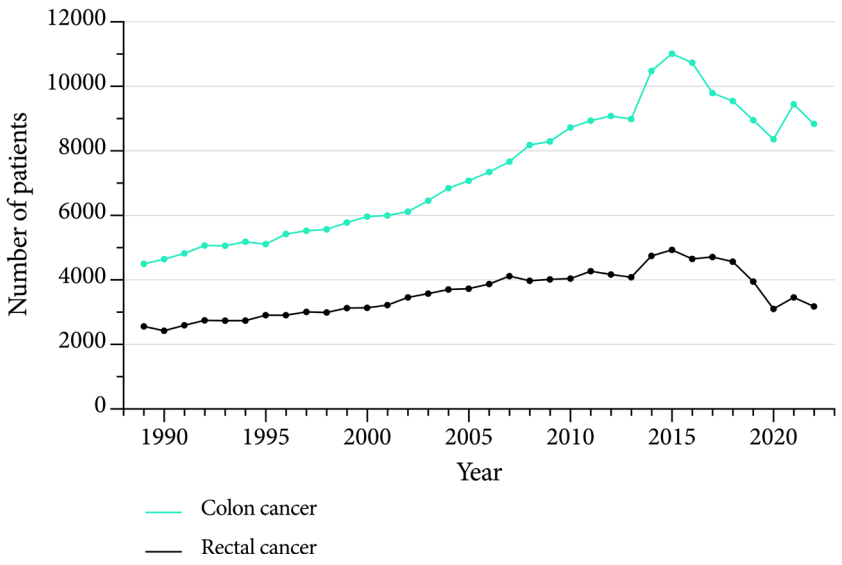

Figure 1 Incidence of colon and rectal cancer in the Netherlands.

The data from 2021 and 2022 is preliminary. Colon cancer also includes cancer of the appendix. Source: NKR, www.iknl.nl, accessed on 26th March 2023.

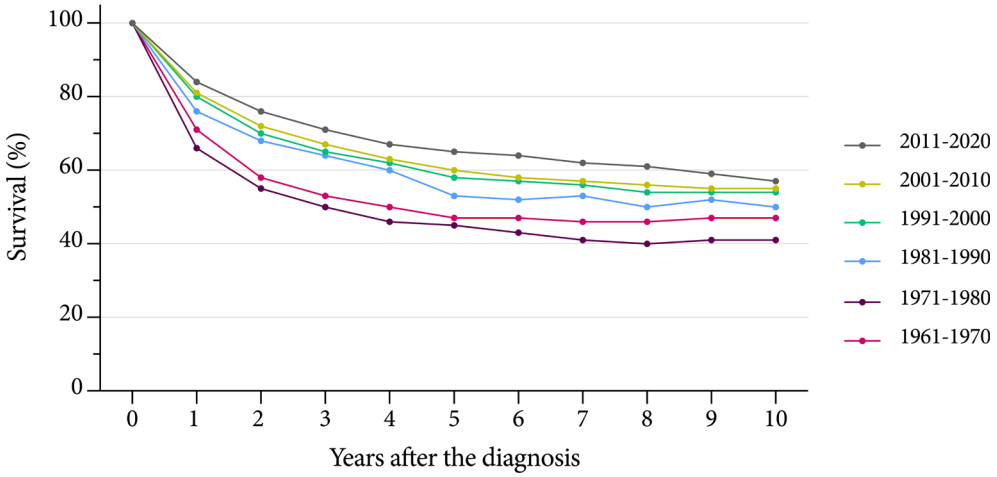

Figure 2a Survival of colon cancer in the Netherlands.

Colon cancer also includes cancer of the appendix. Source: NKR, www.iknl.nl, accessed on 26th March 2023.

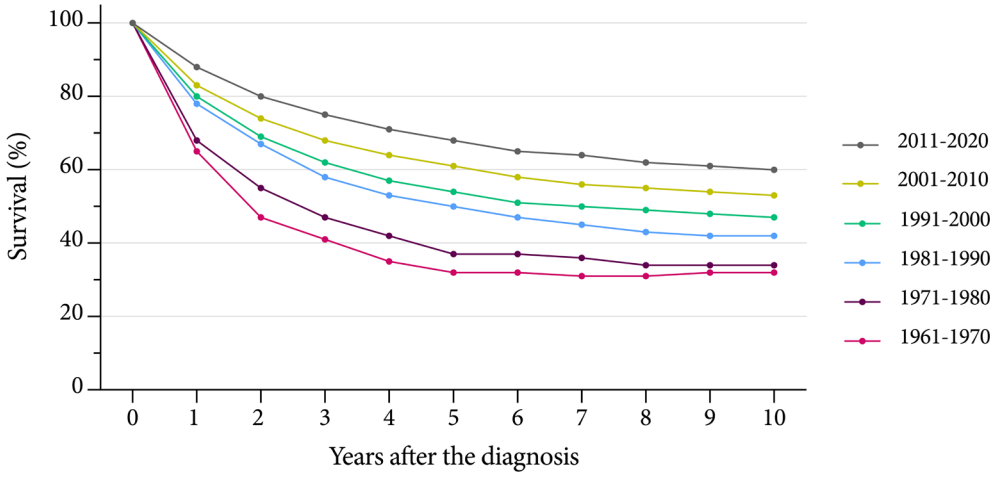

Figure 2b Survival of rectal cancer in the Netherlands.

Source: NKR, www.iknl.nl, accessed on 26th March 2023.

factors such as diet, smoking, and physical activity, might have a different effect; a healthy lifestyle seems to have less impact in preventing rectal cancer compared to colon cancer.[5]

Surgery

Surgery remains the cornerstone in the treatment of colon and rectal cancer although other options are being explored. For rectal cancer, surgery is challenging due to the narrow pelvis. The rectum itself is located in the posterior pelvis and is surrounded by the mesorectal fascia, which envelopes the perirectal fat. The mesorectum is tightly bounded by the sacrum and associated sacral nerves posteriorly, the iliac vessels and branches of the sacral nerves laterally, and the genitourinary structures anteriorly. The introduction of a total mesorectal excision (TME), as first described in 1979 by prof. Heald [7] has reduced the local recurrence rate in rectal cancer drastically and seems suggestive for the survival gains as seen in figure 2b. This technique includes a sharp circumferential resection between the visceral and parietal layers of the mesorectal fascia, including the rectum, tumour and lymphovascular fatty tissue surrounding the rectum to enable radical resection and nerve preservation. For colon cancer, complete mesocolic excision (CME) was introduced in attempt to adopt the same principles as that of TME. However, its additional value is still under debate.[8,9] For both colon and rectal cancer, the introduction of minimal invasive surgery contributed significantly in decreasing morbidity after surgery and has proven to be at least as oncological safe as open surgery.[10-12]

Neoadjuvant and adjuvant therapy

In patients with cT4N0-2M0 colon cancer neoadjuvant (chemo) radiotherapy can be considered according to the Dutch national guidelines.[13] In addition, the added value of neoadjuvant chemotherapy for locally advanced colon cancer is currently being investigated.[14] Patients with stage III colon cancer (pT1-4N1-2M0) are candidates for treatment with three months of adjuvant chemotherapy. In patients with high-risk stage II colon cancer (pT4N0M0) adjuvant chemotherapy should be discussed. When indicated, adjuvant chemotherapy should preferably start within 4-8 weeks after surgery.

Rectal cancer can be categorized as early (cT1-3b, N0, M0, no involvement of the mesorectal

fascia), intermediate (cT3c-dN0 or cT1-3 (no involvement of the mesorectal fascia) N1) and locally advanced rectal cancer (cT4 and/or involvement of the mesorectal fascia and or N2). Early rectal cancer does not require neoadjuvant treatment. Local (endoscopic) excision for T1 tumours or direct surgery is the treatment of choice. For intermediate rectal cancer, preoperative short-course radiotherapy using 5x5 Gy is advised. Currently, for locally advanced rectal cancer chemoradiotherapy followed by surgery according to TME principles after 6–8 weeks is recommended. By contrast with its successful use in colon cancer, adjuvant chemotherapy has not convincingly affected rates of recurrence or survival in rectal cancer.[15] Randomised trials have shown poor tolerability for adjuvant chemotherapy, possibly explaining the absence of an effect.[16] Therefore, the use of adjuvant chemotherapy is not recommended in national Dutch guidelines. However, in several countries such as Belgium and Sweden, adjuvant chemotherapy is part of the standard of care.

Another important change has been the introduction of the multidisciplinary approach including multidisciplinary team meetings, first described in 1975.[17] Patients are individually discussed by several healthcare specialists from different medical specialities involved in the treatment. In the case of colon and rectal cancer these are gastroenterologists, radiologists, radiation and medical oncologists, surgeons and pathologists. The meetings facilitate knowledge exchange between these medical specialists and provides a more extensive understanding regarding the treatment possibilities of other medical specialities. Accurate diagnosing and staging are essential for deciding which treatment strategy to choose for each particular patient. The most current diagnostic capabilities and therapeutic options are easily discussed to ensure the best treatment for each individual patient. A systematic review on the effectiveness of multidisciplinary team meetings reported changes in diagnosis in 18-27% of the evaluated patients, and changes in treatment in 23-42% of the evaluated patients.[18]

Clinical staging

Accurate staging is important in choosing a treatment strategy for colon or rectal cancer. Endoscopy is the first procedure in getting a diagnosis and can be carried out by either sigmoidoscopy or, preferably, a total colonoscopy. A biopsy of the lesion can be performed, the exact location of the tumour can be determined, and in the case of colonoscopy, the presence

or absence of synchronous (pre)cancerous lesions can be evaluated. In addition, preoperative endoscopic marking can help localise flat, small, or subtle colonic lesions that may be difficult to identify by inspection or palpation during surgery.[19]

In addition, for locoregional staging of larger colon tumours, CT-abdomen is used.[20] In rectal cancer to distinguish between cT1 and T2 tumours an Endoscopic Ultra Sound is the preferred method as all individual bowel wall layers are visible. However, it requires expertise and is not available in each hospital. Moreover, it is less accurate for staging larger tumours, in contrast to MRI.[21] MRI has been standardized for staging rectal cancer. With the current MRI techniques, changes in tumour perfusion and microstructure are captured even before morphological changes become apparent.[22]

CT for colon cancer and MRI for rectal cancer are the most accurate modalities to assess the tumour extent and nodal involvement. However, primary nodal staging by imaging remains difficult. This could lead to overstaging which could lead to overtreatment in patients with rectal cancer. For patients with colon cancer, there seems no direct clinical effect of potential overstaging as this will not have an immediate treatment consequence since preoperative treatment is not common.[23,24]

After neoadjuvant treatment, restaging is important in planning further treatment, to plan or even omit surgery. A valuable asset in restaging after neoadjuvant treatment is diffusion-weighted MRI (DWI) which analyses the diffusion of water molecules. Tissues with high cellularity as tumours and lymph nodes have restricted diffusion (high signal), while normal tissue and fibrosis will lead to free diffusion (low signal).[25]

Clinical auditing

Improvement of care by quality assessment was accomplished by clinical auditing: a systematic critical analysis of the quality of medical care, including the procedures used for diagnosis and treatment, and the resulting outcome for the patient, carried out by those personally engaged in the activity concerned. At the beginning of the twentieth-century dr. Ernest Amory Codman described the principles of clinical auditing and conducted the first clinical audit.[26] Today, several national clinical audits have been established that have led to noticeable improvements in patient outcomes.[27-30] Their annual reports are composed with transparency

to patients and insurance companies. Auditing partly works as a result of a response to the awareness of being observed, causing a modification of behaviour.[31]

Thesis outline

EURECCA

The EURECCA (EUropean REgistry of Cancer CAre) platform is the basis for **part I** of this thesis. EURECCA started in 2007 as an initiative of the European Society of Surgical Oncology. It was noticed that considerable variation exists in Europe in cancer management and outcome. This brought forward the need for transparent, uniform international data collection and analysis, to monitor and learn from all aspects of cancer care and to provide feedback and education. The mission of EURECCA is achieving and assuring high quality of multidisciplinary cancer management in Europe with the use of an international multidisciplinary platform of clinicians and epidemiologists aiming to improve the quality of cancer care by data registration, feedback, forming plans for improvement and sharing knowledge of performance and science. Registration of outcome-based quality measurements provides internal feedback, benchmarking, as well as transparency which will rapidly lead to improvements in cancer care. With the audit structure, using anonymous patient data, compliant with national and international laws, the quality of cancer care can be optimized. The ultimate goal with this professional support structure is to minimalize differences in cancer care between European countries.

Since the establishment of EURECCA, various EURECCA comparisons have been undertaken and published, showing a wide variety of treatment strategies across European countries.[32-37] In addition, there are differences across countries regarding survival for colorectal cancer.[38] Thirty-day mortality is usually appointed as an outcome measure to evaluate the postoperative in patients undergoing surgery for colorectal cancer. However, the excess mortality - mortality adjusted for expected mortality in the general population - in the first postoperative year after colorectal cancer surgery is a more accurate reflection of the postoperative risk, especially for older patients.[39,40] This impact of first-year mortality on long-term survival is profound and will impact cancer-related outcomes as well.

Potential differences in one-year excess mortality were investigated using population-based data from four North-European countries; Belgium, the Netherlands, Norway, and Sweden. As these countries have similar expected mortality in all age categories, any disparities between the countries are interesting as they could be consequential to differences in treatment strategies. **Chapter 2** provides an overview of the differences in treatment, 30-day and one-year excess mortality. Mortality was evaluated over time. All analyses were for colon and rectal cancer separated and stratified for stage, age category and country.

As older patients are in general more frail and have more comorbidities, overall survival in older patients is less compared to younger patients. However, to make reliable statements on survival after colorectal cancer, cancer-related survival should be analysed instead of overall survival. To estimate cancer-related survival in the absence of reliable information on the cause of death, relative survival can be calculated, excluding death due to any cause. Different Dutch studies have concluded that the relative survival of older patients with colorectal cancer has improved, leading to almost similar cancer-specific survival compared to the younger population after surviving the first postoperative year.[41,42] Again, emphasising the importance of the first postoperative year. It was not investigated before whether the effect of disappearing age-related differences is also present on a national level for colorectal cancer in other European countries. The results of the analyses, for colon and rectal cancer separated, of one-year relative survival and one-year relative survival with the condition of surviving the first year in Belgium, the Netherlands, Norway, and Sweden are described in **chapter 3**.

RAPIDO

The investigator-driven, international, randomised-controlled RAPIDO trial (Rectal cancer And Pre-operative Induction therapy followed by Dedicated Operation) will be discussed in **part II**. It was hypothesised that delivering chemotherapy preoperatively after radiotherapy (a total neoadjuvant therapy) would increase compliance and reduce distant metastases without compromising locoregional control in patients with locally advanced rectal cancer.

The RAPIDO trial was based on the Dutch M1-trial [43] in which patients with primary metastatic

rectal cancer received short-course radiotherapy, followed by six cycles of capecitabine, oxaliplatin, and bevacizumab, and surgery after 6–8 weeks. Compliance with chemotherapy was 84% (42 of 50 patients received all six cycles) and primary tumour downstaging occurred in 47% (20 of 43 patients who received surgery). Moreover, a pathological complete response of the primary tumour was reported in 11 of 43 patients (26%) who received surgery.[43]

The optimal radiotherapy fractionation and the interval between radiotherapy and surgery were investigated in the Stockholm III trial.[44] Participants were randomly assigned to receive either 5×5 Gy (short-course radiotherapy) with surgery within 1 week or after 4-8 weeks or 25 × 2 Gy (long-course radiotherapy) with surgery after 4-8 weeks. It was concluded that all treatment groups had similar oncological results and that postoperative complications were significantly reduced after short-course radiotherapy with a delay compared to short-course radiotherapy with immediate surgery.[44]

The RAPIDO regimen consisted of short-course radiotherapy (5x5 Gy) followed by 18 weeks of chemotherapy (six cycles of CAPOX or nine cycles of FOLFOX4) followed by total mesorectal excision within 2-4 weeks. It was compared to the standard of care for locally advanced rectal cancer: long-course chemoradiotherapy (28 x 1.8 Gy or 25 x 2.0 Gy, with concomitant twice-daily oral capecitabine) followed by total mesorectal excision within 6-10 weeks. If adjuvant chemotherapy was part of the participating hospitals' policy, adjuvant chemotherapy with eight cycles of CAPOX or 12 cycles of FOLFOX4 was allowed. The primary endpoint was Disease-related Treatment Failure, defined as the first occurrence of locoregional failure, distant metastasis, a new primary colorectal tumour, or treatment-related death. Locoregional failure included locally progressive disease leading to an unresectable tumour, local R2 resection, or local recurrence after an R0–R1 resection. In **chapter 4** the results of the primary aim of the RAPIDO trial are reported and discussed. As the main focus of the RAPIDO trial was to decrease distant metastases, the patterns of distant metastases and prognosis after relapse in the RAPIDO trial were investigated for a better understanding of the clinical nature of locally advanced rectal cancer and whether it is influenced by different treatment modalities. These results are outlined in **chapter 5**.

IWWD

Surgery has always been the cornerstone in the treatment of rectal cancer. However, a trend towards organ-preserving treatment is upcoming and is the focus of **part III**. Patients with a clinical complete response on reassessment imaging after neoadjuvant treatment may refrain from immediate surgery and undergo a strict surveillance strategy, a so-called watch-and-wait (W&W) approach.

After an international consensus meeting in 2014 on W&W for rectal cancer, a network of high-profile clinicians from expert centres around the world established the International Watch & Wait Database (IWWD) under the umbrella of EURECCA and the Champalimaud Foundation in Lisbon.[45] The IWWD is an international, multicentre, partly retrospective and partly prospective cohort database, created to collect all available data to provide an understanding of the risks and benefits of W&W after achieving a clinical complete response after neoadjuvant treatment. Data registration started in April 2015. The ultimate goal for this prospective information is to become the platform for developing best practice guidelines in organ preservation and surveillance.

Together with the rise in older patients, the incidence of colorectal cancer worldwide has increased in young patients (younger than 50 years) over the past decades.[46] The incidence of rectal cancer in adult patients younger than 50 years within Europe has increased annually by 1.6-3.5% between 1990 and 2016.[47] By 2030 nearly one in four diagnoses of rectal cancer will be in patients younger than 50 years.[48] First described by Habr-Gama and colleagues [49] and followed by different cohort series,[50-52] the safety and feasibility of W&W has been confirmed in patients with a clinical complete response after neoadjuvant therapy. Nevertheless, it is questioned whether this approach would be oncological safe for young patients with a longer life expectancy. It seems that there might be more hesitance among treating clinicians to initiate W&W in young patients with a clinical complete response in contrast to older patients. To investigate this thought, as it was not done before for this specific group, data from the IWWD was analysed. In **chapter 6** the results are described.

Finally, **chapter 7** provides a summary and discusses the future perspectives.

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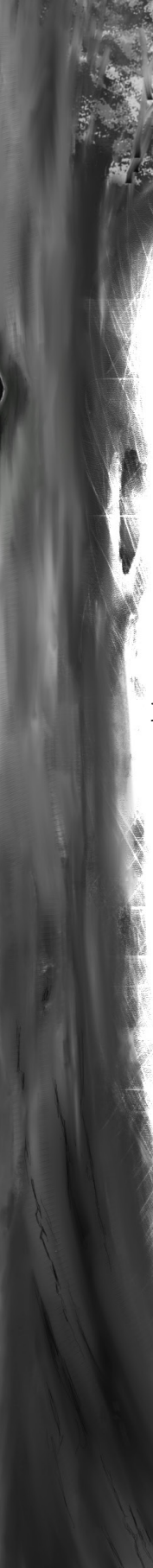
PART I - EURECCA



One-year excess mortality and treatment in surgically treated patients with colorectal cancer: A EURECCA European comparison

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Abstract

Background: Mortality in the first postoperative year represents an accurate reflection of the perioperative risk after colorectal cancer surgery. This research compares one-year mortality after surgery divided into three age-categories (18-64, 65-74, ≥75 years), focusing on time trends and comparing treatment strategies.

Material: Population-based data of all patients diagnosed and treated surgically for stage I-III primary colorectal cancer from 2007 to 2016, were collected from Belgium, the Netherlands, Norway, and Sweden. Stratified for age-category and stage, treatment was evaluated, and 30-day, one-year and one-year excess mortality were calculated for colon and rectal cancer separately. Results were evaluated over two-year time periods.

Results: Data of 206,024 patients were analysed. Postoperative 30-day and one-year mortality reduced significantly over time in all countries and age-categories. Within the oldest age category, in 2015-2016, one-year excess mortality varied from 9% in Belgium to 4% in Sweden for colon cancer and, from 9% in Belgium to 3% in the other countries for rectal cancer. With increasing age, patients were less likely to receive additional therapy besides surgery. In Belgium, colon cancer patients were more often treated with adjuvant chemotherapy ($p<0.001$). For neoadjuvant treatment of rectal cancer, patients in Belgium and Norway were mostly treated with chemoradiotherapy. In the Netherlands and Sweden, radiotherapy alone was preferred ($p<0.001$).

Conclusions: Despite improvement over time in all countries and age-categories, substantial variation exists in one-year postoperative mortality. Differences in one-year excess postoperative mortality could be due to differences in treatment strategies, highlighting the consequences of under- and over-treatment on cancer survival.

Keywords: Colorectal Neoplasms, Mortality, Internationality, epidemiology, treatment

Introduction

Colorectal cancer is the third most common cancer in men and the second most commonly occurring cancer in women.[1] Although other treatment options are being investigated [2], surgery continues to play an essential role in the treatment of colorectal cancer. An important outcome measure for surgery is postoperative mortality and is usually described as 30-day mortality. An earlier study by Dekker et al. revealed that the excess mortality (mortality adjusted for expected mortality in the general population) in the first postoperative year after colorectal cancer surgery is a more accurate reflection of the postoperative risk, in comparison with the 30-day mortality. Death in the first postoperative year, for stage I-III colorectal cancer patients, is in 25% of patients not expected to be from cancer itself or a recurrence but rather an adverse effect of treatment.[3] Across countries survival disparities for colorectal cancer exists.[4] Various EURECCA comparisons have been published, showing a wide variety of treatment strategies across European countries.[5-10]

Considering the importance of the first postoperative year, we used this outcome for comparative purposes of the postoperative course as this may best reflect treatment-related outcomes. The impact of the first-year mortality on long-term survival is profound and will impact cancer-related outcomes as well. Differences in one-year excess mortality between countries are interesting as they could be consequential to differences in treatment strategies. Identifying possible differences in one-year excess mortality and treatment strategies could be a starting point for critical evaluation of national guidelines and their implementation. Using population-based data of four European countries, Belgium, the Netherlands, Norway, and Sweden, the current research aims to make an international comparison of the one-year mortality after surgery and compare time trends and treatment of colorectal patients in three age categories.

Material and methods

Study design and data sources

This project is an observational, international cohort study of consecutively collected population-based data. Data have been collected from the national cancer registries of Belgium, the Netherlands, Norway, and Sweden. Belgian hospitals with care programs for

oncological care, as well as all the pathology labs, are legally required to notify all cancer cases to the Belgian Cancer Registry. In the Netherlands, information about every patient with cancer is gathered in the Netherlands Cancer Registry, managed by the Netherlands Comprehensive Cancer Organisation. Data from Norway have been collected from the Cancer Registry of Norway.[11] All medical doctors in Norway are instructed by law to notify all new cancer cases. This registry is linked to the Norwegian Colorectal Cancer Registry, a specialized registry that contains detailed clinical information on all patients with colorectal cancer nationwide.[12] The Swedish Colorectal cancer registry provided clinical data on patients with colorectal cancer in Sweden.[13] All the cancer registries guaranteed the overall quality of data in terms of completeness (>95% of cancer patients in the population registered) and accuracy. No separate ethical approval was needed, as this study was based on de-identified registry data.

Procedures

Data were collected from all patients ≥18 years, diagnosed with primary colon or rectal cancer from January 2007 to December 2016, and undergoing surgical treatment. In case of patients diagnosed with multiple, simultaneous tumours, the tumour with the worst prognostic characteristics, using stage and grade, was chosen for all analyses. Stage was primarily based on pathological information and completed with clinical stage when necessary, using the 7th edition of the AJCC TNM staging. For rectal cancer, pathological information was based on either pT stage (after primary surgery) or ypT stage (after radiotherapy/chemoradiotherapy and surgery). Belgium and the Netherlands provided their data on stage from 2007 to 2009 using the TNM stage 6th edition, the years 2010-2016 were delivered using the TNM 7th edition. Included were stage I-III, leaving out metastatic disease (stage IV) and unknown stage. Colon cancer was defined by topographical codes C18-C19 and rectal cancer by code C20 of the International Classification of Diseases for Oncology.[14] In Sweden, topographical code C19 (rectosigmoid) was not defined as surgeons decide during surgery whether the tumour is part of the colon or the rectum. Only patients undergoing surgical resection were included in this study. Surgical treatment was defined as surgical removal of the tumour-bearing bowel segment, irrespective of curative or palliative intent. Patients with local excision

of the tumour, including transanal endoscopic microsurgery, were excluded. In Norway, data on chemotherapy was not available. The assumption was made that patients received chemotherapy as per national guidelines.[15] Supplementary table S1 provides an overview of the data selection of each country.

Statistics

Patients were divided into three groups: <65 years, 65-74 years, and ≥75 years. All analyses were performed stratified by tumour location, country, stage, and age category. For the time trend analyses, periods consisting of two years were made. Thirty-day and one-year overall mortality were calculated, as well as treatment characteristics, using SPSS version 25.0. Differences were tested with chi-square tests. Finally, one-year excess mortality was calculated using the following formula: (observed numbers of death in the first year – expected number of deaths in the matched general population) / (number of patients). The expected number of deaths was calculated using national life tables (www.mortality.org) matched for country, age, sex, and year of incidence. Time-trends for mortality were analysed using logistic regression with mortality as outcome and time periods as covariate, p-values over the years are reported.

Results

Patient characteristics

The surgical treatment rate of all patients ≥18 years diagnosed with stage I-III colorectal cancer and reliable follow-up between 2007 and 2016 varied from 64.3% in Belgium and Norway to 66.1% in Sweden and 66.9% in the Netherlands (supplementary table S1). For the current analyses, data of 206,024 patients were included (Belgium 53,071 patients, the Netherlands 88,784 patients, Norway 25,548 patients, Sweden 38,621 patients). Details, stratified by tumour location, on distribution within age-categories, gender, year of diagnosis, and stage are displayed in table 1.

Table 1a Characteristics of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	Belgium			The Netherlands		
	< 65 years (N = 9,645)	65-74 years (N = 11,280)	≥ 75 years (N = 18,063)	< 65 years (N = 17,402)	65-74 years (N = 21,784)	≥ 75 years (N = 24,919)
Gender						
Male	5,362 (55.6)	6,652 (59.0)	8,461 (46.8)	9,298 (53.4)	12,163 (55.8)	11,868 (47.6)
Female	4,283 (44.4)	4,628 (41.0)	9,602 (53.2)	8,104 (46.6)	9,621 (44.2)	13,051 (52.4)
Year of diagnosis						
2007-2008	1,691 (17.5)	1,979 (17.5)	3,489 (19.3)	3,294 (18.9)	3,525 (16.2)	4,863 (19.5)
2009-2010	1,808 (18.7)	2,032 (18.0)	3,525 (19.5)	3,341 (19.2)	3,611 (16.6)	4,991 (20.0)
2011-2012	1,907 (19.8)	2,157 (19.1)	3,717 (20.6)	3,316 (19.1)	4,079 (18.7)	4,952 (19.9)
2013-2014	2,122 (22.0)	2,781 (24.7)	3,762 (20.8)	3,249 (18.7)	4,640 (21.3)	5,338 (21.4)
2015-2016	2,117 (21.9)	2,331 (20.7)	3,570 (19.8)	4,202 (24.1)	5,929 (27.2)	4,775 (19.2)
Stage						
Stage I	2,313 (24.0)	2,856 (25.3)	3,373 (18.7)	3,621 (20.8)	5,326 (24.4)	4,975 (20.0)
Stage II	3,534 (36.6)	4,492 (39.8)	8,434 (46.7)	6,378 (36.7)	8,635 (39.6)	11,534 (46.3)
Stage III	3,798 (39.4)	3,932 (34.9)	6,256 (34.6)	7,403 (42.5)	7,823 (35.9)	8,410 (33.7)

Data are presented as n (%).

Continuation Table 1a Characteristics of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	Norway			Sweden		
	< 65 years (N = 4,564)	65-74 years (N = 5,651)	≥ 75 years (N = 8,698)	< 65 years (N = 5,585)	65-74 years (N = 8,162)	≥ 75 years (N = 12,775)
Gender						
Male	2,312 (50.7)	2,835 (50.2)	3,750 (43.1)	2,955 (52.9)	4,215 (51.6)	5,710 (44.7)
Female	2,252 (49.3)	2,816 (49.8)	4,948 (56.9)	2,630 (47.1)	3,947 (48.4)	7,065 (55.3)
Year of diagnosis						
2007-2008	806 (17.7)	950 (16.8)	1,655 (19.0)	1,131 (20.3)	1,466 (18.0)	2,391 (18.7)
2009-2010	852 (18.7)	1,065 (18.8)	1,715 (19.7)	1,131 (20.3)	1,544 (18.9)	2,497 (19.5)
2011-2012	919 (20.1)	1,118 (19.8)	1,682 (19.3)	1,110 (19.9)	1,677 (20.5)	2,499 (19.6)
2013-2014	973 (21.3)	1,206 (21.3)	1,784 (20.5)	1,053 (18.9)	1,694 (20.8)	2,572 (20.1)
2015-2016	1,014 (22.2)	1,312 (23.2)	1,862 (21.4)	1,160 (20.8)	1,781 (21.8)	2,816 (22.0)
Stage						
Stage I	1,012 (22.2)	1,238 (21.9)	1,826 (21.0)	858 (15.4)	1,492 (18.3)	2,109 (16.5)
Stage II	1,800 (39.4)	2,536 (44.9)	4,156 (47.8)	2,207 (39.5)	3,423 (41.9)	5,952 (46.6)
Stage III	1,752 (38.4)	1,877 (33.2)	2,716 (31.2)	2,520 (45.1)	3,247 (39.8)	4,714 (36.9)

Data are presented as n (%).

Table 1b Characteristics of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	Belgium			The Netherlands		
	< 65 years (N = 5,108)	65-74 years (N = 4,288)	≥ 75 years (N = 4,687)	< 65 years (N = 9,767)	65-74 years (N = 8,757)	≥ 75 years (N = 6,155)
Gender						
Male	3,231 (63.3)	2,852 (66.5)	2,702 (57.6)	6,115 (62.6)	5,840 (66.7)	3,531 (57.4)
Female	1,877 (36.7)	1,436 (33.5)	1,985 (42.4)	3,652 (37.4)	2,917 (33.3)	2,624 (42.6)
Year of diagnosis						
2007-2008	1,023 (20.0)	847 (19.8)	977 (20.8)	1,864 (19.1)	1,453 (16.6)	1.158 (18.8)
2009-2010	1,039 (20.3)	847 (19.8)	959 (20.5)	1,877 (19.2)	1,575 (18.0)	1,194 (19.4)
2011-2012	1,022 (20.0)	846 (19.7)	981 (20.9)	1,949 (20.0)	1,711 (19.5)	1,267 (20.6)
2013-2014	1,058 (20.7)	972 (22.7)	900 (19.2)	1,867 (19.1)	1,918 (21.9)	1,351 (21.9)
2015-2016	966 (18.9)	776 (18.1)	870 (18.6)	2,210 (22.6)	2,100 (24.0)	1.185 (19.3)
Stage						
Stage I	1,750 (34.3)	1,504 (35.1)	1,382 (29.5)	1,784 (18.3)	1,924 (22.0)	1,403 (22.8)
Stage II	1,398 (27.4)	1,290 (30.1)	1,595 (34.0)	2,358 (24.1)	2,402 (27.4)	2,066 (33.6)
Stage III	1,960 (38.4)	1,494 (34.8)	1,710 (36.5)	5,625 (57.6)	4,431 (50.6)	2,686 (43.6)

Data are presented as n (%).

Continuation Table 1b Characteristics of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	Norway			Sweden		
	< 65 years (N = 2,408)	65-74 years (N = 2,153)	≥ 75 years (N = 2,074)	< 65 years (N = 3,936)	65-74 years (N = 4,349)	≥ 75 years (N = 3,814)
Gender						
Male	1,426 (59.2)	1,390 (64.6)	1,153 (55.6)	2,303 (58.5)	2,746 (63.1)	2,204 (57.8)
Female	982 (40.8)	763 (35.4)	921 (44.4)	1,633 (41.5)	1,603 (36.9)	1,610 (42.2)
Year of diagnosis						
2007-2008	452 (18.8)	350 (16.3)	390 (18.8)	791 (20.1)	785 (18.1)	806 (21.1)
2009-2010	480 (19.9)	420 (19.5)	435 (21.0)	759 (19.3)	807 (18.6)	787 (20.6)
2011-2012	436 (18.1)	420 (19.5)	417 (20.1)	802 (20.4)	842 (19.4)	781 (20.5)
2013-2014	537 (22.3)	497 (23.1)	412 (19.9)	789 (20.0)	898 (20.6)	731 (19.2)
2015-2016	503 (20.9)	466 (21.6)	420 (20.3)	795 (20.2)	1,017 (23.4)	709 (18.6)
Stage						
Stage I	586 (24.3)	586 (27.2)	541 (26.1)	1,113 (28.3)	1,325 (30.5)	1,116 (29.3)
Stage II	639 (26.5)	651 (30.2)	758 (36.5)	1,139 (28.9)	1,353 (31.1)	1,275 (33.4)
Stage III	1,183 (49.1)	916 (42.5)	775 (37.4)	1,684 (42.8)	1,671 (38.4)	1,423 (37.3)

Data are presented as n (%).

Colon cancer, time trend analysis, stages

Time trends over the years, stratified for stage, age-category, and country, were all statistically significant (p<0.001). Differences in stage distribution between countries in time period 2015-2016 were all statistically significant except for stage II in the older age category. Stage III disease remained the most common stage within the youngest age-category and stage II within the two other age-categories (details in table 2a).

Rectal cancer, time trend analysis, stages

For stage III disease, a substantial increase was observed within the Netherlands within all age-categories, on average, from 42% to 54% over the years. This is contrary to Belgium, which showed a slight decrease in stage III diagnoses, on average, from 38% to 35%. Time trends over the years, stratified for stage, age-category, and country were all statistically significant (p<0.001), except for stage III in the middle age-category in the Netherlands (p=0.262) and stage III in the youngest age-category in Norway (p=0.392) (details in table 2b).

Colon cancer, treatment differences

In all countries and stages, the use of chemotherapy increased with stage and decreased with age. In Belgium, patients were more often treated with adjuvant chemotherapy in comparison with the other countries. For stage III disease in Belgium, this varied from 91.7% in the youngest age-category to 42.1% in the oldest age category. For the Netherlands, this was 86.6% to 25.7%, respectively, and for Sweden, 78.8% to 20.7%, respectively (figure 1a and supplementary table S2a).

Rectal cancer, treatment differences

In the majority of cases, rectal cancer patients in Belgium and Norway were treated with neoadjuvant chemoradiotherapy, while the Netherlands (stage I, II) and Sweden (all stages) preferred neoadjuvant radiotherapy alone (figure 1b). Furthermore, in Belgium, rectal cancer treatment was more frequently completed with adjuvant chemotherapy compared to the Netherlands and Norway in all stages and compared to stage I and II in Sweden (figure 1c and supplementary table S2b).

Colon cancer, time trend analysis, mortality

Overall, 30-day and one-year mortality, stratified for age-category and country decreased over time (p<0.001), with the largest decrease in the Netherlands (figures 2a and 2b). In time period 2015-2016, one-year overall mortality was statistically different between countries in the middle (p=0.004) and oldest (p<0.001) age-category (table 3a). One-year expected mortality remained stable over the years and was comparable for all countries. The decreases in one-year overall mortality are due to reductions in excess mortality over the years. Within the oldest patient group, Belgium had a higher one-year excess mortality in the most recent years (9%), compared to the Netherlands, Norway, and Sweden (5%).

Rectal cancer, time trend analysis, mortality

Time trends for one-year overall mortality over the years, stratified for age-category and country, were all statistically significant (p<0.001). Here too, one-year expected mortality was similar between the countries and over the years (figures 3a and 3b, table 3b). While excess mortality among the youngest Belgian patients was average, the middle and oldest age-category had three times higher one-year excess mortality compared to the average. In the oldest age-category, one-year excess mortality was 9% in the most recent years compared to, on average, 3% in the other countries. Additional analyses with the most recent years learned that the higher one-year overall mortality was reflected in all stages in the oldest group in Belgium, statistically significant for stage II (p=0.007) and stage III (<0.001) (supplementary table S3). However, it was most pronounced in stage III, where a 20% one-year overall mortality was seen in Belgium, compared to an average of 10% in the other countries.

Table 2a Stage time trends in percentages for colon cancer patients.

	Stage I						Stage II					
	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016	P-value	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016	P-value
< 65 years						<0.001						0.003
Belgium	18.3	20.6	21.3	26.1	31.6		39.8	39.2	38.8	33.5	33.2	
The Netherlands	18.2	17.9	18.1	20.1	27.9		38.6	39.7	37.9	36.5	31.8	
Norway	17.7	18.2	19.4	26.3	27.6		44.0	41.5	41.9	36.9	34.2	
Sweden	13.3	15.9	15.2	14.7	17.6		42.9	40.3	39.5	37.3	37.5	
65-74 years						<0.001						<0.001
Belgium	19.4	20.7	22.3	30.7	30.7		43.4	43.3	40.0	36.5	37.6	
The Netherlands	19.5	21.1	22.3	23.0	32.0		43.4	41.5	40.1	40.8	35.0	
Norway	21.6	22.6	19.7	22.4	23.0		44.7	43.7	46.4	45.1	44.4	
Sweden	17.4	18.6	18.6	18.1	18.6		45.1	42.0	42.3	40.9	40.0	
≥ 75 years						0.006						0.375
Belgium	16.2	17.8	17.8	20.3	21.1		47.4	47.6	47.1	45.3	46.2	
The Netherlands	18.0	18.6	19.1	23.3	20.6		46.9	48.4	47.2	42.8	46.3	
Norway	20.7	19.6	20.6	21.9	22.1		48.3	49.0	48.8	46.7	46.2	
Sweden	16.3	16.0	15.1	16.7	18.2		48.8	48.3	47.5	44.4	44.4	

Percentages are conducted from the stages within the same country and age category. P-values are for differences between countries in time period 2015-2016.

Continuation Table 2a Stage time trends in percent ages for colon cancer patients.

	Stage III					
	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016	P-value
< 65 years						<0.001
Belgium	41.9	40.2	39.9	40.4	35.2	
The Netherlands	43.2	42.4	44.0	43.4	40.3	
Norway	38.2	40.3	38.7	36.8	38.2	
Sweden	43.9	43.8	45.3	48.0	44.9	
65-74 years						<0.001
Belgium	37.2	36.0	37.7	32.8	31.7	
The Netherlands	37.1	37.4	37.6	36.1	32.9	
Norway	33.7	33.7	33.9	32.5	32.5	
Sweden	37.5	39.4	39.1	41.0	41.4	
≥ 75 years						<0.001
Belgium	36.4	34.5	35.1	34.4	32.8	
The Netherlands	35.1	33.0	33.7	33.9	33.1	
Norway	30.9	31.4	30.7	31.4	31.7	
Sweden	35.0	35.6	37.4	38.9	37.4	

Percentages are conducted from the stages within the same country and age category. P-values are for differences between countries in time period 2015-2016.

Table 2b Stage time trends in percentages for rectal cancer patients

	Stage I						Stage II					
	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016	P-value	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016	P-value
< 65 years						<0.001						<0.001
Belgium	30.8	33.8	32.5	36.2	38.2		29.4	26.5	29.3	26.4	25.3	
The Netherlands	22.0	16.4	15.7	16.4	20.5		30.5	28.9	22.3	21.2	18.9	
Norway	20.1	21.9	22.5	26.6	29.6		29.2	25.2	26.1	27.0	25.2	
Sweden	27.7	23.1	32.2	28.3	29.9		29.5	32.4	29.7	26.7	26.5	
65-74 years						<0.001						0.001
Belgium	31.4	31.2	35.3	38.2	39.2		32.1	32.8	29.6	28.3	27.7	
The Netherlands	22.8	22.2	17.8	20.0	26.4		34.6	30.8	27.1	24.8	22.6	
Norway	22.0	22.4	27.1	31.4	31.1		31.4	31.4	31.7	29.8	27.5	
Sweden	28.3	28.9	27.7	32.5	33.9		32.1	31.1	34.6	30.1	28.4	
≥ 75 years						<0.001						<0.001
Belgium	27.5	29.2	27.4	30.2	33.6		33.8	33.7	36.9	32.9	32.6	
The Netherlands	24.9	22.0	21.0	21.5	25.0		39.2	36.8	36.9	29.7	25.7	
Norway	24.4	23.7	24.5	30.3	27.6		40.3	39.8	36.0	32.0	34.8	
Sweden	29.7	28.1	28.3	30.1	30.3		34.9	34.3	33.5	32.3	31.9	

Percentages are conducted from the stages within the same country and age category. P-values are for differences between countries in time period 2015-2016.

Continuation Table 2b Stage time trends in percentages for rectal cancer patients

	Stage III					
	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016	P-value
< 65 years						<0.001
Belgium	39.8	39.7	38.3	37.4	36.5	
The Netherlands	47.5	54.8	62.0	62.3	60.5	
Norway	50.7	52.9	51.4	46.4	45.1	
Sweden	42.9	44.5	38.2	45.0	43.5	
65-74 years						<0.001
Belgium	36.5	36.0	35.1	33.5	33.1	
The Netherlands	42.5	47.0	55.1	55.3	51.0	
Norway	46.6	46.2	41.2	38.8	41.4	
Sweden	39.6	40.0	37.8	37.4	37.7	
≥ 75 years						<0.001
Belgium	38.7	37.1	35.7	36.9	33.8	
The Netherlands	35.9	41.2	42.1	48.9	49.3	
Norway	35.4	36.6	39.6	37.6	37.6	
Sweden	35.5	37.6	38.2	37.6	37.8	

Percentages are conducted from the stages within the same country and age category. P-values are for differences between countries in time period 2015-2016.

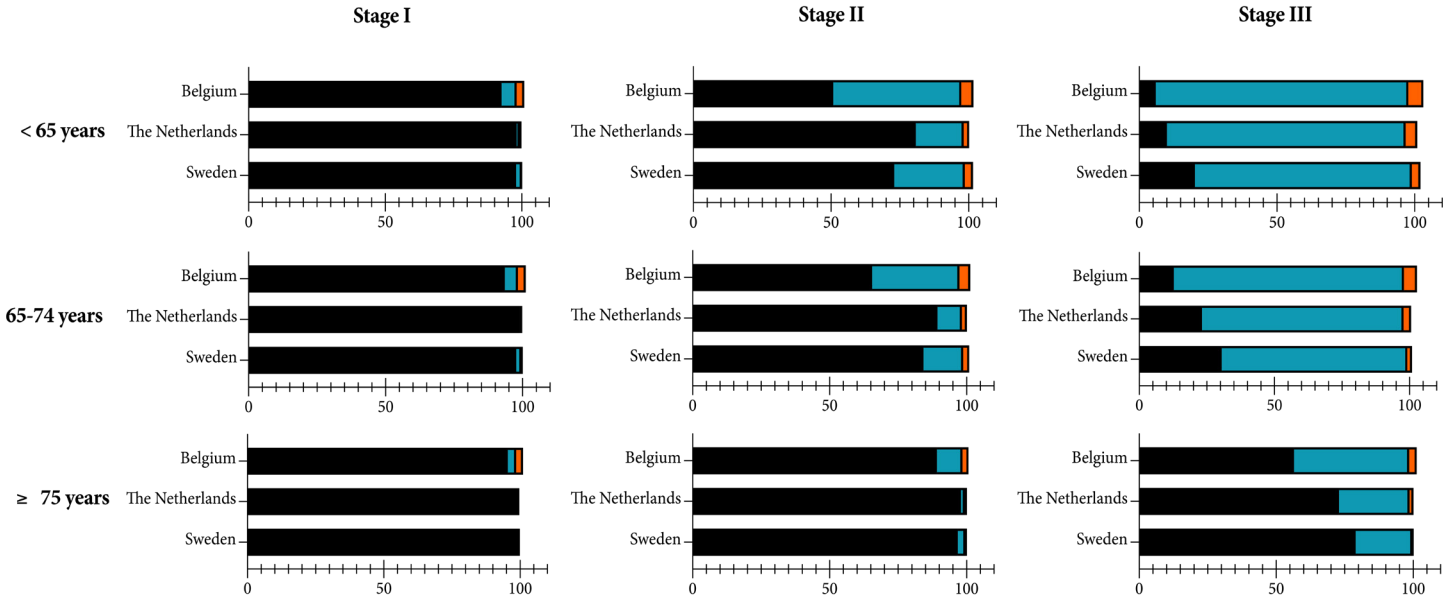

Figure 1a Treatment according to country, age and stage in colon cancer patients. Neoadjuvant and adjuvant treatment are combined; therefore, percentages can be above 100%. Differences between countries for adjuvant chemotherapy, stratified for age category and stage were calculated using chi-square. All differences had a P-value <0.001.

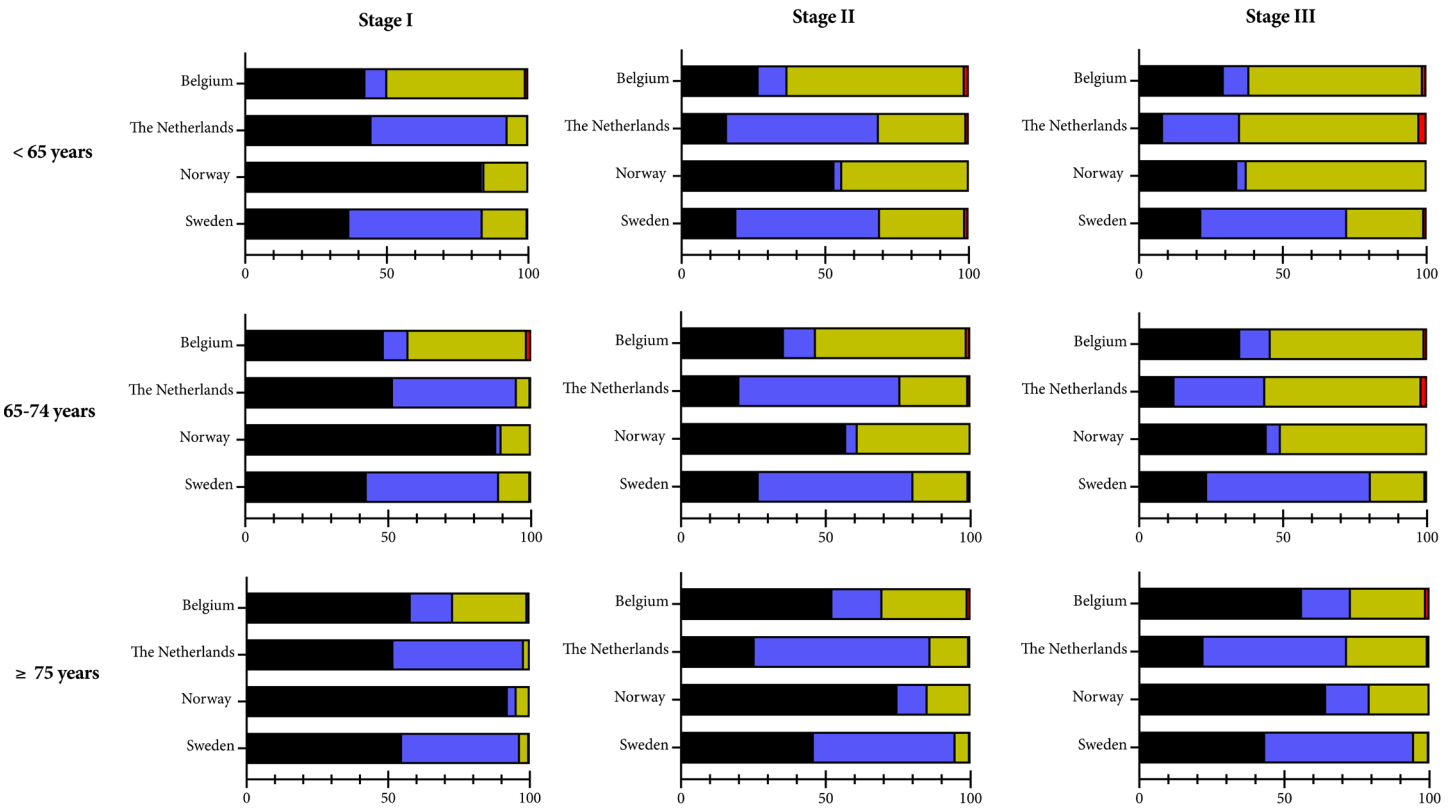

Figure 1b Neoadjuvant treatment, according to country, age and stage in rectal cancer patients. Differences between countries, stratified for age category and stage were calculated using chi-square. All differences between countries for neoadjuvant radiotherapy and chemoradiotherapy had a P-value <0.001.

