Tailored treatment for colon and rectal cancer

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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

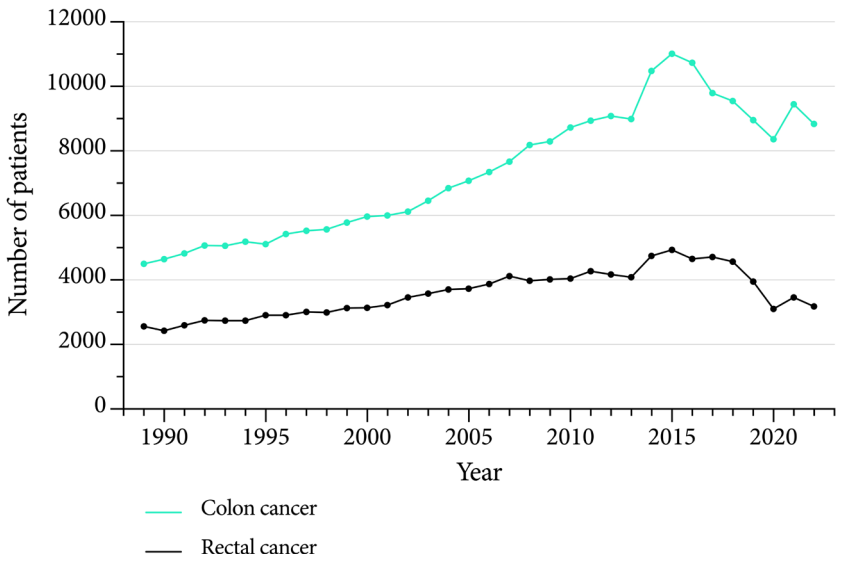

Figure 1 Incidence of colon and rectal cancer in the Netherlands.

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.

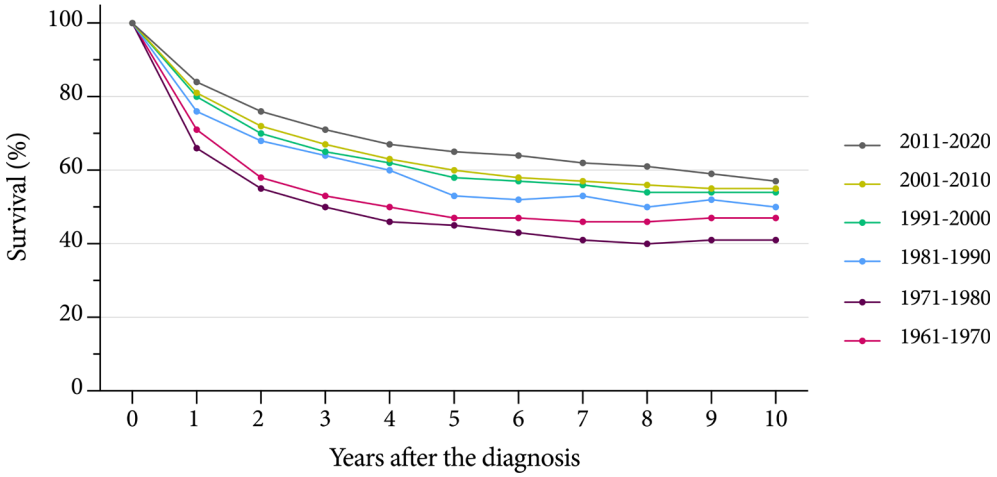

Figure 2a Survival of colon cancer in the Netherlands.

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

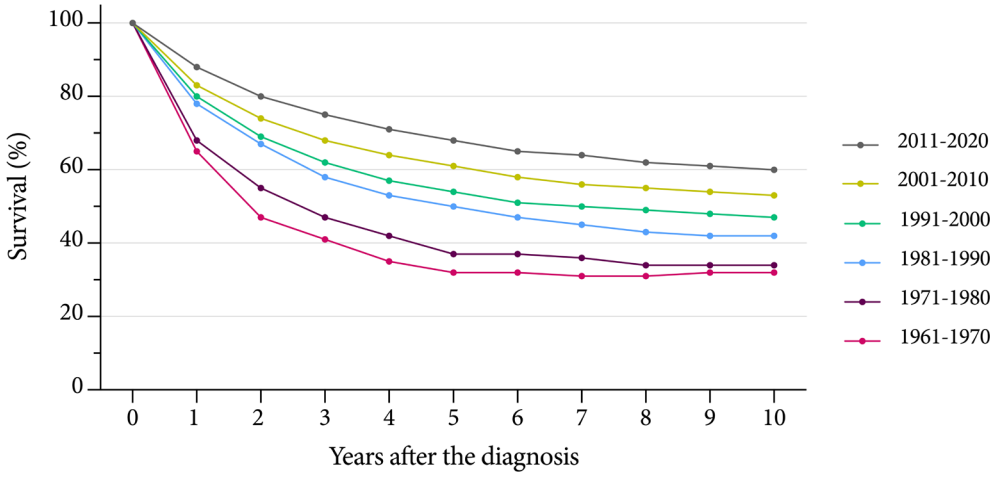

Figure 2b Survival of rectal cancer in the Netherlands.

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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