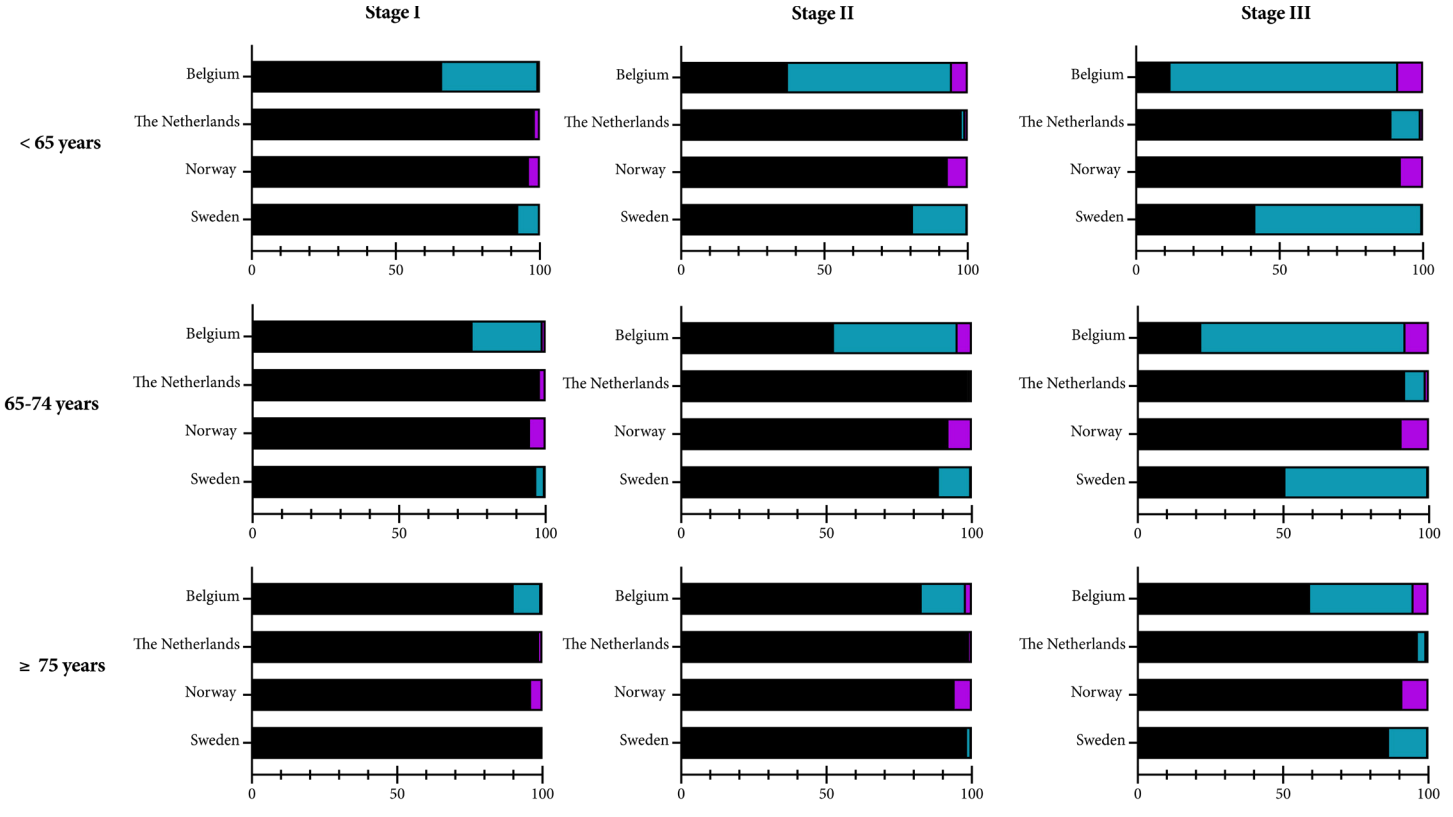

Figure 1c Adjuvant treatment, according to country, age and stage in rectal cancer patients. Differences between countries, stratified for age category and stage were calculated using chi-square. All differences between countries for adjuvant chemotherapy had a P-value <0.001.

Table 3a Mortality time trends in percentages for colon cancer patients.

	≤ 30-day, overall mortality						1st year, overall mortality					
	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016	P-value	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016	P-value
< 65 years						0.70						0.72
Belgium	1.0	1.1	0.9	1.1	0.6		4.7	4.2	3.6	3.0	2.0	
The Netherlands	1.2	1.0	0.8	0.5	0.5		4.2	4.1	3.8	3.1	2.2	
Norway	1.0	0.4	0.1	0.0	0.4		3.8	2.8	2.5	1.5	2.1	
Sweden	0.5	0.6	0.3	0.6	0.3		2.6	2.7	3.0	3.7	2.6	
65-74 years						0.08						0.004
Belgium	2.3	2.3	2.3	1.6	1.6		7.9	7.1	7.8	4.7	5.9	
The Netherlands	3.0	2.5	2.0	1.2	1.0		8.8	7.7	6.3	5.6	4.2	
Norway	1.7	1.8	2.0	1.8	1.1		7.6	6.3	6.4	4.8	3.7	
Sweden	1.2	1.1	1.4	0.9	0.8		5.9	5.2	5.5	5.1	4.8	
> 74 years						<0.001						<0.001
Belgium	6.9	6.1	6.4	5.2	5.6		21.3	18.0	17.9	16.3	16.4	
The Netherlands	9.6	8.7	6.8	5.4	3.9		20.6	18.8	16.2	13.3	11.5	
Norway	6.5	5.8	5.1	4.1	4.1		17.5	16.7	15.3	12.8	11.5	
Sweden	4.2	4.5	4.2	3.8	2.5		14.6	13.9	13.7	12.9	10.5	

P-values are for differences between countries in time period 2015-2016. *No excess mortality.

Continuation Table 3a Mortality time trends in percentages for colon cancer patients.

	1st year, excess mortality				
	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016
< 65 years					
Belgium	4.0	3.5	2.8	2.3	1.3
The Netherlands	3.6	3.6	3.2	2.6	1.5
Norway	3.2	2.3	1.8	1.0	1.6
Sweden	2.0	2.1	2.5	3.2	2.2
65-74 years					
Belgium	6.0	5.2	6.0	2.8	4.1
The Netherlands	6.9	6.0	4.5	3.9	2.5
Norway	5.8	4.6	4.8	2.9	2.0
Sweden	4.2	3.6	4.0	3.5	3.1
> 74 years					
Belgium	15.0	11.6	11.5	9.5	9.4
The Netherlands	14.4	12.7	10.0	7.4	5.3
Norway	10.5	10.0	8.7	5.9	4.7
Sweden	8.0	7.3	7.1	6.6	4.0

P-values are for differences between countries in time period 2015-2016.*No excess mortality.

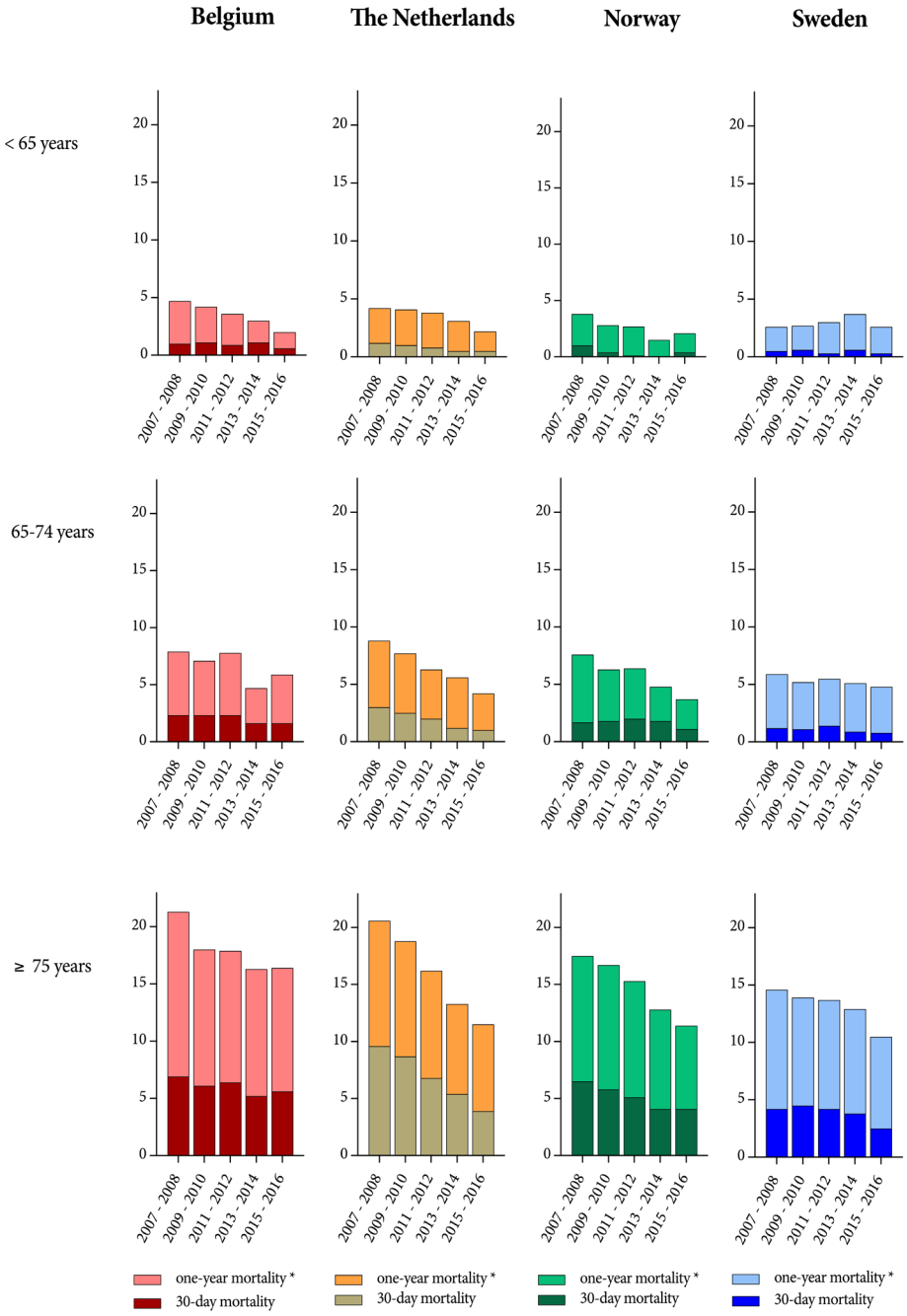

Figure 2 (A) 30-day and one-year overall mortality in colon cancer patients.

* One-year mortality is represented by the full bar.

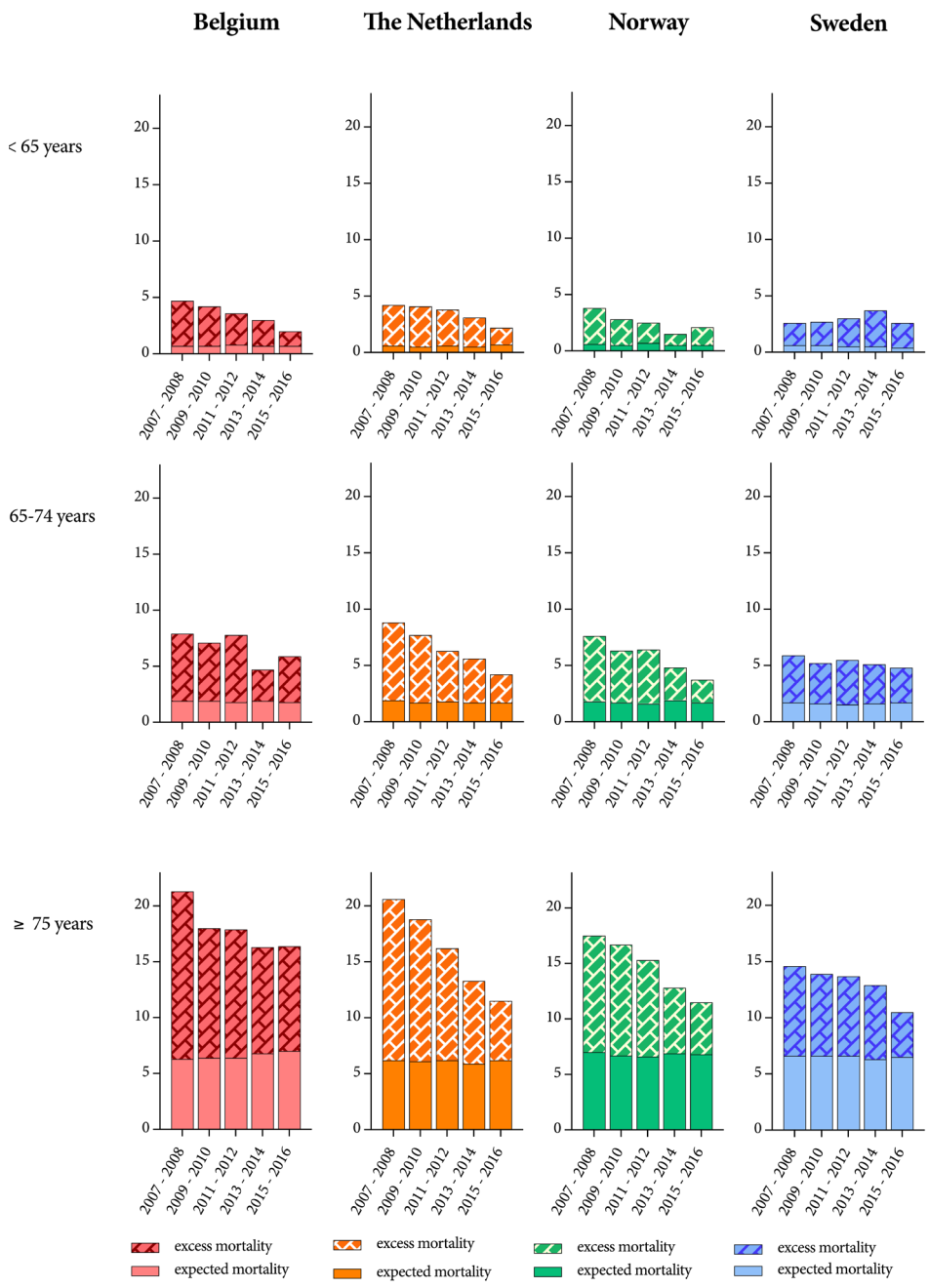

Figure 2 (B) One-year expected and excess mortality in colon cancer patients.

Table 3b Mortality time trends in percentages for rectal cancer patients.

	≤ 30-day, overall mortality						1st year, overall mortality					
	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016	P -value	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016	P-value
< 65 years						0.40						0.20
Belgium	0.4	0.4	0.3	0.2	0.4		3.1	3.0	2.7	2.1	1.7	
The Netherlands	0.8	0.4	0.5	0.4	0.3		3.1	3.0	2.3	2.5	2.0	
Norway	0.2	0.4	0.7	0.4	0.0		2.2	2.5	1.4	1.1	0.8	
Sweden	0.3	0.4	0.4	0.4	0.1		1.9	1.6	2.0	2.4	1.3	
65-74 years						0.06						0.001
Belgium	1.4	0.5	1.8	1.3	1.3		7.0	5.5	7.2	4.9	5.8	
The Netherlands	2.2	1.8	1.8	0.9	1.0		7.1	5.8	6.3	4.2	2.9	
Norway	0.6	1.4	0.7	0.6	0.2		4.3	5.2	4.0	3.0	2.6	
Sweden	1.1	1.1	1.0	1.0	0.4		5.0	4.3	3.8	4.1	3.3	
≥ 75 years						0.005						<0.001
Belgium	6.3	6.9	4.6	4.2	5.3		18.1	19.5	17.8	17.3	15.3	
The Netherlands	7.6	6.0	4.3	3.0	2.8		18.9	14.4	14.0	10.1	8.4	
Norway	3.6	2.8	4.1	1.5	3.1		15.1	9.4	11.3	5.8	9.0	
Sweden	5.6	3.0	2.7	3.7	2.4		14.1	11.3	9.1	8.2	8.7	

P-values are for differences between countries in time period 2015-2016. *No excess mortality.

Continuation Table 3b Mortality time trends in percentages for rectal cancer patients.

	1st year, excess mortality				
	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016
< 65 years					
Belgium	2.4	2.2	2.1	1.4	0.9
The Netherlands	2.5	2.4	1.7	1.8	1.4
Norway	1.8	1.9	0.7	0.6	0.2
Sweden	1.3	1.1	1.5	1.9	0.8
65-74 years					
Belgium	4.7	3.5	5.2	3.1	3.9
The Netherlands	5.2	4.1	4.5	2.3	1.0
Norway	2.6	3.5	2.4	1.4	0.6
Sweden	2.9	2.7	2.3	2.6	1.7
≥ 75 years					
Belgium	12.2	13.6	12.0	11.4	9.0
The Netherlands	13.2	8.8	8.4	4.7	2.5
Norway	9.0	3.4	5.0	*	2.9
Sweden	7.8	5.3	3.3	2.6	3.2

P-values are for differences between countries in time period 2015-2016. *No excess mortality.

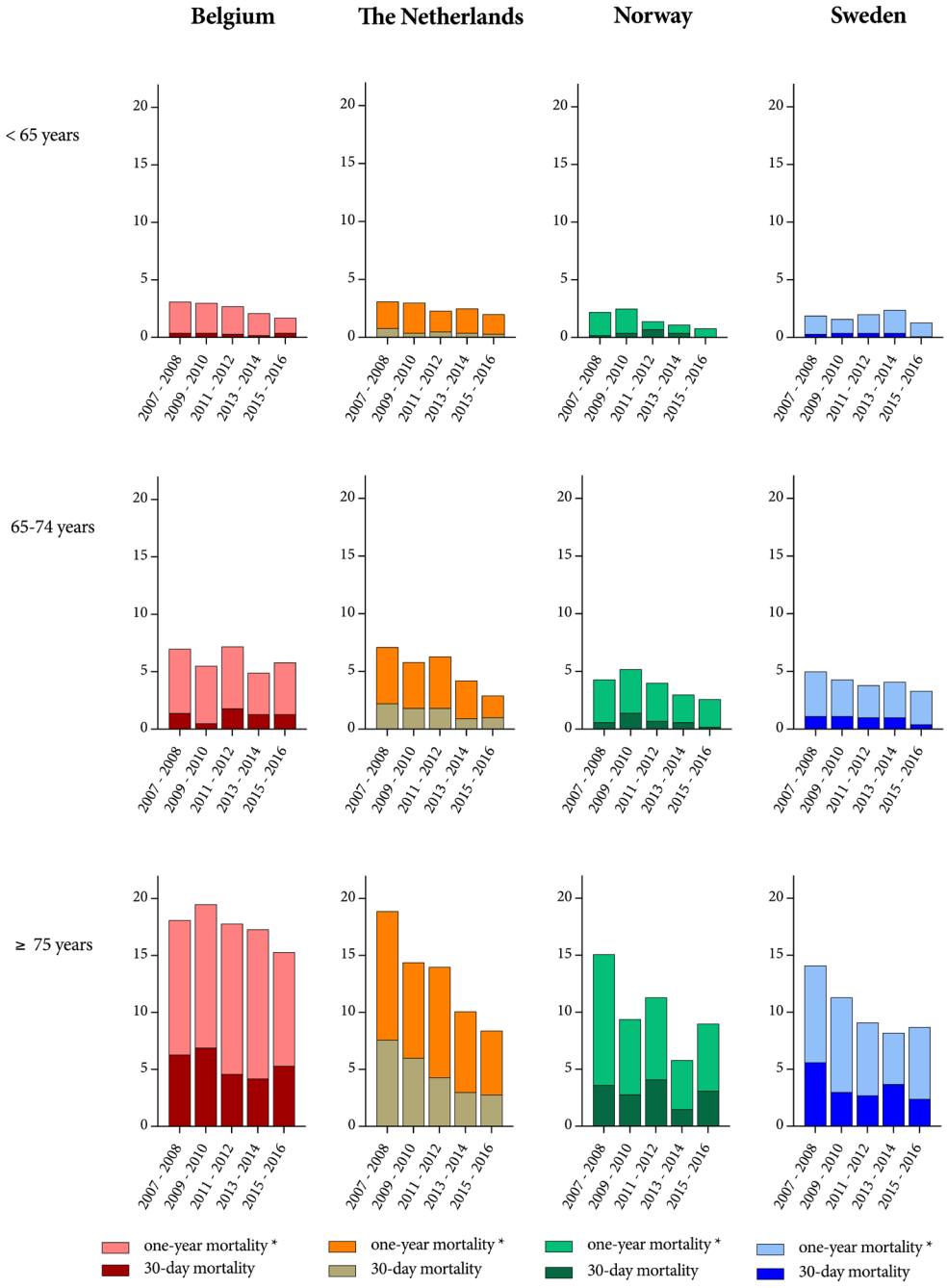

Figure 3 (A) 30-day and one-year overall mortality in rectal cancer patients.

* One-year mortality is represented by the full bar.

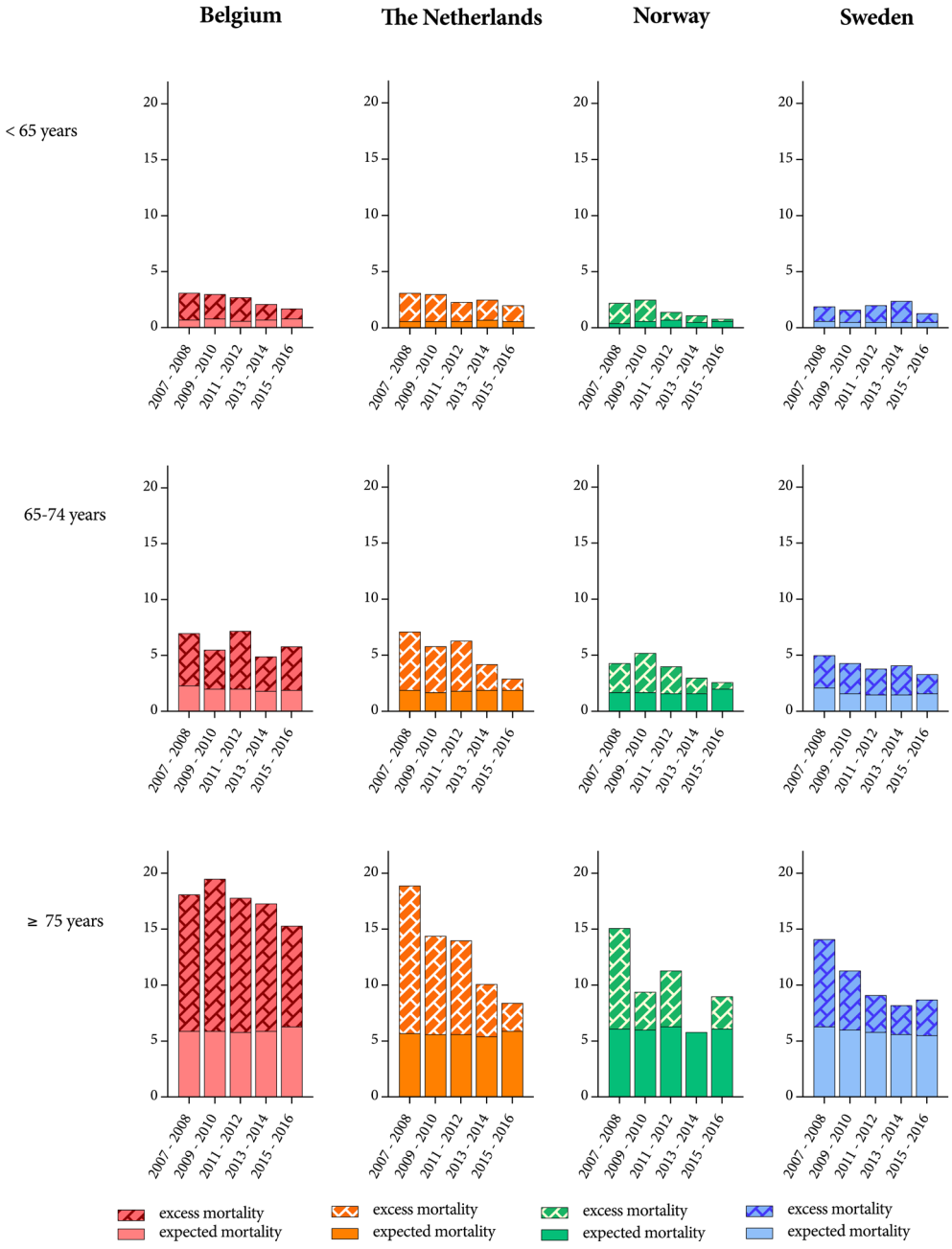

Figure 3 (B) One-year expected and excess mortality in rectal cancer patients.

Discussion

The present study found minor differences in 30-day postoperative mortality and substantial differences in one-year postoperative excess mortality in an international cohort comparing surgically treated colorectal cancer patients. Excess mortality decreased over time in all countries. However, some striking differences across countries persisted over time, which could be related to differences in treatment strategies.

Cancer-related deaths in the first postoperative year are unlikely the result of primary stage I-III colorectal cancer itself, as recurrences usually appear after the first year of treatment.[16,17] Even when they do appear in the first year, they hardly ever lead to mortality in the first year after treatment. Additionally, research found that 25% of deaths in the first postoperative year were attributed to postoperative complications.[3] The one-year mortality reduction over the time periods in this study is most likely due to improvements in surgical procedures (laparoscopy), as well as improved perioperative and postoperative care.[18,19] However, a prolonged impact of treatment which could persist after hospital discharge should not be underestimated.[20] Attention for the time after discharge should be a focus for the improvement of treatment.

Improvement of care and quality assessment can be accomplished by clinical auditing, ultimately leading to demonstrable improvements in patient outcomes, partly as a result of a response to the awareness of being observed, causing a modification of behaviour.[21] The introduction of nationwide audits could partly explain the substantial improvement over time in the investigated countries.[22-25] This improvement is also enhanced by the emergence of multidisciplinary team meetings, where patients are individually discussed by several specialists, leading to a more substantiated treatment plan for each patient.[26] The early introduction of multidisciplinary management in Sweden could also have contributed to the relatively low excess mortality in the early years of the current analyses. The same could be true for the centralization of treatment and further specialization.[13]

It can be beneficial to identify colorectal cancer at an earlier, asymptomatic stage, as screening typically leads to initial greater detection of and shift toward early-stage cancers, which could eventually lead to a decrease in incidence due to the removal of premalignant adenomas.[27] In Norway and Sweden, a pilot of national screening programs has started, without full implementation yet. In Belgium, it was launched in 2009 (on a national level in 2013) and

in the Netherlands in 2014.[28] Its effect is already noticeable by the stage distribution shift over time. Stage III proportion decreased in favour of an important increase of stage I tumours, visible for colon and rectal cancer in Belgium and colon cancer in the Netherlands. For rectal cancer, the increasing use of chemoradiotherapy, and therefore down-staging of the pathological stage could also have been of influence.[29] Despite that, an increase in stage III diagnoses for rectal cancer was seen in the Netherlands. This may be an effect of stage migration, caused by a more thorough examination of lymph nodes.[30]

In general, with increasing age, patients were less likely to be treated with additional therapy. Yet differences in treatment strategies were found. Patients in Belgium received chemotherapy more often in colon cancer and rectal cancer. In the Netherlands and Sweden, patients with rectal cancer were more likely to receive neoadjuvant radiotherapy, while patients in Belgium and Norway were often treated with neoadjuvant chemoradiotherapy. Moreover, in Belgium, and to a lesser extent in Sweden, treatment of rectal cancer patients was frequently completed with adjuvant chemotherapy. A study of Vermeer et al., with colon cancer patients older than 80 years, demonstrated differences in adjuvant chemotherapy for stage III disease from 4% in Norway to 25% in Belgium[6]. In our data, colon cancer patients in Belgium, in all age-categories, received adjuvant chemotherapy more often than patients in the Netherlands or Sweden. Interestingly, the excess mortality was higher in Belgium than in the other countries. For rectal cancer, this difference in excess mortality was even greater (three times) for patients in the middle and oldest age-category with stage III disease, which may suggest the possibility of overtreatment. It has been argued before that it is essential to find a balance between under- and overtreatment, and adjuvant treatment should be considered carefully in older patients.[31,32]. Naturally, this balance should also be sought for young patients. In the current data, young colorectal cancer patients from Belgium and the Netherlands have comparable one-year mortality, while their treatment strategy concerning adjuvant chemotherapy is different.

The results of this study should be interpreted with regard to several limitations. No information on comorbidities and frailty, which significantly affect prognosis and treatment plan, were available for the current analyses. Data on postoperative complications, known for its negative influence on survival, were lacking as well. Also, there was no information on the

number of emergency surgeries. Patients treated in an emergency setting are especially at risk for complications and mortality.[3,33,34] Population-based data with limited detailed patient and treatment information was used to compare treatment strategies, which makes it challenging to understand the entire process of treatment decisions. Age, comorbidities, frailty, but also patient preferences are known to influence treatment choices. Moreover, selection criteria vary per stage, country, hospital, and clinician. In addition, in some cases, maintaining quality of life is more desirable than receiving curative treatment. However, the use of population-based data is also the strength of this study as it provides robust data, compensating for the lack of detail. The data are in line with previous publications on the topic.[4,35-38] Although, the current study is the first one to compare differences in age-categories between four European countries. Due to the mandatory nature of the national cancer registrations, we were able to offer a complete overview of the surgically treated adult patients diagnosed with colorectal cancer in four North-European countries in a period of 10 years.

Conclusion

Postoperative 30-day and one-year mortality of colorectal cancer patients decreased over time in Belgium, the Netherlands, Norway, and Sweden. However, substantial variations between countries exist. As population mortality in these countries is comparable, differences in excess one-year postoperative mortality could be due to differences in treatment strategies. This highlights the consequences of under- and over-treatment on cancer survival, especially in older patients and should be taken into consideration when evaluating national guidelines.

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public, commercial, or non-profit sectors. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

Ethics approval and consent to participate The study was performed in accordance with the Declaration of Helsinki. The national cancer registries provided anonymized patient data. Therefore, informed consent from patients or ethical approval was not required for this study.

Declaration of Competing Interest None declared. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The survival gap between young and older patients after surgical resection for colorectal cancer remains largely based on early mortality: A EURECCA comparison of four European countries

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Abstract

Background: A decade ago, it was demonstrated that the difference in survival between older patients and younger patients with colorectal cancer (CRC) was mainly due to mortality in the first postoperative year. Over the last few years, improvements - especially in perioperative care - have increased survival. The current research investigates whether a survival gap between younger and older patients with CRC still exists on a national level in four European countries.

Methods: Population-based data from Belgium, the Netherlands, Norway, and Sweden were collected from patients that underwent surgical resection for primary stage I-III CRC between 2007 and 2016. Relative survival and conditional relative survival (CS), with the condition of surviving the first postoperative year, were calculated for colon and rectal cancer separately, stratified for country and age category (<65, 65–75, ≥75 years). In addition, relative excess risk of death (RER) was estimated, and one-year excess mortality was calculated.

Results: Data of 206,024 patients were analyzed. In general, compared to patients <65 years, patients ≥75 years had a worse survival during the first year after surgery, which was most pronounced in Belgium (RER colon cancer 2.5 [95% confidence interval (CI) 2.3–2.8] and RER rectal cancer 2.6 [95% CI 2.3–2.9]). After surviving the first year, CS was mostly not statistically different between patients <65 years and patients ≥75 years with stage I-II, with the exception of stage II colon cancer in Belgium. However, CS remained worse in the largest part of the patients ≥75 years with stage III colon or rectal cancer (except for rectal cancer in Norway).

Conclusions: Although differences exist between the countries, the survival gap between young and older patients is based mainly on early mortality and remains only for stage III disease after surviving the first year.

Introduction

As the incidence of colorectal cancer increases with age, and life expectancy of the general population is increasing, a growing proportion of older patients is expected to be diagnosed with colorectal cancer.[1] In the past, surgical treatment options were not offered to older patients as frequently due to an increased complication rate and higher mortality rate in this population.[2,3] Currently, with more frequent use of minimally invasive surgery and improvement of perioperative care within a multidisciplinary setting, these risks have decreased.[4] Analyses of Dutch national data showed that the overall 30-day and one-year survival of older patients operated for colon cancer improved over time. Still, differences in short-term survival remained between the younger and older population[5], although less prominent for relative survival.[6] A recent Dutch study concluded that the relative survival of older patients with colorectal cancer has improved, leading to a similar cancer-specific survival compared with the younger population.[7] In these studies, relative survival was used as an estimation of the cancer-specific survival, and calculated by dividing the observed survival in the cohort by the expected survival calculated from the matched (country, age, sex, and year) general population. This method can be used in the absence of cause of death in the cohort, or when cause of death is hard to establish, which is most often the case in older patients with multiple comorbidities. Calculating the relative survival for patients who survived the first postoperative year, the conditional relative survival, has shown age differences in early mortality. In 2011 Dekker et al. showed, in a regional dataset of the Netherlands, that decreased cancer-specific survival in older patients with colorectal cancer was mainly due to differences in early mortality. For those older patients who survived the first post-operative year, cancer-related survival aligned with younger patients.[8] Correspondingly, Pilleron and colleagues analyzed data from patients with colon cancer aged between 50 and 99 years, and concluded that age-related disparities were no longer evident or considerably reduced if patients with localized disease survived the first six months after diagnosis.[9] Recently, our group studied time-trends with focus on treatment and demonstrated improvement in overall one-year postoperative mortality over time in different age categories (< 65, 65–75, ≥75 years) in Belgium, the Netherlands, Norway, and Sweden. Results showed that substantial differences between countries and age categories still existed.[10] For the current study, our

group focused on conditional relative survival with corresponding one-year excess mortality. It has not been investigated before whether the effect of disappearing age-related differences in conditional survival is also present on a national level for colorectal cancer in other European countries. Therefore, this study compared, with respect to different age categories, the one-year conditional relative survival (overall and according to tumor-stage) and corresponding excess mortality in Belgium, the Netherlands, Norway, and Sweden.

Methods

Study design and data sources

Observational data on consecutive patients have been collected for this international population-based cohort study from the national cancer registries of Belgium, the Netherlands, Norway, and Sweden. These countries were chosen based on their similar cancer incidence and life expectancy. Moreover, their national cancer registries guaranteed the overall quality of data in terms of completeness (>95% of patients with cancer in the population registered) and accuracy.[11] The study was performed in accordance with the Declaration of Helsinki. The national cancer registries provided anonymized patient data. Therefore, informed consent from patients or ethical approval was not required for this study. All countries have a legal foundation that enables the collection of data concerning cancer cases in the context of public health.[12-15]

Procedures

Data were collected from all surgically treated patients diagnosed with primary colon or rectal cancer from January 2007 to December 2016. Colon cancer was defined by topographical codes C18-C19 and rectal cancer by code C20 of the International Classification of Diseases for Oncology.[16] In Sweden, topographical code C19 (rectosigmoid) was not defined as the location of the tumor was decided by the surgeons at the time of surgery. For the current analyses, patients eighteen years and older diagnosed with stage I, II, III disease and recorded follow-up were included. Stage was based on pathological information and completed with clinical stage when necessary, using the 7th edition of the American Joint Committee on Cancer TNM staging. For rectal cancer, pathological information was based on either the

pTN or ypTN category. Belgium and the Netherlands provided their data on stage from 2007 to 2009 using the TNM stage 6th edition and from 2010 to 2016 using the TNM 7th edition. For patients diagnosed with multiple, simultaneous tumors, the tumor with the worst prognostic characteristics, using stage and grade, was chosen for all analyses. Surgical treatment was defined as surgical removal of the tumor-bearing bowel segment, irrespective of curative or palliative intent. Patients with stage IV disease were excluded, as well as patients who underwent local excision of the tumor, including transanal endoscopic microsurgery. Due to the high quality of the national registries there were no missing data on the baseline characteristics.

Statistics

All analyses were performed stratified by tumor location, country, and age category (younger than 65 years, 65–74 years and 75 years and older). To estimate cancer-related survival (in the absence of reliable information on the cause of death), relative survival (RS) was used, calculated by the Ederer II method as the ratio of the survival observed among the patients with cancer and the survival that would have been expected based on the corresponding (country, age, sex, and year) general population.[17] The Ederer II method was used as the matched individuals were considered to be at risk until the corresponding cancer patient died or was censored. National life tables (www.mortality.org) were used to estimate expected survival, and survival time was calculated from the date of surgery to date of death. Afterwards, conditional relative survival (CS) was calculated with the condition of surviving the first postoperative year. With a multivariate generalized linear model, using a Poisson distribution, relative excess risk of death (RER) was estimated based on collapsed relative survival data, using exact survival times.[18] We adjusted the models for overall mortality (OM, mortality in the first year due to any cause) and one-year excess mortality (EM). Expected mortality was based on the matched (country, age, sex, and year) general population, and EM was calculated using the following formula: (observed numbers of death in the first year – expected number of deaths in the first year (in the matched general population)) / (number of patients). The expected number of deaths was calculated by national life tables matched for age, sex, and year of incidence. With respect to the sizeable population of this study, a p-value of <0.001

was considered statistically significant. STATA/SE version 14.0 was used for the analyses.

Results

In Belgium, the Netherlands, Norway, and Sweden, 314,062 patients were diagnosed with colorectal cancer between 2007 and 2016. For the current analyses, the inclusion criteria were met by 53,071 patients from Belgium (64.3%), 88,784 patients from the Netherlands (66.9%), 25,548 patients from Norway (64.3%) and 38,621 patients from Sweden (66.1%). Supplementary Table A provides an overview of the data selection of each country. Patient characteristics, stratified by tumor location and age categories, are displayed in Table 1. The percentages of male patients with colon cancer were 53.6% (< 65 years), 55.2% (65–74 years), 46.2% (≥ 75 years). For patients with rectal cancer, these were 61.6% (< 65 years), 65.6% (65–74 years), and 57.3% (≥ 75 years). The proportion of patients ≥75 years with colon cancer was 43.4% (Belgium 46.3%, the Netherlands 38.9%, Norway 46.0%, Sweden 48.2%), considerably higher than the proportion patients ≥75 years with rectal cancer, 29.1% (Belgium 33.3%, the Netherlands 24.9%, Norway 31.3%, Sweden 31.5%). Patients aged eighteen years or older, diagnosed with stage I-III colorectal cancer and reliable follow-up in the national cancer registries undergoing surgical resection, were 90.2% (53,071 of 58,828) in Belgium, 89.3% (88,784 of 99,464) in the Netherlands, 92.3% (25,548 of 27,679) in Norway and 93.2% (38,621 of 41,437) in Sweden (Supplementary Table A).

Colon cancer, relative survival, and one-year conditional relative survival

As shown in Fig. 1a and Table 2a, in the Netherlands, Norway, and Sweden CS of older patients with stage I, II or III (combined) was similar among patients <65 years and patients 65–74 years after surviving the first postoperative year. Table 2a presents an additional overview of the RERs for RS and CS according to age and stratified for stage, with patients <65 years as a reference category. For stage I, patients ≥75 years in Norway and Sweden had similar RS compared to patients <65 years. In Belgium and the Netherlands, patients ≥75 years initially had a worse survival than patients <65 years, but this difference disappeared after surviving the first postoperative year. For stage II, worse RS of patients ≥75 years were found in Belgium, the Netherlands, and Norway. This difference disappeared after surviving

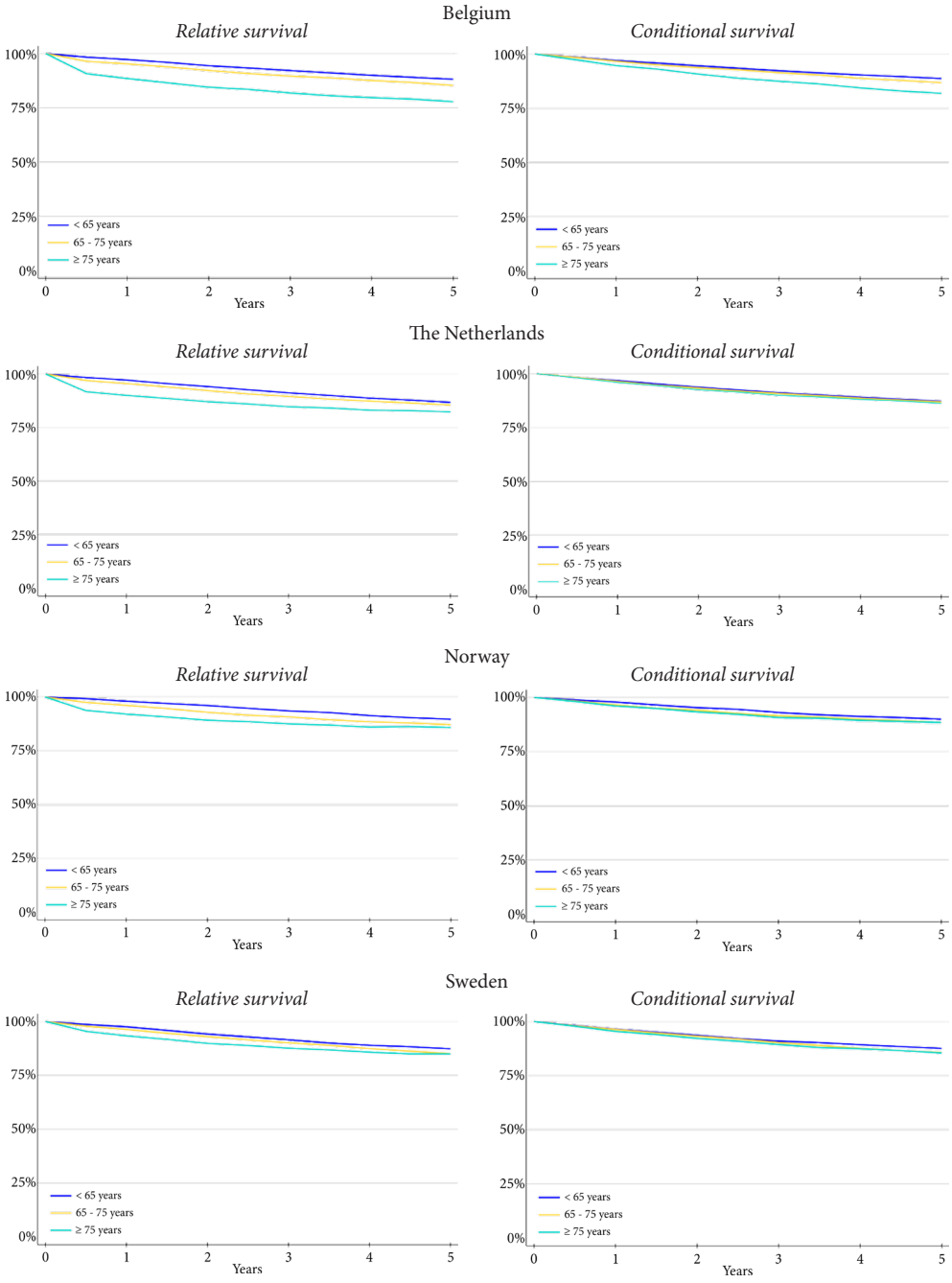

Figure 1a Relative and conditional survival of stage I-III operated colon cancer patients, according to age.

the first postoperative year in the Netherlands and Norway, but remained in Belgium. The difference for the patients 65–74 years remained as well in Belgium and was also present in the Netherlands. For stage III, CS remained worse for patients ≥75 years in all countries. For patients 65–74 years, survival aligned in CS in Belgium, the Netherlands, and Norway.

Rectal cancer, relative survival, and one-year conditional relative survival

Relative survival in patients ≥75 years with stage I, II and III combined improved after surviving the first postoperative year for patients with rectal cancer, leading to comparable CS between age categories (Fig. 1b). Table 2b presents an overview of RERs for RS and CS stratified for stage, with patients <65 years as a reference category. The RS aligned in patients ≥75 years with stage I disease in Belgium and the Netherlands, leading to similar CS in all countries and all age categories. For stage II, the same trend was shown. For stage III, in all countries, RS of older patients was worse compared to patients <65 years. This difference only disappeared in Norway after surviving the first postoperative year. Patients 65–74 years in Belgium and the Netherlands with stage III disease initially had a worse survival, which was similar for patients <65 years after surviving the first postoperative year. (See Fig. 1b.)

One-year excess mortality

Table 3 provides an overview of one-year overall and one-year excess mortality. For colon cancer, in general, higher excess mortality was seen in females, with the exception of Norway, where excess mortality was higher for males. Excess mortality increased with age category. Patients 65–74 years and patients ≥75 years in Belgium and the Netherlands had similar, albeit higher, excess mortality compared to Norway and Sweden. Excess mortality also increased with stage and followed a trend of the lowest excess mortality in Sweden, followed by Norway, the Netherlands, and the highest in Belgium. In rectal cancer, excess mortality was consistently higher among men, increased with age and stage and showed a trend of the lowest excess mortality in Norway, followed by Sweden, the Netherlands, and highest in Belgium.

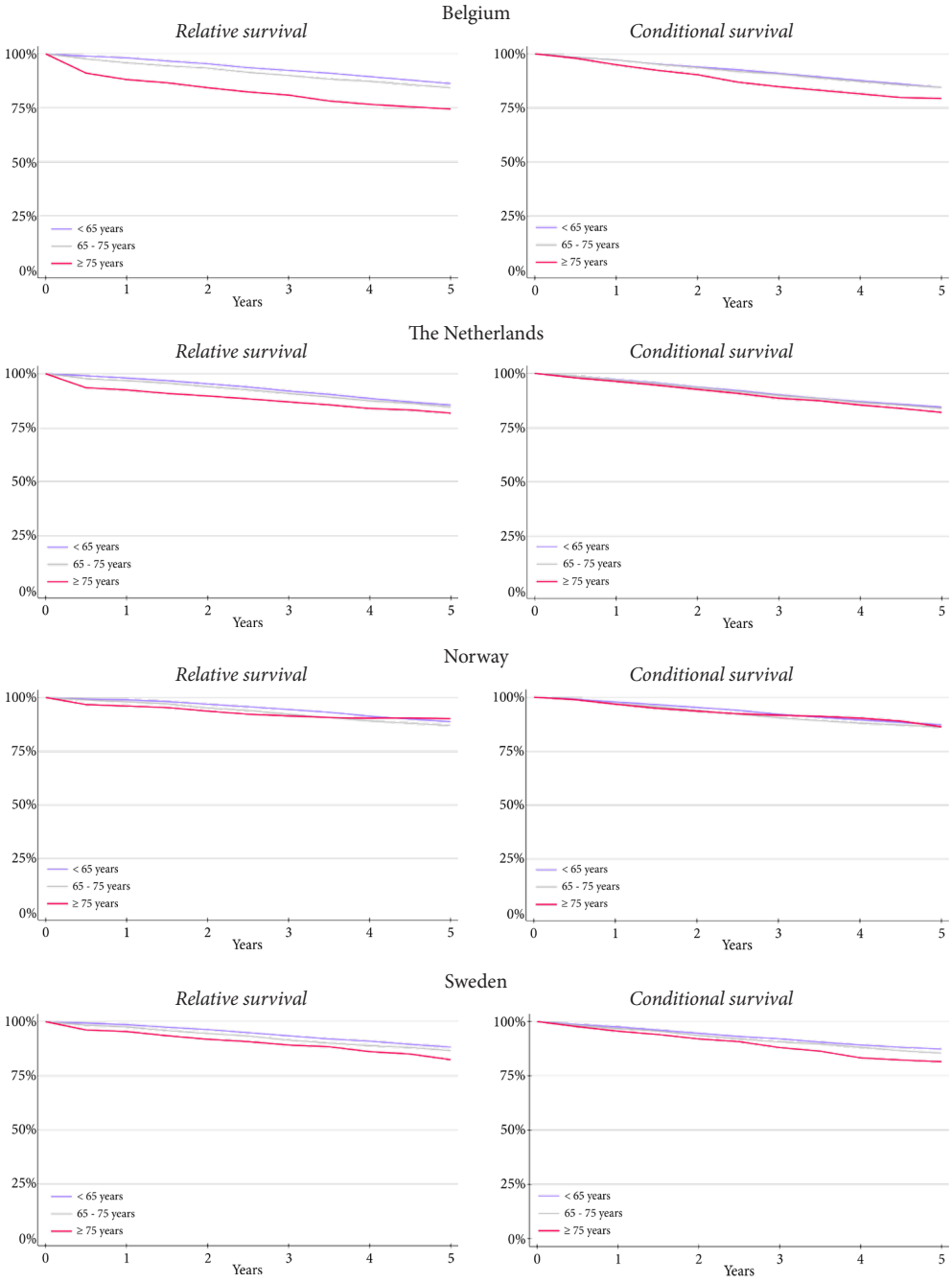

Figure 1b Relative and conditional survival of stage I-III operated rectal cancer patients, according to age.

Table 1 Characteristics of patients operated for colorectal cancer diagnosed in the period 2007 - 2016

	Belgium			The Netherlands		
Colon cancer	< 65 years	65-74 years	≥ 75 years	< 65 years	65-74 years	≥ 75 years
	N = 9,645	N = 11,280	N = 18,063	N = 17,402	N = 21,784	N = 24,919
Gender						
Male	5,362 (55.6)	6,652 (59.0)	8,461 (46.8)	9,298 (53.4)	12,163 (55.8)	11,868 (47.6)
Female	4,283 (44.4)	4,628 (41.0)	9,602 (53.2)	8,104 (46.6)	9,621 (44.2)	13,051 (52.4)
Stage						
Stage I	2,313 (24.0)	2,856 (25.3)	3,373 (18.7)	3,621 (20.8)	5,326 (24.4)	4,975 (20.0)
Stage II	3,534 (36.6)	4,492 (39.8)	8,434 (46.7)	6,378 (36.7)	8,635 (39.6)	11,534 (46.3)
Stage III	3,798 (39.4)	3,932 (34.9)	6,256 (34.6)	7,403 (42.5)	7,823 (35.9)	8,410 (33.7)

	Belgium			The Netherlands		
Rectal cancer	< 65 years	65-74 years	≥ 75 years	< 65 years	65-74 years	≥ 75 years
	N = 5,108	N = 4,288	N = 4,687	N = 9,767	N = 8,757	N = 6,155
Gender						
Male	3,231 (63.3)	2,852 (66.5)	2,702 (57.6)	6,115 (62.6)	5,840 (66.7)	3,531 (57.4)
Female	1,877 (36.7)	1,436 (33.5)	1,985 (42.4)	3,652 (37.4)	2,917 (33.3)	2,624 (42.6)
Stage						
Stage I	1,750 (34.3)	1,504 (35.1)	1,382 (29.5)	1,784 (18.3)	1,924 (22.0)	1,403 (22.8)
Stage II	1,398 (27.4)	1,290 (30.1)	1,595 (34.0)	2,358 (24.1)	2,402 (27.4)	2,066 (33.6)
Stage III	1,960 (38.4)	1,494 (34.8)	1,710 (36.5)	5,625 (57.6)	4,431 (50.6)	2,686 (43.6)

Data are presented as n(%).

Continuation Table 1 Characteristics of patients operated for colorectal cancer diagnosed in the period 2007 - 2016

	Norway			Sweden		
Colon cancer	< 65 years	65-74 years	≥ 75 years	< 65 years	65-74years	≥ 75 years
	N = 4,564	N = 5,651	N = 8,698	N = 5,585	N = 8,162	N = 12,775
Gender						
Male	2,312 (50.7)	2,835 (50.2)	3,750 (43.1)	2,955 (52.9)	4,215 (51.6)	5,710 (44.7)
Female	2,252 (49.3)	2,816 (49.8)	4,948 (56.9)	2,630 (47.1)	3,947 (48.4)	7,065 (55.3)
Stage						
Stage I	1,012 (22.2)	1,238 (21.9)	1,826 (21.0)	858 (15.4)	1,492 (18.3)	2,109 (16.5)
Stage II	1,800 (39.4)	2,536 (44.9)	4,156 (47.8)	2,207 (39.5)	3,423 (41.9)	5,952 (46.6)
Stage III	1,752 (38.4)	1,877 (33.2)	2,716 (31.2)	2,520 (45.1)	3,247 (39.8)	4,714 (36.9)

	Norway			Sweden		
Rectal cancer	< 65 years	65-74 years	≥ 75 years	< 65 years	65-74years	≥ 75 years
	N = 2,408	N = 2,153	N = 2,074	N = 3,936	N = 4,349	N = 3,814
Gender						
Male	1,426 (59.2)	1,390 (64.6)	1,153 (55.6)	2,303 (58.5)	2,746 (63.1)	2,204 (57.8)
Female	982 (40.8)	763 (35.4)	921 (44.4)	1,633 (41.5)	1,603 (36.9)	1,610 (42.2)
Stage						
Stage I	586 (24.3)	586 (27.2)	541 (26.1)	1,113 (28.3)	1,325 (30.5)	1,116 (29.3)
Stage II	639 (26.5)	651 (30.2)	758 (36.5)	1,139 (28.9)	1,353 (31.1)	1,275 (33.4)
Stage III	1,183 (49.1)	916 (42.5)	775 (37.4)	1,684 (42.8)	1,671 (38.4)	1,423 (37.3)

Data are presented as n(%).

Table 2a One-year relative and conditional survival of operated colon cancer patients, stratified by stage, shown as relative excess risk of death (RER) with corresponding 95% CI.

Belgium	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	***1.3 (1.2-1.4)***	1.2 (1.0-1.3)	1.2 (0.7-1.9)	N.A. *
>74 years	***2.5 (2.3-2.8)***	***1.7 (1.5-1.9)***	3.0 (2.0-4.5)	N.A. *

The Netherlands	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	***1.1 (1.1-1.2)***	1.0 (1.0-1.1)	1.9 (0.9-4.0)	1.2 (0.6-2.3)
>74 years	***1.8 (1.7-1.9)***	1.1 (1.0-1.2)	6.8 (3.5-13.3)	0.8 (0.2-3.7)

Norway	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	***1.4 (1.2-1.6)***	1.0 (1.0-1.4)	1.6 (0.6-4.2)	1.5 (0.7-3.4)
>74 years	***2.0 (1.7-2.3)***	1.3 (1.1-1.6)	1.8 (0.5-6.7)	N.A. *

Sweden	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.2 (1.0-1.3)	1.1 (1.0-1.3)	1.4 (0.6-2.9)	1.7 (0.8-3.3)
>74 years	***1.4 (1.3-1.6)***	1.2 (1.1-1.4)	N.A. *	0.9 (0.3-3.3)

RS relative survival, *CS* conditional survival *N.A.** Not addressed due to relative survival above 100%, the results could not be presented in a RER (RS not different from the youngest age). Bold and italic: p-value ≤ 0.001

Continuation Table 2a One-year relative and conditional survival of operated colon cancer patients, stratified by stage, shown as relative excess risk of death (RER) with corresponding 95% CI.

Belgium	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	***1.4 (1.1-1.7)***	***1.4 (1.1-1.8)***	***1.4 (1.2-1.6)***	1.2 (1.1-1.4)
>74 years	***2.5 (2.1-2.9)***	***1.5 (1.2-1.9)***	***2.8 (2.6-3.1)***	***2.1 (1.8-2.3)***

The Netherlands	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	***1.3 (1.1-1.5)***	***1.3 (1.1-1.5)***	***1.2 (1.1-1.3)***	1.1 (1.0-1.2)
>74 years	***1.7 (1.5-2.0)***	1.0 (0.8-1.3)	***2.2 (2.0-2.3)***	***1.5 (1.4-1.6)***

Norway	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	***1.8 (1.3-2.5)***	1.3 (0.9-1.8)	***1.4 (1.2-1.6)***	1.3 (1.1-1.6)
>74 years	***2.7 (1.9-3.7)***	1.7 (1.1-2.4)	***2.2 (1.9-2.6)***	***1.6 (1.3-1.9)***

Sweden	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.2 (0.9-1.6)	1.1 (0.8-1.4)	***1.3 (1.2-1.5)***	***1.3 (1.1-1.4)***
>74 years	1.2 (0.9-1.7)	1.0 (0.7-1.4)	***2.0 (1.8-2.3)***	***1.7 (1.5-1.9)***

RS relative survival, *CS* conditional survival *N.A.** Not addressed due to relative survival above 100%, the results could not be presented in a RER (RS not different from the youngest age). Bold and italic: p-value ≤ 0.001

Table 2b One-year relative and conditional survival of operated rectal cancer patients, stratified by stage, shown as relative excess risk of death (RER) with corresponding 95% CI.

Belgium	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.2 (1.1-1.4)	1.0 (0.9-1.2)	2.7 (1.3-5.8)	2.2 (1.2-3.8)
>74 years	***2.6 (2.3-2.9)***	***1.5 (1.3-1.8)***	***6.9 (3.3-14.4)***	0.6 (0.1-4.2)

The Netherlands	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.1 (1.0-1.2)	1.0 (1.0-1.2)	2.7 (1.1-6.8)	0.9 (0.4-1.9)
>74 years	***1.5 (1.3-1.7)***	1.2 (1.0-1.3)	***6.2 (2.4-15.9)***	0.7 (0.1-4.1)

Norway	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.2 (1.0-1.5)	1.2 (0.9-1.4)	1.0 (0.3-4.3)	0.9 (0.3-3.5)
>74 years	1.0 (0.7-1.5)	1.1 (0.8-1.5)	N.A. *	N.A. *

Sweden	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.2 (1.0-1.4)	1.2 (1.0-1.4)	2.4 (1.0-5.6)	1.7 (0.8-3.5)
>74 years	***1.6 (1.3-1.9)***	***1.5 (1.3-1.8)***	0.4 (0.0-45.9)	0.5 (0.0-8.7)

RS relative survival, *CS* conditional survival *N.A.** Not addressed due to relative survival above 100%, the results could not be presented in a RER (RS not different from the youngest age). Bold and italic: p-value ≤ 0.001

Continuation Table 2b One-year relative and conditional survival of operated rectal cancer patients, stratified by stage, shown as relative excess risk of death (RER) with corresponding 95% CI.

Belgium	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.0 (0.8-1.4)	0.8 (0.6-1.1)	***1.3 (1.1-1.6)***	1.1 (0.9-1.3)
>74 years	***2.6 (2.1-3.2)***	1.5 (1.2-1.9)	***2.4 (2.1-2.8)***	***1.7 (1.5-2.0)***

The Netherlands	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.0 (0.8-1.3)	1.0 (0.8-1.3)	***1.2 (1.1-1.4)***	1.2 (1.1-1.3)
>74 years	***1.5 (1.2-1.9)***	1.0 (0.8-1.4)	***1.8 (1.6-2.1)***	***1.6 (1.4-1.8)***

Norway	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.8 (1.1-2.9)	1.7 (1.1-2.7)	1.2 (0.9-1.5)	1.1 (0.8-1.4)
>74 years	1.5 (0.8-2.8)	1.5 (0.9-2.7)	***1.6 (1.2-2.2)***	1.5 (1.1-2.0)

Sweden	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.2 (0.9-1.6)	1.1 (0.8-1.5)	1.2 (1.0-1.4)	1.2 (1.0-1.4)
>74 years	1.5 (1.0-2.1)	1.3 (0.9-1.9)	***2.1 (1.7-2.5)***	***2.0 (1.7-2.4)***

RS relative survival, *CS* conditional survival *N.A.** Not addressed due to relative survival above 100%, the results could not be presented in a RER (RS not different from the youngest age). Bold and italic: p-value ≤ 0.001

Table 3 One-year overall and excess mortality rates in percentages

Colon cancer	Belgium			The Netherlands		
	N	OM	EM	N	OM	EM
Gender						
Male	20,475	11.0	**6.9**	33,329	9.5	**6.0**
Female	18,513	11.1	**7.7**	30,776	9.1	**6.3**
Age (years)						
< 65	9,645	3.4	**2.7**	17,402	3.4	**2.8**
65 - 74	11,280	6.6	**4.7**	21,784	6.2	**4.5**
≥ 75	18,063	18.0	**11.4**	24,919	16.1	**9.9**
Stage						
Stage I	8,542	6.2	**2.9**	13,922	5.0	**2.1**
Stage II	16,460	10.3	**6.0**	26,547	8.7	**5.2**
Stage III	13,986	15.0	**11.5**	23,636	12.4	**9.5**

Rectal cancer	Belgium			The Netherlands		
	N	OM	EM	N	OM	EM
Gender						
Male	8,785	9.0	**5.9**	15,486	6.7	**4.1**
Female	5,298	8.0	**5.6**	9,193	5.0	**3.1**
Age (years)						
< 65	5,108	2.5	**1.8**	9,767	2.5	**1.9**
65 - 74	4,288	6.1	**4.1**	8,757	5.1	**3.2**
≥ 75	4,687	17.7	**11.7**	6,155	13.1	**7.4**
Stage						
Stage I	4,636	5.4	**2.7**	5,111	4.6	**2.2**
Stage II	4,283	9.6	**6.5**	6,826	6.8	**4.1**
Stage III	5,164	10.7	**7.9**	12,742	6.3	**4.2**

OM overall mortality, *EM* excess mortality

Continuation Table 3 One-year overall and excess mortality rates in percentages

Colon cancer	Norway			Sweden		
	N	OM	EM	N	OM	EM
Gender						
Male	8,897	9.5	**5.4**	12,880	8.5	**4.5**
Female	10,016	8.6	**5.2**	13,642	8.5	**5.1**
Age (years)						
< 65	4,564	2.5	**2.0**	5,424	2.9	**2.5**
65 - 74	5,651	5.6	**3.9**	7,731	5.3	**3.9**
≥ 75	8,698	14.7	**7.9**	11,109	13.0	**7.5**
Stage						
Stage I	4,076	5.2	**1.6**	4,459	3.9	**0.2**
Stage II	8,492	8.5	**4.4**	11,582	7.0	**3.0**
Stage III	6,345	12.2	**8.7**	10,481	12.2	**8.8**

Rectal cancer	Norway			Sweden		
	N	OM	EM	N	OM	EM
Gender						
Male	3,969	5.7	**2.8**	7,253	6.2	**3.4**
Female	2,666	3.8	**1.4**	4,846	4.1	**1.8**
Age (years)						
< 65	2,408	1.6	**1.0**	3,936	1.8	**1.3**
65 - 74	2,153	3.8	**2.0**	4,349	4.1	**2.5**
≥ 75	2,074	10.1	**3.9**	3,814	10.4	**4.5**
Stage						
Stage I	1,713	3.3	**0.6**	3,554	3.5	**1.0**
Stage II	2,048	5.3	**2.2**	3,767	5.4	**2.6**
Stage III	2,874	5.6	**3.2**	4,778	6.6	**4.2**

OM overall mortality, *EM* excess mortality

Patients ≥ 75 years

Fig. 2 focuses on patients ≥75 years, comparing countries. In Belgium and the Netherlands, the RS of patients ≥75 years with colon cancer was worse compared to Norway and Sweden (See Fig. 2a). In Belgium, the RS of patients with rectal cancer was also worse compared to the other countries. The steep decline at the beginning of the RS curves for all countries disappeared in the CS curves for both colon and rectal cancer. This led to a similar survival of this patient group within the investigated countries for the first two years after surviving the first postoperative year. Survival was most favorable in Norway and the least in Belgium. As expected, survival was worse when selecting only patients diagnosed with stage III disease (Fig. 2b).

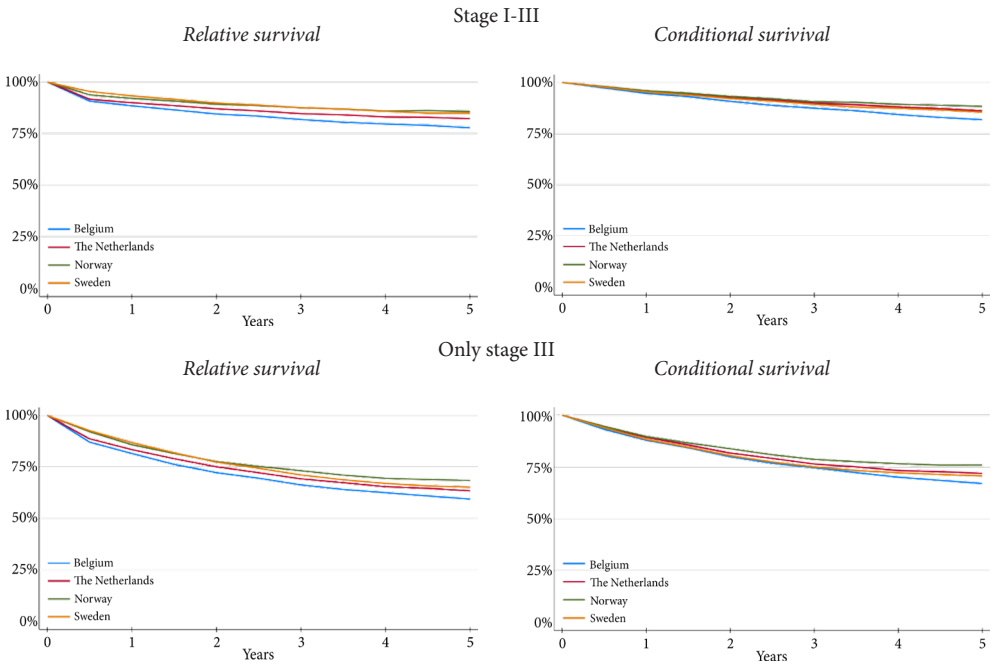

Figure 2a Relative and conditional survival of operated colon cancer patients, 75 years and older.

Discussion

Survival of patients that underwent surgical resection for stage I-III colorectal cancer between 2007 and 2016 in Belgium, the Netherlands, Norway, and Sweden was evaluated by analyzing relative survival. To confirm the importance of the first postoperative year on the survival of older patients, conditional survival was estimated with the condition of surviving the first postoperative year. The current study confirms that the survival of surgically treated older patients with colorectal cancer almost aligned with their younger counterparts (<65 years) after surviving the first postoperative year. The evident decline in survival of older patients during the first year after surgery was most notable in Belgium, followed by the Netherlands, and least in Norway and Sweden.

In line with previous studies,[8,9] the greatest impact of age on survival was seen in stage III disease within all investigated countries, with the exception of patients with rectal cancer in

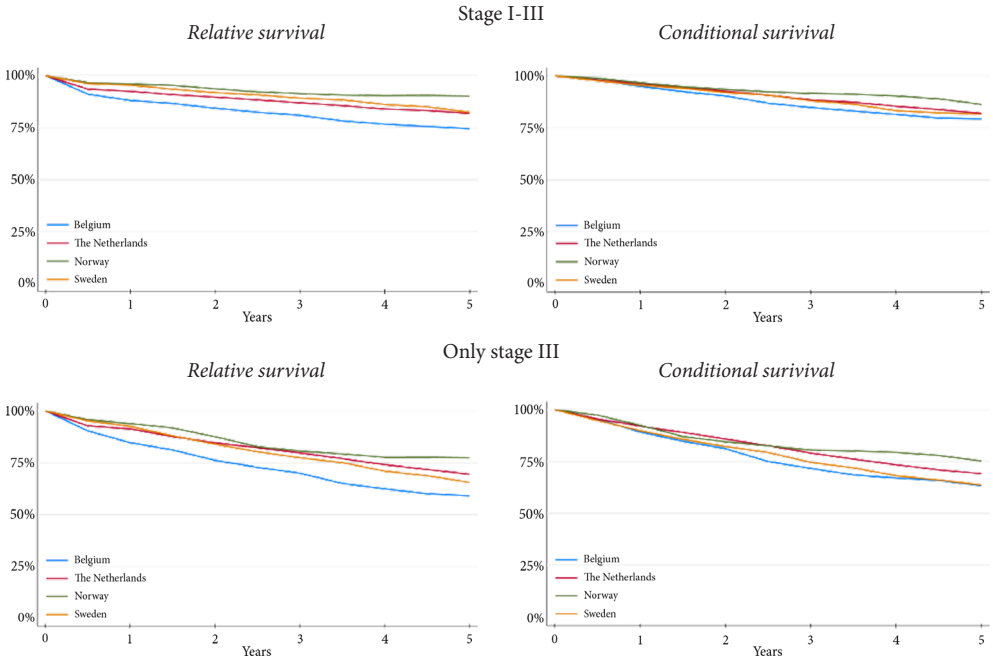

Figure 2b Relative and conditional survival of operated rectal cancer patients, 75 years and older.

Norway. In the last years, efforts have been made to reduce morbidity and mortality in older patients by effectively incorporating geriatric assessments, laparoscopy, enhanced recovery after surgery (ERAS) protocols, and prehabilitation programs.[19] Perhaps the long-term effect of these efforts on a national level are still yet to come, given that large-scale implementation of specific care for the older patients can be a challenge. A single-center study in the Netherlands analyzed patients with colorectal cancer diagnosed between 2006 and 2012 and compared them with patients diagnosed between 2013 and 2017 in two age categories with a cut-off point of 75 years. The difference in one-year relative survival between the old and young group changed from 96.5% and 88.4%, p-value <0.001 (diagnosed 2006–2012) to 95.5% and 94.3%, p-value 0.429 (diagnosed 2013–2017). No distinction was made between stages.[20]

Despite the improved CS for patients ≥75 years, survival remains least favorable in Belgium and most favorable in Norway. Our previous research[10] showed that differences between Belgium, the Netherlands, Norway, and Sweden were most prominent in older patients, particularly for stage III rectal cancer. Patients ≥75 years with rectal cancer in Belgium received relatively less neoadjuvant treatment (less often and predominantly radiotherapy instead of chemoradiotherapy), but more often received adjuvant chemotherapy (36%) in comparison to the Netherlands (3%) and Sweden (13%).[10] Norwegian data concerning the use of adjuvant chemotherapy were not available. However, this was not routinely recommended for patients with stage III colon cancer ≥75 years in the Norwegian guidelines.[21] In addition, patients ≥75 years with colon cancer received adjuvant chemotherapy more often in Belgium than in the Netherlands or Sweden.[10] A previous international study of patients aged 80 years and older, diagnosed between 2007 and 2010, demonstrated that in Belgium, 25% of patients with colon cancer stage III disease were treated with adjuvant chemotherapy, in contrast to 4% in Norway.[22] This suggests for Belgian patients the possibility of undertreatment in case of neoadjuvant treatment for rectal cancer, but overtreatment in the case of adjuvant chemotherapy for colorectal cancer. Adjuvant combination chemotherapy is of uncertain benefit to older patients. Monotherapy is regarded as an appropriate treatment option, and a personalized treatment decision, taking comorbidity and performance status into account, is often recommended.[23] However, the added value of adjuvant chemotherapy in rectal cancer has never been substantiated.[24] The possibility of overtreatment is contrary to previous

literature, which suggested an absolute undertreatment of older patients.[3,25-27] This stresses the importance to finding a good balance between under- and overtreatment. In addition, possible differences in quality of surgery and perioperative care with different degrees of implementation of centralization of care, minimally invasive surgery,[28] and clinical auditing could be partly responsible for the observed differences between countries.

Strikingly enough, a high RER in the first postoperative year among patients ≥75 years diagnosed with stage I colorectal cancer in Belgium and the Netherlands still existed. However, local excisions were more often performed in these countries: Belgium 3.8%, the Netherlands 4.7%, Norway 2.9%, and Sweden 0.6% (supplementary table S1). This procedure is done explicitly for stage I tumors and was not included in the current analyses. The patients ≥75 years diagnosed with stage I that underwent surgical resection were, therefore, probably patients that had tumors with high-risk features.[29] Patients with these high-risk features often require more extensive surgery, which might lead to a more complex recovery after surgery (a "complicated postoperative course") which could explain the higher RER in Belgium and the Netherlands. Next to that, these patients have a higher risk of recurrence, which might also have influenced the mortality.

Not surprisingly, excess mortality increased with age and stage in all investigated countries. Overall, females with colon cancer had a higher excess mortality (compared to men with colon cancer). A possible explanation could be the high percentage of patients ≥75 years (43.4%) in the investigated population, of which the majority were female (56.6%). For rectal cancer, we noted a higher proportion of male patients, and these male patients with rectal cancer had a higher excess mortality (compared to women). A known challenge in the surgical treatment of rectal cancer is the anatomical complexity in the narrow wedge-shaped pelvis of males compared to female patients.[30] This may cause surgical resection to be more difficult, leading to an increased risk of postoperative complications in men and explaining the higher first postoperative year mortality.[31,32]

The variation in surgical resection rate from 89.3% in the Netherlands to 93.2% in Sweden could be explained by differences in patient selection in different countries for patients of all ages.[33] Also, shared-decision-making in older patients may lead to refraining from surgery in case of (severe) comorbidity or a clinical (near) complete response after neoadjuvant

treatment. This watch-and-wait strategy is increasingly being practiced as a treatment for selected patients.[34] Evaluation of older patients demonstrated that they could avoid major surgery and a definitive colostomy, and have a proper anorectal and urinary function, with few cancer-related deaths.[35]

To interpret the results of the present study, a few limitations should be taken into account. For the patients analyzed in this large cohort, information on comorbidities was lacking. Frailty weakens the ability to recover postoperatively and is an important predictor of postoperative morbidity and mortality. This is especially relevant to older patients who have a higher likelihood to be frail.[36] It is also known that patients treated in an emergency setting are more prone to a complicated postoperative course, especially in colon cancer.[37] Patients with emergency surgery were not excluded from the current analyses. As complete information on elective/emergency surgery was not available in this dataset, this subgroup could not be evaluated separately. Fortunately, the rise of national screening programs permits patients to be diagnosed at an earlier stage, presumably reducing the proportion of patients with colorectal cancer undergoing emergency surgery.[38] Despite the completeness of the data on patient and tumor characteristics in the cancer registries, a small percentage of the patients (0.05%) had missing data on follow-up. Due to the fact that information on the cause of death was lacking in this cohort study, we used relative survival as a measure, which has been shown to be a good estimation of the cancer-specific survival. We calculated this by dividing the observed survival in the cohort by the expected survival based on the country, sex, age, and year matched general population. Studying the actual cause of death in the first postoperative year is challenging, especially for older patients, but remains a focus for further research. Last, unfortunately, we did not have information on the yP stage in all countries, so we were not able to stratify the results according to yP or P stage. Despite the lack of these details, the current study was able to demonstrate the importance of the first postoperative year in older patients in four countries. The strength of this paper lies in the mandatory nature of the involved national cancer registries. This provides a robust base for a complete overview of four European countries over a continuous period of ten years, with focus on stage and age-distribution. For further improvement of care for older patients, a starting point for future research could be the first year after surgery. Perhaps improved patient selection, including

shared-decision-making in which the wishes and expectations of patients are carefully considered, could play a role here. In this respect, older patients with stage III disease may have the most to gain.

Conclusion

Although multimodality treatment, perioperative care, and consequently oncological outcome have improved in the past years, older patients with colorectal cancer still have a worse relative survival than their younger counterparts. Despite differences between countries, after surviving the first year, this survival gap is no longer apparent for patients diagnosed with stage I-II but remains for stage III. Together with a focus on early mortality, balancing under- and overtreatment - especially for stage III disease - is key to bridging the survival gap between younger and older patients with colorectal cancer that undergo surgical resection.

Declarations

All authors substantially contributed to the conception and design or analysis and interpretation of the data; drafting the article or revising it critically, and approved the final version. This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred. The authors declare no conflicts of interest.

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Declaration of Competing Interest

None declared

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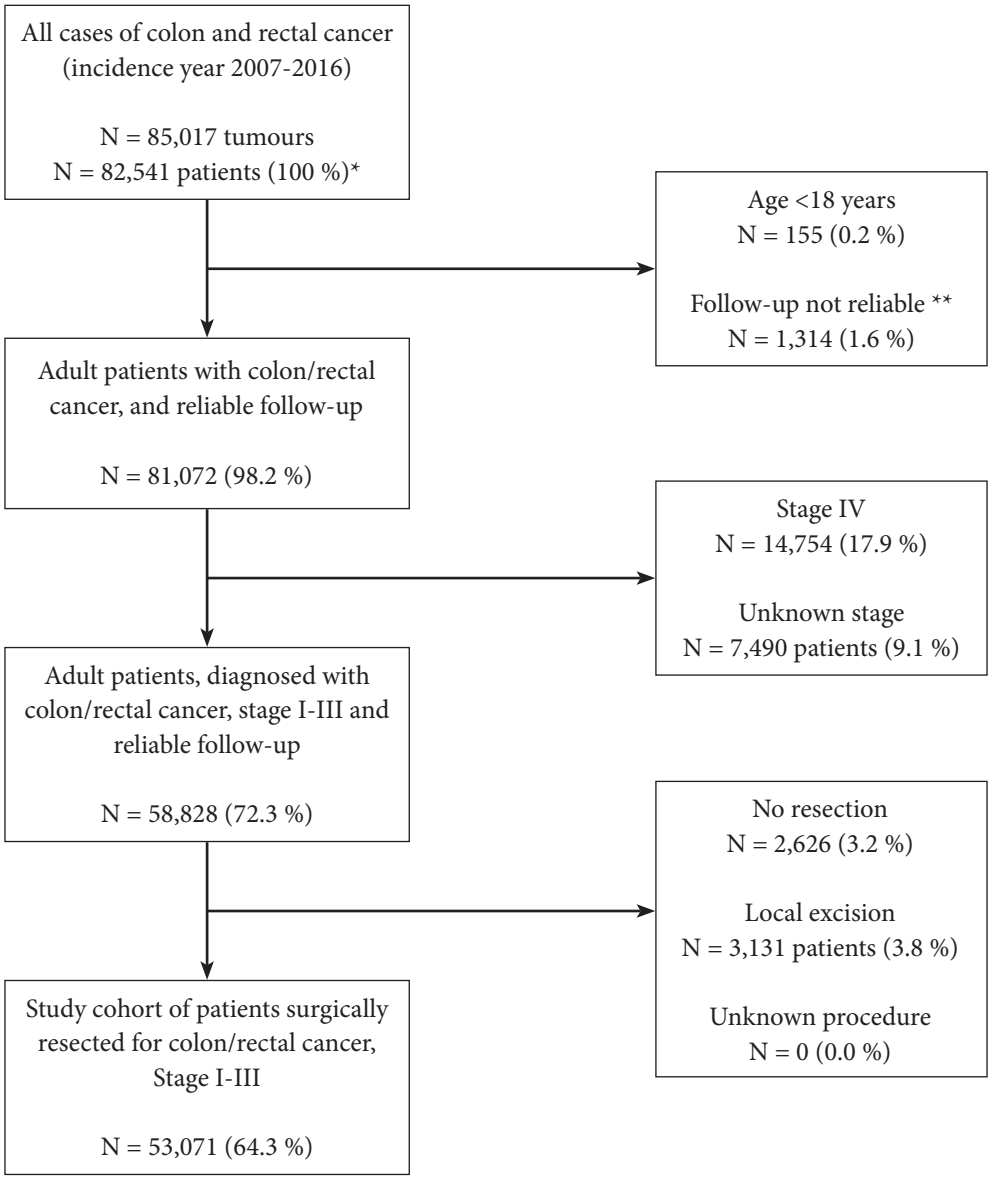
Supplementary Appendix EURECCA

Supplementary Table S1a Flowchart patient selection Belgium.

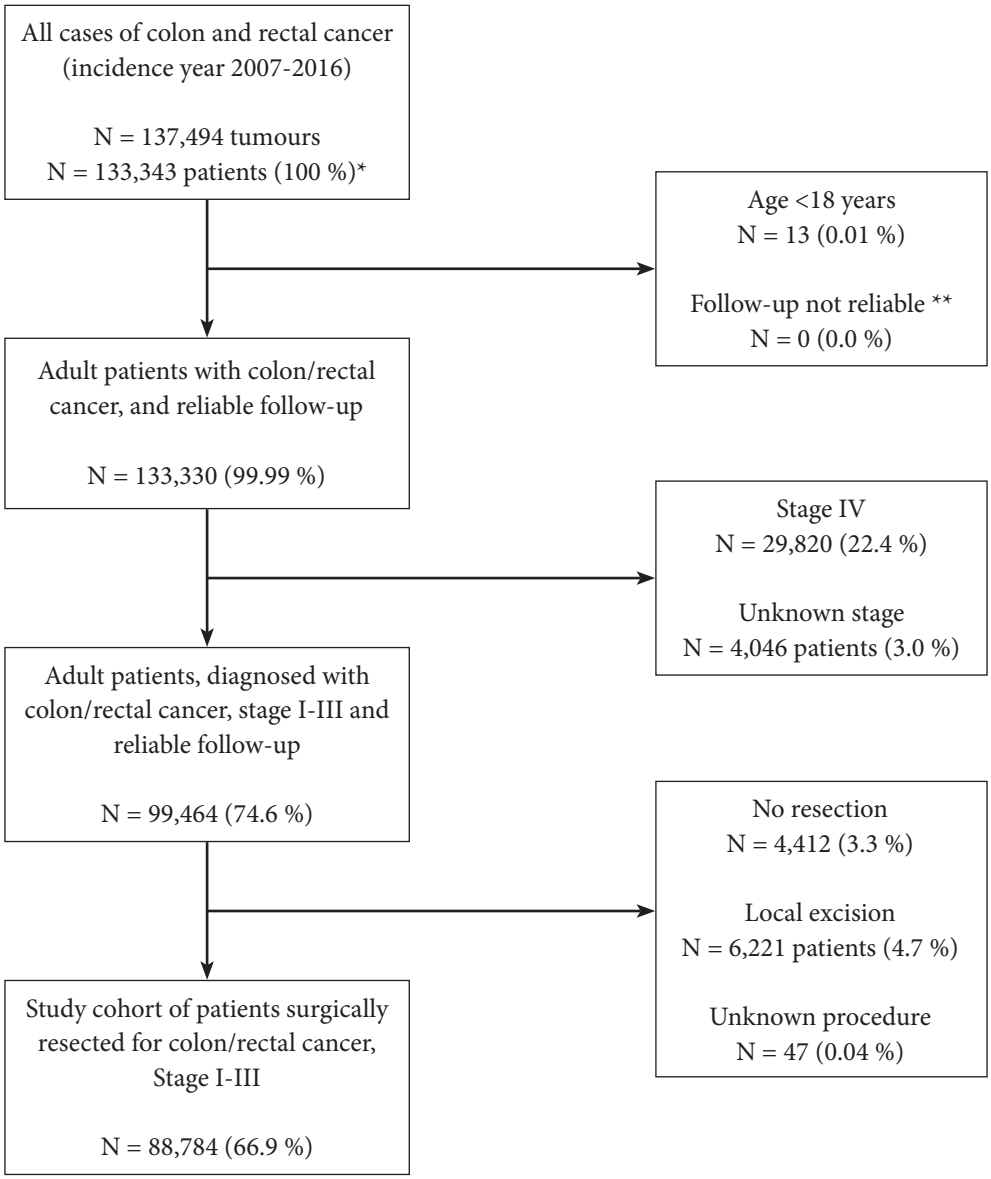


* First primary tumour selected. If multiple tumours were diagnosed on the same day, the highest stage or highest grade was chosen.

** Patients could not be linked with the administrative database, negative follow up (due to registration errors).

In 2018: total population 11,498,527 – number of new colorectal cancer cases 9,346
https://gco.iarc.fr/today/data/factsheets/populations/56-belgium-fact-sheets.pdf - accessed on 28th May 2020.

Supplementary Table S1b Flowchart patient selection The Netherlands.

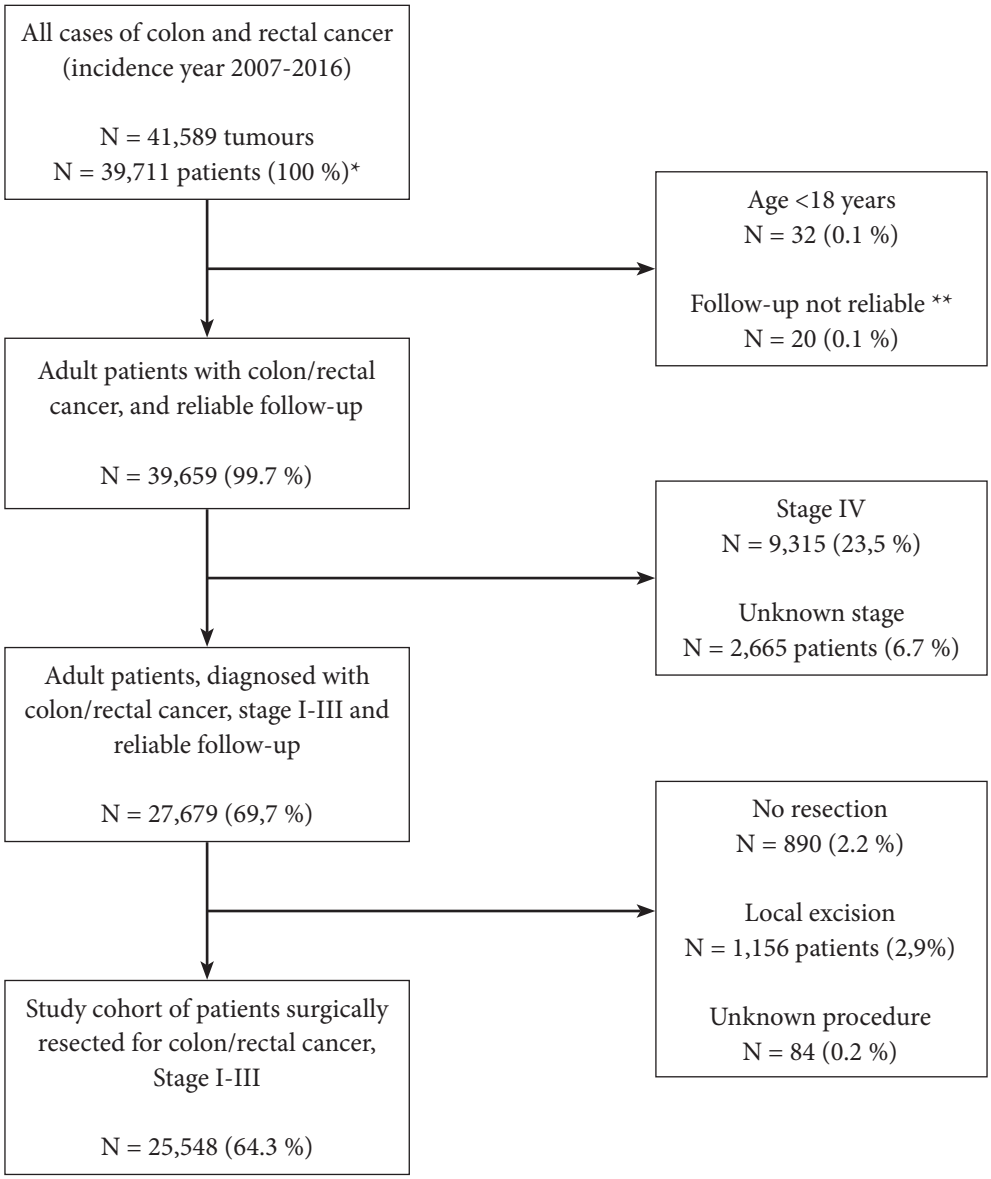


* First primary tumour selected. If multiple tumours were diagnosed on the same day, the highest stage or highest grade was chosen.

** Patients could not be linked with the administrative database, negative follow up (due to registration errors).

In 2018: total population 17,084,467 – number of new colorectal cancer cases 14,921
https://gco.iarc.fr/today/data/factsheets/populations/528-the-netherlands-fact-sheets.pdf - accessed on 28th May 2020.

Supplementary Table S1c Flowchart patient selection Norway.

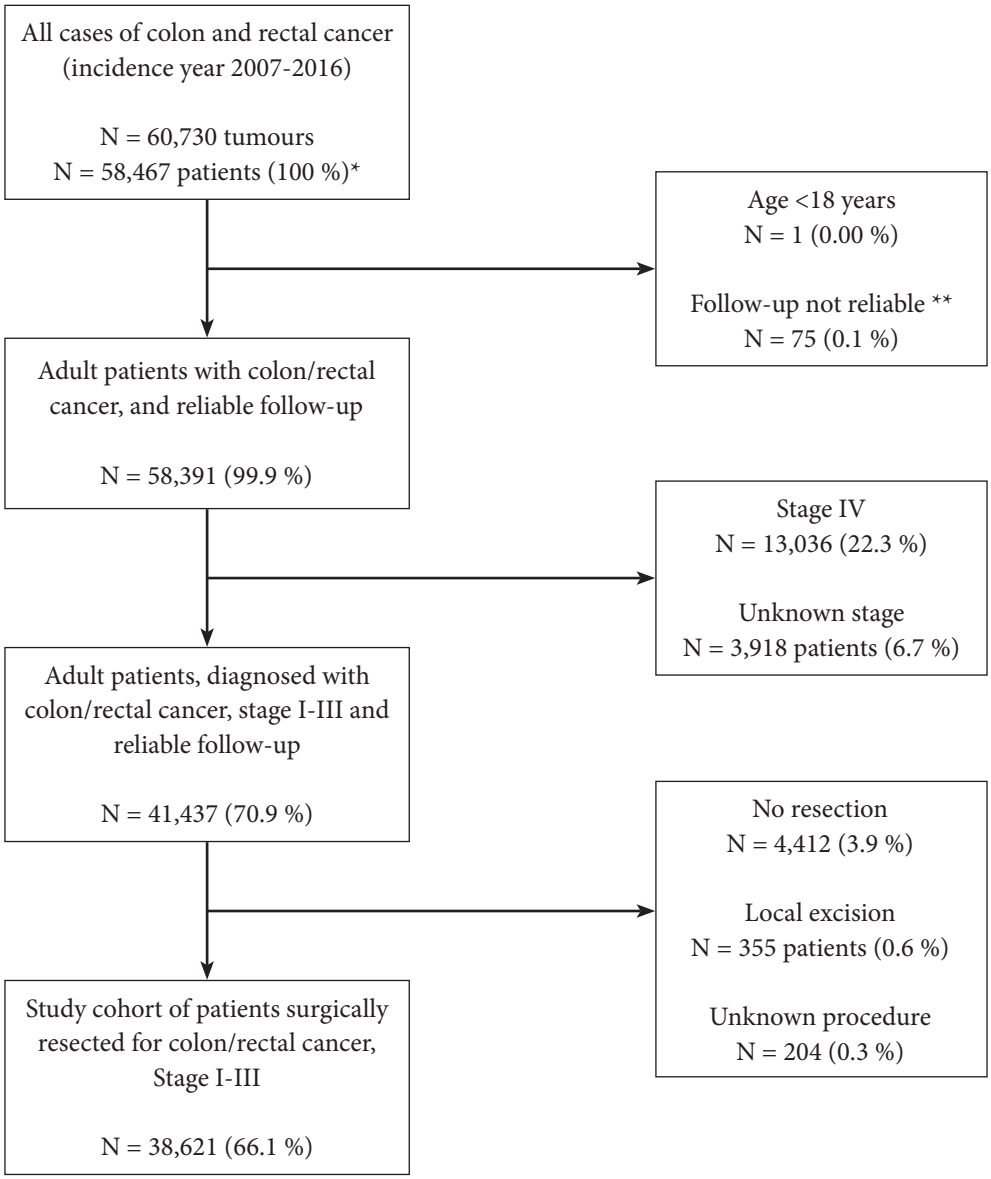


* First primary tumour selected. If multiple tumours were diagnosed on the same day, the highest stage or highest grade was chosen.

** Patients could not be linked with the administrative database, negative follow up (due to registration errors).

In 2018: total population 5,353,365 – number of new colorectal cancer cases 4,887
https://gco.iarc.fr/today/data/factsheets/populations/578-norway-fact-sheets.pdf - accessed on 28th May 2020.

Supplementary Table S1d Flowchart patient selection Sweden.



* First primary tumour selected. If multiple tumours were diagnosed on the same day, the highest stage or highest grade was chosen.

** Patients could not be linked with the administrative database, negative follow up (due to registration errors).

In 2018: total population 9,982,703 – number of new colorectal cancer cases 8,017
https://gco.iarc.fr/today/data/factsheets/populations/752-sweden-fact-sheets.pdf - accessed on 28th May 2020.

Supplementary Table S2a Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	< 65 years			65-74 years		
	Stage I	Stage II	Stage III	Stage I	Stage II	Stage III
Belgium	**(N = 2,313)**	**(N = 3,534)**	**(N = 3,798)**	**(N = 2,856)**	**(N = 4,492)**	**(N = 3,932)**
Only surgery	2142 (92.6)	1796 (50.8)	229 (6.0)	2,670 (93.5)	2,943 (65.5)	502 (12.8)
Additional therapy	171 (7.4)	1,738 (49.2)	3,569 (94.0)	186 (6.5)	1,549 (34.5)	3,430 (87.2)
Neoadjuvant RT	3 (0.1)	6 (0.2)	4 (0.1)	5 (0.2)	9 (0.2)	12 (0.3)
Adjuvant RT	7 (0.3)	7 (0.2)	5 (0.1)	15 (0.5)	19 (0.4)	11 (0.3)
Neoadjuvant CT	28 (1.2)	87 (2.5)	120 (3.2)	41 (1.4)	102 (2.3)	110 (2.8)
Adjuvant CT	127 (5.5)	1,645 (46.5)	3,483 (91.7)	137(4.8)	1,434 (31.9)	3,348 (85.1)
Neoadjuvant CRT	18 (0.8)	15 (0.4)	25 (0.7)	13 (0.5)	21 (0.5)	24 (0.6)
Adjuvant CRT	10 (0.4)	38 (1.1)	52 (1.4)	8 (0.3)	29 (0.6)	36 (0.9)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2a Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I	Stage II	Stage III
Belgium	**(N = 3,373)**	**(N = 8,434)**	**(N = 6,256)**
Only surgery	3,220 (95.5)	7,525 (89.2)	3,533 (56.5)
Additional therapy	153 (4.5)	909 (10.8)	2,723 (43.5)
Neoadjuvant RT	7 (0.2)	18 (0.2)	13 (0.2)
Adjuvant RT	23 (0.7)	39 (0.5)	18 (0.3)
Neoadjuvant CT	44 (1.3)	97 (1.2)	101 (1.6)
Adjuvant CT	102 (3.1)	787 (9.3)	2,632 (42.1)
Neoadjuvant CRT	9 (0.3)	12 (0.1)	11 (0.2)
Adjuvant CRT	1 (0.0)	18 (0.2)	26 (0.4)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2a Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	< 65 years			65-74 years		
	Stage I	Stage II	Stage III	Stage I	Stage II	Stage III
The Netherlands	**(N = 3,621)**	**(N = 6,378)**	**(N = 7,403)**	**(N = 5,326)**	**(N = 8,635)**	**(N = 7,823)**
Only surgery	3554 (98.1)	5155 (80.8)	747 (10.1)	5,275 (99.0)	7,724 (89.4)	1,817 (23.2)
Additional therapy	67 (1.9)	1,223 (19.2)	6,656 (89.9)	51 (1.0)	911 (10.6)	6,006 (76.8)
Neoadjuvant RT	26 (0.7)	54 (0.8)	80 (1.1)	21 (0.4)	60 (0.7)	71 (0.9)
Adjuvant RT	-	5 (0.1)	5 (0.1)	1 (0.0)	7 (0.1)	3 (0.0)
Neoadjuvant CT	1 (0.0)	37 (0.6)	95 (1.3)	2 (0.0)	41 (0.5)	61 (0.8)
Adjuvant CT	39 (1.1)	1,107 (17.4)	6,427 (86.6)	24 (0.5)	771 (8.9)	5,839 (74.6)
Neoadjuvant CRT	1 (0.0)	32 (0.5)	121 (1.6)	2 (0.0)	42 (0.5)	79 (1.0)
Adjuvant CRT	-	3 (0.0)	14 (0.2)	1 (0.0)	3 (0.0)	5 (0.1)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2a Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I	Stage II	Stage III
The Netherlands	**(N = 4,975)**	**(N = 11,534)**	**(N = 8,410)**
Only surgery	4957 (99.6)	11,299 (98.0)	6,140 (73.0)
Additional therapy	18 (0.4)	235 (2.0)	2,270 (27.0)
Neoadjuvant RT	12 (0.2)	44 (0.4)	58 (0.7)
Adjuvant RT	-	11 (0.1)	5 (0.1)
Neoadjuvant CT	-	15 (0.1)	16 (0.2)
Adjuvant CT	5 (0.1)	156 (1.4)	2,164 (25.7)
Neoadjuvant CRT	1 (0.0)	11 (0.1)	35 (0.4)
Adjuvant CRT	-	3 (0.0)	-

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2a Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	< 65 years			65-74 years		
	Stage I	Stage II	Stage III	Stage I	Stage II	Stage III
Norway	**(N = 1,012)**	**(N = 1,800)**	**(N = 1,752)**	**(N = 1,238)**	**(N = 2,536)**	**(N = 1,877)**
Only surgery *	-	-	-	-	-	-
Additional therapy *	-	-	-	-	-	-
Neoadjuvant RT	-	-	2 (0.1)	-	2 (0.1)	2 (0.1)
Adjuvant RT	12 (1.2)	53 (2.9)	135 (7.7)	13 (1.1)	80 (3.2)	130 (6.9)
Neoadjuvant CT *	-	-	-	-	-	-
Adjuvant CT *	-	-	-	-	-	-
Neoadjuvant CRT	1 (0.1)	8 (0.4)	12 (0.7)	1 (0.1)	1 (0.0)	9 (0.5)
Adjuvant CRT	-	-	-	-	-	-

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2a Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I	Stage II	Stage III
Norway	**(N = 1,826)**	**(N = 4,156)**	**(N = 2,716)**
Only surgery *	-	-	-
Additional therapy *	-	-	-
Neoadjuvant RT	-	-	1 (0.0)
Adjuvant RT	11 (0.6)	73 (1.8)	121 (4.5)
Neoadjuvant CT *	-	-	-
Adjuvant CT *	-	-	-
Neoadjuvant CRT	-	3 (0.1)	2 (0.1)
Adjuvant CRT	-	-	-

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2a Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	< 65 years			65-74 years		
	Stage I	Stage II	Stage III	Stage I	Stage II	Stage III
Sweden	**(N = 858)**	**(N = 2,207)**	**(N = 2,520)**	**(N = 1,492)**	**(N = 3,423)**	**(N = 3,247)**
Only surgery	840 (97.9)	1,612 (73.0)	510 (20.2)	1,457 (97.7)	2,885 (84.3)	990 (30.5)
Additional therapy	18 (2.1)	595 (27.0)	2,010 (79.8)	35 (2.3)	538 (15.7)	2,257 (69.5)
Neoadjuvant RT	-	5 (0.2)	4 (0.2)	2 (0.1)	13 (0.4)	4 (0.1)
Adjuvant RT	-	-	-	-	-	-
Neoadjuvant CT	1 (0.1)	47 (2.1)	61 (2.4)	3 (0.2)	44 (1.3)	48 (1.5)
Adjuvant CT	18 (2.1)	564 (25.6)	1,985 (78.8)	28 (1.9)	495 (14.5)	2,230 (68.7)
Neoadjuvant CRT	1 (0.1)	15 (0.7)	12 (0.5)	3 (0.2)	12 (0.4)	3 (0.1)
Adjuvant CRT	-	-	-	-	3 (0.1)	1 (0.0)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2a Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I	Stage II	Stage III
Sweden	**(N = 2,109)**	**(N = 5,952)**	**(N = 4,714)**
Only surgery	2,102 (99.7)	5,760 (96.8)	3,723 (79.0)
Additional therapy	7 (0.3)	192 (3.2)	991 (21.0)
Neoadjuvant RT	1 (0.0)	14 (0.2)	4 (0.1)
Adjuvant RT	-	-	1 (0.0)
Neoadjuvant CT	-	13 (0.2)	18 (0.4)
Adjuvant CT	5 (0.2)	165 (2.8)	976 (20.7)
Neoadjuvant CRT	1 (0.0)	6 (0.1)	-
Adjuvant CRT	-	-	-

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Supplementary Table S2b Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	< 65 years			65-74 years		
	Stage I	Stage II	Stage III	Stage I	Stage II	Stage III
Belgium	**(N = 1,750)**	**(N = 1,398)**	**(N = 1,960)**	**(N = 1,504)**	**(N = 1,290)**	**(N = 1,494)**
Only surgery	703 (40.2)	183 (13.1)	38 (1.9)	692 (46.0)	302 (23.4)	95 (6.4)
Additional therapy	1,047 (59.8)	1,215 (86.9)	1,922 (98.1)	812 (54.0)	988 (76.6)	1,399 (93.6)
Neoadjuvant RT	134 (7.7)	141 (10.1)	175 (8.9)	130 (8.6)	142 (11.0)	158 (10.6)
Adjuvant RT	4 (0.2)	5 (0.4)	5 (0.3)	4 (0.3)	13 (1.0)	5 (0.3)
Neoadjuvant CT	15 (0.9)	19 (1.4)	26 (1.3)	23 (1.5)	15 (1.2)	14 (0.9)
Adjuvant CT	585 (33.4)	800 (57.2)	1,555 (79.3)	360 (23.9)	548 (42.5)	1,048 (70.1)
Neoadjuvant CRT	855 (48.9)	863 (61.7)	1,182 (60.3)	622 (41.4)	672 (52.1)	798 (53.4)
Adjuvant CRT	6 (0.3)	71 (5.1)	164 (8.4)	10 (0.7)	50 (3.9)	116 (7.8)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2b Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I	Stage II	Stage III
Belgium	**(N = 1,382)**	**(N = 1,595)**	**(N = 1,710)**
Only surgery	778 (56.3)	745 (46.7)	611 (35.7)
Additional therapy	604 (43.7)	850 (53.3)	1,099 (64.3)
Neoadjuvant RT	206 (14.9)	276 (17.3)	287 (16.8)
Adjuvant RT	4 (0.3)	20 (1.3)	20 (1.2)
Neoadjuvant CT	13 (0.9)	16 (1.0)	21 (1.2)
Adjuvant CT	131 (9.5)	243 (15.2)	608 (35.6)
Neoadjuvant CRT	362 (26.2)	469 (29.4)	443 (25.9)
Adjuvant CRT	2 (0.1)	11 (0.7)	66 (3.9)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2b Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	< 65 years			65-74 years		
	Stage I	Stage II	Stage III	Stage I	Stage II	Stage III
The Netherlands	**(N = 1,784)**	**(N = 2,358)**	**(N = 5,625)**	**(N = 1,924)**	**(N = 2,402)**	**(N = 4,431)**
Only surgery	768 (43.0)	348 (14.8)	265 (4.7)	958 (49.8)	467 (19.4)	397 (9.0)
Additional therapy	1,016 (57.0)	2,010 (85.2)	5,360 (95.3)	966 (50.2)	1,935 (80.6)	4,034 (91.0)
Neoadjuvant RT	858 (48.1)	1,248 (52.9)	1,504 (26.7)	834 (43.3)	1,336 (55.6)	1,396 (31.5)
Adjuvant RT	29 (1.6)	14 (0.6)	28 (0.5)	34 (1.8)	14 (0.6)	34 (0.8)
Neoadjuvant CT	1 (0.1)	21 (0.9)	138 (2.5)	4 (0.2)	20 (0.8)	86 (1.9)
Adjuvant CT	6 (0.3)	31 (1.3)	574 (10.2)	2 (0.1)	16 (0.7)	313 (7.1)
Neoadjuvant CRT	129 (7.2)	717 (30.4)	3,509 (62.4)	93 (4.8)	561 (23.4)	2,406 (54.3)
Adjuvant CRT	2 (0.1)	4 (0.2)	15 (0.3)	2 (0.1)	3 (0.1)	12 (0.3)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2b Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I	Stage II	Stage III
The Netherlands	**(N = 1,403)**	**(N = 2,066)**	**(N = 2,686)**
Only surgery	714 (50.9)	522 (25.3)	541 (20.1)
Additional therapy	689 (49.1)	1,544 (74.7)	2,145 (79.9)
Neoadjuvant RT	647 (46.1)	1,255 (60.7)	1,327 (49.4)
Adjuvant RT	15 (1.1)	18 (0.9)	17 (0.6)
Neoadjuvant CT	-	8 (0.4)	16 (0.6)
Adjuvant CT	1 (0.1)	2 (0.1)	78 (2.9)
Neoadjuvant CRT	28 (2.0)	274 (13.3)	748 (27.8)
Adjuvant CRT	-	1 (0.0)	4 (0.1)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2b Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	< 65 years			65-74 years		
	Stage I	Stage II	Stage III	Stage I	Stage II	Stage III
Norway	**(N = 586)**	**(N = 639)**	**(N = 1,183)**	**(N = 586)**	**(N = 651)**	**(N = 916)**
Only surgery *	468 (79.8)	296 (46.3)	314 (26.5)	484 (82.6)	320 (49.1)	320 (34.9)
Additional therapy *	118 (20.2)	343 (53.7)	869 (73.5)	102 (17.4)	331 (50.9)	596 (65.1)
Neoadjuvant RT	5 (0.9)	17 (2.7)	39 (3.3)	11 (1.9)	26 (4.0)	45 (4.9)
Adjuvant RT	22 (3.8)	44 (6.9)	91 (7.7)	31 (5.3)	52 (8.0)	86 (9.4)
Neoadjuvant CT *	-	-	-	-	-	-
Adjuvant CT *	-	-	-	-	-	-
Neoadjuvant CRT	91 (15.5)	282 (44.1)	739 (62.5)	60 (10.2)	253 (38.9)	465 (50.8)
Adjuvant CRT	-	-	-	-	-	-

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2b Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I	Stage II	Stage III
Norway	**(N = 541)**	**(N = 758)**	**(N = 775)**
Only surgery *	478 (88.4)	522 (68.9)	430 (55.5)
Additional therapy *	63 (11.6)	236 (31.1)	345 (44.5)
Neoadjuvant RT	17 (3.1)	79 (10.4)	116 (15.0)
Adjuvant RT	21 (3.9)	45 (5.9)	69 (8.9)
Neoadjuvant CT *	-	-	-
Adjuvant CT *	-	-	-
Neoadjuvant CRT	25 (4.6)	112 (14.8)	160 (20.6)
Adjuvant CRT	-	-	-

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2b Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	< 65 years			65-74 years		
	Stage I	Stage II	Stage III	Stage I	Stage II	Stage III
Sweden	**(N = 1,113)**	**(N = 1,139)**	**(N = 1,684)**	**(N = 1,325)**	**(N = 1,353)**	**(N = 1,671)**
Only surgery	397 (35.7)	184 (16.2)	95 (5.6)	551 (41.6)	325 (24.0)	154 (9.2)
Additional therapy	716 (64.3)	955 (83.8)	1,589 (94.4)	774 (58.4)	1,028 (76.0)	1,517 (90.8)
Neoadjuvant RT	524 (47.1)	570 (50.0)	854 (50.7)	614 (46.3)	723 (53.4)	951 (56.9)
Adjuvant RT	-	-	2 (0.1)	0 (0.1)	2 (0.1)	2 (0.1)
Neoadjuvant CT	3 (0.3)	14 (1.2)	14 (0.8)	4 (0.3)	9 (0.7)	10 (0.6)
Adjuvant CT	83 (7.5)	216 (19.0)	979 (58.1)	40 (3.0)	152 (11.1)	818 (49.0)
Neoadjuvant CRT	176 (15.8)	337 (29.6)	452 (26.8)	144 (10.9)	257 (19.0)	316 (18.9)
Adjuvant CRT	-	1 (0.1)	3 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2b Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I	Stage II	Stage III
Sweden	**(N = 1,116)**	**(N = 1,275)**	**(N = 1,423)**
Only surgery	609 (54.6)	579 (45.4)	550 (38.7)
Additional therapy	507 (45.4)	696 (54.6)	873 (61.3)
Neoadjuvant RT	465 (41.7)	623 (48.9)	730 (51.3)
Adjuvant RT	1 (0.1)	1 (0.1)	2 (0.1)
Neoadjuvant CT	2 (0.2)	3 (0.2)	3 (0.2)
Adjuvant CT	5 (0.4)	19 (1.5)	191 (13.4)
Neoadjuvant CRT	36 (3.2)	64 (5.0)	72 (5.1)
Adjuvant CRT	-	-	-

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Supplementary Table S3 Mortality time trends in percentages for patients with rectal cancer ≥ 75 years.

	≤ 30 day, overall mortality					
	2007 - 2008	2009 - 2010	2011 - 2012	2013 - 2014	2015 - 2016	P-value
Stage I						0.204
Belgium	4.5	6.4	2.6	4.0	3.4	
The Netherlands	7.3	6.1	4.5	2.4	3.7	
Norway	0.0	1.9	4.9	0.8	0.9	
Sweden	5.4	1.8	0.9	3.6	1.4	
Stage II						0.082
Belgium	7.0	8.7	7.2	5.1	6.0	
The Netherlands	8.4	5.2	4.3	3.5	2.0	
Norway	4.5	2.9	4.0	3.8	5.5	
Sweden	5.0	3.0	3.1	4.2	4.0	
Stage III						0.009
Belgium	7.1	5.6	3.4	3.6	6.5	
The Netherlands	7.0	6.7	4.3	3.0	2.7	
Norway	5.1	3.1	3.6	0.0	2.5	
Sweden	6.3	4.1	3.7	3.3	1.9	

P-values are for differences between countries in time-period 2015-2016.

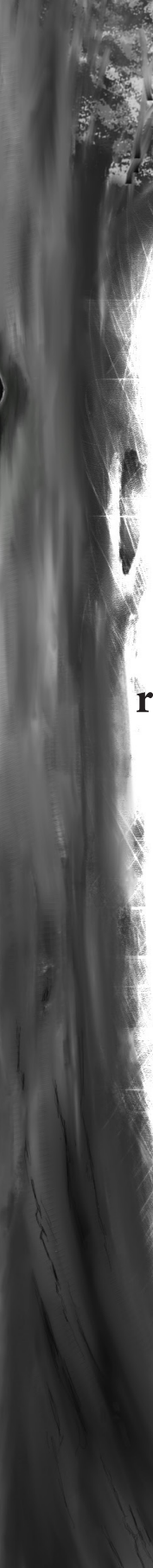
Continuation Supplementary Table S3 Mortality time trends in percentages for patients with rectal cancer ≥ 75 years.

	1st year, overall mortality					
	2007 - 2008	2009 - 2010	2011 - 2012	2013 - 2014	2015 - 2016	P-value
Stage I						0.122
Belgium	10.8	16.4	13.8	13.2	9.2	
The Netherlands	16.7	9.5	11.7	6.6	7.4	
Norway	8.4	7.8	11.8	2.4	3.4	
Sweden	11.3	8.1	5.0	5.0	5.1	
Stage II						0.007
Belgium	19.4	19.5	18.2	18.2	16.2	
The Netherlands	18.9	14.6	12.8	11.7	7.5	
Norway	14.6	8.1	9.3	7.6	13.7	
Sweden	14.2	10.0	8.4	9.3	9.7	
Stage III						<0.001
Belgium	22.2	21.9	20.6	19.9	20.4	
The Netherlands	20.4	16.9	16.3	10.8	9.4	
Norway	20.3	11.9	12.7	7.1	8.9	
Sweden	16.4	14.9	12.8	9.8	10.8	

P-values are for differences between countries in time-period 2015-2016.

PART II - RAPIDO


4



Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, multicentre, phase 3 trial

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Abstract

Background: Systemic relapses remain a major problem in locally advanced rectal cancer. Using short-course radiotherapy followed by chemotherapy and delayed surgery, the Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation (RAPIDO) trial aimed to reduce distant metastases without compromising locoregional control.

Methods: In this multicentre, open-label, randomised, controlled, phase 3 trial, participants were recruited from 54 centres in the Netherlands, Sweden, Spain, Slovenia, Denmark, Norway, and the USA. Patients were eligible if they were aged 18 years or older, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, had a biopsy-proven, newly diagnosed, primary, locally advanced rectal adenocarcinoma, which was classified as high risk on pelvic MRI (with at least one of the following criteria: clinical tumour [cT] stage cT4a or cT4b, extramural vascular invasion, clinical nodal [cN] stage cN2, involved mesorectal fascia, or enlarged lateral lymph nodes), were mentally and physically fit for chemotherapy, and could be assessed for staging within 5 weeks before randomisation. Eligible participants were randomly assigned (1:1), using a management system with a randomly varying block design (each block size randomly chosen to contain two to four allocations), stratified by centre, ECOG performance status, cT stage, and cN stage, to either the experimental or standard of care group. All investigators remained masked for the primary endpoint until a pre-specified number of events was reached. Patients allocated to the experimental treatment group received short-course radiotherapy (5 × 5 Gy over a maximum of 8 days) followed by six cycles of CAPOX chemotherapy (capecitabine 1000 mg/m² orally twice daily on days 1–14, oxaliplatin 130 mg/m² intravenously on day 1, and a chemotherapy-free interval between days 15–21) or nine cycles of FOLFOX4 (oxaliplatin 85 mg/m² intravenously on day 1, leucovorin [folinic acid] 200 mg/m² intravenously on days 1 and 2, followed by bolus fluorouracil 400 mg/m² intravenously and fluorouracil 600 mg/m² intravenously for 22 h on days 1 and 2, and a chemotherapy-free interval between days 3–14) followed by total mesorectal excision. Choice of CAPOX or FOLFOX4 was per physician discretion or hospital policy. Patients allocated to the standard of care group received 28 daily fractions of 1.8 Gy up to 50.4 Gy or 25 fractions of 2.0 Gy up to 50.0 Gy (per physician discretion or

hospital policy), with concomitant twice-daily oral capecitabine 825 mg/m² followed by total mesorectal excision and, if stipulated by hospital policy, adjuvant chemotherapy with eight cycles of CAPOX or 12 cycles of FOLFOX4. The primary endpoint was 3-year disease-related treatment failure, defined as the first occurrence of locoregional failure, distant metastasis, new primary colorectal tumour, or treatment-related death, assessed in the intention-to-treat population. Safety was assessed by intention to treat. This study is registered with the EudraCT, 2010-023957-12, and ClinicalTrials.gov, NCT01558921, and is now complete.

Findings: Between June 21, 2011, and June 2, 2016, 920 patients were enrolled and randomly assigned to a treatment, of whom 912 were eligible (462 in the experimental group; 450 in the standard of care group). Median follow-up was 4.6 years (IQR 3.5–5.5). At 3 years after randomisation, the cumulative probability of disease-related treatment failure was 23.7% (95% CI 19.8–27.6) in the experimental group versus 30.4% (26.1–34.6) in the standard of care group (hazard ratio 0.75, 95% CI 0.60–0.95; p=0.019). The most common grade 3 or higher adverse event during preoperative therapy in both groups was diarrhoea (81 [18%] of 460 patients in the experimental group and 41 [9%] of 441 in the standard of care group) and neurological toxicity during adjuvant chemotherapy in the standard of care group (16 [9%] of 187 patients). Serious adverse events occurred in 177 (38%) of 460 participants in the experimental group and, in the standard of care group, in 87 (34%) of 254 patients without adjuvant chemotherapy and in 64 (34%) of 187 with adjuvant chemotherapy. Treatment-related deaths occurred in four participants in the experimental group (one cardiac arrest, one pulmonary embolism, two infectious complications) and in four participants in the standard of care group (one pulmonary embolism, one neutropenic sepsis, one aspiration, one suicide due to severe depression).

Interpretation: The observed decreased probability of disease-related treatment failure in the experimental group is probably indicative of the increased efficacy of preoperative chemotherapy as opposed to adjuvant chemotherapy in this setting. Therefore, the experimental treatment can be considered as a new standard of care in high-risk locally advanced rectal cancer.

Funding: Dutch Cancer Foundation, Swedish Cancer Society, Spanish Ministry of Economy and Competitiveness, and Spanish Clinical Research Network.

Introduction

Standard of care for locally advanced rectal cancer consists of chemoradiotherapy followed by surgery according to total mesorectal excision principles after 6–8 weeks. In several countries, adjuvant chemotherapy is also part of the standard of care. Preoperative chemoradiotherapy aims to downstage tumours, leading to improved locoregional control with local recurrence rates of approximately 5–9%.[1,2] However, unfortunately the occurrence of distant metastases has not decreased accordingly.

Downstaging also occurs after short-course radiotherapy followed by delayed surgery, as found in the Stockholm III trial.[3] Although the evidence is not entirely conclusive, many centres administer adjuvant chemotherapy intended to reduce systemic relapses, but compliance is suboptimal.[2,4,5] Surgery can safely be delayed after short-course radiotherapy, creating a window of opportunity to deliver chemotherapy preoperatively instead of postoperatively—an approach that is expected to increase compliance.[6,7] We hypothesised that this approach might result in a decreased number of distant metastases without increasing the risk of locoregional failure, ultimately improving survival outcomes.

The Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation (RAPIDO) trial is based on the Dutch M1-trial[8] in which patients with metastatic primary rectal cancer received short-course radiotherapy, followed by six cycles of capecitabine, oxaliplatin, and bevacizumab, and surgery after 6–8 weeks. High chemotherapy compliance (42 [84%] of 50 patients received six cycles) and primary tumour downstaging in 20 (47%) of

Research in context:

Evidence before this study

On May 15, 2020, we searched PubMed, without any language or date restrictions, using terms related to rectal cancer, short- course radiotherapy, and preoperative chemotherapy. We found no randomised trials that used the approach of 5 × 5 Gy radiotherapy followed by 18 weeks of preoperative chemotherapy and curative surgery in patients with locally advanced rectal cancer. Research in the past two decades has resulted in improved categorisation of rectal cancer, especially by MRI. More precise surgery and appropriate use of preoperative radiotherapy or chemoradiotherapy have yielded considerably lower rates of local recurrence than has been

seen before. However, distant metastases have not decreased and, as a result, overall survival has not improved proportionally. By contrast with its successful use in colon cancer, adjuvant chemotherapy, although used extensively in many countries, has not convincingly affected rates of recurrence or survival in rectal cancer. Randomised trials have shown poor tolerability for adjuvant chemotherapy, possibly explaining the absence of effect. Therefore, we hypothesised that delivering preoperative chemotherapy after radiotherapy would increase compliance, reduce distant metastases, and ultimately improve survival. This approach, called total neoadjuvant therapy, resulted in the initiation of several phase 2 trials, with favourable outcomes.

Added value of this study

The experimental treatment of the RAPIDO trial decreased the rate of disease-related treatment failure compared with standard of care, mainly due to fewer distant metastases. Moreover, this approach doubled the rate of pathological complete response compared with the standard of care treatment. No differences regarding locoregional failure and overall survival after 3 years of follow-up were observed. The results also suggested that the experimental treatment could have additional benefits, such as fewer visits to specialised health-care facilities, a prominent advantage in the context of the COVID-19 pandemic.

Implications of all the available evidence

Preoperative short-course radiotherapy followed by chemotherapy and total mesorectal excision could be considered as a new standard of care. The PRODIGE 23 trial has also reported improved results with a total neoadjuvant therapy approach compared with a similar standard of care treatment as used in the RAPIDO trial, although with a more demanding experimental treatment with triplet chemotherapy and conventional chemoradiotherapy. These trials add strong evidence to support the proposal that total neoadjuvant therapy should replace the current standard treatment since it decreases the risk of systemic relapse and could potentially improve overall survival. In future research, data from the RAPIDO trial will be used to explore dose-effect associations for tumour control and toxicity of the radiotherapy and chemotherapy regimens, quality of MRIs, quality of life, local recurrence, and metastatic patterns. Furthermore, in the context of the growing interest in organ preservation in rectal cancer treatment, the high rate of pathological complete response observed in the experimental treatment group of RAPIDO is encouraging.

43 patients were reported. Moreover, a pathological complete response of the primary tumour occurred in 11 (26%) of 43 patients.[8] Similarly, favourable experiences of combining short-course radiotherapy and subsequent chemotherapy have been reported in Sweden.[6]

The main objective of the RAPIDO trial was to reduce disease-related treatment failure at 3 years with short-course radiotherapy followed by chemotherapy and total mesorectal excision compared with standard chemoradiotherapy, total mesorectal excision, and optional adjuvant chemotherapy (predefined by hospital policy). Data on compliance, toxicity, and postoperative complications in the RAPIDO trial have been published previously.[9] Here we present the primary endpoint after a median follow-up of 4.6 years.

Methods

Study design and participants

The RAPIDO trial was an investigator-driven, open-label, randomised, controlled, phase 3 trial, done at in 54 hospitals and radiotherapy centres in seven countries (the Netherlands, Sweden, Spain, Slovenia, Denmark, Norway, and the USA). The study was coordinated by the Clinical Research Center (Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands), including randomisation, trial and database management, quality assurance, and quality control (EM-KK and AGHR).

Patients were eligible for inclusion if they were aged 18 years or older, with a biopsyproven, newly diagnosed, primary, locally advanced rectal adenocarcinoma with distal extension less than 16 cm from the anal verge. A pelvic MRI with at least one of the following highrisk criteria was required: clinical tumour (cT) stage cT4a or cT4b, extramural vascular invasion, clinical nodal (cN) stage cN2, involved mesorectal fascia (tumour or lymph node ≤1 mm from the mesorectal fascia), or enlarged lateral lymph nodes considered to be metastatic. For all staging, the TNM5 classification was used.[10] Other inclusion criteria were that the patient must be mentally and physically fit for chemotherapy, have an Eastern Cooperative Oncology Group (ECOG) performance score of 0–1, be assessed for staging within 5 weeks before randomisation, be available for follow-up, and provide written informed consent. Additionally the following laboratory results were required: a white blood cell count of 4.0×10^9 cells per L or higher, platelet count of 100×10^9 per L or higher, a clinically acceptable haemoglobin level,

a creatinine level indicating renal clearance of 50 mL/min or higher, and bilirubin level below 35 µmol/L. Comorbidities were permitted. Exclusion criteria included extensive growth of the rectal tumour into the cranial part of the sacrum or the lumbosacral nerve roots indicating that surgery will never be possible even if substantial tumour downsizing is seen and presence of metastatic disease or recurrent rectal cancer.

The trial was carried out in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. Surgery was mandatory; therefore, a watch andwait strategy was considered a protocol violation. After central evaluation by the medical ethics committee of University Medical Center Groningen (Groningen, Netherlands [2011/098]), the boards of directors or local ethics committees of all participating centres approved the protocol.

Randomisation and masking

Patients were recruited at the participating hospitals before commencement of any treatment and randomly assigned (1:1) by use of the ProMISe data management system (version 4.0) using a stratified and randomly varying block design (each block size was randomly chosen to contain two to four allocations), to either the experimental group or standard of care group. Stratification factors were institution, ECOG performance status (0 or 1), cT stage (cT2–cT3 or cT4), and cN stage (cN– or cN+). Randomisation was coordinated by the Clinical Research Center. All investigators remained masked to treatment assignment for the primary endpoint until the pre-specified number of events was reached. Due to the nature of the intervention, patients and clinical staff were not masked to group assignment.

Procedures

A high-resolution, three-dimensional T2 weighted sequence MRI was mandatory before and after preoperative treatment. The protocol specified details on MRI reporting. MRI reports minimally included the following details: tumour height from the anorectal junction, morphology of the tumour, depth of extramural spread, presence or absence of extramural vascular invasion, mesorectal fascia involvement, breach of the peritoneal reflection by the tumour, presence or absence of mesorectal or extra mesorectal lymph node metastases, and, at restaging, the response to preoperative treatment. Mesorectal lymph nodes with a short

axis diameter of more than 10 mm and round shape, and those with a short axis of 5–9 mm and meeting at least two criteria of round shape, irregular border, or heterogeneous signal intensity on MRI were defined as metastatic.[11] Extramesorectal lymph nodes with an irregular border or heterogeneous signal intensity, or both, or round lymph nodes with a short axis diameter of more than 10 mm, or a combination of these factors, were considered to be metastatic.

An overview of both treatment regimens is provided in the appendix (p 160). Patients in the experimental group were assigned to short-course radiotherapy (5 × 5 Gy), administered over a maximum of 8 days. Chemotherapy was preferably started within 11–18 days after the last radiotherapy fraction, but within at least 4 weeks. Chemotherapy consisted of six cycles of CAPOX (capecitabine 1000 mg/m² orally twice daily on days 1–14, oxaliplatin 130 mg/m² intravenously on day 1, and a chemotherapy-free interval between days 15–21) or nine cycles of FOLFOX4 (oxaliplatin 85 mg/m² intravenously on day 1, leucovorin [folinic acid] 200 mg/m² intravenously on days 1 and 2, followed by bolus fluorouracil 400 mg/m² intravenously and fluorouracil 600 mg/m² intravenously for 22 h on days 1 and 2, and a chemotherapy-free interval between days 3–14). After completion of chemotherapy, surgery according to total mesorectal excision principles was planned after 2–4 weeks. The choice of CAPOX or FOLFOX4 was determined by the treating physician and according to hospital policy.

In the standard of care group, patients received radiotherapy in 28 daily fractions of 1.8 Gy up to 50.4 Gy or 25 fractions of 2.0 Gy up to 50.0 Gy, as per the decision of the treating physician and hospital policy, with concomitant twicedaily oral capecitabine 825 mg/m². Optional field reduction was recommended after 45 Gy (1.8 Gy schedule) or 46 Gy (2.0 Gy schedule), with the last fractions delivered to the tumour bed. Surgery according to total mesorectal excision principles was planned 6–10 weeks after the last radiotherapy fraction. If protocolised by the participating centre, adjuvant chemotherapy was admin istered within 6–8 weeks using eight cycles of CAPOX or 12 cycles of FOLFOX4.

In both groups, the clinical target volume for radiotherapy included the entire mesorectum with the primary tumour and relevant regional lymph nodes; an additional boost dose was optional. The clinical target volume of the boost was the assessable tumour with a 1 cm margin within the same anatomical compartment as where the tumour is located. In case of toxicity

(according to Common Terminology Criteria for Adverse events [CTCAE] version 4) a dose reduction of 25% or more (relative to the previous chemotherapy cycle) was protocolised (appendix p 161-162). Laboratory and adverse event monitoring during preoperative therapy was done before all cycles in the experimental group and weekly in the standard of care group. Adverse events related to preoperative and adjuvant therapy were assessed and graded by the local investigator using CTCAE version 4 and postoperative complications using the Clavien Dindo classification.[12] Surgery was done according to total mesorectal excision principles; a partial mesorectal excision was accepted for proximal tumours. Open and laparoscopic approaches were allowed and at the surgeon's discretion. The completeness of resection was assessed using the residual tumour classification.[13] Pathological assessment of the resected sample was done according to national guidelines of each participating country and included standardised work up and reporting. The involvement of circumferential resection margins, quality of the sample, and complete tumour response (yes or no) were recorded. Quality of the resection was assessed at two different levels for abdominoperineal excision (mesorectum and anal canal) and at one level for anterior resection (mesorectum). A serious adverse event was defined as any untoward medical occurrence or effect that at any dose: results in death; is life threatening (at the time of the event); requires admission to hospital or extension of ongoing hospital stay; results in persistent or clinically significant disability or incapacity; is a congenital anomaly or birth defect; or is a new event of the trial likely to affect the safety of the participants, such as an unexpected outcome of an adverse reaction, lack of efficacy of a study drug used for the treatment of a life threatening disease, and major safety finding from a newly completed animal study.

A standardised, minimal follow-up schedule was defined, with clinical assessments at 6, 12, 24, 36, and 60 months after surgery, including carcinoembryonic antigen measurement. Total colonoscopy was obligatory within the first year unless done preoperatively. The study protocol mandated chest x-ray or CT of the thorax and liver ultrasound or CT of the abdomen at 12 and 36 months as a minimum. A colonoscopy was mandatory 60 months postoperatively. On indication, other diagnostics (eg, PET CT scan) were allowed, to confirm or detect recurrent disease. Functional outcome and health-related quality of life of patients who did not have a disease-related treatment failure event within 36 months

after surgery were measured once, using three European Organisation for Research and treatment of Cancer (EORTC) questionnaires: the quality-of-life questionnaire for patients with cancer (QLQC30), the quality-of-life questionnaires for patients with colorectal cancer (QLQCR29; supplemented with questions related to sexual functioning from the prostate cancer [QLQPR25] and endometrial cancer [QLQEN24] modules) and the quality-of-life questionnaire to assess chemotherapy-induced peripheral neuropathy (QLQCIPN20). The low anterior resection syndrome (LARS) scores, regarding bowel function, were also measured.14 These questionnaires were available in the official languages of each country, except Slovenian. Hence patients from Slovenia were not assessable for the 3year endpoint of quality of life.

Outcomes

The primary endpoint was disease-related treatment failure, defined as the first occurrence of locoregional failure, distant metastasis, a new primary colorectal tumour, or treatment-related death. Loco regional failure included locally progressive disease leading to an unresectable tumour, local R2 resection, or local recurrence after an R0–R1 resection. Locoregional regrowth after a clinical complete response and a watch-and-wait period was not considered a locoregional failure when followed by an R0–R1 resection. Disease-related treatment failure events were not centrally reviewed. Data collection continued after the first disease-related treatment failure event for separate analyses of locoregional failure and distant metastases. Although these were not protocolised secondary end points, the stated aim of RAPIDO to reduce systemic relapses without compromising local control justifies these analyses as separate outcomes. Other secondary end points were completion rate of neoadjuvant treatment, toxicity, R0 resection rate (resection margin of >1 mm), pathological complete response rate (no residual tumour at pathological assessment after surgery), surgical complications within 30 days, quality of life (in patients alive without disease related treatment failure, 3 years after surgery), functional outcome, overall survival (time from randomisation to death from any cause), and local recurrence. Toxicity and surgical complications within 30 days have been reported elsewhere.[9] Quality-of-life outcomes will be reported in depth elsewhere.

Statistical analysis

After two protocol amendments, the primary endpoint was changed from disease-free survival to disease-related treatment failure. Around 1 year before the end of the inclusion period, it became apparent that disease-free survival, commonly used in adjuvant trials, was an inappropriate endpoint in a neoadjuvant trial, because patients are not disease free at randomisation and some will never become disease free. For this reason, the protocol was amended (version 3.1; Jan 8, 2016) and a new primary endpoint was formulated: time to diseaserelated treatment failure. The change to this new endpoint was approved by the medical ethics committee and data safety monitoring board (DSMB), which did ongoing safety surveillance and evaluated interim analyses. The first planned and blinded efficacy interim analysis was done on Oct 17, 2017, after 226 disease-related treatment failure events. The second interim analysis was planned after 339 events. However, after a median follow-up exceeding 3 years, the total number of events (for which investigators were masked to treatment group assignment) was lower than anticipated and the required number of events (n=452) was expected to never be reached. Potential reasons for this situation are as follows: alteration of the endpoint (death due to other reasons and a new primary tumour, other than colorectal, are not events), a finite period of follow-up (statistical programs assume endless follow-up), and possibly better overall outcomes than projected. Therefore, the hypo thesis changed from a decrease in events from 50% to 40%, to a decrease in the probability of disease-related treatment failure events from 30% to 22.5% with the experimental treatment, approved by the medical ethics committee and DSMB (protocol version 3.2; June 13, 2019).

To detect a decrease in 3year cumulative probability of disease-related treatment failure from 30% to 22.5%, corresponding to a hazard ratio (HR) of 0.715, a two sided log-rank test with 280 events would achieve 80% power at a two-sided α significance level of 0.05.

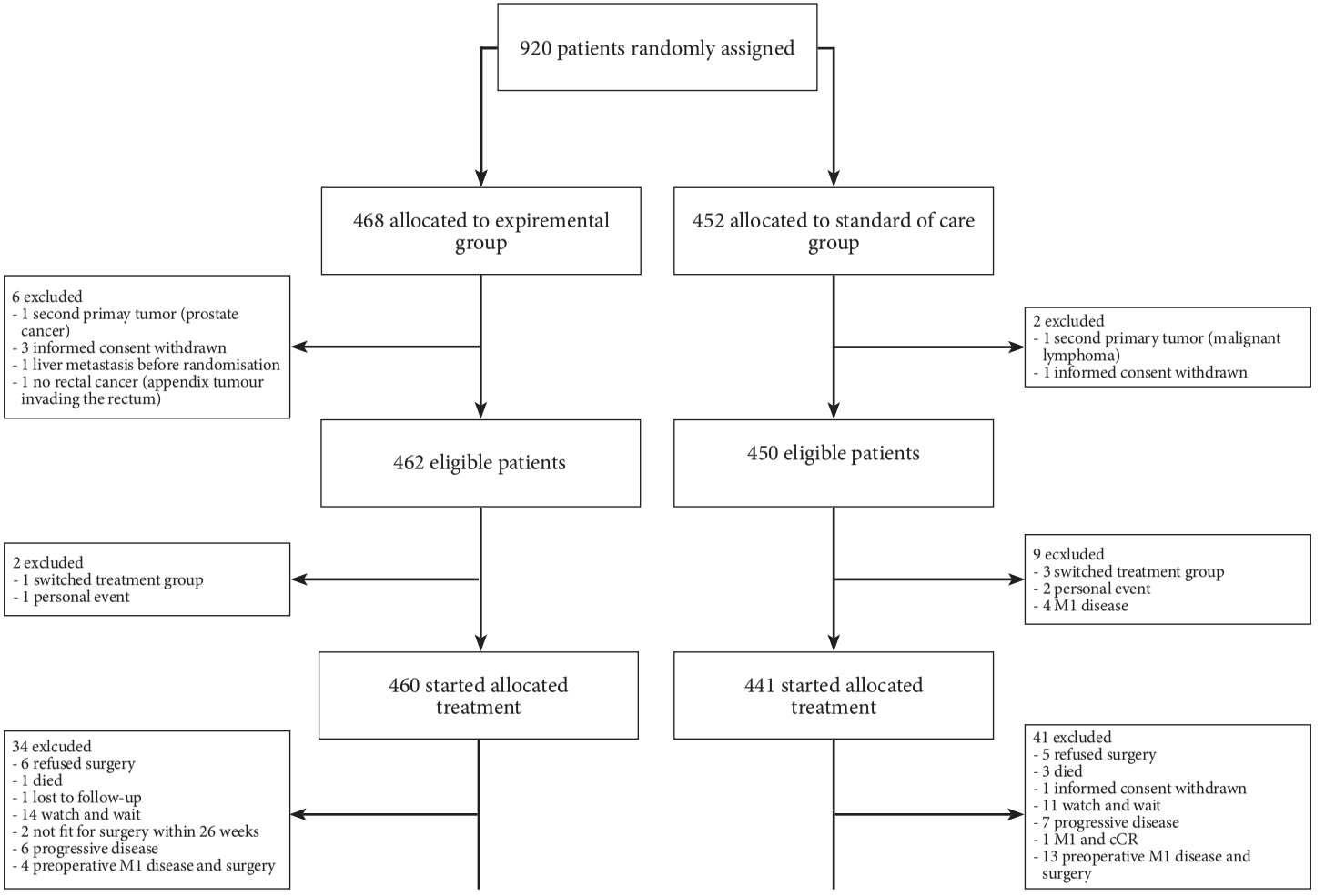
The primary analysis and the secondary endpoint analysis of overall survival were done in the intention-to-treat population (all patients randomly assigned to treatment, excluding those who withdrew informed consent or were ineligible), as were the analyses of locoregional failure and distant metastases. The secondary endpoints of R0 resection and pathological complete response were analysed in patients who had a resection; surgical complications were analysed in patients who had surgery with curative intent within 6 months; quality of life

was assessed in patients who had resection, did not already develop a disease-related treated failure event, and responded in full to the questionnaires; and toxicity was analysed in all patients who started on their allocated treatment.

Using IBM SPSS Statistics (version 25.0), we compared proportions using the χ^2 test and continuous data, depending on the distribution, with Student's t test or the Mann-Whitney U test. All calculated median values are accompanied by an IQR and means with SDs. Using R (version 3.6.1), we did all survival analyses using the Kaplan-Meier method on an intention-to-treat basis. We calculated HRs and 95% CIs using Cox regression. Visual inspection of the cumulative hazards showed no evidence of violation of the proportional hazards assumption. For our separate analyses of locoregional failure, all patients, with and without distant metastases, were included, and for the separate analyses of distant metastases all patients, with and without locoregional failure, were included. Patients who were alive and disease free at last follow-up were censored. We used the reverse Kaplan-Meier method to calculate median follow-up. We calculated cumulative incidence of disease-related treatment failure accounting for non-treatment-related death as a competing risk. For distant metastases and locoregional failure, we calculated cumulative incidences accounting for all causes of death as a competing risk. For all competing risks analyses, we calculated and report cause-specific HRs. We calculated p values for all survival analyses on the basis of (cause specific) logrank tests.[15,16] For pathological complete response, we calculated odds ratios (ORs) and 95% CIs.

To assess whether the main results were robust, we did sensitivity analyses to study the effect of timing of disease staging (ie, time-related bias), and to adjust for stratification factors. Additionally, in sensitivity analyses, we analysed the influence of hospital policy on adjuvant chemotherapy within the standard of care group on the endpoints of disease-related treatment failure, distant metastases, and locoregional failure using the Kaplan Meier method. We did subgroup analyses on associations between the primary endpoint and baseline characteristics and present these analyses in a forest plot.

We did a post-hoc analysis of disease-free survival from surgery. Additionally, we calculated disease-free survival, as defined by Fokas and colleagues,[17] which is similar to our definition of disease-related treatment failure but includes a second primary cancer, other than colorectal, and death from all causes as events. According to this definition, patients are not disease free


920 patients randomly assigned
468 allocated to expiremental group
452 allocated to standard of care group
6 excluded
- 1 second primay tumor (prostate cancer)
- 3 informed consent withdrawn
- 1 liver metastasis before randomisation
- 1 no rectal cancer (appendix tumour invading the rectum)
2 excluded
- 1 second primary tumor (malignant lymphoma)
- 1 informed consent withdrawn
462 eligible patients
450 eligible patients
2 excluded
- 1 switched treatment group
- 1 personal event
9 ecxluded
- 3 switched treatment group
- 2 personal event
- 4 M1 disease
460 started allocated treatment
441 started allocated treatment
34 exlcuded
- 6 refused surgery
- 1 died
- 1 lost to follow-up
- 14 watch and wait
- 2 not fit for surgery within 26 weeks
- 6 progressive disease
- 4 preoperative M1 disease and surgery
41 excluded
- 5 refused surgery
- 3 died
- 1 informed consent withdrawn
- 11 watch and wait
- 7 progressive disease
- 1 M1 and cCR
- 13 preoperative M1 disease and surgery

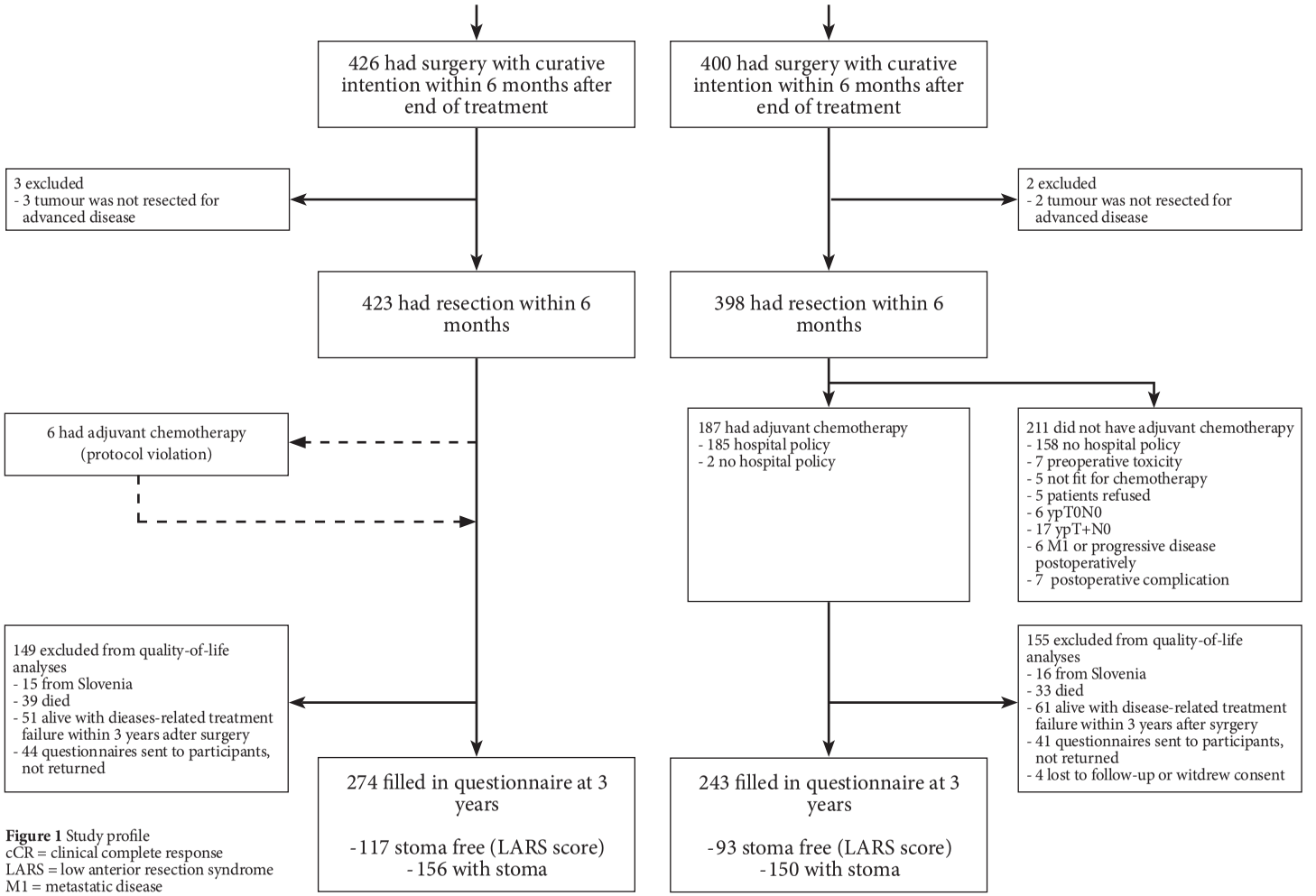


Figure 1 Study profile
cCR = clinical complete response
LARS = low anterior resection syndrome
M1 = metastatic disease

at the start of the curves; rather they are event free. The starting point for all analyses was date of randomisation. The significance threshold for all p values was 0.05. The RAPIDO trial is registered with EudraCT (201002395712) and ClinicalTrials.gov (NCT01558921).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

Between June 21, 2011, and June 2, 2016, 920 patients were randomly assigned to the experimental group (468) or standard of care group (452), of whom 912 (99%) were eligible (462 in the experimental group and 450 in the standard of care group; figure 1). Baseline characteristics of eligible participants are shown in table 1. Information on the proportion of participants in each group by year and country of inclusion is provided in the appendix (p 163). At the time of analyses (database lock was on June 19, 2020), median follow-up was 4.6 years (IQR 3.5–5.5). The median time between randomisation and surgery was 25.5 weeks (IQR 24.0–27.9) in the experimental group and 15.9 weeks (14.6–17.6) in the standard of care group.

After reaching 128 disease-related treatment failure events in the experimental group and 152 events in the standard of care group, the difference between groups in disease-related treatment failure at 3 years was significant, with fewer disease-related treatment failure events in the experimental group than in the standard of care group (3year cumulative probability of 23.7% [95% CI 19.8–27.6] vs 30.4% [26.1–34.6]; HR 0.75 [95% CI 0.60–0.95]; p=0.019; figure 2). Distant metastasis caused most disease-related treatment failures (table 2). At 3 years, the cumulative probability of distant metastases was 20.0% (95% CI 16.4–23.7) in the experimental group compared with 26.8% (22.7–30.9) in the standard of care group (HR 0.69 [95% CI 0.54–0.90]; p=0.0048; figure 2). The cumulative probability of locoregional failure at 3 years was 8.3% (95% CI 5.8–10.8) in the experimental group compared with 6.0% (3.8–8.2) in the standard of care group (HR 1.42 [95% CI 0.91–2.21]; p=0.12; figure 2). The post-hoc

subgroup analysis of disease-free survival from surgery, in patients with an R0 (>1 mm) resection within 6 months after the end of preoperative treatment is provided in the appendix (p 164). Notably, randomisation in this subgroup comparison (743 of 902 eligible patients) is no longer guaranteed to be balanced with respect to important prognostic factors. Therefore, the comparison could be biased due to possible differences in type of resection and approach, resection rate, pathological response, and other factors, between the treatment groups. The adjusted disease-free survival according to a different definition by Fokas et al,[17] which was similar to our definition of disease-related treatment failure but included a second primary cancer, other than colorectal, and death from all causes as events, had a hazard ratio of 0.75 (95% CI 0.60–0.93; p=0.010). However, according to this definition, patients are not disease free at the start of the curves, rather they are event free. Sensitivity analyses adjusting for possible time-related bias and separately for stratification factors showed similar results as the original analyses (appendix pp 163, 166). Local recurrence in each group is shown in table 2. In the experimental group, median time between conclusion of radiotherapy and start of chemotherapy was 14 days (IQR 12–17) in patients who started allocated treatment. In the standard of care group, the optional field reduction after 45 or 46 Gy, as described in the protocol, was done for 102 (23%) of 441 patients who started treatment. Among patients who started allocated treatment, one (<1%) of 460 patients in the experimental group and ten (2%) of 441 in the standard of care group were given an external beam boost. Dose reduction of chemotherapy occurred in 201 (44%) of 460 patients in the experimental group, in 25 (6%) of 441 patients in the standard of care group during preoperative therapy, and in 64 (34%) of 187 patients during adjuvant chemotherapy in the standard of care group. Of the patients who started allocated treatment in the experimental group, 454 (99%) of 460 started with CAPOX. In the experimental group, 71 (15%) of 460 patients prematurely stopped pre-operative chemo therapy. In the standard of care group, 40 (9%) of 441 patients prematurely stopped chemo therapy during preoperative (neoadjuvant) treatment and 69 (37%) of 187 who started adjuvant chemotherapy prematurely stopped chemotherapy during adjuvant treatment. Thus, in the experimental group, 389 (85%) patients completed preoperative chemotherapy compared with 401 (90%) patients in the standard of care group who completed chemotherapy. Reasons for stopping chemo therapy were toxicity (in 65 [14%] patients in the

Table 1 Baseline characteristics of eligible patients

	Experimental group (n=462)		Standard of care group (n=450)	
Sex				
Male	300	(65%)	312	(69%)
Female	162	(35%)	138	(31%)
Age at randomisation, years				
(median, IQR)	62	(55-68)	62	(55-68)
Range		31-83		23-84
Age category				
< 65	280	(61%)	270	(60%)
≥ 65	182	(39%)	180	(40%)
Clinical T-stage * †				
cT2	14	(3%)	14	(3%)
cT3	301	(65%)	299	(66%)
cT4	147	(32%)	137	(30%)
Clinical N-stage * †				
cN0	42	(9%)	35	(8%)
cN1	118	(26%)	120	(27%)
cN2	302	(65%)	295	(66%)
Other high-risk criteria †				
Enlarged lateral nodes	66	(14%)	69	(15%)
EMVI +	148	(32%)	125	(28%)
MRF +	285	(62%)	271	(60%)
Number of high-risk criteria per patient †				
1	158	(34%)	168	(37%)
2	160	(35%)	146	(32%)
3	98	(21%)	96	(21%)
4	39	(8%)	29	(6%)
5	7	(2%)	11	(2%)
ECOG performance status				
0	369	(80%)	365	(81%)
1	93	(20%)	85	(19%)

Continuation Table 1 Baseline characteristics of eligible patients

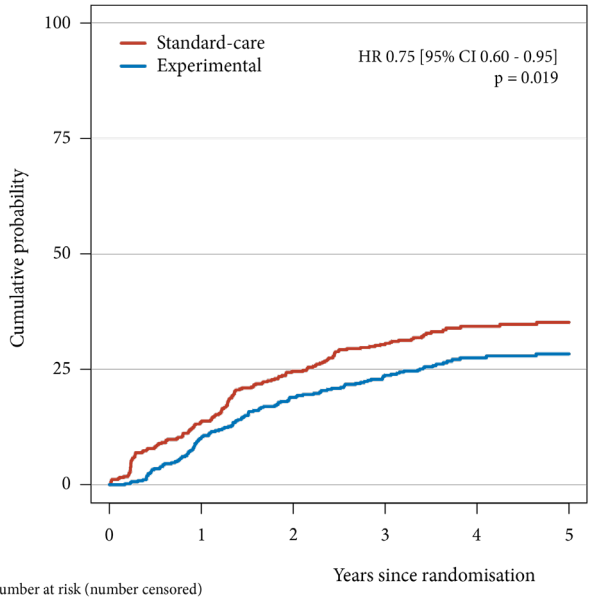
	Experimental group (n=462)	Standard of care group (n=450)
Distance from anal verge on endoscopy, cm		
< 5	103 (22%)	115 (26%)
5 – 10	181 (39%)	153 (34%)
≥ 10	146 (32%)	151 (34%)
Unknown	32 (7%)	31 (7%)
Treated in a hospital with policy for adjuvant chemotherapy		
Yes	273 (59%)	265 (59%)
No	189 (41%)	185 (41%)

Data are n (%), unless otherwise indicated. Percentages might not equal 100 due to rounding. IQR = interquartile range. T-stage = tumour stage. N-stage = nodal stage. EMVI = extramural vascular invasion. MRF = mesorectal fascia. ECOG = Eastern Cooperative Oncology Group. *According TNM 5. † MRI defined.

experimental group, 32 [7%] in the standard of care group during preoperative treatment, and 60 [32%] in the standard of care group during adjuvant therapy), disease progression (in one [<1%] in the experimental group, two [<1%] in the standard of care group during preoperative treatment, and one [1%] in the standard of care group during adjuvant therapy), and other (in one [<1%] in the experimental group, one [<1%] in the standard of care group during preoperative treatment, and three [2%] in the standard of care group during adjuvant therapy). Additional reasons in the experimental group were non-compliance (one [<1%]), patient withdrew from study (two [<1%]), and unknown (one [<1%]). In the standard of care group, during preoperative treatment the reasons for prematurely stopping chemotherapy were unknown (five [1%]) and during adjuvant chemotherapy reasons were noncompliance (two [1%]), patient withdrew from study (two [1%]), and unknown reasons (one [1%]).

Overall, 426 (92%) of 462 patients in the experimental group and 400 (89%) of 450 patients in the standard of care group (p=0.086) had surgery with curative intent within 6 months from the end of preoperative treatment. No differences were seen between the groups regarding type of approach (p=0.31) or type of resection (p=0.56; appendix pp 167-168). The

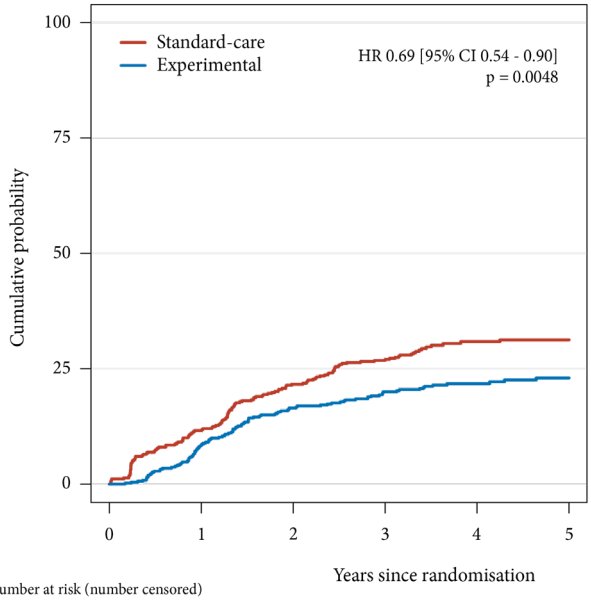
Disease-related treatment failure



Number at risk (number censored)

Standard-care: 450 (0)	450 (2)	385 (3)	334 (7)	300 (133)	159 (160)
Experimental: 462 (0)	462 (1)	411 (2)	367 (8)	339 (150)	179 (182)

Distant metastases



Number at risk (number censored)

Standard-care: 450 (0)	450 (2)	390 (3)	343 (7)	311 (138)	164 (166)
Experimental: 462 (0)	462 (1)	414 (2)	372 (9)	349 (156)	189 (188)

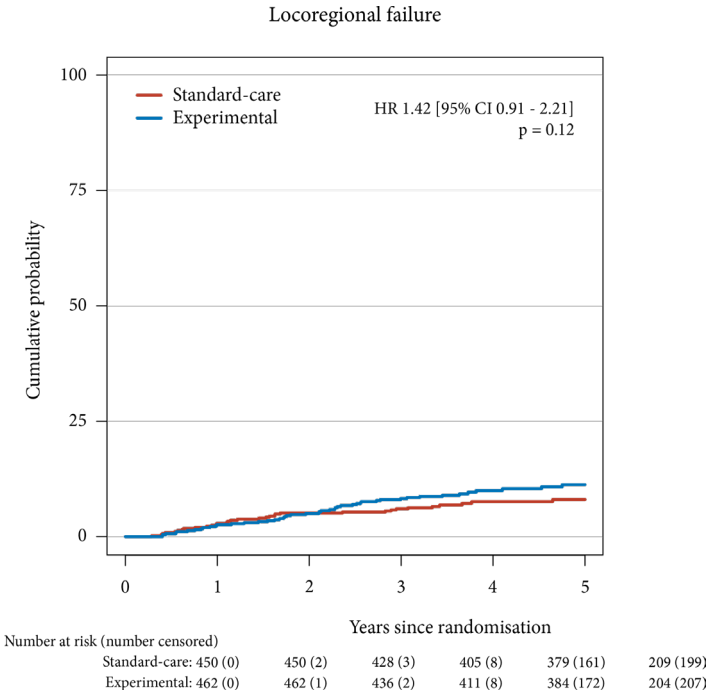


Figure 2 Cumulative probability of disease-related treatment failure, distant metastases, and locoregional failure. HR=hazard ratio.

proportion of patients with R0 resection was high and similar in the two groups (table 2). Of the 826 patients who had surgery with curative intent, the tumour was unresectable in five (1%) patients (three in the experimental group and two in the standard of care group), leading to exclusion of these patients from pathological analyses. 120 (28%) of 423 patients in the experimental group had a pathological complete response compared with 57 (14%) of 398 in the standard of care group (OR 2.37 [95% CI 1.67–3.37]; p<0.0001; table 2). 3year overall survival was 89.1% (95% CI 86.3–92.0) in the experimental group and 88.8% (85.9–91.7) in the standard of care group (HR 0.92 [95% CI 0.67–1.25]; p=0.59; figure 3).

An overview of adverse events is provided in table 3. Grade 3 or higher adverse events during preoperative treatment occurred in 219 (48%) of 460 patients in the experimental group, compared with 109 (25%) of 441 patients in the standard of care group and during adjuvant chemotherapy in 63 (34%) of 187 patients in the standard of care group. The most common

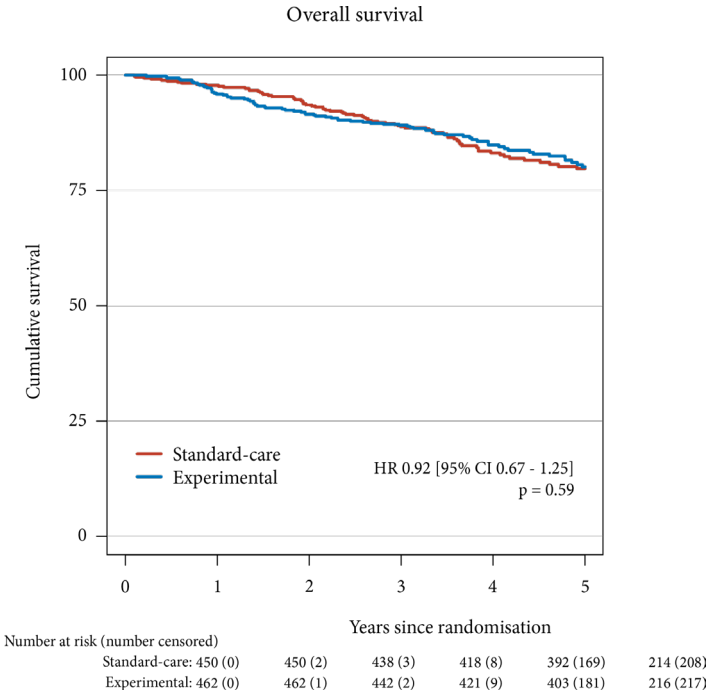


Figure 3 Overall survival. HR=hazard ratio.

grade 3 or higher adverse event was diarrhoea in both treatment groups (table 3). Serious adverse events occurred in the experimental group in 177 (38%) of 460 patients and, in the standard of care group, in 87 (34%) of 254 patients without adjuvant chemotherapy and in 64 (34%) of 187 with adjuvant chemotherapy (appendix pp 169-172). Diarrhoea was the most common serious adverse event in the experimental group during preoperative chemotherapy (41 [9%] of 460) and in the standard of care group during preoperative chemoradiotherapy (11 [3%] of 441). During adjuvant chemotherapy, the most common serious adverse event in the standard of care group was infectious complications (eight [4%] of 187). Postoperatively, the most common serious adverse events in both groups were wound-related events (appendix p 172).

At the time of database lock, 161 patients had died, including 80 (17%) of 462 patients in the experimental group (four [5%] deaths were treatment related [one cardiac arrest, one pulmonary embolism, two infectious complications]; 63 [79%] were rectal cancer related; six

Table 2 Number of surgeries with curative intent, disease-related treatment failures, and pathological outcomes

	Experimental		Standard-care		P-value
All eligible patients					
Surgery with curative intent within 6 months after the end of preoperative treatment					
Yes	426/462	(92%)	400/450	(89%)	0.086 *
No	36/463	(8%)	50/450	(11%)	..
Disease-related treatment failure, first occurring	128	(23.7 †)	152	(30.4 †)	0.019 †
Locoregional failure					
Local progression, unresectable tumour	1/128	(1%)	1/152	(1%)	..
R2 resection	0		0		..
Local recurrence	22/128	(17%)	13/152	(10%)	..
Locoregional failure and distant metastasis ‡					
Local progression, unresectable tumour	4/128	(3%)	2/152	(1%)	..
R2 resection	1/128	(1%)	0		..
Local recurrence	7/128	(5%)	4/152	(3%)	..
Distant metastasis	86/128	(67%)	123/152	(81%)	..
New primary colorectal tumour	3/128	(2%)	5/152	(3%)	..
Treatment-related death	4/128	(3%)	4/152	(3%)	..
Patients with a resection within six months after the end of preoperative treatment					
Residual tumour classification					
R0 > 1 mm	382/423	(90%)	360/398	(90%)	0.87 *
R1 ≤ 1 mm	38/423	(9%)	37/398	(9%)	..
R2	3/423	(1%)	1/398	(<1%)	..
Circumferential resection margin					
>1 mm	385/423	(91%)	363/398	(91%)	0.92 *
≤1 mm	38/423	(9%)	35/398	(9%)	..

Continuation Table 2 Number of surgeries with curative intent, disease related treatment failures, and pathological outcomes

	Experimental		Standard-care		P-value
Differentiation grade during pathological assessment					
Well differentiated	62/423	(15%)	82/398	(21%)	0.09 *§
Moderately differentiated	167/423	(39%)	189/398	(47%)	..
Poorly differentiated	44/423	(10%)	35/398	(9%)	..
No tumour	129/423	(30%)	69/398	(17%)	..
Not assessed	21/423	(5%)	23/398	(6%)	..
Pathological complete response					
Yes	120/423	(28%)	57/398	(14%)	<0.0001*
No	303/423	(72%)	341/398	(86%)	..
Pathological T-stage ¶					
ypT0	129/423	(30%)	69/398	(17%)	<0.0001*
ypTis	2/423	(<1%)	1/398	(<1%)	..
ypT1	17/423	(4%)	17 /398	(4%)	..
ypT2	82/423	(19%)	96/398	(24%)	..
ypT3	157/423	(37%)	190/398	(48%)	..
ypT4	36/423	(9%)	25/398	(6%)	..
Pathological N-stage ¶					
ypN0	317/423	(75%)	273/398	(69%)	0.017 *
ypN1	75/423	(18%)	78/398	(20%)	..
ypN2	31/423	(7%)	47/398	(12%)	..
Postoperative M-stage ¶					
ypM0	420/423	(99%)	396/398	(99%)	0.70 *
ypM1	3/423	(1%)	2/398	(1%)	..

Data are n (%). Proportions might not equal 100% due to rounding. M stage=metastasis stage. N stage=nodal stage. R0=clear resection margins. R1=resection margin of 0–1 mm. R2=macroscopic residual tumour. T stage=tumour stage.

*P-value calculated using χ^2 test. †3-year cumulative probability; p-value calculated using the log-rank test. ‡Locoregional failure and distant metastasis diagnosed simultaneously within 30 days of each other. §p-value calculated on the basis of well, moderately, and poorly differentiated. ¶ According to TNM 5.

[8%] were due to a second primary tumour; four [5%] were due to other causes; and three [4%] were due to unknown reasons) and 81 (18%) of 450 patients in the standard of care group (four [5%] were treatment related [one pulmonary embolism, one neutropenic sepsis, one aspiration, one suicide due to severe depression]; 66 [82%] were related to rectal cancer; seven [9%] were due to a second primary tumour; and four [5%] were due to other causes; appendix p 173).

Analyses of quality-of-life data are to presented in a subsequent publication; here, we present the number of respondents. 3 years after resection, 602 (73%) of 821 patients received quality-of-life questionnaires (318 in the experimental group and 284 in the standard of care group; figure 1). Responses were obtained from 517 (86%) of 602 patients (274 in the experimental group and 243 in the standard of care group), of whom four (1%) did not respond in full. Among 211 (26%) of 821 patients who did not have a disease-related treatment failure and who did not have a stoma, 207 (98%) responded to the LARS questionnaire on bowel function (116 in the experimental group and 91 in the standard of care group). In total, 402 (78%) of 517 patients completed the QLQCIPN20 questionnaire on neurotoxicity (217 in the experimental group, 109 in the standard of care group without adjuvant chemotherapy, and 76 in the standard of care group with adjuvant chemotherapy). The questionnaire responses are to be reported in a subsequent publication.

Subgroup analyses of disease-related treatment failure according to baseline characteristics were consistently in favour of the experimental group (appendix p 174). Of the 54 participating centres, 28 (52%) opted to administer adjuvant chemotherapy in the standard of care group. In sensitivity analyses, within the standard of care group, hospital policy on adjuvant chemotherapy did not affect the probability of disease-related treatment failure at 3 years (HR 1.18 [95% CI 0.85–1.64]; p=0.32). Comparing hospitals with and without adjuvant chemotherapy policies in the standard of care group, similar probabilities of distant metastases (28.5% [95% CI 23.1–34.0] vs 24.4% [18.2–30.6]; p=0.34) and locoregional failure (7.2% [4.1–10.4] vs 4.3% [1.7–7.3]; p=0.20) were seen.

Among the 912 eligible patients, 25 (3%) were followed up according to the watch-and-wait strategy due to a clinical complete response (14 in the experimental group and 11 in the standard of care group). In the experimental group, two (14%) of 14 patients developed

distant metastasis and one (7%) developed local regrowth; and in the standard of care group, one (9%) of 11 patients developed distant metastasis, one (9%) developed local regrowth, and one (9%) simultaneously developed distant metastasis and local regrowth (appendix p 175).

Discussion

In this study, we found that patients treated with short course radiotherapy followed by 18 weeks of systemic chemotherapy before surgery have a significantly lower probability of disease-related treatment failure at 3 years after randomisation than do patients undergoing standard of care chemoradiotherapy followed by optional adjuvant chemotherapy after surgery. Hospital policy regarding the use of adjuvant chemotherapy did not affect disease-related treatment failure in the standard of care group. Additionally, with the experimental treatment, the pathological complete response rate was double that in the standard of care group. Given the increased tendency to refrain from surgery in patients with a clinical complete response after pre-operative treatment, the experimental treatment offers the potential opportunity for patients seeking organ preservation.

The lower probability of disease-related treatment failure in the experimental group than in the standard of care group can mainly be attributed to a decreased rate of distant metastases. A possible explanation for this reduction in distant metastases might be better compliance to preoperative chemotherapy in the experimental group than with adjuvant chemotherapy when offered in the standard of care group;[9] patients are generally in better condition before than after surgery. Fewer weeks of chemotherapy (18 weeks preoperatively vs 24 weeks postoperatively) could also have contributed to better compliance in the experimental group than in the standard of care group, and did not result in reduced efficacy. Justification for a reduced number of chemotherapy cycles has emerged in several adjuvant colon cancer trials, showing that 3 months of CAPOX is non inferior to 6 months of CAPOX in terms of disease-free survival.[18,19] Predefined hospital policy regarding the use of adjuvant chemotherapy did not affect disease-related treatment failure in the standard of care group, suggesting that the efficacy of postoperative chemo therapy might be low.[20,21] Systemic chemotherapy in the experimental group started approximately 18 weeks earlier than in the standard of care group, potentially leading to more effective eradication of possible micro metastases.

Although some guidelines exclude proximal rectal cancers from preoperative radiotherapy or chemo radiotherapy, we believe exceptions exist (eg, in the presence of high-risk criteria). The randomised Polish II study,[22] which included 515 patients with locally advanced rectal cancer, also compared preoperative short-course radio therapy followed by chemotherapy with chemoradiotherapy. No significant difference in the 3year cumulative incidence of distant metastases between the experimental (30%) and standard groups (27%) was reported (relative risk 1.21 [95% CI 0.59–1.15] p=0.25).[22] In the RAPIDO trial, the rate of distant metastases (20.0%) was lower in the experimental group than in the standard of care group (26.8%), which was similar to the standard group in the Polish II study. Although MRI was not mandatory in the Polish II study, this similarity in outcome indicates that the two trials enrolled similar patient populations. An explanation for the difference between the two experimental groups in these two studies might be the duration of preoperative chemo therapy: six cycles of CAPOX or nine cycles of FOLFOX4 in the RAPIDO trial versus three cycles of FOLFOX4 in the Polish II study. Further insight into how the number of chemotherapy cycles affects this outcome will come from the ongoing randomised STELLAR trial.[23] In the STELLAR trial, patients with MRI-staged non-metastatic locally advanced rectal cancer are given six cycles of CAPOX, divided into four preoperative cycles after short-course radiotherapy and two adjuvant chemo therapy cycles.[23]

The overall probability of locoregional failure in the RAPIDO trial at 3 years is similar to previously published data.[1,2,4,24] A longer period between radiotherapy and surgery in the experimental group than in the standard of care group might have led to increased downstaging, and possibly a higher proportion of patients with a pathological complete response. However, for patients who had little or no response to therapy, the extended interval between randomisation and surgery in the experimental group compared with the standard of care group (median time 25.5 weeks [IQR 24.0–27.9] vs 15.9 weeks [14.6–17.6]) might be disadvantageous. The higher number of residual pathological T4 (ypT4) tumours in the experimental group than in the standard of care group (9% vs 6%) could indicate the presence of a small proportion of nonresponding tumours that might actually progress during preoperative treatment. Hence, early response imaging could be advocated, enabling alterations in therapeutic approach.

Table 3 Adverse events

	Experimental group During preoperative therapy (n=460)			
	Grade 1–2	Grade 3	Grade 4	Grade 5
General adverse events				
Allergic reaction	19 (4%)	5 (1%)	1 (<1%)	0
Alopecia	9 (2%)	0	0	0
Cystitis	38 (8%)	1 (<1%)	0	0
Fatigue or lethargy	297 (65%)	14 (3%)	0	0
Febrile neutropenia	0	5 (1%)	0	0
Hand-foot syndrome	134 (29%)	8 (2%)	0	0
Neurological toxicity	362 (79%)	19 (4%)	1 (<1%)	0
Radiation dermatitis	24 (5%)	2 (<!%)	0	0
Rash maculopapular	18 (4%)	0	0	0
Weight loss	78 (17%)	3 (1%)	0	0
Other*	266 (58%)	111 (24%)	20 (4%)	1 (<1%)

In the standard of care group, no grade 5 adverse events occurred during adjuvant chemotherapy. *According to Common Terminology Criteria for Adverse events version 4.0 (ear and labyrinth disorders, endocrine disorders, eye disorders, general disorders and administration site conditions, hepatobiliary disorders, immune system disorders, injury, poisoning and procedural complications, investigations, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, neoplasms benign, malignant and unspecified [including cysts and polyps], nervous system disorders, psychiatric disorders, renal and urinary disorders, reproductive system and breast disorders, respiratory, thoracic and mediastinal disorders; and skin and subcutaneous tissue disorders). †Due to constipation, obstruction, or other causes.

Continuation Table 3 Adverse events

	Experimental group During preoperative therapy (n=460)			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Gastrointestinal toxicity				
Abdominal pain†	213 (16%)	25 (5%)	2 (<1%)	0
Diarrhoea	225 (49%)	75 (16%)	6 (1%)	0
Faecal incontinence	37 (8%)	0	0	0
Nausea	232 (50%)	16 (3%)	0	0
Oral mucositis	49 (11%)	3 (1%)	0	0
Proctitis	44 (10%)	4 (1%)	0	0
Rectal bleeding	103 (22%)	1 (<1%)	0	0
Rectal mucositis	43 (9%)	3 (1%)	0	0
Rectal pain	106 (23%)	4 (1%)	0	0
Vomiting	99 (22%)	9 (2%)	0	0

In the standard of care group, no grade 5 adverse events occurred during adjuvant chemotherapy. *According to Common Terminology Criteria for Adverse events version 4.0 (ear and labyrinth disorders, endocrine disorders, eye disorders, general disorders and administration site conditions, hepatobiliary disorders, immune system disorders, injury, poisoning and procedural complications, investigations, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, neoplasms benign, malignant and unspecified [including cysts and polyps], nervous system disorders, psychiatric disorders, renal and urinary disorders, reproductive system and breast disorders, respiratory, thoracic and mediastinal disorders; and skin and subcutaneous tissue disorders). †Due to constipation, obstruction, or other causes.

Continuation Table 3 Adverse events

	Standard of care group						
	During preoperative therapy (n=441)				During adjuvant therapy (n=187)		
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4
General adverse events							
Allergic reaction	3 (1%)	0	0	0	6 (3%)	1 (1%)	0
Alopecia	6 (1%)	0	0	0	3 (2%)	0	0
Cystitis	97 (22%)	0	0	0	9 (5%)	0	0
Fatigue or lethargy	255 (58%)	6 (1%)	0	0	118 (63%)	10 (5%)	0
Febrile neutropenia	0	1 (<1%)	0	1 (<1%)	0	1 (1%)	0
Hand-foot syndrome	77 (17%)	5 (1%)	0	0	68 (36%)	4 (2%)	0
Neurological toxicity	30 (7%)	1 (<1%)	0	0	119 (64%)	16 (9%)	0
Radiation dermatitis	112 (25%)	14 (3%)	0	0	1 (1%)	0	0
Rash maculopapular	16 (4%)	2 (<1%)	0	0	5 (3%)	0	0
Weight loss	48 (11%)	1 (<1%)	0	0	22 (12%)	0	0
Other*	235 (53%)	46 (10%)	8 (2%)	2 (<1%)	106 (57%)	26 (14%)	7 (4%)

In the standard of care group, no grade 5 adverse events occurred during adjuvant chemotherapy. *According to Common Terminology Criteria for Adverse events version 4.0 (ear and labyrinth disorders, endocrine disorders, eye disorders, general disorders and administration site conditions, hepatobiliary disorders, immune system disorders, injury, poisoning and procedural complications, investigations, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, neoplasms benign, malignant and unspecified [including cysts and polyps], nervous system disorders, psychiatric disorders, renal and urinary disorders, reproductive system and breast disorders, respiratory, thoracic and mediastinal disorders; and skin and subcutaneous tissue disorders). †Due to constipation, obstruction, or other causes.

Continuation Table 3 Adverse events

	Standard of care group						
	During preoperative therapy (n=441)				During adjuvant therapy (n=187)		
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4
Gastrointestinal toxicity							
Abdominal pain†	161 (37%)	6 (1%)	2 (<1%)	0	40 (21%)	4 (2%)	0
Diarrhoea	220 (50%)	40 (9%)	1 (<1%)	0	95 (51%)	13 (7%)	0
Faecal incontinence	43 (10%)	0	0	0	2 (1%)	0	0
Nausea	139 (32%)	3 (1%)	0	0	90 (48%)	4 (2%)	0
Oral mucositis	23 (5%)	0	0	0	21 (11%)	0	0
Proctitis	48 (11%)	6 (1%)	0	0	3 (2%)	0	0
Rectal bleeding	93 (21%)	3 (1%)	0	0	2 (1%)	1 (1%)	0
Rectal mucositis	52 (12%)	3 (1%)	0	0	5 (3%)	0	0
Rectal pain	135 (31%)	5 (1%)	0	0	22 (12%)	0	0
Vomiting	38 (9%)	3 (1%)	0	0	38 (20%)	3 (2%)	0

In the standard of care group, no grade 5 adverse events occurred during adjuvant chemotherapy. *According to Common Terminology Criteria for Adverse events version 4.0 (ear and labyrinth disorders, endocrine disorders, eye disorders, general disorders and administration site conditions, hepatobiliary disorders, immune system disorders, injury, poisoning and procedural complications, investigations, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, neoplasms benign, malignant and unspecified [including cysts and polyps], nervous system disorders, psychiatric disorders, renal and urinary disorders, reproductive system and breast disorders, respiratory, thoracic and mediastinal disorders; and skin and subcutaneous tissue disorders). †Due to constipation, obstruction, or other causes.

In the Stockholm III trial,[25] with less advanced tumours than in our study population, pathological complete response was seen in 29 (10.4%) of 285 participants following short-course radiotherapy with delayed surgery compared with two (2.2%) of 94 participants after long-course radiotherapy.[25] In the experimental group of the RAPIDO trial, the pathological complete response rate was 28%. Apart from the longer interval between radiotherapy and surgery in RAPIDO than in Stockholm III (>18 weeks vs 4–8 weeks), the addition of chemotherapy in RAPIDO is likely to have contributed to the higher rate of pathological complete response. In a study with four consecutive series of patients with intermediate-risk rectal cancer, pathological complete response rates increased from 18% (95% CI 10–30) after chemoradiotherapy alone to 38% (27–51) in patients receiving six cycles of modified FOLFOX6 in the interval between chemo radiotherapy and surgery.[26] Delivering additional cycles of chemotherapy and extending the interval between chemo radiotherapy and surgery seems to have added value in achieving pathological complete response, and is associated with a survival benefit.[27] A pooled analysis showed that patients with a pathological complete response after chemoradiotherapy have favour able outcomes regarding local control and overall survival.[28] Although no studies have yet shown that a pathological complete response achieved by the additional effect of chemotherapy is associated with improved prognosis, this outcome seems possible. Additionally, an adequately assessed clinical complete response followed by a watch-and-wait strategy is increasingly being used as an alternative to major surgery.[29] The experimental RAPIDO regimen resulted in a high rate of pathological complete response and could potentially be used to initiate a watch-and-wait strategy.

After a median follow-up of 4.6 years, no difference in overall survival was observed, but might be revealed with longer follow-up that will continue until 10 years after randomisation, according to the trial protocol.

The optimal timing of chemotherapy in a total neoadjuvant approach remains a matter of debate. The fear of local progression could justify a radiotherapy-first approach, whereas prioritising the early control of potential micrometastases would justify a chemotherapy first strategy. The chemotherapy-first strategy is under investigation in the PRODIGE 23 trial[30] (preoperative chemotherapy before chemoradiotherapy, followed by total mesorectal excision and adjuvant chemotherapy). The initial results showed significantly increased 3-year disease-

free survival, metastasis-free survival, and pathological complete response rate compared with chemoradiotherapy followed by total mesorectal excision and adjuvant chemotherapy.[30] An obvious advantage of short-course radiotherapy as part of a total neoadjuvant approach is its short duration with minimal delay between the end of radiotherapy and start of systemic chemotherapy. To our knowledge, optimal timing for chemotherapy has been investigated in only one published randomised study so far.[31] In that study, patients having preoperative chemotherapy after chemo radiotherapy had fewer adverse events, better compliance to chemoradiotherapy, and higher pathological complete response rates than did patients who started with preoperative chemotherapy.[31] The long-term results on oncological outcomes are awaited.[31] Currently, chemoradiotherapy before preoperative chemotherapy appears to be the preferred option.

To exclude the potential bias of recurrent disease and treatment thereof, only patients without disease-related treatment failure at 3 years will be analysed in the RAPIDO trial with respect to quality of life, results of which will be published elsewhere.

In the experimental group of the RAPIDO trial, more serious adverse events of diarrhoea and neurological toxicity occurred than in the standard of care group, probably due to preoperative treatment with CAPOX. Another possible contributing factor to diarrhoea could be the longer period between diagnosis and removal of the tumour. Despite differences in toxicity between treatment groups during preoperative treatment, no effect on surgery was observed in our previous report of compliance, toxicity, and postoperative complications in the RAPIDO trial.[9]

Concerns have been raised about short-course radiotherapy having lower efficacy than conventional chemoradiotherapy; however, to our knowledge, no randomised trials have compared the anti-tumour or downstaging effect of short-course radiotherapy and delayed surgery to chemoradiotherapy with a similar delay. Therefore, we cannot draw firm conclusions about relative efficacy between short-course radiotherapy and chemoradiotherapy. In the Stockholm III trial,[25] more downstaging and a higher pathological complete response rate were observed after short-course radio therapy than after long course radiotherapy, indicating that the tumour-cell kill effect is probably higher from five fractions of 5 Gy than from 25 fractions of 2 Gy, and not less, as the commonly used coefficients in the linear-quadratic formula

indicate.[32] Additionally, the long-term consequences of short-course radiotherapy are under debate. Evidence indicates that short-course radiotherapy results in long-term morbidity.[33] However, the long-term morbidity caused by chemoradiotherapy is less studied than short-course radiotherapy, making a comparison difficult. Moreover, at least two randomised trials indicate no differences in late complications (ie, at 3–5 years) between the two treatments. [34,35] Notably, most data on long-term consequences originate from trials using either two anterior-posterior portals or the conventional three dimensional-conformal radiotherapy technique instead of the currently used intensity-modulated radiation therapy or volumetric modulated arc therapy techniques. Furthermore, the target volumes have been reduced compared with the many studies on which our present knowledge of radiotherapy-induced late effects (ie, at 4–10 years) after rectal cancer radiotherapy has been based.[33] With these newer techniques and the possibilities of daily adaptive therapy, doses to relevant organs at risk are substantially reduced. Therefore, the ultimate effects on longterm functional outcomes and morbidity require careful assessment in the coming years.

Our study has several limitations. Alteration of the primary endpoint during a trial is undesirable but was considered necessary because disease-ree survival was inappropriate in a neoadjuvant trial on patients with high-risk locally advanced rectal cancer. Another potential limitation was the absence of a central review of baseline MRIs. Patients could have been under-staged or over staged, although over-staging was most probably predominant.[36] However, bias towards one group is unlikely to have occurred because randomisation was stratified.

A prominent benefit of the experimental treatment reported here, especially in the context of the COVID19 pandemic, is the decrease in the number of treatment days spent in healthcare facilities, 12 days in the experimental group versus 25–28 days in the standard of care group for the preoperative period on the basis of typical treatment regimens. If adjuvant chemotherapy is given (8 treatment days in 24 weeks if CAPOX, 24 days if FOLFOX4), the reduction is even more pronounced. This reduction in time spent in hospital minimises the risk for these susceptible patients and improves hospitals' ability to implement physical distancing during the COVID19 pandemic situation.[37]

In summary, in patients with high-risk locally advanced rectal cancer, the RAPIDO trial shows

that short-course radiotherapy followed by 18 weeks of chemotherapy before surgery decreases the probability of disease related treatment failure compared with chemo radiotherapy with or without adjuvant chemotherapy, mainly by reducing the probability of distant metastases. Additionally, the high rate of pathological complete response in the experimental group can potentially contribute to organ preservation. Supported by previously reported high compliance and tolerability,[9] this treatment could be considered as a new standard of care for patients with high-risk locally advanced rectal cancer. Future research could focus on assessing tumour response to preoperative treatment at an early stage and improving the efficacy of systemic therapy with the aim of decreasing distant metastases even further.

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Supplementary Appendix Chapter 4

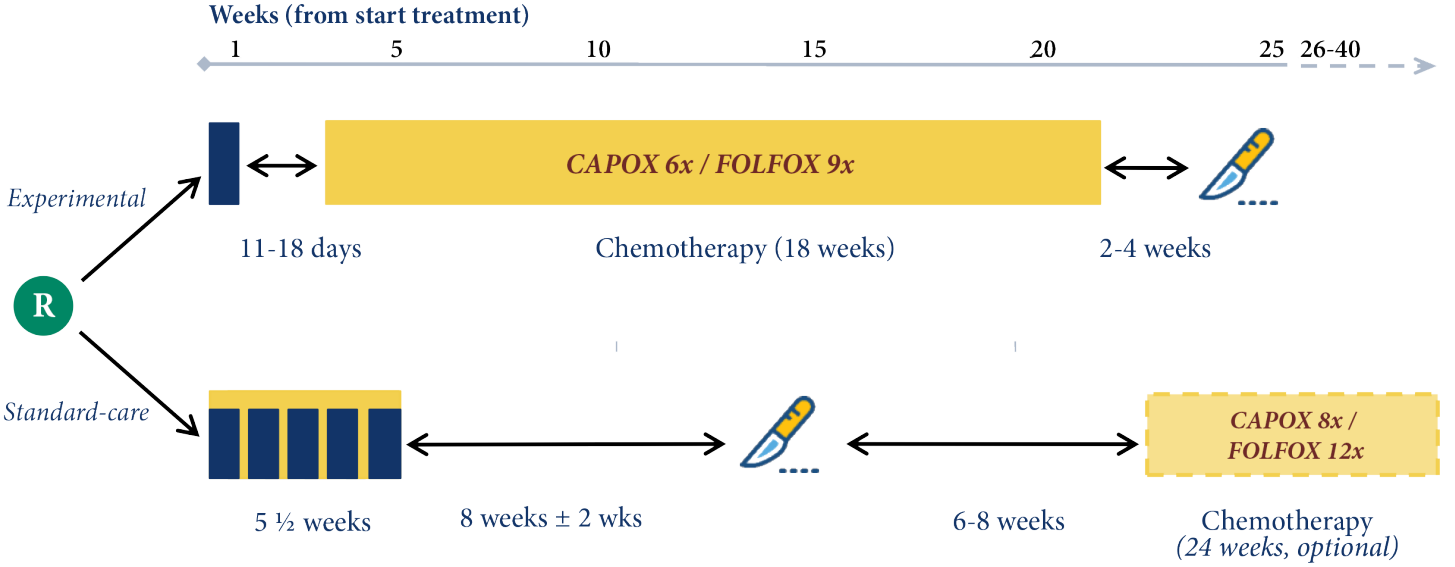

Figure S1 Treatment regimen.

Table S2a Dose reductions capecitabine, 5-FU, leucovorin.

	Grade 2	Grade 3	Grade 4
1st occurrence	Interrupt treatment until recovery to grade 0-1 → continue with no dose reduction	Interrupt treatment until recovery to grade 0-1 → continue with 25% dose reduction	Interrupt treatment until recovery to grade 0-1 → continue with 50% dose reduction
2nd occurrence	Interrupt treatment until recovery to grade 0-1 → continue with 25% dose reduction	Interrupt treatment until recovery to grade 0-1 → continue with 50% dose reduction	Discontinue treatment
3rd occurrence	Interrupt treatment until recovery to grade 0-1 → continue with 50% dose reduction	Discontinue treatment	
4th occurrence	Discontinue treatment		

Table S2b Dose reductions for oxaliplatin for sensory neuropathy.

Sensory neuropathy	Oxaliplatin dose
Non-painful paresthesia ≥ 14 days or temporary (7-14 days) painful paresthesia/ functional impairment	25% reduction
Persistent (pain≥ 14 days) painful paresthesia/ functional impairment	Omit until recovery, then restart at 50%
Recurrent neurotoxicity after 50% dose reduction	Permanently discontinued

Table S2c Dose reductions for specific toxicity.

Toxicity during previous cycle	Grade	Next dose oxaliplatin	Next dose capecitabine, 5-FU, leucovorin
Diarrhoea	3/4	75%	75-50%
Mucositis	3/4	Full dose	75-50%
Skin	3/4	Full dose	75-50%
Hand-foot-syndrome	2/3	Full dose	According to table S2a
Neurotoxicity	According to table S2b	According to table S2b	Full dose
Other non-haematologic toxicities	3/4	75%	75-50%

Table S3 Addition table 1, inclusion characteristics of eligible patients.

	Experimental (n = 462)		Standard-care (n = 450)	
Year of randomization				
2011	7	(1·5)	10	(2·2)
2012	34	(7·4)	30	(6·7)
2013	96	(20·8)	107	(23·8)
2014	129	(27·9)	103	(22·9)
2015	148	(32·0)	142	(31·6)
2016	48	(10·4)	58	(12·9)
Country				
Denmark	16	(3·5)	12	(2·7)
The Netherlands	180	(39·0)	180	(40·0)
Norway	12	(2·6)	11	(2·4)
Slovenia	18	(3·9)	17	(3·8)
Spain	58	(12·5)	60	(13·3)
Sweden	168	(36·4)	160	(35·6)
United States	10	(2·2)	10	(2·2)

Data are n (%). Percentages may not equal 100 due to rounding.

Table S4 Sensitivity analyses adjusting for stratification factors.

	Hazard Ratio	95% confidence interval	p-value
Adjusted disease-related treatment failure	0·76	0·60-0·96	0·024
Adjusted overall survival	0·94	0·74-1·19	0·68
Adjusted distant metastases	0·70	0·55-0·89	0·0063
Adjusted locoregional failure	1·45	1·15-1·84	0·099

As sensitivity analyses a Cox (cause-specific) proportional hazards frailty model was fitted with treatment, using ECOG, T- and N-stage as adjusting covariates, and with institution as a random (frailty) effect. The reason for adding institution as random effects rather than covariates is the large number of (often small) institutions.

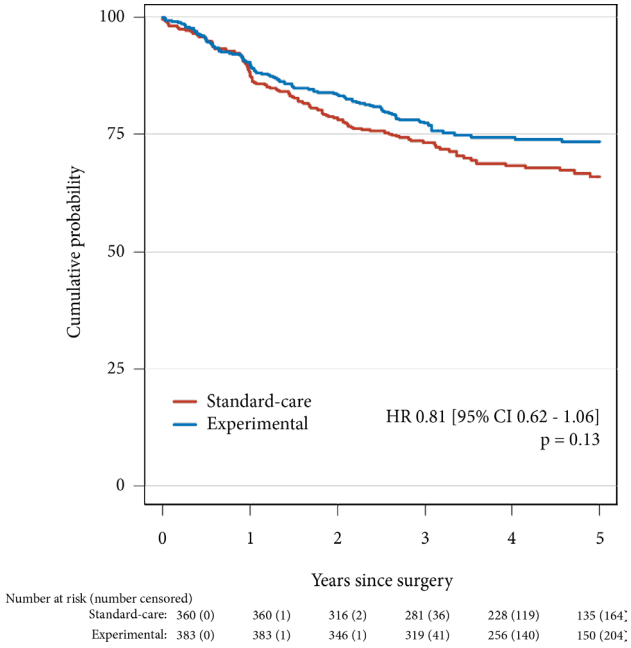

Figure S2 Subgroup analysis of disease-free survival from surgery, in patients with an R0 (> 1 mm) resection within six months after end of preoperative treatment. Note that the randomisation in this subgroup comparison (743 out of 902 eligible patients) is no longer guaranteed to be balanced with respect to important prognostic factors. The comparison could therefore be biased due to possible differences in type of resection and approach, resection rate, pathological response, etc. between the treatment groups.

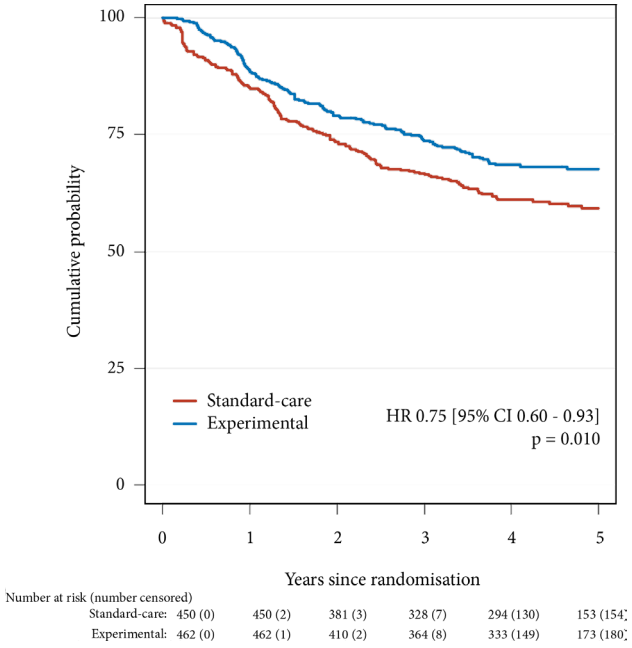

Figure S3 Recently, Fokas et al.[1] brought forward an adjusted DFS, similar to our DrTF but including a second primary cancer, other than colorectal, and death from all causes as events as well. Note that with this definition, patients are not disease-free at the start of the curves, rather event-free.

1. Fokas E, Glynne-Jones R, Appelt A, *et al.* Outcome measures in multimodal rectal cancer trials. *Lancet Oncol* 2020; 21: e252–64.

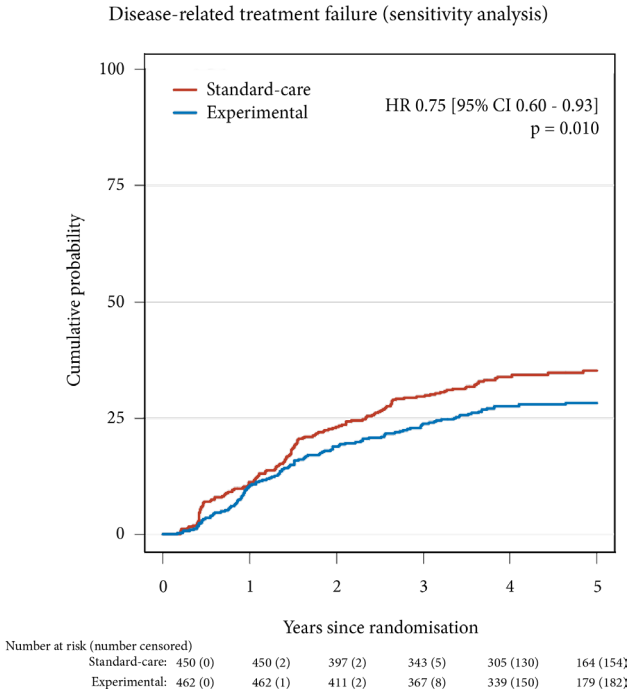

Figure S4 Sensitivity analysis adjusting for possible time-related bias (DrTF). Re-staging and surgery after preoperative treatment occurs approximately 10 weeks earlier (median time) in the standard-care group. To adjust for possible time-related bias, a sensitivity analysis was performed in which the timing of DrTF in the standard-care group was moved to 10 weeks later. Note that this sensitivity analysis overcorrects, since not all DrTF events are detected by imaging or during surgery (e.g. treatment-related death). The steep rise in the standard-care group still appears with the same rate of events, but at a later moment. The difference between the two groups remains statistically significant.

Table S5a Surgical details.

Patients with surgery with curative intent within six months after the end of preoperative treatment	Experimental (n = 426)		Standard-care (n = 400)		p-value
Time to surgery since randomisation (weeks) (median, [IQR])	25·5	[24·0 – 27·9]	15·9	[14·6 – 17·6]	<0·0001 *
Type of approach					0·31 †
Laparoscopic	178	(41·8)	182	(45·5)	
Laparoscopic converted to open	42	(9·9)	29	(7·2)	
Open	206	(48·4)	189	(47·3)	
Type of resection					0·56 †
No resection	3	(0·7)	2	(0·5)	
Anterior resection, PME	41	(9·6)	33	(8·3)	
Low anterior resection, TME	207	(48·6)	190	(47·5)	
Abdominoperineal excision	149	(35·0)	160	(40·0)	
Hartmann's procedure	20	(4·7)	12	(3·0)	
Posterior pelvic exenteration	1	(0·2)	1	(0·3)	
Total pelvic exenteration	2	(0·5)	2	(0·5)	
Intersphincteric resection	3	(0·7)	-		

Data are n (%). Percentages may not equal 100 due to rounding. * P-value calculated with the Mann-Whitney U test. † P-values are calculated with chi-square.
IQR = interquartile range. PME = partial mesorectal excision. TME = total mesorectal excision.

Table S5b Additional surgical resections, as reported in the CRFs.

	Experimental (n = 426)		Standard-care (n = 400)	
Number of additional organs/structures resected				
None	393	(92·3)	364	(91·0)
1 organ/structure	16	(3·8)	24	(6·0)
2 organs/structure	15	(3·5)	7	(1·8)
3 organs/structure	2	(0·5)	3	(0·8)
4 organs/structure	-	-	1	(0·3)
5 organs/structure	-	-	1	(0·3)
Resected organ/structure (or part of)	**(n=52)**		**(n=56)**	
Ovarium/uterus	20	(38·5)	16	(28·6)
Vagina	4	(7·7)	3	(5·4)
Vesiculae seminales/prostate/funiculus spermaticus	11	(21·2)	20	(35·7)
Urether/bladder	5	(9·6)	7	(12·5)
Colon/appendix	2	(3·8)	3	(5·4)
Short bowel	2	(3·8)	2	(3·6)
Spleen	1	(1·9)	-	-
Liver	2	(3·8)	-	-
Lateral lymph nodes	2	(3·8)	3	(5·4)
Sacrum/coccyx	1	(1·9)	-	-
Levator/endopelvic fascia	1	(1·9)	2	(3·6)
Vertebral wall	1	(1·9)	-	-

Data are n (%). Percentages may not equal 100 due to rounding.

Table S6 Adverse events: highest grade reported per patient.

	Experimental	Standard-care	
	During preoperative therapy	*During preoperative therapy*	*During postoperative therapy*
Highest grade adverse event reported per patient	(n = 460)	(n = 441)	(n = 187)
None	4 (0·9)	14 (3·2)	6 (3·2)
Grade 1-2	237 (51·5)	318 (72·1)	118 (63·1)
Grade 3	188 (40·9)	96 (21·8)	56 (29·9)
Grade 4	30 (6·5)	10 (2·3)	7 (3·7)
Grade 5	1 (0·2)	3 (0·7)	-

Toxicity was graded according to the Common Terminology Criteria for adverse events (CTCAE) version 4.0. Data are n (%). Percentages may not equal 100 due to rounding.

Table S7a Number of serious adverse events per patient.

	Experimental	Standard-care	
		No adjuvant chemotherapy	Adjuvant chemotherapy started
	(n = 460)	(n = 254)	(n = 187)
None	283 (61·5)	167 (65·7)	124 (66·3)
1	125 (27·2)	70 (27·6)	51 (27·3)
2	35 (7·6)	12 (4·7)	7 (3·7)
3	15 (3·3)	5 (2·0)	3 (1·6)
4	1 (0·2)	-	3 (1·6)
5	1 (0·2)	-	-

Table S7b Number of serious adverse events per treatment period.

	Experimental	Standard-care
Before start of treatment	(n = 460) 3 (0·7)	(n = 441) 2 (0·5)
During short-course radiotherapy	(n = 460) 17 (3·7)	-
During preoperative chemo(radio)therapy	(n = 460) 155 (33·7)	(n=441) 73 (16·6)
Postoperatively	(n = 426) 73 (17·1)	(n = 400) 80 (20·0)
During adjuvant chemotherapy	(n = 6) 1*	(n = 187) 40 (21·4)

* Preoperative chemotherapy had to be stopped early (after four cycles of CAPOX) due to serious adverse events. After surgery, chemotherapy was continued.

Table S7c Specification of serious adverse events.

Before start of treatment	Experimental (n = 460)	Standard-care (n = 441)
Fever	1 (0·2)	1 (0·2)
Ileus	-	1 (0·2)
Obstipation	1 (0·2)	-
Rectal hemorrhage	1 (0·2)	-

	Experimental		Standard-care
During preoperative treatment	Short-course radiotherapy (n = 460)	Chemotherapy (n = 460)	Chemoradiotherapy (n = 441)
Abdominal pain/ obstipation obstruction	5 (1·1)	22 (4·8)	10 (2·3)
Blood loss (oral, rectal, urine)	2 (0·4)	4 (0·9)	2 (0·5)
Cardiovascular disease	-	8 (1·7)	10 (2·3)
Dehydration/laboratory deviations	-	3 (0·7)	5 (1·1)
Diarrhoea	4 (0·9)	41 (8·9)	11 (2·5)
General weakness/fatigue	-	1 (0·2)	3 (0·7)
Infectious, abdominal	-	11 (2·4)	6 (1·4)
Infectious, other	4 (0·9)	14 (3·0)	8 (1·8)
Nausea/vomiting/anorexia	-	8 (1·7)	1 (0·2)
Psychological	-	1 (0·2)	2 (0·5)
Pulmonary	-	6 (1·3)	2 (0·5)
Thromboembolic	1 (0·2)	12 (2·6)	6 (1·4)
Other, abdominal	1 (0·2)	15 (3·3)	4 (0·9)
Other	-	9 (2·0)	3 (0·7)

Continuation Table S7c Specification of serious adverse events.

Postoperatively	Experimental (n = 426)	Standard-care (n = 400)
Anastomotic leak	5 (1·2)	6 (1·5)
Cardiovascular disease	1 (0·2)	1 (0·3)
Dehydration/high output stoma/diarrhoea	7 (1·6)	5 (1·3)
Ileus	8 (1·9)	10 (2·5)
Pain	4 (0·9)	1 (0·3)
Stoma-related	1 (0·2)	2 (0·5)
Thromboembolic	2 (0·5)	2 (0·5)
Urinary	3 (0·7)	3 (0·8)
Vomiting/anorexia/general weakness	3 (0·7)	3 (0·8)
Wound related	28 (6·6)	41 (10·3)
Other	11 (2·6)	6 (1·5)

During adjuvant chemotherapy	Experimental (n = 6)	Standard-care (n = 187)
Abdominal pain/ obstipation /obstruction	-	3 (1·6)
Blood loss (oral, rectal, urine)	-	1 (0·5)
Cardiovascular disease	-	1 (0·5)
Dehydration/laboratory deviations	-	4 (2·1)
Diarrhoea	-	5 (2·7)
General weakness/fatigue	-	2 (1·1)
Infectious, abdominal	-	-
Infectious, other	1	8 (4·3)
Nausea/vomiting/anorexia	-	2 (1·1)
Psychological	-	-
Pulmonary	-	2 (1·1)
Thromboembolic	-	2 (1·1)
Other, abdominal	-	6 (3·2)
Other	-	4 (2·1)

Table S8 Causes of death.

	Experimental (n = 80)	Standard-care (n = 81)
Treatment-related death		
Preoperative		
Cardiac arrest *	1 (1·3)	-
Neutropenic sepsis	-	1 (1·2)
Aspiration after a fall	-	1 (1·2)
Suicide †	-	1 (1·2)
Postoperative		
Pulmonary embolism	1 (1·3)	1 (1·2)
Infectious complications	2 (2·5)	
Rectal cancer	63 (78·8)	66 (81·5)
Second primary tumour	6 (7·5)	7 (8·6)
Other	4 (5·0)	4 (4·9)
Unknown	3 (3·8)	-

* In the presence of electrolyte disturbances due to diarrhoea.

† Due to a severe depression after rectal cancer diagnosis

		Experimental		Standard-care		Experimental versus standard-care	
		Event/ patients	DrTF probability at 3 year [95% CI]	Event/ patients	DrTF probability at 3 year [95% CI]	HR [95% CI]	$P_{interaction}$
Gender	Male	61/300	26% [21-31]	57/312	32% [26-37]	0·78 [0·59-1·03]	0·75
	Female	19/162	20% [14-26]	24/138	28% [20-35]	0·73 [0·47-1·12]	
Age	< 65	47/280	25% [20-30]	54/270	31% [26-37]	0·75 [0·56-1·02]	0·99
	≥ 65	33/182	22% [16-28]	27/180	29% [22-36]	0·75 [0·51-1·10]	
Clinical T-stage	cT2-T3	47/315	22% [17-27]	55/313	29% [24-35]	0·77 [0·57-1·03]	0·63
	cT4	33/147	27% [20-34]	26/137	32% [25-40]	0·74 [0·50-1·09]	
Clinical N-stage	cN0	6/42	14% [4-25]	7/35	23% [9-38]	0·93 [0·34-2·52]	0·78
	cN+	74/420	25% [21-29]	74/415	31% [27-35]	0·75 [0·59-0·95]	
Lateral nodes	-	63/395	22% [18-26]	71/380	32% [27-36]	0·70 [0·54-0·91]	0·14
	+	17/66	33% [22-45]	10/69	25% [15-35]	1·13 [0·64-2·01]	
EMVI	-	50/313	22% [17-26]	54/323	27% [23-32]	0·73 [0·55-0·99]	1·00
	+	30/148	29% [21-36]	27/125	38% [29-46]	0·75 [0·50-1·12]	
MRF	-	27/176	21% [15-27]	28/178	29% [22-36]	0·72 [0·49-1·07]	0·77
	+	53/285	26% [21-31]	53/271	32% [26-37]	0·77 [0·58-1·04]	
ECOG	0	60/369	23% [19-27]	66/365	30% [26-35]	0·74 [0·57-0·96]	0·78
	1	20/93	27% [18-36]	15/85	31% [21-41]	0·82 [0·48-1·39]	
Distance from anal verge	< 5 cm	16/103	25% [16-33]	19/115	30% [21-38]	0·77 [0·48-1·25]	0·93
	5-10 cm	34/181	21% [15-27]	27/153	28% [20-35]	0·77 [0·52-1·15]	
	≥ 10 cm	24/146	27% [20-35]	28/151	35% [27-43]	0·72 [0·48-1·08]	
Standard-care group adjuvant hospital policy	No	30/189	24% [18-31]	33/185	28% [22-35]	0·85 [0·59-1·24]	0·38
	Yes	50/273	23% [18-28]	48/265	32% [26-38]	0·70 [0·51-0·94]	
Overall estimate		128/462	24% [20-28]	125/450	30% [26-35]	0·75 [0·60-0·95]	

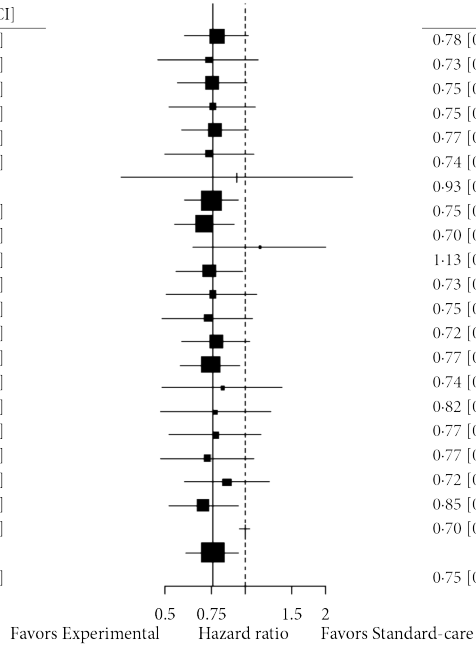

Figure S5 Forest plot of the effect of treatment on DrTF according to randomisation characteristics and predefined hospital policy in the standard-care group on adjuvant chemotherapy.

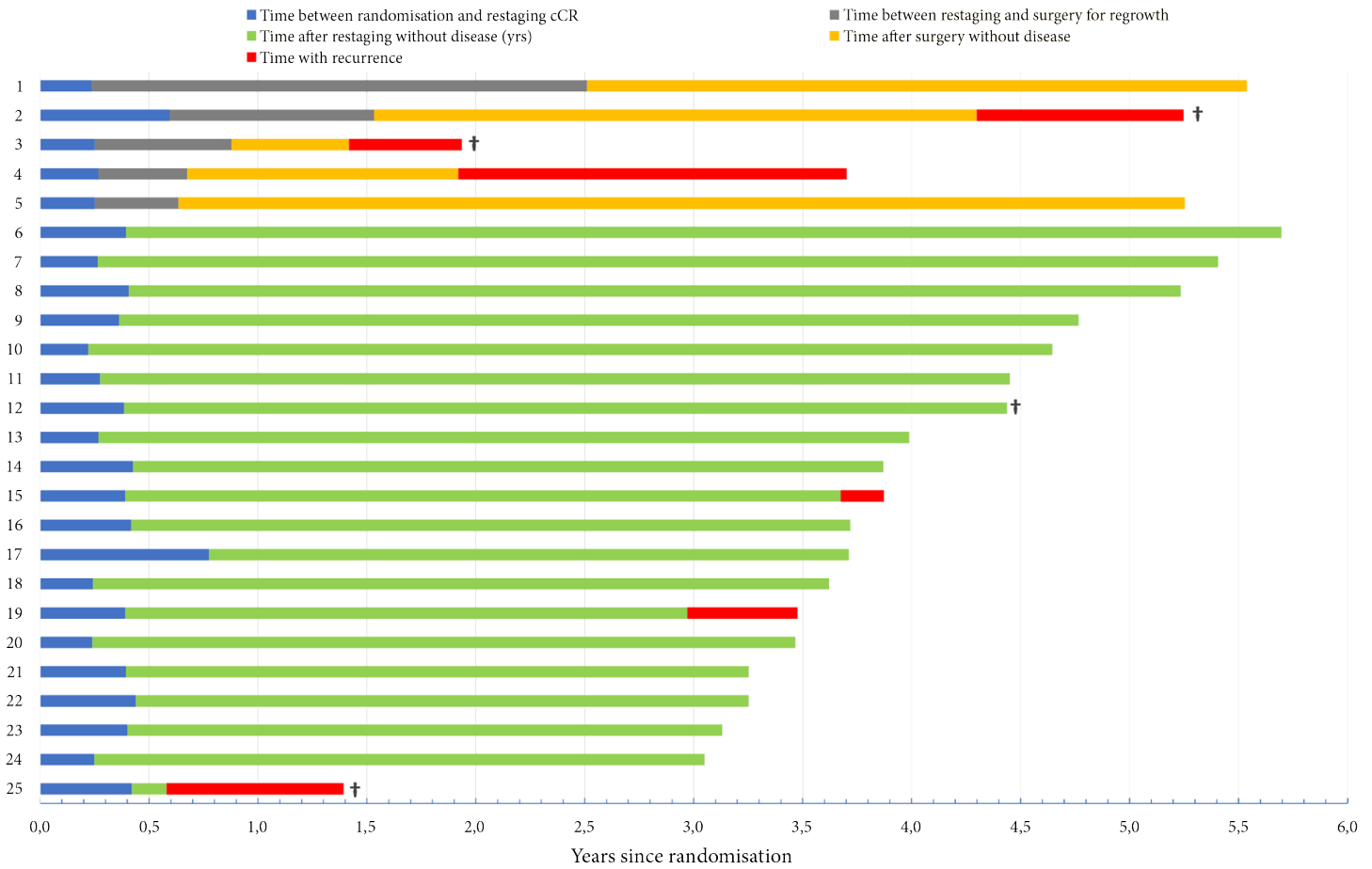

Figure S6 Follow-up of patients with a W&W strategy.


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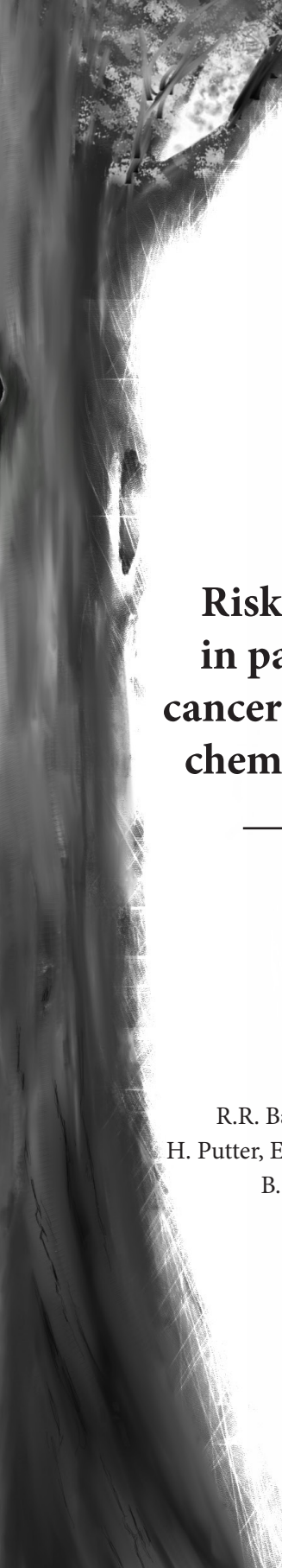

Risk and location of distant metastases in patients with locally advanced rectal cancer after total neoadjuvant treatment or chemoradiotherapy in the RAPIDO trial

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Abstract

Introduction: Although optimising rectal cancer treatment has reduced local recurrence rates, many patients develop distant metastases (DM). The current study investigated whether a total neoadjuvant treatment strategy influences the development, location, and timing of metastases in patients diagnosed with high-risk locally advanced rectal cancer included in the RAPIDO trial.

Material and methods: Patients were randomly assigned to short-course radiotherapy followed by 18 weeks of CAPOX or FOLFOX4 before surgery (EXP), or long-course chemoradiotherapy with optional postoperative chemotherapy (STD). Assessments for metastatic disease were performed pre- and post-treatment, during surgery, and 6, 12, 24, 36, and 60 months postoperatively. From randomisation, differences in the occurrence of DM and first site of metastasis were evaluated.

Results: In total, 462 patients were evaluated in the EXP and 450 patients in the STD groups. Cumulative probability of DM at 5 years after randomization was 23% [95%CI 19-27] and 30% [95%CI26-35] (HR 0.72 [95%CI 0.56-0.93];P=0.011) in the EXP and STD, respectively. Median time to DM was 1.4 (EXP) and 1.3 years (STD). After diagnosis of DM, median survival was 2.6 years [95%CI 2.0-3.1] in the EXP and 3.2 years [95%CI 2.3-4.1] in the STD groups (HR 1.39 [95%CI 1.01-1.92];P=0.04). First occurrence of DM was most often in the lungs (60/462 (13%) EXP and 55/450 (12%) STD) or the liver (40/462 (9%) EXP and 69/450 (15%) STD). A hospital policy of postoperative chemotherapy did not influence the development of distant metastases.

Conclusions: Compared to long-course chemoradiotherapy, total neoadjuvant treatment with short-course radiotherapy and chemotherapy significantly decreased the occurrence of metastases, particularly liver metastases.

Trial registration: EudraCT, 2010-023957-12, and ClinicalTrials.gov, NCT01558921

Keywords: rectal cancer, total neoadjuvant therapy, distant metastases, metastatic pattern

Introduction

Treatment of locally advanced rectal cancer (LARC) has evolved during the past decades. Irradiation has shifted from postoperative to preoperative, leading to fewer local recurrences. (1, 2) The effectiveness of short-course radiotherapy has been demonstrated next to long-course radiotherapy.(3-5) Moreover, the addition of chemotherapy to radiotherapy has proven to be effective in further reducing local recurrence rates in more advanced tumours but it has not improved survival except possibly in the most LARCs.(6-8) Improved preoperative imaging has contributed in selecting patients for neoadjuvant treatment. Moreover, due to improvements in surgical technique, local recurrence is no longer a major problem after treatment of LARC. In contrast, up to 30-40% of the patients still develop distant metastases (DM).(9, 10)

The RAPIDO trial enrolled patients diagnosed with LARC including at least one high-risk criterion. A decrease in the probability of disease-related treatment failure at 3 years from 30% to 24% after treatment with preoperative short-course radiotherapy followed by chemotherapy compared to preoperative long-course chemoradiotherapy and optional postoperative chemotherapy was demonstrated.(11) Although this difference could mainly be attributed to fewer DM in the experimental group, no improvement in overall survival was observed after a median follow-up of 4.6 years.

The current study aims to investigate whether a total neoadjuvant treatment strategy influences the development, location and timing of DM and the prognosis thereafter in patients diagnosed with high-risk LARC included in the RAPIDO trial after a median follow-up of 5.6 years.

Material and methods

Study population and design

The RAPIDO trial is an investigator-driven, international, open-label, phase III, randomized trial. The design, inclusion and exclusion criteria and results of the primary endpoint were published previously. (11) Eligible patients had non-metastasized locally advanced rectal cancer fulfilling at least one high-risk criteria on pelvic MRI (clinical tumour stage T4, clinical nodal stage N2, extramural vascular invasion (EMVI+), involved mesorectal fascia (MRF+),

or enlarged lateral lymph nodes) indicating high risk of failing locally and/or systemically. Between June 21, 2011, and June 2, 2016, 920 patients were assigned to either short-course radiotherapy (5x5 Gy), followed by six cycles of CAPOX or nine cycles of FOLFOX4 and surgery after a recovery period of two to four weeks (n=462, experimental group) or long-course radiotherapy (28-25 x 1.8-2.0 Gy) with concurrent capecitabine, followed by surgery after eight ± two weeks (n=450, standard-care group). Administration of postoperative chemotherapy in the standard-care group was allowed when recommended by the hospitals' local policy. The RAPIDO trial was carried out in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. After central evaluation and approval by the medical ethics committee of University Medical Center Groningen, the boards of directors or local ethics committees of all participating centres approved the protocol. The RAPIDO trial is registered with EudraCT (2010-023957-12) and ClinicalTrials.gov (NCT01558921).

Evaluation of the primary tumour and during follow-up

Pre-treatment screening included CEA, CT thorax-abdomen-pelvis and an MRI of the pelvis. Re-staging before surgery was mandatory (in the experimental group 1-2 weeks after the last chemotherapy cycle; in the standard-care group 2-3 weeks prior to planned surgery). After surgery, a standardised, minimal follow-up schedule was defined, with clinical assessments at 6, 12, 24, 36, and 60 months postoperatively, including CEA measurement. A chest x-ray and liver ultrasound or CT of thorax and abdomen were required at least at 12 and 36 months. Evidence of recurrent disease was accepted in case of positive histology or cytology, or with metastases on ultrasound, X-ray, (PET)CT, bone-scintigraphy and/or pelvic pathology on PET. Distant metastses were defined as relapse of the tumour outside the pelvic region. Analyses were based on information from the case report forms and corresponding copies of imaging and/or pathology reports in which the first occurrence of DM was documented. Type of imaging modality used all involved subsites at that assessment, and treatment of the metastases were recorded.

Statistical analyses

The reverse Kaplan-Meier method was used for the calculation of median follow-up.

Proportions were compared with chi-square tests. Survival analyses were performed on an intention-to-treat basis. For calculation of the cumulative incidence of DM, competing risks analyses were performed with death as competing risk. For calculation of the cumulative incidence of different sites of DM competing risks analyses were also performed, with time as the time of the first occurrence of distant metastasis, death or last follow-up, and the different sites of DM (liver-only, lung-only, liver+lung, other), and death as competing risks. Patients alive and DM-free at last follow-up were censored. A Cox proportional hazards regression, with the time-interval of DM after randomization as a continuous variable (in years), was performed to investigate the influence of time of first occurrence of DM on subsequent survival. Patients with locoregional failure prior to the diagnosis of DM were excluded when calculating the risk of developing locoregional failure after the diagnosis of DM. Locoregional failure and DM diagnosed within 90 days of each other were considered to occur synchronously. HRs and 95% confidence intervals (CI) were computed using Cox regression (for competing risks analyses based on the cause-specific hazards). Violation of the proportional hazards assumption was checked by visual inspection. P-values were calculated based on (cause-specific) log-rank tests.(12, 13) Univariate Cox regressions were performed to investigate the influence of baseline characteristics on the development of DM. Variables with a p-value <0.10 were included in a multivariate Cox regression, with the exception of 'number of high-risk criteria' as the high-risk criteria were already included in the multivariate analyses. Subgroup analyses of the effect of treatment on associations between prognostic factors of DM and the development thereof were performed and presented in a forest plot. The significance threshold for all P-values was 0.05. All analyses were performed using IBM SPSS Statistics version 25.0 or 'R' version 4.0.1.

Results

Clinical characteristics of eligible patients are demonstrated in table 1. At the time of analyses (data lock: 11March, 2022), median follow-up was 5.6 years (IQR 5.4-7.5).

Distant metastases

At 5 years after randomization the cumulative probability of DM was 23% [95%CI 19-27]

Table 1 Clinical characteristics

	All eligible patients			
	Experimental (n = 462)		Standard-care (n = 450)	
Gender				
Male	300	(65%)	312	(69%)
Female	162	(35%)	138	(31%)
Age at randomization (years)				
(median, range)	62	31-83	62	23-84
High-risk criteria *				
cT4	149	(32%)	139	(31%)
cN2	318	(69%)	314	(70%)
enlarged lateral nodes	70	(15%)	74	(16%)
EMVI +	166	(36%)	151	(34%)
MRF +	311	(67%)	312	(69%)
Number of high-risk criteria per patient *				
None	2	(<1%)	-	-
1	132	(29%)	136	(30%)
2	166	(36%)	155	(34%)
3	107	(23%)	106	(24%)
4	46	(10%)	39	(9%)
5	9	(2%)	14	(3%)
Distance from anal verge on endoscopy				
< 5 cm	103	(22%)	114	(25%)
5 – 10 cm	181	(39%)	153	(34%)
≥ 10 cm	146	(32%)	152	(34%)
Unknown	32	(7%)	31	(7%)
Treated in a hospital with a policy for postoperative chemotherapy (standard-care group)				
Yes	-	-	265	(59%)
No	-	-	185	(41%)

Continuation Table 1 Clinical characteristics

	All eligible patients	
	Experimental (n = 462)	Standard-care (n = 450)
Number of postoperative chemotherapy courses (standard-care group)		
None, no hospital policy		183 (41%)
None, despite hospital policy	- -	80 (18%)
1-3	- -	65 (14%)
≥ 4	- -	122 (27%) ‡

Data are n (%), unless otherwise indicated. Percentages might not equal 100% due to rounding. * MRI defined, according to radiology reports. ‡ Two patients without a hospital policy are also included.

and 30% [95%CI 26-35] in the experimental and standard-care groups, respectively (HR 0.72 [95%CI 0.56-0.93];P=0.011, figure 1A). Median time from randomization to the diagnosis of DM was 1.4 years (IQR 0.9-2.5) in the experimental group and 1.3 years (IQR 0.5-2.2) in the standard-care group. The moment of diagnosis of the first appearance of DM is described in table 2. From diagnosis of DM, patients in the experimental group had a worse prognosis than those in the standard-care group (HR 1.39 [95%CI 1.01-1.92];P=0.04) with a median survival of 2.6 years [95%CI 2.0-3.1] and 3.2 years [95%CI 2.3-4.1], respectively, figure 1B. A hospital policy of postoperative chemotherapy in the standard-care group did not influence the development of DM (Supplementary Figure A). Table 3 describes the occurrence of DM and locoregional failure in relation to each other. Supplementary Figure B contains additional information on the timing of development of DM and/or locoregional failure. At 5 years the cumulative probability of developing locoregional failure synchronously or after being diagnosed with DM was 25% [95%CI 15-35] in the experimental group and 13% [95%CI 7-19] in the standard-care group (HR 2.02 [95%CI 1.07-3.81];P=0.03). The cumulative probability of disease-related treatment failure at five years was 28% [95%CI 24–32] in the experimental group and 34% [95%CI 30–38) in the standard-care group (HR 0.79 [95%CI 0.63–1.00];P=0.048. Overall survival of all eligible patients in the RAPIDO trial at 5 years was 82% [95%CI 78-85] for the experimental group and 80% [95%CI 77-84] for the standard-care group (HR 0.91 [95%CI 0.70-1.19];P=0.50). For all analyses, visual inspection showed no evidence of violation of the proportional hazards assumption.

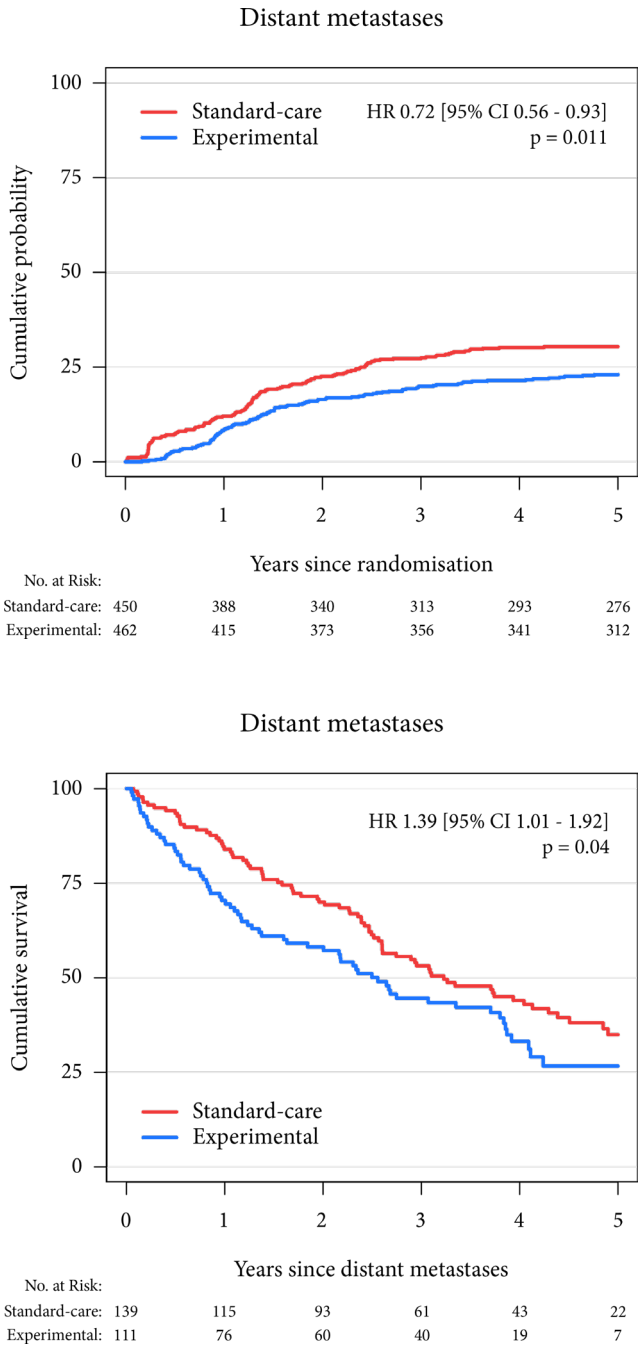

Figure 1 The risk of distant metastases (A) and survival after diagnosis of metastases (B).

First metastasized organ-site

In the experimental and standard-care groups, 73% (81/111) and 78% (109/139) of patients were initially diagnosed with DM in one organ-site, 22% (24/111) and 17% (23/139) had DM in two organ-sites, and 5% (6/111) and 5% (7/139) in 3-6 organ-sites, respectively (P=0.58). DM were most often located in the liver or the lungs (figure 2,3). In the experimental group, 9% (40/462) of patients were diagnosed with liver metastases compared to 15% (69/450) of patients in the standard-care group (P=0.002). Lung metastases were equally common in both groups, 13% (60/462) in the experimental group and 12% (55/450) in the standard-care group (P=0.73). Survival after lung-only versus liver-only metastases was not statistically significantly different, stratified for treatment group or for the treatment groups combined (Supplementary Figure C). Tumour level did not influence first metastatic organ-site (Supplementary Table A).

Treatment of distant metasases

Of the patients with DM, 46% (51/111) and 52% (72/139) underwent surgery for metastatic disease (P=0.36), 14% (15/111) and 16% (22/139) received radiotherapy (P=0.61), 45% (50/111) and 58% (81/139) received chemotherapy (P=0.037), and 6% (7/111) and 9% (12/139) received other or no treatment (P=0.49) in the experimental and standard-care groups, respectively. Treatment according to the location of DM is displayed in table 4 (in more detail, Supplementary Table B).

Prognostic factors for the development of distant metastases

Treatment group, all high-risk criteria except cT4, and the total number of high-risk criteria were associated with the development of DM. In the multivariate analyses, treatment group, EMVI+, cN2 and MRF+ were statistically significant (table 5). No interaction between risk factors and treatment groups could be demonstrated (figure 4).

Discussion

The RAPIDO trial demonstrates that short-course radiotherapy followed by chemotherapy before surgery decreases the cumulative probability of DM at five years to 23% compared to

30% after chemoradiotherapy before surgery and optional postoperative chemotherapy in patients with LARC who are considered to have a high risk of systemic recurrence. Median time to appearance of DM was the same and median survival after DM was six months longer in the standard-care group than in the experimental group (3.1 vs 2.6 years, p=0.04).The decrease in DM is mainly caused by a reduction in liver-only metastases.

The appearance of distant metastases

As reported earlier from the RAPIDO trial, compliance with systemic chemotherapy was increased when this was delivered pre-operatively.(14) With the TNT approach, the intended dose of chemotherapy could be given to more patients resulting in a lower DM rate. In colon cancer, an early start of adjuvant chemotherapy is more effective than starting more than 10 weeks after surgery, the latter negatively impacts disease-free survival.(15) By bringing forward chemotherapy as part of a TNT in rectal cancer, micrometastases, when susceptible to chemotherapy, can be combatted earlier in the treatment process, preventing development of detectable metastases. This is supported by our finding that DM were more often diagnosed during re-staging in the standard-care group than in the experimental group, where restaging was after a longer interval. The follow-up schedule after surgery was standardised leading to clear increases of DM at set times. Merely postponement of DM does not seem to be the case as median time to DM is comparable between treatment groups.

Decrease in liver metastases

It is unknown why neoadjuvant chemotherapy appears more effective in decreasing liver metastases than lung metastases in the RAPIDO trial. The literature is not unequivocal regarding the most common metastasised organ in rectal cancer. Some studies have reported the liver as most common metastasized organ(16), other retrospective and prospective single-centre studies have reported the lungs as the most common metastasized organ-site.(17, 18) However, this finding may be explained by the inclusion of mostly mid-, and lower rectal cancers in those studies.(17, 19-21) Tumour height did not influence first-metastasised organ-site in the RAPIDO trial as distance from the anal verge was equal between the treatment groups (supplementary table A).

Table 2 Moment for the diagnosis of the first appearance of distant metastases

	All patients		
	Experimental (n = 462)	Standard-care (n = 450)	P-value
			0.040
Before start of treatment *	0 (0%)	5 (1%)	
At restaging after the end of the neoadjuvant treatment	8 (2%)	20 (4%)	
During surgery	6 (1%)	4 (1%)	
After surgery or sustained cCR	97 (21%)	110 (24%)	

* At planning CT-scan for radiotherapy. Data are presented as n (absolute %).

Table 3 Events of disease-related treatment failure

	All patients	
	Experimental (n = 462)	Standard-care (n = 450)
DM only	74 (16%)	106 (24%)
LRF only	15 (3%)	6 (1%)
DM + LRF synchronously *	15 (3%)	11 (2%)
DM before LRF	11 (2%)	8 (2%)
DM after LRF	9 (2%)	5 (1%)
New primary tumor (without DM or LRF)	21 (5%)	28 (6%)
Treatment-related death	4 (1%)	4 (1%)

* Locoregional failure and distant metastases diagnosed within 90 days of each other.
Data are presented as n (absolute %).

Prognosis after distant metastases

In the experimental group, 84% (387 of 462) of patients received at least 75% of the prescribed courses of systemic chemotherapy before the diagnosis of DM compared to 24% (108 of 450) of patients in the standard-care group.(14) As a consequence, patients in the experimental group with metastatic disease who progressed after this systemic treatment had already received a nearly cumulative maximum dose of oxaliplatin, hampering administration of oxaliplatin-

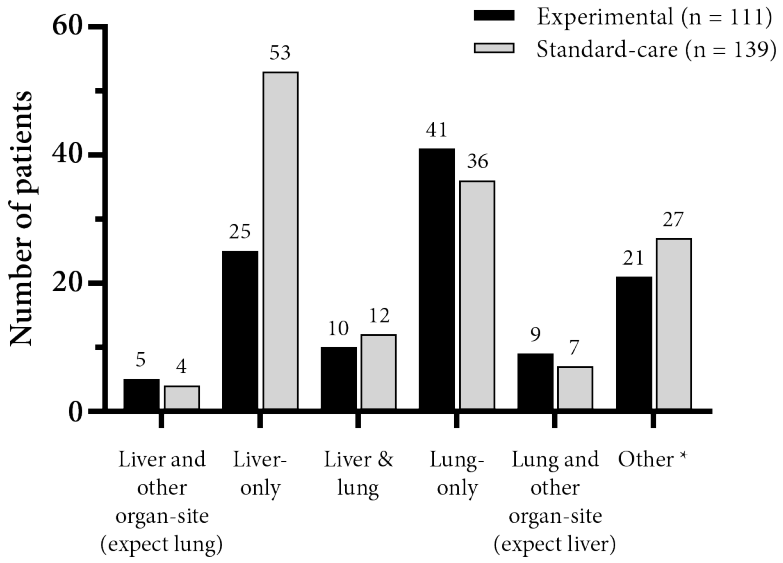

Figure 2 First metastasized organ-site.

**Other includes bone, brain, peritoneum, distant lymph nodes, and pleura.*

containing chemotherapy in the metastatic setting. These patients often received second-line chemotherapy, known to be less effective in the palliative setting, as tumour cells that cause relapse after treatment with systemic chemotherapy can have a worse biological profile and could therefore be partly responsible for a poorer prognosis.(22) In contrast, patients developing metastatic disease in the standard-care group who had not received adjuvant chemotherapy could be treated with first-line oxaliplatin-containing chemotherapy. The gain in fewer DM from preoperative chemotherapy may be counterbalanced by shortening of survival after recurrence, as recently stressed in a systematic review.(23)

Also, a more aggressive treatment with multiple interventions creates survival advantages for chemo-resistant tumour cells after each successful intervention. A combined treatment as the RAPIDO schedule (radiotherapy and chemotherapy) is more effective than only one local intervention (chemoradiotherapy in the standard-care group) resulting in a higher pCR rate. (11) However, the most aggressive and invasive cancer cells will survive after each intervention if not eliminated.(24) This selection effect was observed in the experimental group with

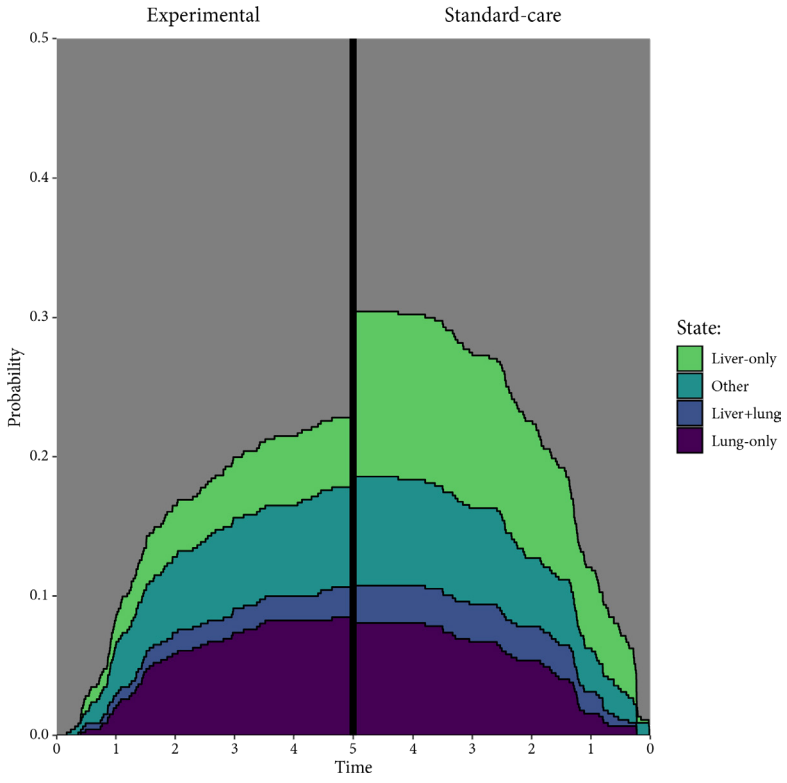

Figure 3 First diagnosis of distant metastases over time, based on cumulative probabilities according to the first metastasized organ-site. Other includes liver and another organ-site, lung, and another organ-site.

worse survival and a higher probability of developing locoregional failure synchronously or after the diagnosis of DM.

The experimental treatment possibly prevented the DM with very little tumour burden, which was still present in the standard-care group. These patients may be the ones cured by local treatment being another reason for the better survival after DM in the standard-care group. Metastases with the worst prognosis (non-resectable, non-responsive to chemotherapy etc) were the ones remaining in both treatment groups influencing overall survival. Possibly explaining why overall survival of the whole group is comparable at 5 years. However, another

		Experimental Events/patients		Standard-care Events/patients		HR [95% CI]	*P*interaction
mr cT4	yes	39/149	(26%)	50/139	(36%)	0.68 [0.44-1.03]	0.68
	no	72/313	(23%)	89/311	(29%)	0.75 [0.55-1.02]	
mr cN2	yes	86/318	(27%)	103/314	(33%)	0.77 [0.58-1.03]	0.44
	no	25/144	(17%)	36/136	(26%)	0.60 [0.36-1.00]	
mr lat LN +	yes	22/70	(31%)	28/74	(38%)	0.82 [0.47-1.43]	0.66
	no	89/392	(23%)	111/376	(30%)	0.71 [0.54-0.94]	
mr EMVI +	yes	50/166	(30%)	60/151	(40%)	0.68 [0.47-1.00]	0.76
	no	61/296	(21%)	79/299	(26%)	0.73 [0.52-1.02]	
mr MRF +	yes	82/311	(26%)	105/312	(34%)	0.73 [0.55-0.98]	0.94
	no	29/151	(19%)	34/138	(25%)	0.72 [0.44-1.18]	
High-risk criteria per patient	1	20/132	(15%)	29/136	(21%)	0.67 [0.38-1.19]	0.89
	2	37/166	(22%)	48/155	(31%)	0.64 [0.42-0.99]	
	3	30/107	(28%)	34/106	(32%)	0.78 [0.45-1.35]	
	4-5	23/55	(42%)	28/53	(53%)	0.77 [0.45-1.35]	
Overall estimate							

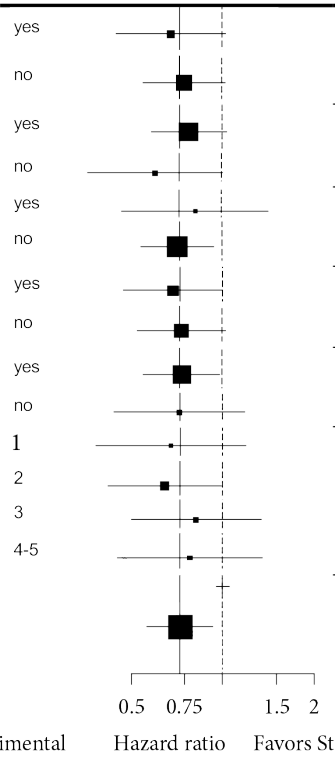

Figure 4 Forest plot of the effect of high-risk factors present at abseline MRI on the development of distant metastases.

Table 4 Treatment according to location of distant metastases

	Liver-only		Lung-only	
	EXP (n=25)	STD (n=53)	EXP (n=41)	STD (n=36)
No treatment	3 (12%)	3 (6%)	3 (7%)	5 (14%)
Surgery only	8 (32%)	18 (34%)	17 (41%)	9 (25%)
Surgery + CT	7 (28%)	17 (32%)	2 (5%)	2 (6%)
Surgery + RT	- -	2 (4%)	2 (5%)	- -
CT only	4 (16%)	4 (8%)	10 (24%)	13 (36%)
RT only	- -	1 (2%)	5 (12%)	5 (14%)
CT + RT	- -	- -	1 (2%)	2 (6%)
Other treatment*	3 (12%)	8 (15%)	1 (2%)	- -

	Liver + lung		Other	
	EXP (n=10)	STD (n=12)	EXP (n=21)	STD (n=27)
No treatment	4 (40%)	1 (8%)	3 (14%)	2 (7%)
Surgery only	1 (10%)	- -	3 (14%)	3 (11%)
Surgery + CT	2 (20%)	1 (8%)	3 (14%)	6 (22%)
Surgery + RT	- -	1 (8%)	1 (5%)	1 (4%)
CT only	2 (20%)	7 (58%)	7 (33%)	10 (37%)
RT only	- -	- -	1 (5%)	1 (4%)
CT + RT	1 (10%)	1 (8%)	- -	1 (4%)
Other treatment*	- -	1 (8%)	3 (14%)	3 (11%)

EXP = experimental group; STD = standard-care group; CT = chemotherapy;
RT = radiotherapy.
*Other treatment also includes: (a combined treatment using) microwave ablation, radiofrequency ablation, HIPEC, electrochemotherapy.

possible explanation is that the RAPIDO trial was not powered to address overall survival. The gain in DM rate (7%-unites) may be too small to detect a difference in overall survival with the number of patients included.

Table 5 Univariate and multivariate cox regression analyses for distant metastases

Variable	Number of patients at risk	Univariate		Multivariate	
		Hazard ratio (CI 95%)	P-value	Hazard ratio (CI 95%)	P-value
Treatment			0.011		0.011
Experimental	462	1.00		1.00	
Standard-care	450	1.39 (1.08-1.78)		1.39 (1.08-1.78)	
Gender			0.138		
Male	612	1.00		-	
Female	300	0.81 (0.62-1.07)		-	
Age			0.703		
	912	1.00 (0.99-1.02)		-	
Distance from anal verge (endoscopy)			0.689		
≤ 5cm	217	1.00		-	
5-10 cm	334	0.92 (0.66-1.27)		-	
≥10 cm	298	1.05 (0.75-1.45)		-	
High risk factors					
mr cT4			0.060		0.285
No	624	1.00		1.00	
Yes	288	1.28 (0.99-1.66)		1.16 (0.88-1.53)	
mr cN2			0.008		0.005
No	280	1.00		1.00	
Yes	632	1.48 (1.11-1.98)		1.53 (1.14-2.06)	
mr Lat LN +			0.025		0.081
No	768	1.00		1.00	
Yes	144	1.43 (1.05-1.94)		1.32 (0.97-1.81)	

Continuation Table 5 Univariate and multivariate cox regression analyses for distant metastases

Variable	Number of patients at risk	Univariate		Multivariate	
		Hazard ratio (CI 95%)	P-value	Hazard ratio (CI 95%)	P-value
mr EMVI +			<0.001		<0.001
No	595	1.00		1.00	
Yes	317	1.66 (1.29-2.13)		1.64 (1.28-2.12)	
mr MRF +			0.007		0.013
No	289	1.00		1.00	
Yes	623	1.48 (1.11-1.97)		1.46 (1.08-1.97)	
Number of high-risk criteria			<0.001		
	912	1.41 (1.26-1.57)			

Strengths and limitations

To our knowledge, this study is the first to compare the first metastatic organ-site in LARC while comparing TNT to conventional chemoradiotherapy and to report a changed metastatic pattern with the different treatment regimens. A limitation of the current study is that further diagnostics of the occurrence of DM were not always fully performed after an LRF had been established and vice versa. This has not been checked and corrected for in the analyses as this differs per hospital and country. In addition, comparisons with regard to systemic chemotherapy were more challenging as the standard-care group was not evenly distributed because adjuvant chemotherapy was allowed according to the hospital protocol. Although the results of the RAPIDO trial are promising with respect to a decrease in DM, a higher pCR rate, and therewith a possible organ-saving strategy, an important clinical dilemma still concerns the selection of LARC patients who will most likely benefit from this new treatment schedule. Recently our study group published that enlarged lateral lymph nodes, a positive circumferential resection margin, tumour deposits, node positivity at pathology and experimental treatment were significant predictors for developing locoregional recurrence. No statistically significant association was found in the multivariate analysis regarding distance from the anal verge. (25) In the current manuscript, we demonstrated that EMVI,

cN2, MRF and standard-care treatment are prognostic factors for the development of DM, yet, identification of patients who would benefit the most from the RAPIDO schedule or other TNT schedules is not yet possible. Although health-related quality of life and bowel function were not compromised and no increase in grade ≥ 3 toxicity was observed,(26) the benefits and harms of a total neoadjuvant treatment should be carefully balanced, as some patients are overtreated.

Further research is needed to predict clinical response, for example, via biomarkers and to define the optimal selection criteria for total neoadjuvant treatment. In addition, standardised follow-up schedules should be applied to future studies to provide comparable results.

Conclusion

In summary, compared to standard care with long-course chemoradiotherapy, short-course radiotherapy in combination with systemic chemotherapy effectively decreases liver metastases in patients with high-risk LARC without influencing the time of diagnosis of DM. With the experimental TNT, an effective dose of chemotherapy can be given to eliminate more micrometastases, when susceptible to chemotherapy, early in the treatment process, preventing development into detectable metastases. Why this effect mainly occurs in liver metastases cannot be fully explained based on the current data.

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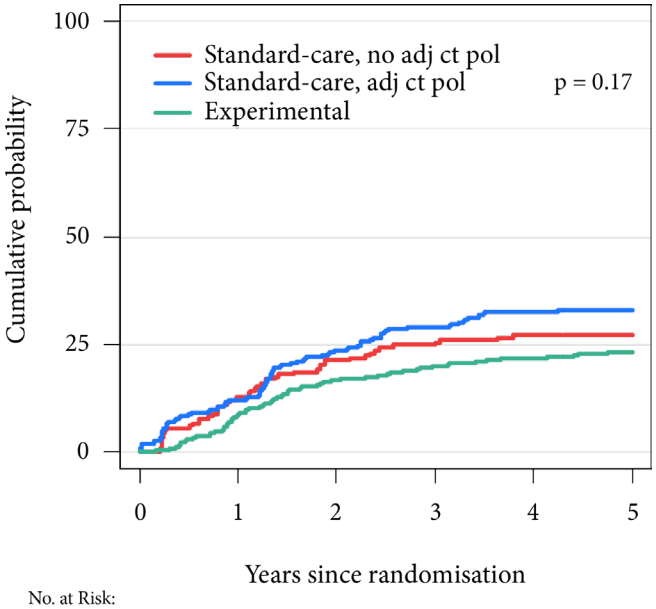
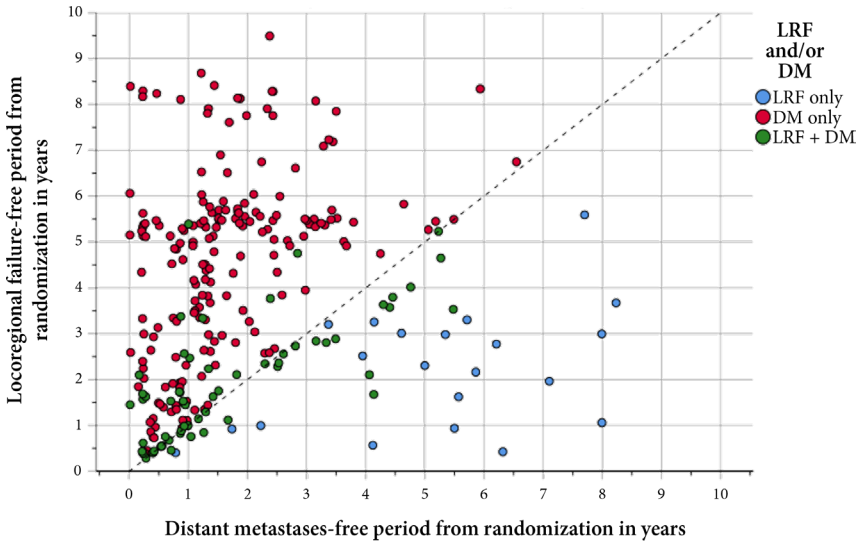
Supplementary Appendix Chapter 5



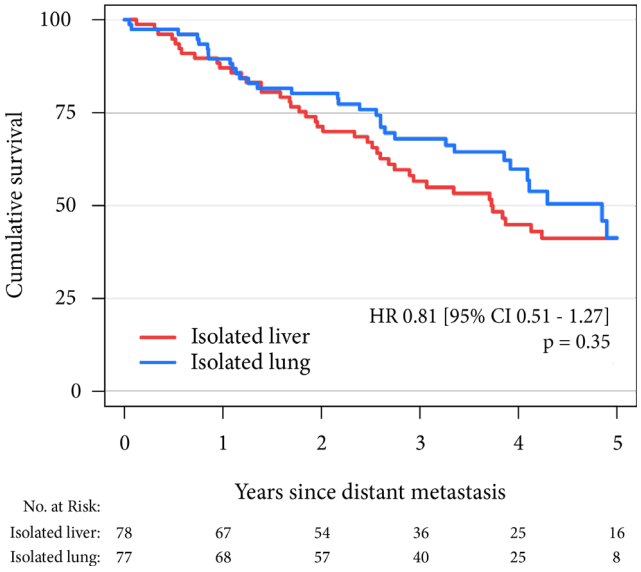
No. at Risk:						
Standard-care, no adj ct pol:	185	158	141	133	124	117
Standard-care, adj ct pol:	265	230	199	180	169	159
Experimental:	462	415	373	356	341	312

Supplementary Figure A The development of distant metastases stratified for the experimental group and the standard-care group with or without a hospital policy for postoperative chemotherapy.

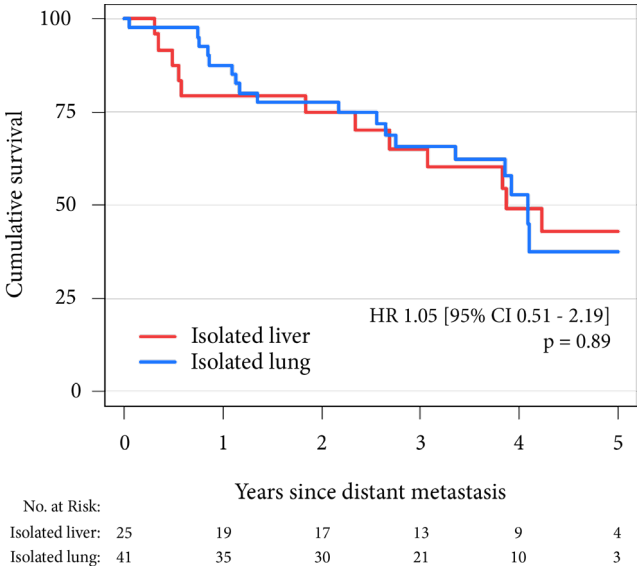
Cumulative probabilities at five years after randomization were 33% [95% CI 27-38] and 27% [95% CI 21-34] with or without hospital policy, respectively (HR 1.22 [95% CI 0.86-1.72]; P=0.019). In total, 187 patients started adjuvant chemotherapy in the standard-care group; two patients were from the group without a hospital policy for adjuvant chemotherapy.



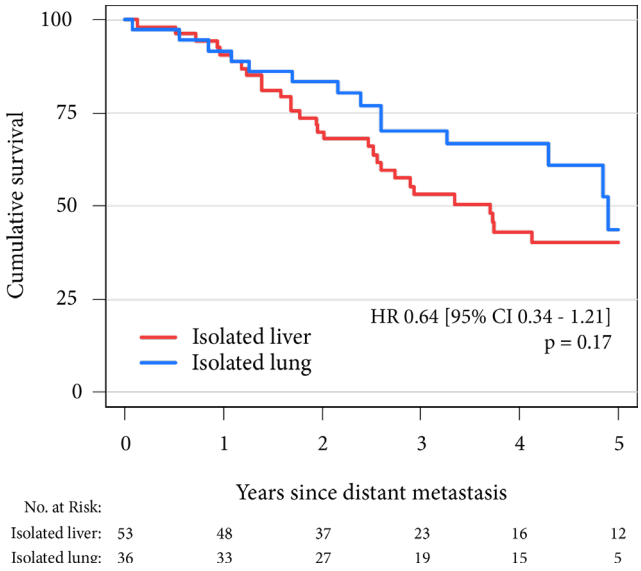
Supplementary Figure B Timing of distant metastases and/or locoregional failure.
LRF = locoregional failure DM = distant metastases.



Supplementary Figure C.1 Survival after isolated lung metastases versus after isolated liver metastases (both treatment groups).



Supplementary Figure C.2 Survival after isolated lung metastases versus after isolated liver metastases (experimental group).



Supplementary Figure C.3 Survival after isolated lung metastases versus after isolated liver metastases (standard-care group).

Supplementary Table A First metastatic organ-sites according distance from anal verge.

	Whole group				Whole group			
	Experimental		Standard		Experimental		Standard	
	< 5cm				5-10 cm			
No metastases	154	(71%)			247	(74%)		
	75	(73%)	79	(71%)	139	(77%)	108	(71%)
Isolated liver	14	(22%)			31	(36%)		
	4	(4%)	10	(9%)	11	(6%)	20	(13%)
Liver and other organ-site (except lung)	1	(1%)			3	(1%)		
	1	(1%)	-	-	1	(1%)	2	(1%)
Isolated lung	24	(11%)			29	(9%)		
	13	(13%)	11	(10%)	17	(9%)	12	(8%)
Lung and other organ-site (except liver)	6	(3%)			5	(2%)		
	2	(2%)	4	(4%)	4	(2%)	1	(1%)
Other	13	(6%)			13	(4%)		
	5	(5%)	8	(7%)	7	(4%)	6	(4%)
Liver + lung	5	(2%)			6	(2%)		
	3	(3%)	2	(2%)	2	(1%)	4	(3%)

None of the differences are statistically significant

Continuation

Supplementary Table A First metastatic organ-sites according distance from anal verge.

	Whole group				Whole group			
	Experimental		Standard		Experimental		Standard	
	≥ 10 cm				unknown			
No metastases	212	(71%)			49	78%)		
	111	(76%)	101	(66%)	26	(81%)	23	(74%)
Isolated liver	32	(37%)			1	(7%)		
	10	(7%)	22	(15%)	-	-	1	(3%)
Liver and other organ-site (except lung)	4	(1%)			1	(2%)		
	2	(1%)	2	(1%)	1	(3%)	-	-
Isolated lung	21	(7%)			3	(5%)		
	10	(7%)	11	(7%)	1	(3%)	2	(7%)
Lung and other organ-site (except liver)	2	(1%)			3	(5%)		
	1	(1%)	1	(1%)	2	(6%)	1	(3%)
Other	18	(6%)			4	(6%)		
	8	(6%)	10	(7%)	1	(3%)	3	(10%)
Liver + lung	9	(3%)			2	(3%)		
	4	(3%)	5	(3%)	1	(3%)	1	(3%)

None of the differences are statistically significant

Supplementary Table B Treatment according to location of distant metastases

	Liver-only		Lung-only		Liver + lung		Other	
	EXP (n=25)	STD (n=53)	EXP (n=41)	STD (n=36)	EXP (n=10)	STD (n=12)	EXP (n=21)	STD (n=27)
No treatment	3 (12%)	3 (6%)	3 (7%)	5 (14%)	4 (40%)	1 (8%)	3 (14%)	2 (7%)
Surgery only	8 (32%)	18 (34%)	17 (41%)	9 (25%)	1 (10%)	- -	3 (14%)	3 (11%)
Surgery + CT	7 (28%)	17 (32%)	2 (5%)	2 (6%)	2 (20%)	1 (8%)	3 (14%)	6 (22%)
Surgery + RT	- -	2 (4%)	2 (5%)	- -	- -	1 (8%)	1 (5%)	1 (4%)
CT only	4 (16%)	4 (8%)	10 (24%)	13 (36%)	2 (20%)	7 (58%)	7 (33%)	10 (37%)
RT only	- -	1 (2%)	5 (12%)	5 (14%)	- -	- -	1 (5%)	1 (4%)
CT + RT	- -	- -	1 (2%)	2 (6%)	1 (10%)	1 (8%)	- -	1 (4%)
Other treatment*	3 (12%)	8 (15%)	1 (2%)	- -	- -	1 (8%)	3 (14%)	3 (11%)

EXP = experimental group; STD = standard-care group; CT = chemotherapy; RT = radiotherapy.

Continuation Supplementary Table B Treatment according to location of distant metastases

Other treatment*

Experimental liver only:1x MWA, 1x surgery + RFA, 1x surgery + CT + RT

Standard-care liver only:1x electrochemotherapy, 3x surgery + RFA, 2x CT + RFA, 1x surgery + CT + RFA, 1x surgery + RT + chemo + RFA

Experimental lung only: 1x microwave ablation

Standard-care liver + lung: 1x RT + CT + RFA

Experimental other: 2x surgery, including HIPEC, 1x RT + pain relief,

Standard-care other: 1x surgery, including HIPEC, 1x surgery + RT + CT + HIPEC, 1x surgery + CT + RT

Treatment liver + other

Experimental: 1x surgery + CT, 4x only CT

Standard-care: 1x CT + RT, 2x surgery + CT, 1x surgery + CT + RT

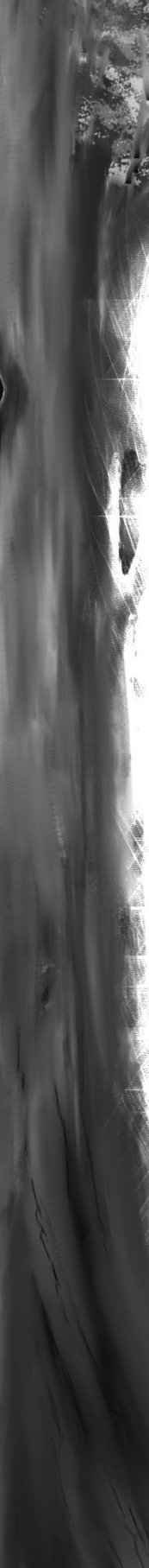
Treatment lung + other

Experimental: 3x no treatment, 4x only CT, 1x only RT, 1x CT + RT

Standard-care: 1x no treatment, 4x only CT, 1x CT + RT, 1x surgery + CT + HIPEC

PART III - IWWD


6



Watch and wait after a clinical complete response in rectal cancer patients younger than 50 years

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Abstract

Background: Young-onset rectal cancer, in patients less than 50 years, is expected to increase in the coming years. A watch-and-wait strategy is nowadays increasingly practised in patients with a clinical complete response (cCR) after neoadjuvant treatment. Nevertheless, there may be reluctance to offer organ preservation treatment to young patients owing to a potentially higher oncological risk. This study compared patients aged less than 50 years with those aged 50 years or more to identify possible differences in oncological outcomes of watch and wait.
Methods: The study analysed data from patients with a cCR after neoadjuvant therapy in whom surgery was omitted, registered in the retrospective–prospective, multicentre International Watch & Wait Database (IWWD).

Results: In the IWWD, 1552 patients met the inclusion criteria, of whom 199 (12.8 per cent) were aged less than 50 years. Patients younger than 50 years had a higher T category of disease at diagnosis (P =0.011). The disease-specific survival rate at 3 years was 98 (95 per cent c.i. 93 to 99) per cent in this group, compared with 97 (95 to 98) per cent in patients aged over 50 years (hazard ratio (HR) 1.67, 95 per cent c.i. 0.76 to 3.64; P =0.199). The cumulative probability of local regrowth at 3 years was 24 (95 per cent c.i. 18 to 31) per cent in patients less than 50 years and 26 (23 to 29) per cent among those aged 50 years or more (HR 1.09, 0.79 to 1.49; P =0.603). Both groups had a cumulative probability of distant metastases of 10 per cent at 3 years (HR 1.00, 0.62 to 1.62; P =0.998).

Conclusion: There is no additional oncological risk in young patients compared with their older counterparts when following a watch-and-wait strategy after a cCR. In light of a shared decision-making process, watch and wait should be also be discussed with young patients who have a cCR after neoadjuvant treatment.

Introduction

Colorectal cancer is generally thought to be a disease of the elderly. However, together with the rise in older patients, the incidence in young patients (aged less than 50 years) has increased worldwide over recent decades[1]. Between 1990 and 2016, the incidence of rectal cancer in adults younger than 50 years in Europe increased annually from 1.6 to 3.5 per cent[2]. It is estimated that by 2030 nearly one in four diagnoses of rectal cancer will be in patients aged less than 50 years[3]. Young patients often receive more intensive treatment, presumably related to better overall performance status and possibly more advanced disease stage at presentation[4]. In addition, clinicians expect relatively more survival gain for young patients. Treatment of clinical stage II and III rectal cancers consists of total or partial mesorectal excision, often preceded by neoadjuvant treatment, resulting in complete disappearance of the rectal tumour and tumour-positive lymph nodes—termed a pathological complete response (pCR)—in 10–15 per cent of patients after chemoradiotherapy and almost 30 per cent of patients when smaller tumours are included[5]. This has led to the question of whether rectal resection could be considered overtreatment for this subgroup, as there is no longer evidence of tumour or involved lymph nodes. In addition, patients with a pCR have a particularly favourable oncological outcome, with a low risk of local or distant recurrences[5].

In an attempt to avoid potentially unnecessary surgery and its detrimental side-effects, a watch-and-wait strategy has been developed. Patients with a clinical complete response (cCR) on reassessment imaging after neoadjuvant therapy may avoid immediate surgery and be subjected to a strict surveillance strategy. Championed by Habr-Gama and colleagues[6] and followed by different cohort series[7,8], the safety and feasibility of watch and wait has been established in patients with a cCR after neoadjuvant therapy. The largest series of pooled individual data was published by the International Watch & Wait Database (IWWD) Consortium[9] in 2018, in an analysis of 880 patients worldwide with a cCR treated according to a watch-and-wait strategy. The 5-year overall survival rate was 85 per cent, corresponding to a disease-specific survival rate of 97 per cent, indicating that the vast majority of deaths were not cancer-related. Nevertheless, there may be more hesitance among treating clinicians to initiate watch and wait after a cCR in patients with young-onset disease than in older patients. It is questioned whether this approach would be oncologically safe for such young patients

with a longer life expectancy, and thus potentially more considerable loss of life-years. The aim of the present study was to investigate the oncological outcomes of a watch-and-wait strategy in patients aged less than 50 years with a cCR after neoadjuvant therapy, and to compare them with outcomes among patients aged 50 years or older.

Methods

Study design

The IWWD is an international multicentre, partly retrospective and partly prospective cohort database, established in 2014 to collect all available data to provide an understanding of the risks and benefits of a watch-and-wait strategy after achieving a cCR following neoadjuvant treatment. Data registration started in April 2015. Patient consent and ethical and institutional review board approval were handled according to the local requirements of participating centres. Data were entered online by local research staff or the participating investigator, and stored in a highly secured NEN7510 certified and encrypted research data server (ProMISe) (Leiden, the Netherlands). To analyse the data, a data set without identifiable patient parameters was extracted from PRoMISe in compliance with the General Data Protection Regulation (EU 2016/679). The Clinical Research Centre of the Leiden University Medical Centre was responsible for overall data management and performed data quality checks in case of missing or data irregularities. All participating centres retain full ownership of their data and responsibility for accuracy of the information provided.

Patients

Data registered in the observational IWWD from all patients achieving a cCR after neoadjuvant treatment, and not undergoing surgery, were analysed. Patients with distant metastases at diagnosis or concurrently with the start of watch and wait, and those for whom age was missing, were excluded. The indication for and type of neoadjuvant therapy, the decision to watch and wait, and all restaging and follow-up assessments were done according to the local protocol of the participating institutions. A cCR was defined by the absence of signs of residual tumour or involved lymph nodes at clinical reassessment after neoadjuvant therapy, which consisted of digital rectal examination, endoscopy, MRI, CT, and/or other

imaging modalities according to each institution's policy. Local regrowth was defined as any reappearance of the tumour at the original tumour location or regional
lymph nodes. Distant metastases were defined by the presence of radiological evidence or histological confirmation of metastatic disease.

Statistical analysis

Currently, most national screening programmes start from age 50 years[10]. Therefore, patients were divided into two groups: those younger than 50 years and patients aged 50 years or more. Baseline characteristics were described. Differences were tested with c^2 tests. Statistical analyses were performed using SPSS® version 25.0 (IBM, Armonk, NY, USA). Data on all imaging modalities at baseline were combined to determine stage, with MRI as the leading modality. The reverse Kaplan–Meier method was used for calculation of median follow-up. All survival analyses were done using the Kaplan–Meier survival method in Stata® version 16.1 (StataCorp, College Station, TX, USA). Differences were assessed by means of the log rank test. Hazard ratios (HRs) and 95 per cent confidence intervals were computed using Cox regression. Patients alive and disease-free at last follow-up were censored. To evaluate overall survival, disease-specific survival, the development of local regrowth, and the development of distant metastases from the moment a cCR was diagnosed, the date of decision to watch and wait was used as starting point for all survival analyses.

Results

Of 1924 patients registered in the IWWD between 14 April 2015 and 9 April 2021, 1552 met the inclusion criteria for the present study. Median follow-up was 3.2 (i.q.r. 1.8–5.1) years. In total, 199 patients (12.8 per cent) were aged less than 50 years. Before 2011, 17.3 per cent of patients (34 of 196) were younger than 50 years, between 2011–2015 this was 11.7 per cent (69 of 592 patients), and after 2015 this was 12.6 per cent (96 of 764 patients). Baseline characteristics are shown in Table 1. Patients younger than 50 years had fewer co-morbidities and a higher T category at diagnosis. Baseline diagnostics in this group more often consisted of digital rectal examination and CEA measurement, whereas those aged 50 years and over underwent MRI of the pelvis more often. The same pattern was observed for reassessment

Table 1 Baseline characteristics

	< 50 years (n= 199)	≥ 50 years (n=1353)	P§
Age at diagnosis (years)*			
	45 (40-48, 21-49)	66 (60-73, 50-98)	
Gender			0.145
M	123 (61.8%)	907 (67.0%)	
F	76 (38.2%)	446 (33.0%)	
Comorbidity			<0.001
Yes	30 (16.9%)	453 (47.6%)	
No	148 (83.1%)	499 (52.4%)	
Unknown	21	401	
Clinical tumour category†			0.011
T0-1 ‡	-	22 (1.8%)	
T2	34 (20.5%)	349 (28.1%)	
T3	119 (71.7%)	789 (63.5%)	
T4	13 (7.8%)	82 (6.6%)	
Unknown †	33	111	
Clinical node category†			0.198
N0	54 (32.1%)	477 (37.8%)	
N1	68 (40.5%)	471 (37.4%)	
N2	46 (27.4%)	313 (24.8%)	
Unknown	31	92	

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r., range). †Information from ultrasonography, CT, and MRI combined; MRI was the leading modality in determining stage. ‡A tumour was clearly present based on imaging, or other clinical examination (such as endoscopy). §$\chi 2$ test.

after induction therapy (Table 2). Induction therapy was mandatory for inclusion in the IWWD, and the majority of patients received chemoradiotherapy. Among the patients younger than 50 years, 15 (7.5 per cent) received induction chemotherapy (7 combined with induction chemoradiotherapy and 8 with induction external beam radiotherapy). Of patients aged 50 years or more, 67 (5.0 per cent) received induction chemotherapy (34 combined with

induction chemoradiotherapy, 24 with induction external beam radiotherapy, and 9 with only induction chemotherapy).

Three- and 5-year overall survival rates were higher among young patients (97 (95 per cent c.i. 93 to 99) and 93 (86 to 96) per cent respectively) in comparison to those in the older group (93 (91 to 94) and 85 (82 to 88) per cent) (HR 2.51, 95 per cent c.i. 1.36 to 4.63; P =0.003) (Fig. 1). A statistically significant difference was no longer evident in the disease-specific survival rates in patients aged less than 50 years (98 (93–99) and 95 (88 to 98) per cent) compared with those aged 50 years or more (97 (95–98) and 92 (89–94) per cent) (HR 1.67, 0.76–3.64; P =0.199) (Fig. 2).

Table 2 Diagnostic procedures at baseline and at reassessment after induction therapy

	< 50 years (n= 199)	≥ 50 years (n=1353)	P†
Baseline			
Digital rectal examination	157 (78.9%)	946 (69.9%)	0.009
Endoscopy/rectoscopy	126 (63.3%)	805 (59.9%)	0.305
Endorectal ultrasound imaging	26 (13.1%)	200 (14.8%)	0.522
MRI of pelvis	163 (81.9%)	1201 (88.8%)	0.006
Carcinoembryonic antigen	147 (73.9%)	860 (63.6%)	0.004
Dissemination investigations*	187 (94.0%)	1221 (90.2%)	0.091
Reassessment after induction therapy			
Digital rectal examination	169 (84.9%)	978 (72.3%)	<0.001
Endoscopy/rectoscopy	180 (90.5%)	1197 (88.5%)	0.409
Endorectal ultrasound	18 (9.0%)	84 (6.2%)	0.132
MRI of pelvis	152 (76.4%)	1139 (84.2%)	0.006
Carcinoembryonic antigenCEA	76 (38.2%)	354 (26.2%)	<0.001
Dissemination investigations*	110 (55.3%)	708 (52.3%)	0.437

Values in parentheses are percentages. *At least one of the following: X-ray of thorax, CT of thorax, CT of abdomen, ultrasonography of liver, CT of liver, MRI of liver, CT of pelvis, PET. †X^2 test.

The cumulative probability of local regrowth at 3 and 5 years was 24 (18 to 31) and 25 (19 to 32) per cent respectively in patients younger than 50 years, compared with 26 (23 to 29) and 28 (25 to 31) per cent in those age 50 years or older (HR 1.09, 0.79 to 1.49; P =0.603)

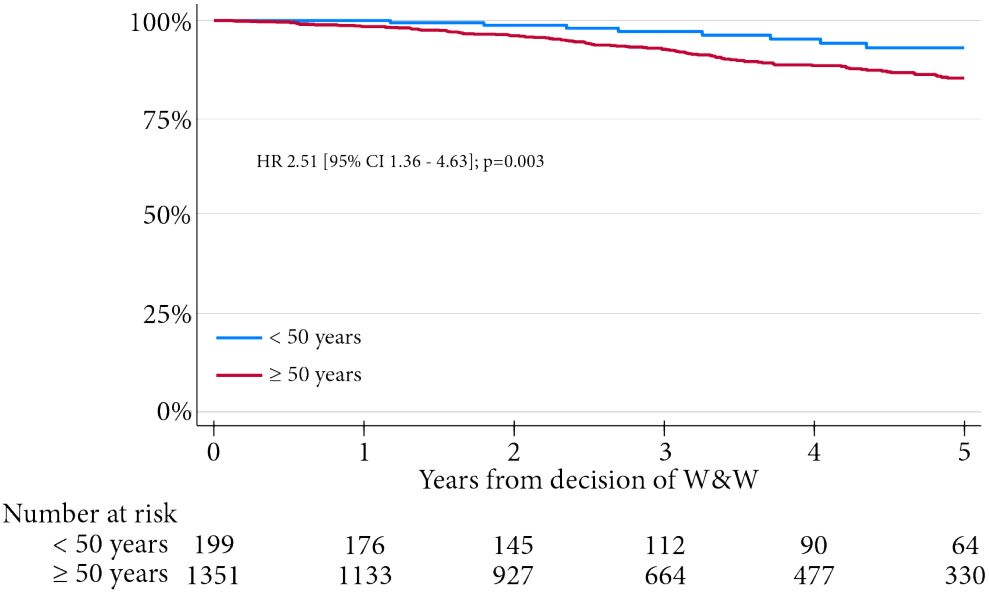

Figure 1 Overall survival after the decision to watch and wait.

P ¼ 0.003 (log rank test).

(Fig. 3). Among patients younger than 50 years who developed local regrowth, this occurred during the first 6 months, the first year, and the first 2 years in 47.7, 75.0, and 90.9 per cent respectively; respective values in the older group were 37.1, 70.8, and 90.8 per cent (Table 3). At 3 and 5 years, the cumulative probability of distant metastases was 10 (6 to 16) and 11 (7 to 17) per cent in patients younger than 50 years, and 10 (8 to 12) and 13 (10 to 15) per cent among those aged 50 years or more (HR 1.00, 0.62 to 1.62; P =0.998) (Fig. 4). At least 68.4 per cent of all distant metastases occurred in the first 2 years among patients under 50 years, compared with 62.5 per cent of those in the older group (Table 3). Of the young patients with local regrowth, 18 per cent (8 of 44) developed distant metastases, which was comparable to the 22 per cent (70 of 315) in the older group (P =0.543).

Treatment of local regrowth in 44 young patients consisted of low anterior resection in 14 patients (93 per cent R0 rate), of whom three also received chemotherapy, abdominoperineal resection in 14 (R0 rate 71 per cent), of whom one also received brachytherapy and one chemotherapy, radiotherapy, and targeted therapy. Nine patients underwent local excision

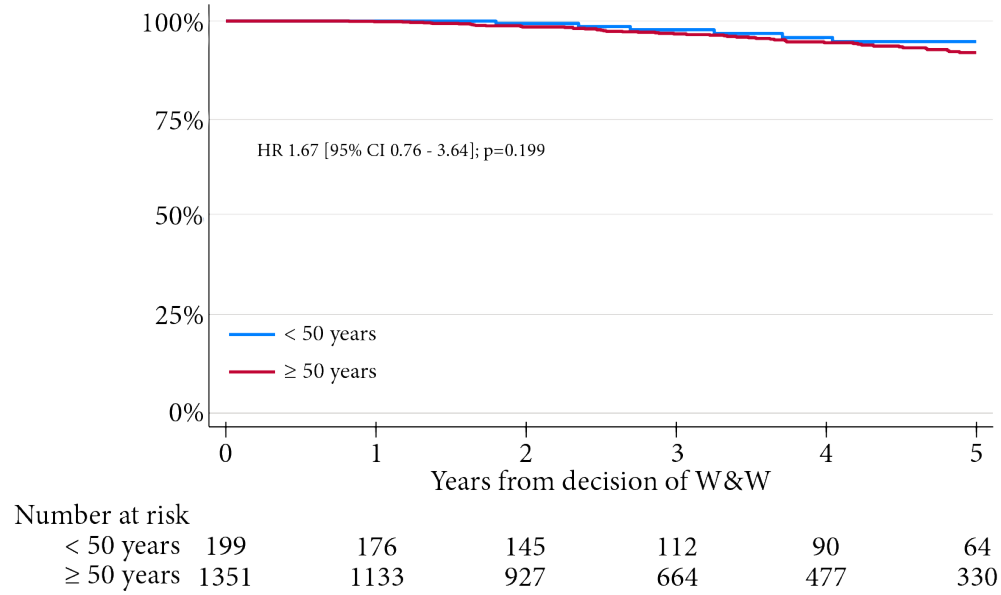

Figure 2 Disease-specific survival after the decision to watch and wait.

P ¼ 0.199 (log rank test).

(100 per cent R0 rate), two had chemotherapy only, and information regarding treatment of local regrowth was not available for five patients.

Additional analyses demonstrated that patients who were diagnosed before 2010 accounted for the difference in diagnostic procedures between patients younger than 50 years and those aged 50 years or more. The statistically significant difference disappeared in the subgroup of patients who started watch and wait in 2010 or later. All survival analyses were repeated for patients enrolled from 2010 and staged by MRI. This selection did not change the outcomes.

Discussion

The present study aimed to evaluate the outcome of a watch-and-wait strategy in patients younger than 50 years with a cCR after neoadjuvant treatment, compared with outcomes in patients aged 50 years or more. Based on current data from patients in the IWWD, the young patients had comparable disease-specific survival, and a risk of local regrowth and distant metastases similar to that of older patients undergoing watch and wait.

Table 3 Oncological outcomes

	< 50 years (n= 199)		≥ 50 years (n=1353)		P
Follow-up after decision to watch and wait (years)*	3.5	(2.9-4.2)	3.1	(3.0-3.3)	
Alive at end of registered follow-up					0.016
Yes	188	(94.5%)	1203	(88.9%)	
No	11	(5.5%)	152	(11.2%)	
Local regrowth †					0.715
Yes	44	(22.1%)	315	(23.3%)	
Within 6 months	21/44	(48%)	117/315	(37%)	
Within 7-12 months	12/44	(27%)	106/315	(34%)	
Within 13-24 months	7/44	(16%)	63/315	(20%)	
After 2 years	4/44	(9%)	28/315	(9%)	
Timing unknown	0	(0%)	1/315	(<1%)	
No	155	(77.9%)	1038	(76.7%)	
Distant metastases †					0.754
Yes	19	(9.5%)	120	(8.9%)	
Within 12 months	8/19	(42%)	43/120	(36%)	
Within 13-24 months	5/19	(26%)	32/120	(27%)	
After 2 years	0	(0%)	6/120	(5%)	
Timing unknown	6/19	(32%)	39/120	(32%)	
No	180	(90.5%)	1233	(91.1%)	

Values in parentheses are percentages unless indicated otherwise; *values are median (95 per cent c.i.). †Time calculated from decision to watch and wait. ‡X^2 test.

In line with the present findings, young patients often present with more advanced disease stage at diagnosis, more aggressive tumours, and unfavourable histopathological features[11]. As colorectal cancer is often perceived as a disease of the elderly, this now-frequent diagnosis in young patients may be overlooked by both patients and physicians. Young patients wait longer before the initial symptoms lead them to search for a healthcare provider. In addition, the duration of diagnostic evaluation is longer for young compared with older patients[11,12] owing to a low level of suspicion of malignancy. Symptoms as rectal blood loss are frequently

ascribed to benign conditions such as haemorrhoids. In this study, patients younger than 50 years less often underwent diagnostic MRI of the pelvis, currently the most important staging modality[13]. However, this did not appear to affect survival compared with that of patients aged over 50 years. National screening programmes are helpful in identifying tumours at an early, asymptomatic stage. However, as the minimum age for inclusion in a national screening programme is 50 years in general, this will not help in identifying young-onset rectal cancer[10]. Zaborowski and colleagues[4] evaluated cancer-specific outcomes of patients with stage III or high-risk stage II rectal cancer, treated with neoadjuvant long-course chemoradiotherapy, total mesorectal excision, and optional postoperative chemotherapy, and compared patients younger than 50 years with those aged 50 years or older. Although young patients were more often diagnosed with stage III disease and more often received neoadjuvant and postoperative therapy, disease-free survival rates at 1, 3, and 5 years were similar in the two age groups: 96, 87, and 81 per cent in the younger group, and 95, 85, and 81 per cent in the older group (P =0.711); this is consistent with the present findings. Nevertheless, the present cohort had

Figure 3 Development of local regrowth after the decision to watch and wait.

P ¼ 0.603 (log rank test).

favourable tumour biology as the patients responded well to neoadjuvant treatment, and were even capable of obtaining a cCR. Patients with a cCR have better overall survival, comparable to that of patients with a pCR.

Offering watch and wait to patients with a cCR after neoadjuvant treatment is very appealing. Nonetheless, there might be an additional oncological risk, which is not yet entirely known. In a systematic review and meta-analysis, Socha and co-workers[14] calculated that patients treated according to a watch-and-wait strategy have a risk of developing distant metastases of between 0 and 6.5 per cent owing to the omission of immediate surgery. However, they suggested that the maximum risk of 6.5 per cent might be overestimated because of assumptions made in the calculation. In a pooled analysis of patients with a pCR after chemoradiation for rectal cancer, Maas et al.[5] reported a 5-year distant metastasis-free survival rate of 89 per cent. This is close to the risk of distant metastases found in the present study. It is likely that the additional risk of distant metastases resulting from omission of immediate surgery is very small. In the present study, the risk of metastases was similar in both age groups, despite a higher T category at initial diagnosis among younger patients. Achieving a cCR after neoadjuvant therapy may be a stronger prognostic factor than baseline stage on MRI. A recent study[15] has shown that, when patients have a sustained cCR for 3 years, the probability of developing local regrowth or distant metastases is less than 3 per cent.

For young patients, considerations regarding the choice of surgery or organ preservation by watch and wait may be different from those for the elderly. Postoperative morbidity and mortality rates are lower in young patients, favouring surgery[16]. Therefore, it feels more logical to operate on these patients as surgery provides more oncological certainty. However, urinary and sexual dysfunction can seriously affect quality of life for an excess of life-years, which may be highly relevant for younger patients. In addition, patients managed by a watch-and-wait strategy have a significantly better 3-year colostomy-free survival rate than those who undergo immediate surgery[8]. Having a stoma can affect body image and lead to less self-confidence because of the shame and fear of being stigmatized by others. In contrast, specific to young patients is that they may have children who are still emotionally and financially dependent on them. It is known that the patient's quality of life can also influence the quality of life of their family[17]. As there is no histological confirmation of tumour response with a watch-and-

wait policy, the inherent uncertainty about residual disease might reduce patients' willingness to take risks. However, with 3-monthly follow-up, which was considered acceptable by 95 per cent of patients a study by Gani and colleagues[18], 83 per cent of patients would consider deferral of surgery in the event of a cCR. Moreover, 94 per cent of patients would accept a local regrowth risk of 25 per cent, especially when facing permanent colostomy as an alternative. Kennedy and colleagues[19] found that patients were willing to accept a 20 per cent absolute increase in local regrowth and a 20 per cent absolute decrease in overall survival (from 80 to 60 per cent) if that would mean organ preservation instead of major surgery. In contrast, medical physicians were willing to accept a 5 per cent absolute increase in local regrowth and decrease in overall survival. This highly reflects the difference in point of view between patients and their treating physicians. Patients are willing to accept a higher oncological risk as they have other priorities. The option of watch and wait should, therefore, be discussed with the patient in a shared decision-making setting. It has been demonstrated that better understanding of a patient's situation after appropriate provision of information will help the patient to cope with cancer, and reduces stress, anxiety, and depression. This improved mental health also translates into better quality of life[20].

A few limitations should be taken into account when interpreting the present results. The IWWD provides data on patients treated according to a watch-and-wait strategy in many centres worldwide. However, this also led to considerable variability between participating centres in baseline characteristics, neoadjuvant therapy, and imaging strategies[9]. Also important, it is unclear how many patients with young-onset rectal cancer with a cCR were actually treated according to a watch-and-wait strategy, possibly introducing a selection bias. The IWWD does not provide information on how many patients with or without a cCR were actually treated in each centre. Patients with late-onset rectal cancer could have been offered watch and wait in a more liberal fashion (owing to the high risk of postoperative morbidity/mortality), whereas patients with young-onset rectal cancer could have been selected more strictly. Another limitation could be the absence of baseline information regarding microsatellite stability status. It could be argued that a large population of patients aged below 50 years could actually represent those with microsatellite stability-high status/Lynch syndrome[4], a subgroup of cancers with distinct biological behaviour. In addition, no

information on functional outcome and quality of life was available in the IWWD, although this is thought to be an important consideration for patients younger than 50 years when deciding on either organ preservation or surgery. It should also be kept in mind that the IWWD includes patients who started watch and wait in 1991. Over time, assessment modalities and neoadjuvant treatment strategies have evolved substantially, which might have influenced oncological outcomes. Nevertheless, the IWWD is a proper reflection of real-world clinical practice.

The present analysis of oncological outcomes of a watch-and-wait strategy in patients younger than 50 years compared with older patients has highlighted aspects of proposing watch and wait in young-onset rectal cancer from different angles. Although patient preferences and concerns regarding different aspects will vary widely, the authors strongly believe that the possibility of organ preservation should always be discussed, even in young patients who have a longer life expectancy. They should be able to make their own decisions based on well founded information. Wishes and expectations of patients in the context of their future,

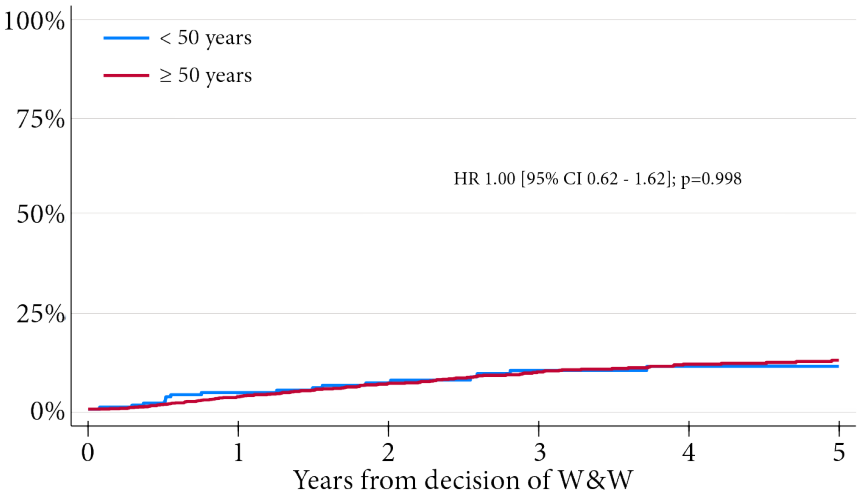

Figure 4 Development of distant metastases after the decision to watch and wait

P ¼ 0.998 (log rank test).

taking into consideration their social life, family, career, and quality of life, should be discussed openly, enabling patients to make a well considered decision. However, it is critical that watch and wait is practised in a dedicated centre with the expertise to make a careful risk assessment and where sufficient follow-up modalities are available to ensure high quality of care.

When a cCR is determined after neoadjuvant treatment for rectal cancer, offering watch and wait as a treatment option may be consistent with the values and preferences of patients. There is no difference in oncological risk between young patients and older ones, so there should not be a reason to dissuade young patients from an organ-preserving treatment. A watch-and-wait strategy should certainly be considered and at least be discussed with the patient.

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Summary, general discussion and future perspectives

Summary, general discussion and future perspectives

Summary

For **chapters 2 and 3**, population-based data from the national cancer registries of Belgium, the Netherlands, Norway, and Sweden were collected. Between January 2007 and December 2016, 314,062 patients were diagnosed with stage I-III colon or rectal cancer. Data were analysed of all adult patients undergoing surgical treatment, which was defined as surgical removal of the tumour-bearing bowel segment, irrespective of curative or palliative intent. The inclusion criteria were met by 53,071 patients from Belgium (64.3%), 88,784 patients from the Netherlands (66.9%), 25,548 patients from Norway (64.3%) and 38,621 patients from Sweden (66.1%). Patients were divided into three age categories: <65 years, 65-74 years, and ≥75 years.

In **chapter 2** treatment strategies and 30-day and one-year mortality were compared. In all countries, the use of chemotherapy increased with stage and decreased with age. Patients with colon cancer in Belgium were more often treated with adjuvant chemotherapy. Patients with rectal cancer in the Netherlands and Sweden were more likely to receive neoadjuvant radiotherapy, while patients in Belgium and Norway were more frequently treated with neoadjuvant chemoradiotherapy. Moreover, in Belgium, and to a lesser extent in Sweden, treatment was frequently complemented with adjuvant chemotherapy. In all countries, 30-day and one-year excess mortality decreased over the years for colon and rectal cancer. The one-year expected mortality remained stable over the years and was comparable for the investigated countries. Despite more often (neo)adjuvant therapy in Belgium, the excess mortality for older patients with colon or rectal cancer was interestingly enough higher than in the other countries. This may suggest the possibility of overtreatment. Patients in the youngest age category had comparable one-year mortality with different treatment strategies implying the high compensating abilities of younger patients.

Using the same dataset, conditional one-year relative survival was evaluated in **chapter 3** to investigate whether age-related differences disappeared after surviving the first postoperative year as this would confirm the importance of the first postoperative year. The evident decline in survival of older patients during the first year after surgery was most notable in Belgium, followed by the Netherlands, and least in Norway and Sweden. After surviving the first postoperative year, the survival of surgically treated older patients aligned with their younger

counterparts (< 65 years), except for patients with stage III disease. The survival gap between young and older patients after surgical resection for colon and rectal cancer remains largely based on early (first year) mortality.
The key to bridging this survival gap between young and older patients would be balancing under- and overtreatment, especially for patients with stage III disease with a focus on preventing early mortality.

The following chapters focus on patients with rectal cancer.

The RAPIDO trial included 920 patients with locally advanced rectal cancer and at least one of the following high-risk criteria: clinical tumour [cT] stage cT4a or cT4b, extramural vascular invasion, clinical nodal [cN] stage cN2, involved mesorectal fascia, or enlarged lateral lymph nodes. Of the 912 eligible patients, 462 received the experimental treatment (short-course radiotherapy (5x5 Gy) followed by 18 weeks of chemotherapy (six cycles of CAPOX or nine cycles of FOLFOX4) followed by total mesorectal excision within 2-4 weeks) and 450 patients received standard-care treatment (long-course chemoradiotherapy (28 x 1.8 Gy or 25 x 2.0 Gy, with concomitant twice-daily oral capecitabine followed by total mesorectal excision within 6-10 weeks and optional adjuvant chemotherapy). **Chapter 4** describes the results of the analyses of the primary endpoint Disease-related Treatment Failure (DRTF), defined as the first occurrence of locoregional failure, distant metastasis, a new primary colorectal tumour, or treatment-related death. Locoregional failure included locally progressive disease leading to an unresectable tumour, local R2 resection, or local recurrence after an R0–R1 resection. After a median follow-up of 4·6 years (IQR 3.5–5.5), the cumulative probability of DRTF decreased from 30% in the standard-care group to 24% in the experimental group at 3 years after randomisation, mainly due to a decrease in distant metastases. **Chapter 5** focuses on differences in metastatic pattern between the two treatment groups. A changed metastatic pattern with less metastases due to less liver metastases in the experimental treatment was observed. The decrease in distant metastases is probably due to better compliance preoperatively and perhaps due the earlier treatment of micrometastases in the treatment process. A hospital policy for adjuvant chemotherapy did not influence the development of

distant metastases. Although patients with distant metastases in the experimental group had worse survival compared to patients in the standard-care group, the cumulative probability of overall survival remained comparable for both treatment groups; 82% in the experimental group and 80% in the standard-care group (HR 0.91 [95%CI 0.70-1.19];P=0.50), at five years after randomisation.

In addition, with the experimental RAPIDO treatment, the pathological complete response rate doubled from 14% to 28%. If the patients with a complete response can be identified during reassessment after neoadjuvant therapy, surgery may be omitted. As reported in **chapter 6**, a Watch-and-Wait strategy (W&W) after a clinical complete response with an appropriate follow-up has no additional oncological risk in young patients (younger than 50 years) compared to older patients. This opens the door for potential organ preservation. Therefore, W&W should be considered and at least be discussed with the patients with a clinical complete response.

General discussion and future perspectives

For a long period, the oncological outcome for patients with rectal cancer was inferior compared to patients with colon cancer due to inadequate staging, blunt dissection and therefore irradical resections and a high locoregional failure. As the result of standardisation of total mesorectal excision (TME), improved staging and therewith more targeted neoadjuvant therapy, the local recurrence rate for rectal cancer has decreased and survival for colon and rectal cancer has become comparable (figure 2 – chapter 1). After the improvement of locoregional control, distant metastases have become the main cause of treatment failure. Key challenges for the next decade are prolongation of survival by preventing distant metastases and improvement of the patients' quality of life.

Surgery – Minimally invasive surgery

Although laparoscopic surgery has been successfully introduced in the past decade, minimally invasive surgery is still developing. Robotic assistance has the potential to overcome some of the limitations of laparoscopic surgery, providing a three-dimensional depth of field, effective counter traction with articulating motion, tremor elimination, a stable camera platform, and

improved ergonomics for the surgeon. It has been actively applied to surgery performed in narrow spaces where the benefits of a surgical robotic system can be maximized, such as the pelvic cavity. In the field of colorectal surgery, the development of robotic surgery has mainly focused on rectal surgery. Colon cancer surgery is mainly performed in a wide abdominal cavity, so the advantage of robotic technology compared to laparoscopy is not particularly evident.[1]

A concern of robotic surgery is the significantly longer operation time. Even after going through the learning curve,[2] little gain will be made as additional time is required for docking the robotic arms. Moreover, robotic surgery allows for more precise movements which also takes time.[1] Regarding surgical outcome, there is no difference in the overall conversion rates, but in obese patients and male patients with low rectal cancer in the ROLARR trial, the conversion rate was significantly lower with robotic surgery.[3] The first results on pathological and oncological outcomes show similarities between robotic and laparoscopic surgery.[3] However, more studies reporting on oncologic outcomes after robotic surgery are awaited. As a result of the more precise surgery less urogenital and sexual dysfunction seems reasonable. However, to date, the superiority of robotic surgery in terms of functional outcomes remains controversial as it is not only affected by nerve injury during surgery but also by radiotherapy.[1,4,5]

Surgery - Image guided surgery

The implementation of minimally invasive surgery requires improvement of optical systems as optimal tactile feedback lacks. Visualisation techniques such as near-infrared fluorescence using indocyanine green can be very useful. It can provide imaging of the tumour, sentinel lymph node, distant metastases (peritoneal and liver, lung and brain are being investigated), vital structures, and perfusion.[6] Poor perfusion of the anastomosis is a risk factor for anastomotic leakage as complete anastomosis healing requires adequate perfusion. Using indocyanine green, vascular perfusion at the anastomotic site can be assessed to determine the optimal site for the anastomosis.[7] The phase III AVOID trial aims to include almost 1000 patients to investigate the role of indocyanine green in a randomised controlled setting. It is hypothesised that intraoperative assessment of bowel perfusion using near-infrared

fluorescence imaging with indocyanine green will lower the incidence of clinically relevant anastomotic leakage within 90 days after colorectal resection.[8]

Surgery - Prehabilitation

On the same note, identification of preoperative risk factors for complications or impaired recovery after surgery has given rise to different prehabilitation programmes, conveying the impression of improved postoperative outcome.[9,10] The goal is to boost the functional capacity of patients before surgery and includes enhancing physical performance and nutritional status. Meantime, focusing on getting as fit and strong as possible before surgery can also help prepare mentally for the treatment and thus contribute to patient empowerment. Especially patients who qualify for neoadjuvant treatment can use this time to invest in improving their physical status. Medical prehabilitation also includes the management and optimisation of comorbidities, such as diabetes and cardiovascular disease, likewise the promotion of smoking cessation. In the future, more emphasis should be placed on patient-specific risk factors during prehabilition. In a randomized blinded controlled trial, physical endurance training and promotion of physical activity of patients older than 70 years, ASA III-IV, reduced the number of patients with postoperative complications by 51%.[11] This indicates that preoperative care should be patient specific, targeting appropriate risk factors. Results of two randomised controlled trials are awaited. One, on whether multimodal prehabilitation could enhance postoperative outcomes.[12] The other, a three-way randomisation, also investigating the difference between hospital-supervised and home-supported exercise.[13]

Peri-operative treatment - Neoadjuvant and adjuvant treatment

In the field of rectal cancer bringing forward systemic chemotherapy has been successful as demonstrated by the RAPIDO trial. Traditionally, systemic chemotherapy was offered after surgery for rectal cancer. However, the evidence on its benefits after surgery is inconclusive if neoadjuvant radiotherapy and high-quality surgery are carried out.[14,15] Moving systemic chemotherapy from the adjuvant to the neoadjuvant setting ensures better compliance as demonstrated by the RAPIDO trial.[16] Besides, delayed surgery after radiotherapy is considered safe and creates an opportunity window that encourages the delivery of sequential neoadjuvant

chemotherapy and targeting micrometastases early and therewith more efficiently.[17,18]

The RAPIDO trial [19] the PRODIGE-23 trial [20] both demonstrate that total neoadjuvant treatment (TNT) reduces the risk of distant metastases and doubles complete response rates, creating the opportunity for organ preservation which will be explained later. The Polish-II trial initially showed a survival advantage after three years when patients were treated with TNT that disappeared after eight years of follow-up.[21,22] The RAPIDO and PRODIGE-23 trial [20] also showed no improvement in overall survival.[19] However, none of the trials were powered to address this question. The STELLAR trial, on the contrary, found a survival advantage at three years of patients treated with short-course radiotherapy followed by four cycles of chemotherapy compared to patients treated with long-course chemoradiotherapy (75% versus 87%; P=0.033).[23]

With all these developments, an important question arises: what would be the optimal duration of chemotherapy? Should this be continued for 18 weeks as in the RAPIDO trial, or could a shorter duration be equally effective? In the adjuvant setting of colon cancer, 12 weeks of oxaliplatin-based chemotherapy is non-inferior to 24 weeks of the same treatment for most patients with stage III colon cancer.[24] A prospective study enrolled 259 patients with stage II-III rectal cancer into four sequential treatment arms. In one arm only chemoradiotherapy was given, in the other three chemoradiotherapy was followed by 2, 4 or 6 cycles of chemotherapy (mFOLFOX6).[25] The pathological complete response rate was directly proportional to the number of chemotherapy cycles (18%-25%-30%-38%). It remains questionable whether the chemotherapy was solely responsible for the higher pCR rate. The results might have been largely influenced by the longer interval between radiotherapy and surgery. This is a highly relevant and interesting topic as the increasing number of chemotherapy cycles is accompanied by an equivalent rise in toxicity. Within the RAPIDO trial (18 weeks of chemotherapy), 48% of patients in the experimental group experienced adverse events grade III or higher. In the standard-care group, this was 25% of patients during neoadjuvant treatment with chemoradiotherapy only and 34% in patients who received adjuvant chemotherapy (24 weeks). The Polish II trial reported 23% grade III-IV adverse events in the group with short-course radiotherapy followed by three weeks of chemotherapy, and 21% in the group treated with chemoradiotherapy only. Optimising treatment and finding a good balance in the right

amount of treatment with minimal unnecessary side effects remains a challenge.

For patients with stage III colon cancer, adjuvant chemotherapy has gradually been implemented as the standard of care from the first trial [26] investigating it and is associated with improved survival.[27] However, R0 resection is not always possible in patients with locally advanced colon cancer.[28] Given the success in rectal cancer, curiosity was aroused whether neoadjuvant chemotherapy would be a feasible treatment option for inoperable colon cancer. Growing evidence supports the oncological benefit of neoadjuvant chemotherapy in the treatment of locally advanced colon cancer as it seems to be safe, leads to tumour downstaging and an increase in R0 resection rate.[29]

Peri-operative treatment - Organ preservation

Patients with a pathological complete response (pCR) after neoadjuvant therapy have a favourable oncological outcome with a low risk of local or distant recurrences.[30] As there is no longer evidence of tumour or involved lymph nodes, rectal resection could be considered overtreatment for this subgroup. To avoid potentially unnecessary surgery, a strict surveillance strategy was developed refraining patients with a clinical complete response (cCR) from surgery. For these selected patients this Watch-and-Wait strategy (W&W) as a form of organ preservation is nowadays increasingly being utilised as a treatment option. Different cohort series from all over the world have been published, confirming the oncological safety and feasibility of W&W.[31-34]

A challenge of W&W is to accurately identify patients with a complete response who can safely avoid surgery. MRI provides additional information next to traditional endoscopy but is hampered by the difficulty of distinguishing fibrosis from a viable tumour, often leading to incorrectly classifying fibrosis as residual tumour.[35,36] Fluorescent tumour labelling of patients after neoadjuvant treatment is currently being investigated, preliminary results show that visualisation using this technique can distinguish residual tumour from normal rectal tissue and fibrosis. It improves staging by 16% compared to standard MRI and white-light endoscopy.[37] Fluorescence labelling and imaging could therefore be incorporated, after research on a larger scale, into the decision-making process of patients with rectal cancer who qualify for organ preservation.

Another challenge of W&W constitutes the optimal timing for determining the achievement of a cCR. Tumour response to treatment is a dynamic phenomenon affected by tumour size, histology, biology, treatment strategy and the time interval from neoadjuvant treatment. The first follow-up assessments typically occur 6–8 weeks after completion of neoadjuvant treatment. It is important to find a balance between a time period where is it oncologically safe and meaningful to wait before assessing tumour response and on the other hand waiting too long before identifying poor responders where it could be oncological hazardous. For the latter group, surgery should be offered immediately after restaging. An interim assessment during prolonged total neoadjuvant therapy could be advocated, especially because these patients have a significantly higher risk of distant metastases compared to patients with a good response.[38] Another subgroup contains patients with a near-complete response after the first restaging. Proponents of a W&W strategy advocate that waiting beyond 16 weeks could be beneficial when patients have a near-complete response. Patients with a more advanced T status (T3b-d/T4) may take longer to achieve a cCR than those with T2/T3a tumours.[39] The OPAXX trial is investigating whether these patients would benefit from a boost of contact brachytherapy or extending the waiting interval by 6 weeks and potential local excision.[40]
Different organ preservation strategies, using different neoadjuvant treatments and follow-up schedules might complicate the assessment of the clinical value and safety of W&W. Consensus on treatment and follow up schedules is key to facilitate accurate comparisons of data from ongoing and future organ preservation trials. In December 2021, international consensus recommendations on key outcome measures for organ preservation after (chemo) radiotherapy in patients with rectal cancer were published.[38] 88% of all local regrowth is diagnosed in the first two years, and 97% of local regrowth is located in the bowel wall.[34] Regarding follow-up, a five-year follow-up is advised including serum carcinoembryonic antigen testing (every 3 months the first 3 years, year 4-5 every 6 months), digital rectal examination, endoscopy and pelvic MRI (every 3 months the first 2 years, year 3-5 every 6 months). For the follow-up of distant metastases chest and abdominal CT is advised annually (first year every 6 months).[38] Analyses of data from the International Watch and Wait Database showed that the probability of remaining local-regrowth-free for an additional 2 years after a sustained cCR of 1 year or 3 years was 88.1% and 97.3%, respectively. With these results,

the intensity of active surveillance could theoretically be reduced if patients maintain a cCR within the first 3 years.[41]

Peri-operative treatment - Immunotherapy

In recent years, the tumour microenvironment has emerged as an important source of potential therapeutic targets. Immune dysfunction caused by immunosuppression or autoimmune disease is associated with a high incidence of various cancers. Immunotherapy is an emerging tumour treatment, it can eliminate tumour cells and inhibit tumour growth and metastases by activating the immune system.[42] Immune checkpoint inhibitors (ICIs), such as ipilimumab (anti- CTLA-4 antibody), nivolumab (anti-PD-L1 antibody), toripalimab (anti-PD-L1 antibody) and atezolizumab (anti-PD-L1 antibody) are the most common. Microsatellite instability (MSI) is the result of the accumulation of nucleotide insertions or deletions in the genome. MSI can be divided into microsatellite instability-high (MSI-H) or microsatellite instability-low/microsatellite-stable (MSS).[43] The MSI-H group accounts for 15% of all colorectal cases and is characterized by defects in the DNA mismatch repair program. At present, immunotherapy with an ICI has only proven effective for patients with MSI-H [44] and seems predictive for the benefit of postoperative chemotherapy in stage III colon cancer.[45] Recently, the use of a an anti–PD-1 monoclonal antibody – dostarlimab - was investigated in a phase II study in mismatch repair deficient (MSI-H) LARC. All 12 patients developed a clinical complete response. No patients had received chemoradiotherapy or undergone surgery, and no cases of progression or recurrence had been reported during follow-up (range 6 to 25 months). In addition, no adverse events of grade 3 or higher have been reported.[46] The NICHE trial [47] combined immunotherapy (nivolumab and ipilimumab) with the cyclooxygenase (COX)-2 inhibitor celecoxib in patients with stage I-III colon cancer. The first results showed a 100% (20/20) complete response in patients with MSI and 27% (4/15) in patients with MSS. A promising outcome given that 85% of all patients with non-metastasised colon cancer are MMS.[47] Preclinical data suggest that celecoxib increases tumour-promoting inflammation.[48] Reversing the inhibitory immune microenvironment and improving the immunotherapeutic sensitivity of MSS patients has become an urgent task.[49] Radiotherapy is also responsible for increasing the expression of immune checkpoints. The

release of immune-stimulating signals and neoantigens following radiotherapy induces profound changes in the tumour microenvironment and promotes anti-tumour immune responses that could be enhanced by systemic immune-stimulating agents. Because of the differences in the dynamic progression of immunological responses upon radiotherapy and immune checkpoint inhibitors, it might be important to determine the most effective sequence of treatments. Radiation before immunotherapy can produce more tumour neoantigens to promote the effects of subsequent immunotherapy. On the other hand, the use of immunotherapy can change the microenvironment of tumours to promote the effects of radiotherapy.[50] TORCH [51], a randomized, multicentre, phase II trial investigates the correct sequence in patients with locally advanced rectal cancer. Their consolidation arm consists of short-course radiotherapy followed after two weeks by 18 weeks of CAPOX and toripalimab, whereas their induction arm consists of six weeks of CAPOX and toripalimab, followed by short-course radiotherapy and is completed after two weeks with 12 weeks of CAPOX and toripalimab. Patients will be reassessed 2-4 weeks after completion of the neoadjuvant therapy and will, depending on the results, start a W&W or undergo surgery. The first results are expected in 2023.[51]

Prevention - Population screening

Most national screening strategies use the faecal immunochemical test.[52] Participants are invited to collect a faeces sample at home and return it by mail. Individuals with a positive test outcome are referred for diagnostic colonoscopy. In the Netherlands in 2020, 1.2% of participants had a (pre)cancerous lesion. Partly as a result of the screening, the mortality from colon and rectal cancer in the Netherlands has been reduced.[53] Other, less invasive methods are also being investigated for screening, for example volatile organic compounds (VOC), which are present in various excreted biological materials. VOC are the final products of cellular metabolism probably produced by the oxidative stress of cell-membranes as a consequence of gene or protein alterations in cancer cells. These metabolites are released into the blood stream and excreted.[54] Analyses of breath samples suggest that VOC detection with sensor technology could have comparable or even better accuracy for colon and rectal cancer detection and possibly also precancerous lesion detection than the currently recommended

FIT test.[55]

Prevention - Early tumours

With the emergence of population screening, tumours will more often be detected in a lower, asymptomatic stage.[56] As a result, in the coming years a lot of focus will be on early - cT-3N0M0 - tumours. Standard treatment now includes immediate TME surgery. However, the success of organ preservation in tumours with a cCR after clearly indicated neoadjuvant therapy has prompted a desire to introduce organ preservation for early-stage tumours as well. Moreover, it is also a good alternative for patients who are considered not fit for surgery. Avoiding surgery can provide important benefits such as reduced morbidity, a better quality of life, 2,5 times lower health care costs, and most importantly, oncological outcomes seem not to be compromised.[57,58]

When patients with these early tumours are pre-treated with (chemo)radiotherapy, restaging is performed 6–8 weeks thereafter. This could have three possible outcomes: (1) a cCR after which strict surveillance such as the earlier described W&W could be started, (2) a good response with sufficient downstaging after which a local excision can be performed to remove residual tumour, and option (3) no or a bad response, which means that the patient still has to undergo surgery.

The GRECCAR-2 trial [59] confirmed that local excision instead of surgery after downstaged early rectal cancer is equally feasible in terms of oncological outcome. There was no difference between the local excision and total mesorectal excision groups in 5-year local recurrence (7% vs 7%), metastatic disease (18% vs 19%), overall survival (84% vs 82%) and disease-free survival (70% vs 72%).[59] In the phase II CARTS study [4] patients were treated with neoadjuvant chemoradiotherapy followed by local excision in case of good or complete response. In case of a bad or no response, they were assigned to surgery. Oncological outcomes of the whole group at 5 years were a local recurrence rate of 8%, disease-free survival of 82% and overall survival of 83%. Of patients with successful organ preservation major, minor, and no low anterior resection syndrome (LARS) symptoms were experienced in 50%, 28%, and 22%, respectively. However, one-third of the included patients still needed surgery and were overtreated by chemoradiotherapy.[4]

In the STAR-TREC study [60], shared-decision making is being embraced. Patients with cT1-3N0M0 rectal cancer can choose immediate TME surgery (standard treatment), or opt for randomization between short-course radiotherapy or chemoradiotherapy in an attempt to determine the ideal treatment for inducing optimal response while simultaneously aiming to identify the treatment with the least treatment-related toxicity. 11-13 weeks after the start of treatment, response assessment will take place, patients with a poor response are immediately referred for surgery. The remaining patients will have a second reassessment 16-20 weeks after starting treatment. Patients with an incomplete response will receive local excision (and possibly TME surgery if necessary) and patients with a cCR will be followed with a W&W. The results are awaited.

The gain of strict surveillance instead of major surgery after achieving a cCR is clear in patients with a solid indication for neoadjuvant therapy but adding radiotherapy when not strictly necessary is debatable. The addition of radiation to treatment is associated with increased toxic effects. The risk of bowel dysfunction is increased in irradiated patients compared to patients undergoing surgery alone.[61] In addition, anorectal functions after neoadjuvant radiotherapy and local excision may be worse than expected. Irradiation of the rectum is known to cause injury to the rectal wall and related autonomic nerves resulting in impaired long-term functional outcomes.[5] However, it is often difficult to differentiate between radiation and surgery-induced damage. A recent study showed that after a median follow-up of two years, one-third of patients with W&W still experience major LARS complaints, with the most frequent complaints being clustering of defaecation and faecal urgency.[62] Although a cCR occurs more often in patients with lower tumour stages, patients who respond poorly to neoadjuvant treatment could be overtreated as they still need rectal surgery. These patients will endure the downsides of neoadjuvant treatment and surgery without having any benefit. In addition, there is evidence that radiation might cause impaired wound healing. Careful selection of patients is very important but at the same time also the biggest challenge. New developments in selecting patients who will most likely respond are extremely valuable, such as the use of zebrafish avatars. By injecting tumour cells, obtained from the diagnostic tumour biopsy, into zebrafish who are then exposed to radiation, we will be able to distinguish radiosensitive from radioresistant tumours within 12 days.[63] This information can be taken

into consideration during the multidisciplinary meetings where the optimal treatment for each individual patient is discussed.

Prevention – Lifestyle

Although the developments in the field of treating colon and rectal cancer are exceptional, there is no doubt that the ideal approach is prevention of the disease itself. A Western, sedentary lifestyle with a high-caloric diet including high consumption of processed or red meats and sugar, leading to type II diabetes and obesity, increases the risk of colon cancer. In addition, alcohol and tobacco use, often associated with this lifestyle, contribute negatively.[64] Although the overall relation between physical activity and the risk of colon cancer is clear, the opposite is true for rectal cancer, no association has been found.[65] Nevertheless, educating people and actively promoting a healthy lifestyle is very important. From an early age, this self-awareness should be advocated. The consumption of fruit, vegetables and a fibre-rich diet should be promoted along with encouraging more physical activity. Examples of this are the introduction of healthy lunches and snacks at schools and work, at an affordable price or even funded by the government. Next to education, affordability is crucial. Healthy food happens to be a lot more expensive. The right approach would be not by making unhealthy products more expensive, but by making healthy food more affordable. Physical activity should also be made more attractive. More importantly, it should be prioritised by people of all levels of socioeconomic status. In this area, it might help by promoting physical activity as a social occasion, a joint activity, rather than an obligation. The importance of motivating and helping patients to cope with these unhealthy lifestyle habits is still meaningful whatsoever after the diagnosis of colon or rectal cancer. Physical activity and a healthy diet also have a favourable influence on healing capacity and rehabilitation. More benefits can be expected when started early. It is also effective to fight common cancer symptoms such as fatigue and could improve quality of life as a result of patient empowerment. When a healthy lifestyle is started after diagnosis, its effect on tumour control is indistinct. However, health gains are still obtained since it has proven to reduce all-cause mortality.[66]

Prevention – Health-care costs

In addition, prevention will be of great importance to maintain a sustainable and affordable health-care system. In the coming years, a large increase in health-care cost is expected, partly due to the aging population. Although cancer can occur in the younger patient, it is mainly a disease of the elderly. However, developments in oncological treatment are also responsible for the rising costs. [67]

Altogether

In contemporary medicine, the patient is the centre of the treatment. All aspects, from an attempt at prevention to diagnosing the tumour as early as possible and as accurately as possible from cellular to macroscopic level, have led to optimisation of treatment for colon and rectal cancer. Different (medical) disciplines have joined strengths to compose the most appropriate treatment for each individual patient, taking into account tumour characteristics and patient preferences, balancing between under-and overtreatment. Many steps have already been taken with shared decision making. It is important not only to decide together about the treatment but to delve into what the patient really wants. Perhaps other endpoints will become more important than the well-known oncological endpoints such as overall survival and recurrence.[68] Quality of life has also priority for many patients. In this, an open discussion with the patient is key. After all, every patient deserves a tailored treatment as cancer is as unique as the person fighting it.

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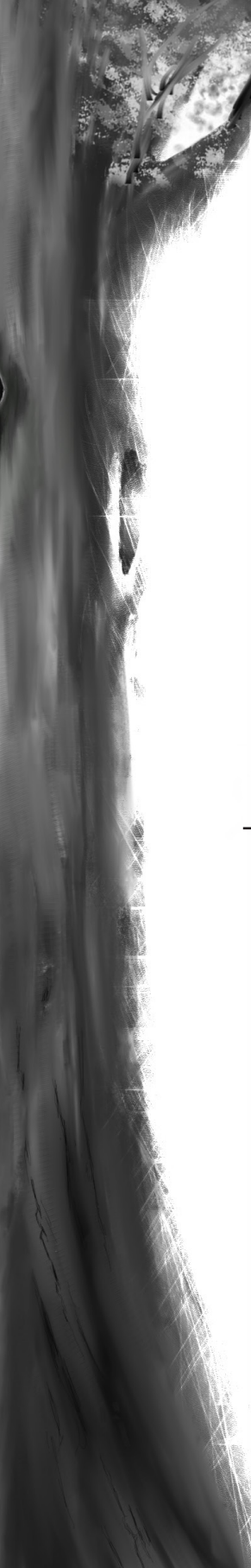
APPENDICES



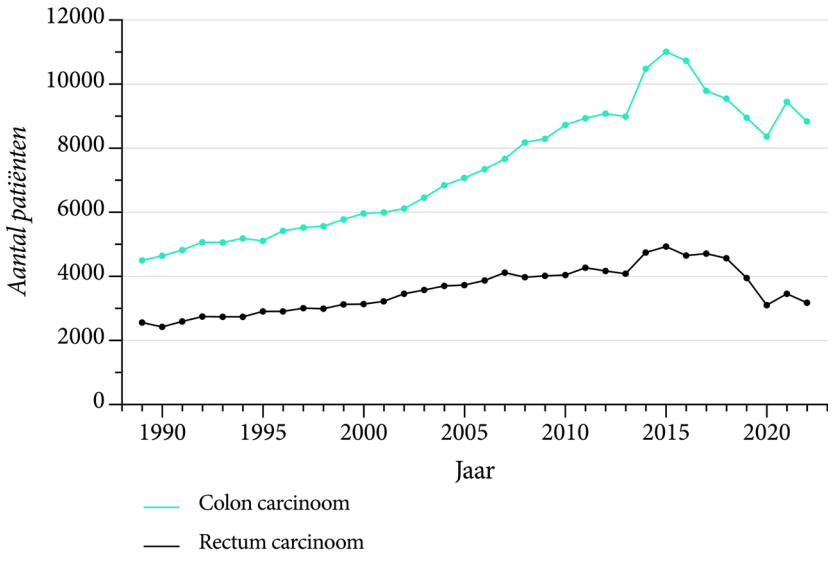
Nederlandse samenvatting

Epidemiologie

Darmkanker is de derde meest voorkomende kanker bij mannen en de tweede meest voorkomende kanker bij vrouwen. Het komt op de tweede plaats wat betreft sterfte. In 2020 waren er wereldwijd respectievelijk ongeveer 1,1 miljoen en 732.000 nieuwe gevallen van colon- en rectumcarcinoom. Dit heeft geleid tot 577.000 sterfgevallen van patiënten met coloncarcinoom en 339.000 sterfgevallen van patiënten met rectumcarcinoom.[1] In Nederland werd in 2020 bij 8.100 patiënten coloncarcinoom vastgesteld en bij 3.100 patiënten rectumcarcinoom. De incidentie nam in de loop van de tijd toe met een piek in 2014 na de introductie van het bevolkingsonderzoek[2], en een daling in 2020, hoogstwaarschijnlijk als gevolg van de COVID-19-pandemie [3] (figuur 1).

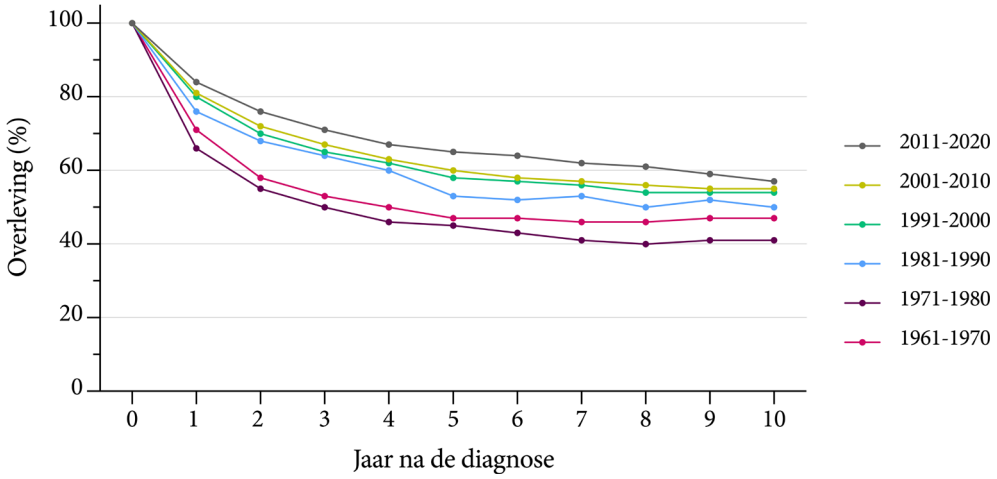
Door verbeteringen in diagnostiek en behandeling is de algehele overleving in de loop der jaren toegenomen, met de grootste winst voor rectumcarcinoom (figuur 2).

Het colon en het rectum verschillen wat betreft embryologische oorsprong, anatomie en functie. Als gevolg hiervan is er verschil in de behandeling van colon- en rectumcarcinoom.[4-6]



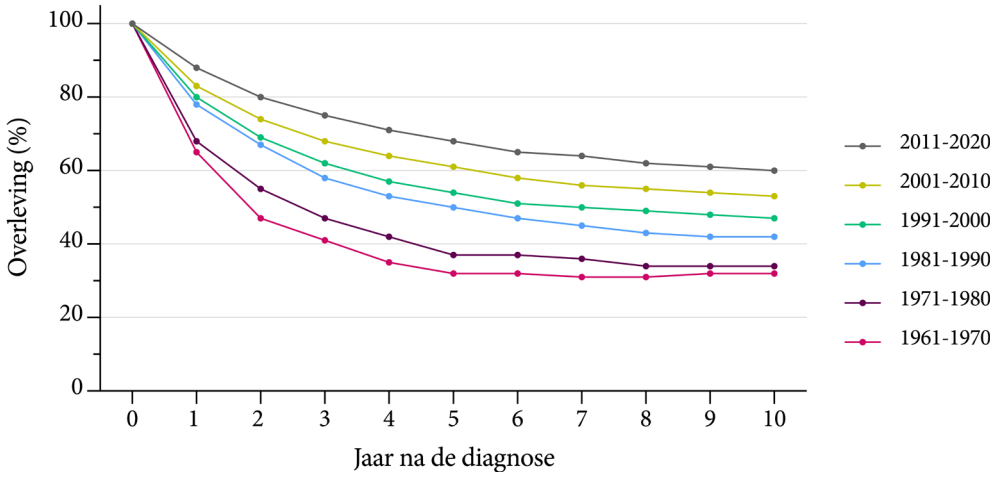
Figuur 1 Incidentie van colon-en rectumcarcinoom in Nederland.

De gegevens van 2021 en 2022 zijn voorlopig. Coloncarcinoom omvat ook kanker van de blinde darm. Bron: NKR, www.iknl.nl, geraadpleegd op 26 maart 2023.



Figuur 2a Overleving na de diagnose coloncarcinoom in Nederland.

Bron: NKR, www.iknl.nl, geraadpleegd op 26 maart 2023.



Figuur 2b Overleving na de diagnose rectumcarcinoom in Nederland.

Bron: NKR, www.iknl.nl, geraadpleegd op 26 maart 2023.

Bovendien kunnen factoren zoals voeding, roken en lichaamsbeweging een ander effect hebben; een gezonde levensstijl lijkt minder impact te hebben op het voorkomen van rectumcarcinoom in tegenstelling tot coloncarcinoom.[5]

Chirurgie

Chirurgie blijft de hoeksteen in de behandeling van colon- en rectumcarcinoom. Voor rectumcarcinoom is een operatie een uitdaging vanwege het smalle bekken. Het rectum zelf bevindt zich in het achterste bekken en wordt omgeven door de mesorectale fascie die het perirectale vet omhult. Het mesorectum wordt strak begrensd door het sacrum en de bijbehorende sacrale zenuwen aan de achterkant, de iliacale vaten en takken van de sacrale zenuwen aan de zijkant en de urogenitale structuren aan de voorkant. De introductie van een totale mesorectale excisie (TME), zoals voor het eerst beschreven in 1979 door prof. Heald [7] heeft het lokaal recidiefpercentage bij rectumcarcinoom drastisch verminderd en lijkt suggestief voor de overlevingswinsten zoals te zien in figuur 2b. Deze techniek omvat een scherpe circumferentiële resectie tussen de viscerale en pariëtale lagen van de mesorectale fascia, inclusief het rectum, tumor en lymfovasculair vetweefsel rondom het rectum, om zo radicale resectie en zenuwbehoud mogelijk te maken. Voor coloncarcinoom werd een complete mesocolische excisie (CME) geïntroduceerd in een poging dezelfde principes over te nemen. De toegevoegde waarde ervan staat echter nog ter discussie.[8,9] Voor zowel colon- als rectumcarcinoom heeft de introductie van minimaal invasieve chirurgie aanzienlijk bijgedragen aan het verminderen van de morbiditeit na chirurgie en is oncologisch gezien minstens even veilig als open chirurgie.[10-12]

Neoadjuvante en adjuvante behandeling

Als behandeling voor cT4N0-2M0 coloncarcinoom kan volgens de Nederlandse landelijke richtlijn neoadjuvante (chemo)radiotherapie worden overwogen.[13] Daarnaast wordt momenteel de meerwaarde van neoadjuvante chemotherapie bij lokaal gevorderd coloncarcinoom onderzocht.[14] Patiënten met stadium III (pT1-4N1-2M0) coloncarcinoom komen in aanmerking voor behandeling met drie

maanden adjuvante chemotherapie. Bij patiënten met hoog-risico stadium II (pT4N0M0) coloncarcinoom dient adjuvante chemotherapie te worden besproken. Indien geïndiceerd, wordt adjuvante chemotherapie bij voorkeur binnen 4-8 weken na de operatie gestart.

Rectumcarcinoom kan worden ingedeeld in vroege (cT1-3b, N0, M0, geen aantasting van de mesorectale fascia), intermediaire (cT3c-dN0 of cT1-3 (geen aantasting van de mesorectale fascia) N1) en lokaal gevorderd rectumcarcinoom (cT4 en/of betrokkenheid van de mesorectale fascia en/of N2). Vroege rectumcarcinoom vereist geen neoadjuvante behandeling. Lokale (endoscopische) excisie voor T1-tumoren of directe chirurgie is de voorkeursbehandeling. Voor intermediair rectumcarcinoom wordt preoperatieve kortdurende radiotherapie met 5x5 Gy geadviseerd. Momenteel wordt voor lokaal gevorderd rectumcarcinoom chemoradiotherapie gevolgd door chirurgie volgens TME-principes na 6-8 weken aanbevolen. In tegenstelling tot het succesvolle gebruik ervan bij coloncarcinoom heeft adjuvante chemotherapie geen overtuigende invloed gehad op het aantal recidieven of de overleving bij rectumcarcinoom.[15] Gerandomiseerde onderzoeken hebben aangetoond dat adjuvante chemotherapie slecht wordt verdragen, wat mogelijk de afwezigheid van een effect verklaart.[16] Daarom wordt het gebruik van adjuvante chemotherapie in de landelijke Nederlandse richtlijnen niet aanbevolen. Echter, in sommige landen, zoals België en Zweden, maakt adjuvante chemotherapie wel deel uit van de standaard behandeling.

Een andere belangrijke verandering is de introductie van de multidisciplinaire aanpak, inclusief het multidisciplinair overleg (MDO), voor het eerst beschreven in 1975.[17] Patiënten worden individueel besproken door meerdere zorgspecialisten van verschillende medische specialismen die betrokken zijn bij de behandeling. In het geval van colon- en rectumcarcinoom zijn dat maagdarmlever-artsen, radiologen, radiotherapeuten, medisch oncologen, chirurgen en pathologen. Deze MDO's faciliteren kennisuitwisseling tussen verschillende medisch specialisten en geven meer inzicht in de behandelmogelijkheden van andere medische specialismen. De meest actuele diagnostische mogelijkheden en therapeutische opties worden besproken om de beste behandeling voor elke individuele patiënt te garanderen. Een systematische review over de effectiviteit van MDO's liet een verandering in diagnose zien bij 18-27% van de geëvalueerde patiënten en een verandering in de behandeling bij 23-42% van de geëvalueerde patiënten.[18]

Klinische stadiëring

Om te beslissen welke behandelingsstrategie voor elke specifieke patiënt moet worden gekozen is nauwkeurige diagnostiek en stadiëring essentieel. Endoscopie is de eerste stap in de diagnostiek en kan worden uitgevoerd door middel van sigmoïdoscopie of, bij voorkeur, een totale colonoscopie. Een

biopsie van de laesie kan worden uitgevoerd, de exacte locatie van de tumor kan worden bepaald en in het geval van colonoscopie kan de aan- of afwezigheid van synchrone (pre) maligne laesies worden beoordeeld. Bovendien kan preoperatieve endoscopische markering helpen bij het lokaliseren van platte, kleine of subtiele colonlaesies die tijdens de operatie moeilijk te identificeren zijn.[19]

Daarnaast wordt voor locoregionale stadiëring van grotere colontumoren gebruik gemaakt van een CT-abdomen.[20] Om onderscheid te maken tussen cT1- en T2- rectumtumoren heeft een EUS (Endoscopic UltraSound) de voorkeur; hiermee zijn alle individuele darmwandlagen zichtbaar. Het vereist echter expertise en is niet in elk ziekenhuis aanwezig. Bovendien is het minder nauwkeurig voor het stadiëren van grotere tumoren, in tegenstelling tot MRI.[21] MRI is tegenwoordig gestandaardiseerd voor de stadiëring van rectumcarcinoom. Met de huidige MRI-technieken worden veranderingen in tumorperfusie en microstructuur vastgelegd, nog voordat morfologische veranderingen zichtbaar zijn.[22] Naast de beoordeling van tumorgrootte zijn een CT voor coloncarcinoom en een MRI voor rectumcarcinoom de meest accurate diagnostische methoden om lymfeklier betrokkenheid te beoordelen. Primaire lymfeklier stadiëring door middel van beeldvorming blijft echter moeilijk. Dit zou kunnen leiden tot overstadiëring, met mogelijke overbehandeling van patiënten met rectumcarcinoom als gevolg. Voor patiënten met coloncarcinoom lijkt er geen direct klinisch effect van mogelijke overstadiëring aangezien dit geen onmiddellijk gevolg voor de behandeling zal hebben gezien preoperatieve behandeling niet gebruikelijk is.[23,24]

Na neoadjuvante behandeling is restadiering belangrijk voor het plannen van verdere behandeling en het plannen of zelfs achterwege laten van een operatie. Een waardevolle troef bij restadiering na neoadjuvante behandeling is diffusie gewogen MRI (DWI), waarbij diffusie van watermoleculen wordt geanalyseerd. Weefsels met een hoge cellulariteit zoals tumoren en lymfeklieren hebben een beperkte diffusie (hoog signaal), terwijl normaal weefsel en fibrose

leidt tot vrije diffusie (laag signaal).[25]

Klinische auditing

Klinische auditing heeft gezorgd voor een verbetering van de zorg door middel van een systematische en kritische analyse van de kwaliteit van medische zorg. Dit is inclusief de procedures die worden gebruikt voor diagnose en behandeling en het resultaat voor de patiënt, uitgevoerd door degenen die persoonlijk betrokken zijn bij de betreffende activiteit. Aan het begin van de twintigste eeuw beschreef dr. Ernest Amory Codman de principes van klinische auditing en voerde de eerste klinische audit uit.[26] Hedendaags zijn er verschillende nationale klinische audits opgezet die hebben geleid tot merkbare verbetering in de patiëntenzorg.[27-30] De jaarverslagen zijn opgesteld met transparantie voor patiënten en verzekeringsmaatschappijen. Auditing werkt gedeeltelijk als gevolg van een reactie op het besef geobserveerd te worden, waardoor gedragsverandering optreedt.[31]

Inhoud proefschrift

EURECCA

Het EURECCA-platform (EUropean REgistry of Cancer CAre) vormde de basis voor **deel I** van dit proefschrift. EURECCA begon in 2007 als een initiatief van de European Society of Surgical Oncology. Er werd opgemerkt dat er in Europa aanzienlijke variatie bestond in behandeling van kanker en de uitkomst daarvan. Hierdoor ontstond de behoefte aan transparante, uniforme internationale dataverzameling en -analyse, om alle aspecten van kankerzorg te monitoren en hiervan te leren, en om feedback en educatie te bewerkstelligen. Het doel van EURECCA is het bereiken en het garanderen van hoge kwaliteit multidisciplinaire kankerzorg in Europa met behulp van een internationaal multidisciplinair platform van clinici en epidemiologen. Gezamenlijk zijn zij gericht op het verbeteren van de kwaliteit van kankerzorg door gegevensregistratie, feedback, het opstellen van verbeterplannen en het delen van kennis en wetenschap. Met de auditstructuur, waarbij gebruik wordt gemaakt van anonieme patiëntgegevens en die voldoet aan de nationale en internationale wetgeving, kan de kwaliteit van de kankerzorg worden geoptimaliseerd. Het uiteindelijke doel van deze

professionele ondersteuningsstructuur is om verschillen in kankerzorg tussen Europese landen te minimaliseren.

Sinds de oprichting van EURECCA zijn er verschillende EURECCA studies uitgevoerd en gepubliceerd. Hieruit komt een grote diversiteit aan behandelstrategieën in Europese landen naar voren.[32-37] Bovendien zijn er verschillen tussen landen met betrekking tot overleving voor colon- en rectumcarcinoom gevonden.[38]

Voor **hoofdstukken 2 en 3** werd gebruik gemaakt van gegevens van de nationale kankerregistraties van België, Nederland, Noorwegen en Zweden. Tussen januari 2007 en december 2016 werden 314.062 patiënten gediagnosticeerd met stadium I-III colon- of rectumcarcinoom. Er werden gegevens geanalyseerd van alle volwassen patiënten die een chirurgische behandeling ondergingen, welke werd gedefinieerd als chirurgische verwijdering van het tumor dragende darmsegment, ongeacht curatieve of palliatieve intentie. Aan de inclusiecriteria werd voldaan door 53.071 patiënten uit België (64,3%), 88.784 patiënten uit Nederland (66,9%), 25.548 patiënten uit Noorwegen (64,3%) en 38.621 patiënten uit Zweden (66,1%). Aangezien deze landen vergelijkbare verwachte sterftecijfers hebben in alle leeftijdscategorieën, zijn eventuele verschillen tussen de landen interessant omdat ze het gevolg kunnen zijn van verschillen in behandelingsstrategie.

30-dagen mortaliteit wordt meestal als uitkomstmaat gekozen om het postoperatieve beloop te evalueren bij patiënten die een operatie ondergaan voor colon- en rectumcarcinoom. Echter, de oversterfte - sterfte gecorrigeerd voor verwachte sterfte in de algemene bevolking - in het eerste postoperatieve jaar na chirurgie is een betere afspiegeling van het postoperatieve risico, vooral voor oudere patiënten.[39,40] De impact van sterfte in het eerste jaar op de overleving op lange termijn is groot en zal ook gevolgen hebben voor kanker-gerelateerde uitkomsten.

In **hoofdstuk 2** werden behandelstrategieën en postoperatieve mortaliteit na 30-dagen en na 1-jaar vergeleken. In alle landen nam het gebruik van chemotherapie toe met het stadium en nam het af met de leeftijd. Patiënten met coloncarcinoom in België werden vaker behandeld met adjuvante chemotherapie. Patiënten met rectumcarcinoom in Nederland en Zweden kregen vaker neoadjuvante radiotherapie, terwijl patiënten in België en Noorwegen vaker neoadjuvante chemoradiotherapie kregen. Bovendien werd de behandeling in België, en in mindere mate in Zweden, vaker aangevuld met adjuvante chemotherapie. In alle landen nam

de 30-dagen- en 1-jaars-oversterfte in de loop der jaren af voor colon- en rectumcarcinoom. De 1-jaars-verwachte sterfte bleef door de jaren heen stabiel en was vergelijkbaar voor de onderzochte landen. Ondanks vaker (neo)adjuvante therapie in België, was de oversterfte voor oudere patiënten met colon- en rectumcarcinoom interessant genoeg hoger dan in de andere landen. Dit kan wijzen op de mogelijkheid van overbehandeling. Patiënten in de jongste leeftijdscategorie hadden een vergelijkbare mortaliteit na één jaar na verschillende behandelingsstrategieën, wat wijst op het hoge compenserende vermogen van jongere patiënten.

Aangezien oudere patiënten over het algemeen kwetsbaarder zijn en meer comorbiditeit hebben, is de algehele overleving bij oudere patiënten lager dan bij jongere patiënten. Echter, om betrouwbare uitspraken te doen over de overleving na colon- of rectumcarcinoom zou de kanker-gerelateerde overleving moeten worden geanalyseerd in plaats van de totale overleving. Hiervoor wordt de relatieve survival berekend waarbij algehele overleving wordt gecorrigeerd voor de normale levensverwachting op basis van de sterftetafels naar leeftijd en geslacht. Verschillende Nederlandse studies hebben geconcludeerd dat de relatieve overleving van oudere patiënten met colon- en rectumcarcinoom is verbeterd, wat heeft geleid tot bijna vergelijkbare kanker-specifieke overleving in vergelijking met de jongere populatie na het overleven van het eerste postoperatieve jaar.[41,42] Hiermee wordt het belang van het eerste postoperatieve jaar benadrukt. Of het effect van verdwijnen van leeftijdsverschillen ook op nationaal niveau aanwezig is voor colon- en rectumcarcinoom in andere Europese landen, is niet eerder onderzocht.

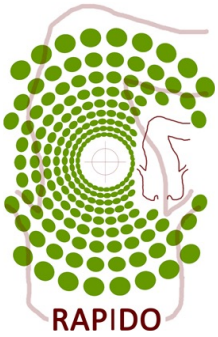
De resultaten van de analyses (voor colon- en rectumcarcinoom apart) van relatieve overleving na 1-jaar en relatieve overleving na 1-jaar met de voorwaarde om het eerste jaar te overleven in België, Nederland, Noorwegen en Zweden werden beschreven in **hoofdstuk 3**. Op deze manier werd onderzocht of leeftijd gerelateerde verschillen verdwenen na het overleven van het eerste postoperatieve jaar.

Afname in overleving van oudere patiënten tijdens het eerste postoperatieve jaar was het duidelijkst in België, gevolgd door Nederland, en het minst in Noorwegen en Zweden. Na het overleven van het eerste postoperatieve jaar was de overleving van chirurgisch behandelde

oudere patiënten gelijk aan die van hun jongere tegenhangers (< 65 jaar), behalve voor patiënten met stadium III ziekte. Hierdoor kan geconcludeerd worden dat de overlevingskloof tussen jonge en oudere patiënten na chirurgische resectie van colon- en rectumcarcinoom grotendeels gebaseerd is op vroege (eerstejaars) sterfte. De sleutel tot het overbruggen van deze overlevingskloof tussen jonge en oudere patiënten zou een evenwicht zijn tussen onder- en overbehandeling kunnen zijn. Dit is met name belangrijk voor patiënten met stadium III-ziekte. Hierbij is aandacht op het voorkomen van vroege sterfte essentieel.

RAPIDO

De onderzoeker-aangestuurde, internationale, gerandomiseerde RAPIDO-studie (Rectal cancer And Pre-operative Induction therapy followed by Dedicated Operation) werd besproken in **deel II**. Er werd verondersteld dat het preoperatief toedienen van chemotherapie na radiotherapie (een totale neoadjuvante therapie) de therapietrouw zou verhogen en metastasen op afstand zou verminderen zonder de locoregionale controle in gevaar te brengen bij patiënten met lo kaal gevorderd rectumcarcinoom.



De RAPIDO-studie was gebaseerd op de Nederlandse M1-studie [43] waarbij patiënten met primair gemetastaseerd rectumcarcinoom kortdurende radiotherapie kregen, gevolgd door zes cycli capecitabine, oxaliplatine en bevacizumab, en een operatie na 6-8 weken. Therapietrouw aan chemotherapie was 84% (42 van de 50 patiënten kregen alle zes cycli) en in 47% van de gevallen werd de tumor kleiner (20 van de 43 patiënten die een operatie ondergingen). Bovendien werd een pathologische complete respons van de primaire tumor gerapporteerd bij 11 van de 43 patiënten (26%) die een operatie ondergingen.[43]

De optimale radiotherapiefractionering en het interval tussen radiotherapie en chirurgie werden onderzocht in de Stockholm III studie.[44] De studiedeelnemers werden willekeurig toebedeeld aan ofwel 5 × 5 Gy (kortdurende radiotherapie) en een operatie binnen 1 week of na 4-8 weken danwel 25 × 2 Gy (langdurige radiotherapie) en een operatie na 4-8 weken. Er werd geconcludeerd dat de drie verschillende behandelgroepen leiden tot dezelfde oncologische resultaten. Kortdurende radiotherapie heeft als voordeel, uiteraard, dat het

een kortere behandelduur heeft vergeleken met langdurige radiotherapie. Daarnaast waren er minder postoperatieve complicaties bij een langere periode tussen radiotherapie en een operatie, waardoor kortdurende radiotherapie en een operatie na 4-8 weken geprefereerd werd. [44]

Het RAPIDO-regime bestond uit kortdurende radiotherapie (5x5 Gy) gevolgd door 18 weken chemotherapie (zes cycli CAPOX of negen cycli FOLFOX4) gevolgd door TME binnen 2-4 weken. Het werd vergeleken met de standaard behandeling voor lokaal gevorderd rectumcarcinoom: langdurige chemoradiotherapie (28 x 1,8 Gy of 25 x 2,0 Gy, met gelijktijdig tweemaal daags oraal capecitabine) gevolgd door TME binnen 6-10 weken. Als adjuvante chemotherapie deel uitmaakte van het beleid van de deelnemende ziekenhuizen, was adjuvante chemotherapie met 8 kuren CAPOX of 12 kuren FOLFOX4 toegestaan. Het primaire eindpunt was Disease-related Treatment Failure (DrTF), gedefinieerd als het eerste optreden van locoregionaal falen, metastasen op afstand, een nieuwe primaire colorectale tumor of overlijden als gevolg van de behandeling. Locoregionaal falen omvatte lokaal progressieve ziekte die leidde tot een inoperabele tumor, lokale R2-resectie of lokaal recidief na een R0-R1-resectie.

In **hoofdstuk 4** werden de resultaten van het primaire eindpunt van de RAPIDO studie gerapporteerd en besproken. Na een mediane follow-up van 4,6 jaar (IQR 3,5–5,5) daalde de cumulatieve kans op DrTF, 3 jaar na randomisatie, van 30% in de groep met standaardbehandeling tot 24% in de groep met de experimentele behandeling, voornamelijk als gevolg van een afname van metastasen op afstand.

Aangezien de belangrijkste focus van de RAPIDO-studie het verminderen van metastasen op afstand was, richtte **hoofdstuk 5** zich op verschillen in metastaseringspatroon tussen de twee behandelgroepen. Hiermee werd een beter begrip van de klinische aard van lokaal gevorderd rectumcarcinoom nagestreefd en werd onderzocht of deze wordt beïnvloed door verschillende behandelingen. Een veranderd metastaseringspatroon met minder metastasen door minder levermetastasen in de experimentele behandeling werd waargenomen. De afname van metastasen op afstand is waarschijnlijk te danken aan een betere therapietrouw preoperatief en wellicht aan de eerdere behandeling van micrometastasen in het behandeltraject. Een ziekenhuisbeleid voor adjuvante chemotherapie had geen invloed op het ontstaan van

metastasen op afstand. Hoewel patiënten met metastasen op afstand in de experimentele groep een slechtere overleving hadden dan patiënten in de standaardbehandeling groep, bleef de cumulatieve kans op overleving op basis van de behandeling vergelijkbaar voor beide behandel groepen; 82% voor de experimentele groep en 80% voor de standaardbehandeling groep (HR 0.91 [95%CI 0.70-1.19];P=0.50) 5 jaar na randomisatie.

Verder verdubbelde met de experimentele RAPIDO-behandeling het pathologische complete responspercentage van 14% naar 28%. Als de patiënten met een klinisch complete respons kunnen worden geïdentificeerd tijdens de herbeoordeling na neoadjuvante therapie, kan een operatie achterwege blijven. Dit werd verder toegelicht in **deel III**.

IWWD

Chirurgie is altijd de hoeksteen geweest van de behandeling van rectumcarcinoom. Er is echter, zoals beschreven in **deel III**, een trend in de richting van een orgaan-sparende behandeling. Patiënten met een klinisch complete respons tijdens restadiering na neoadjuvante behandeling kunnen afzien van onmiddellijke chirurgie en een strikte surveillancestrategie ondergaan, een zogenaamde watch-and-wait (W&W)-benadering.

Na een internationale consensusbijeenkomst in 2014 over W&W voor rectumcarcinoom heeft een netwerk van experts van over de hele wereld de International Watch & Wait Database (IWWD) opgericht onder de paraplu van EURECCA en de Champalimaud Foundation in Lissabon.[45] De IWWD is een internationale, multicenter, deels retrospectieve en deels prospectieve cohort database, opgezet om alle beschikbare gegevens te verzamelen om zo inzicht te krijgen in de risico's en voordelen van W&W na het bereiken van een klinisch complete respons na neoadjuvante behandeling. De data verzameling is gestart in april 2015. Het uiteindelijke doel van deze prospectieve informatie is om het platform te worden voor het ontwikkelen van best practice-richtlijnen voor orgaan-sparende behandeling.

De afgelopen decennia is naast de toename bij oudere patiënten de incidentie van colon- en rectumcarcinoom wereldwijd toegenomen bij jonge patiënten (jonger dan 50 jaar).[46] De incidentie van rectumcarcinoom bij volwassen patiënten jonger dan 50 jaar in Europa, is tussen

1990 en 2016 jaarlijks met 1,6-3,5% gestegen.[47] Tegen 2030 zal bijna een op de vier diagnoses van rectumcarcinoom worden gesteld bij patiënten jonger dan 50 jaar.[48] Voor het eerst beschreven door Habr-Gama en collega's [49] en gevolgd door verschillende cohort reeksen,[50-52] is de veiligheid en haalbaarheid van W&W bevestigd bij patiënten met een klinisch complete respons na neoadjuvante therapie. Toch is het de vraag of deze benadering oncologisch veilig is voor jongere patiënten gezien zij over het algemeen een langere levensverwachting hebben. Het lijkt erop dat er meer aarzeling bestaat onder artsen om W&W te starten bij jonge patiënten met een klinisch complete respons in tegenstelling tot bij oudere patiënten. Om deze gedachte te onderzoeken, gezien dit nog niet eerder onderzocht was voor deze specifieke groep, werden gegevens uit de IWWD geanalyseerd. In **hoofdstuk 6** werden de resultaten beschreven. Er werd geen verhoogd oncologisch risico gevonden bij patiënten jonger dan 50 jaar in vergelijking met oudere patiënten die waren gestart met een W&W-strategie met een adequate follow-up na een klinisch complete response. Dit opent de deur voor potentieel orgaanbehoud. Daarom moet W&W worden overwogen en minstens worden besproken met de patiënten met een klinisch complete respons.

Samengevat

In de hedendaagse geneeskunde staat de patiënt centraal in de behandeling. Alle aspecten, van een poging tot preventie, tot het zo vroeg mogelijk en zo nauwkeurig mogelijk diagnosticeren van de tumor, van cel tot macroscopisch niveau, hebben geleid tot optimalisatie van de behandeling van colon- en rectumcarcinoom. Verschillende (medische) disciplines hebben hun krachten gebundeld om voor elke individuele patiënt de meest geschikte behandeling samen te stellen, rekening houdend met tumorkenmerken en patiëntvoorkeuren, balancerend tussen onder- en overbehandeling. Met shared-decision-making zijn al veel stappen gezet. Het is belangrijk om niet alleen samen te beslissen over de behandeling, maar ook om te verdiepen in wat de patiënt echt wil. Wellicht worden andere eindpunten belangrijker dan de bekende oncologische eindpunten zoals overleving en recidiefkans.[53] Kwaliteit van leven staat bij veel patiënten ook voorop. Hierbij staat een open gesprek met de patiënt centraal. Elke patiënt verdient immers een behandeling op maat, want kanker is net zo uniek als de persoon die ertegen vecht.

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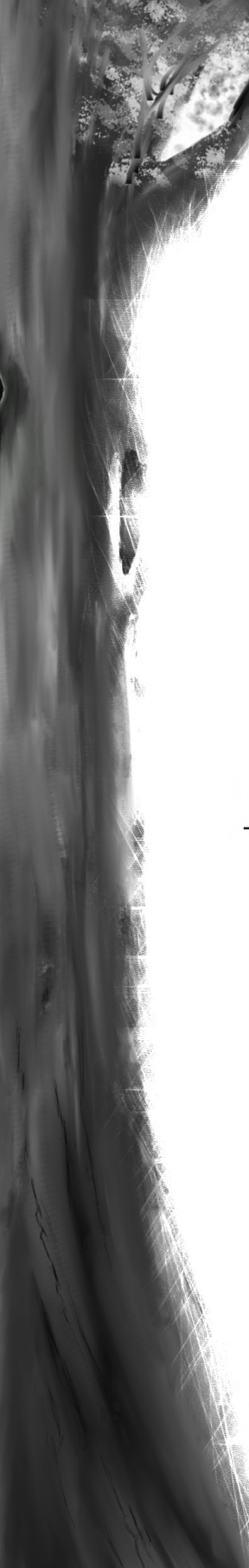

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List of publications

Bahadoer RR, Hospers GAP, Marijnen CAM, Peeters KCMJ, Putter H, Dijkstra EA, Meershoek-Klein Kranenbarg E, Roodvoets AGH, van Etten B, Nilsson PJ, Glimelius B, van de Velde CJH, and collaborative investigators. *"Risk and Location of Distant Metastases in Patients With Locally Advanced Rectal Cancer After Total Neoadjuvant Treatment or Chemoradiotherapy in The RAPIDO Trial."* Eur J Cancer. 2023 Mar 7;185:139-149. Online ahead of print.

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Collaborations

"Practice variation in anastomotic leak after esophagectomy: Unravelling differences in failure to rescue."
Eur J Surg Oncol. 2023 Jan 20:S0748-7983(23)00032-X. Online ahead of print.

"Retrospective evaluation of national MRI reporting quality for lateral lymph nodes in rectal cancer patients and concordance with prospective re-evaluation following additional training."
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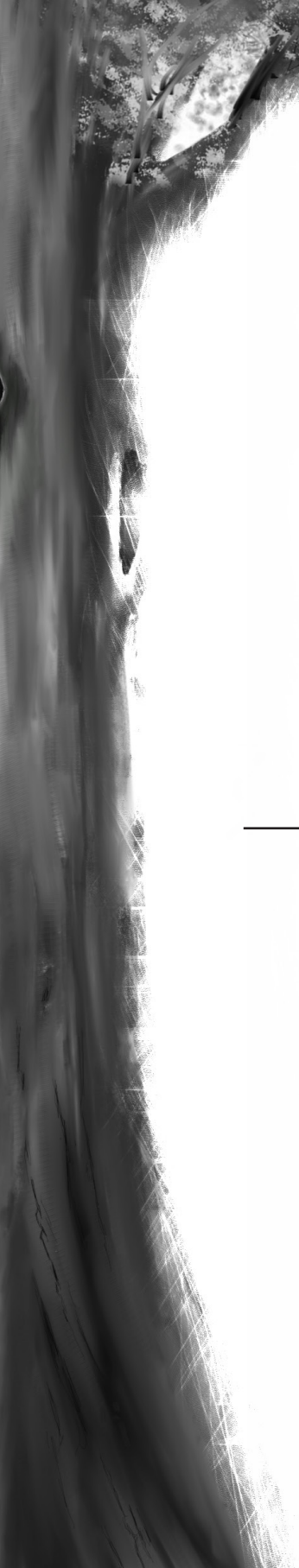
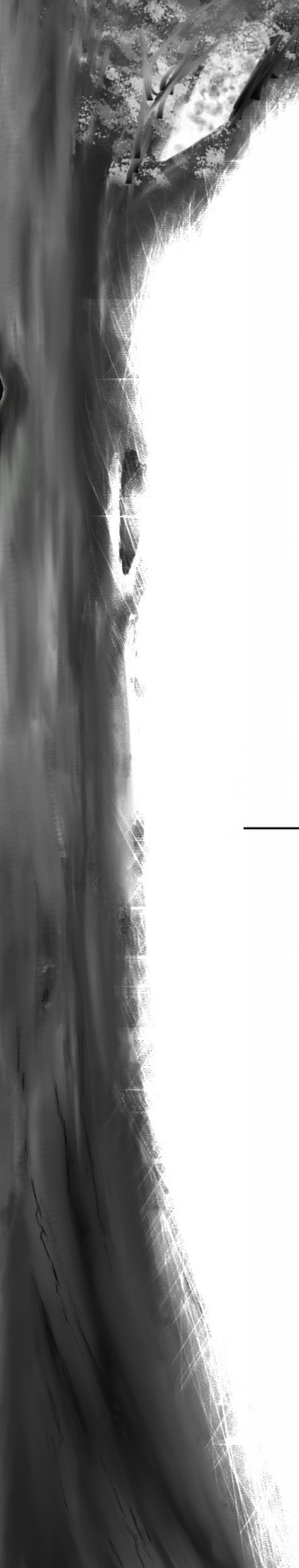


Curriculum Vitae

Curriculum Vitae

Renu Ragini Bahadoer werd op 2 december 1992 geboren in Den Haag. In 2010 behaalde ze haar VWO diploma aan het Segbroek college waarna ze meteen startte met de geneeskunde opleiding aan de universiteit Leiden. In 2017 behaalde ze haar geneeskunde diploma en startte als ANIOS chirurgie in het Leids Universitair Medisch Centrum waar ook haar interesse voor wetenschappelijk onderzoek werd gewekt. Een jaar later, in 2018, startte ze met fulltime onderzoek onder leiding van prof. dr. C.J.H van de Velde (LUMC) en prof. dr. G.A.P Hospers (UMCG). Voor haar onderzoek heeft Renu de Schoemaker prijs van de Nederlandse vereniging voor Heelkunde voor beste publicatie in 2020 in ontvangst mogen nemen en is zij genomineerd voor Best Proffered Paper op het congres van de European Society of Surgical Oncology (ESSO) in 2021. Na 3 jaar fulltime onderzoek startte ze in 2021 met de opleiding tot chirurg in het HagaZiekenhuis te Den Haag en daarna in het Alrijne Ziekenhuis te Leiderdorp. Echter is zij sinds 2023 begonnen aan een carrière switch en is nu werkzaam als ANIOS dermatologie in het Groene Hart Ziekenhuis te Gouda.



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En pap, hoe vind je mijn werkstuk geworden?