Tailored treatment for colon and rectal cancer

Bahadoer, R.R.

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.

References

1. Baek SJ, Kim CH, Cho MS, et al. Robotic surgery for rectal cancer can overcome difficulties associated with pelvic anatomy. Surg Endosc 2015; 29(6): 1419-24.
2. Corrigan N, Marshall H, Croft J, Copeland J, Jayne D, Brown J. Exploring and adjusting for potential learning effects in ROLARR: a randomised controlled trial comparing robotic-assisted vs. standard laparoscopic surgery for rectal cancer resection. Trials 2018; 19(1): 339.
3. Jayne D, Pigazzi A, Marshall H, et al. Effect of Robotic-Assisted vs Conventional Laparoscopic Surgery on Risk of Conversion to Open Laparotomy Among Patients Undergoing Resection for Rectal Cancer: The ROLARR Randomized Clinical Trial. JAMA 2017; 318(16): 1569-80.
4. Stijns RCH, de Graaf EJR, Punt CJA, et al. Long-term Oncological and Functional Outcomes of Chemoradiotherapy Followed by Organ-Sparing Transanal Endoscopic Microsurgery for Distal Rectal Cancer: The CARTS Study. JAMA Surg 2019; 154(1): 47-54.
5. Petersen S, Jongen J, Petersen C, Sailer M. Radiation-induced sequelae affecting the continence organ: incidence, pathogenesis, and treatment. Dis Colon Rectum 2007; 50(9): 1466-74.
6. Galema HA, Meijer RPJ, Lauwerends LJ, et al. Fluorescence-guided surgery in colorectal cancer; A review on clinical results and future perspectives. Eur J Surg Oncol 2022; 48(4): 810-21.
7. Zocola E, Meyer J, Christou N, et al. Role of near-infrared fluorescence in colorectal surgery. World J Gastroenterol 2021; 27(31): 5189-200.
8. Meijer RPJ, Faber RA, Bijlstra OD, et al. AVOID; a phase III, randomised controlled trial using indocyanine green for the prevention of anastomotic leakage in colorectal surgery. BMJ Open 2022; 12(4): e051144.
9. van Kooten RT, Bahadoer RR, Peeters K, et al. Preoperative risk factors for major postoperative complications after complex gastrointestinal cancer surgery: A systematic review. Eur J Surg Oncol 2021; 47(12): 3049-58.
10. Trepanier M, Minnella EM, Paradis T, et al. Improved Disease-free Survival After Prehabilitation for Colorectal Cancer Surgery. Ann Surg 2019; 270(3): 493-501.
11. Barberan-Garcia A, Ubre M, Roca J, et al. Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery: A Randomized Blinded Controlled Trial. Ann Surg 2018; 267(1): 50-6.
12. van Rooijen S, Carli F, Dalton S, et al. Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation. BMC Cancer 2019; 19(1): 98.
13. Collaborative P-AT. SupPoRtive Exercise Programmes for Accelerating REcovery after major ABdominal Cancer surgery trial (PREPARE-ABC): Study protocol for a multicentre randomized controlled trial. Colorectal Dis 2021; 23(10): 2750-60.
14. Breugom AJ, Swets M, Bosset JF, et al. Adjuvant chemotherapy after preoperative (chemo)

radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2015; 16(2): 200-7.
15. Breugom AJ, van Gijn W, Muller EW, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. Ann Oncol 2015; 26(4): 696-701.
16. van der Valk MJM, Marijnen CAM, van Etten B, et al. Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer - Results of the international randomized RAPIDO-trial. Radiother Oncol 2020; 147: 75-83.
17. Glynne-Jones R, Anyamene N, Moran B, Harrison M. Neoadjuvant chemotherapy in MRI-staged high-risk rectal cancer in addition to or as an alternative to preoperative chemoradiation? Ann Oncol 2012; 23(10): 2517-26.
18. Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol 2017; 18(3): 336-46.
19. Bahadoer RR, Dijkstra EA, van Etten B, et al. 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, phase 3 trial. Lancet Oncol 2021; 22(1): 29-42.
20. Conroy T, Bosset JF, Etienne PL, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2021; 22(5): 702-15.
21. Bujko K, Wyrwicz L, Rutkowski A, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 x 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol 2016; 27(5): 834-42.
22. Cisel B, Pietrzak L, Michalski W, et al. Long-course preoperative chemoradiation versus 5 x 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: long-term results of the randomized Polish II study. Ann Oncol 2019; 30(8): 1298-303.
23. Jin J, Tang Y, Hu C, et al. Multicenter, Randomized, Phase III Trial of Short-Term Radiotherapy Plus Chemotherapy Versus Long-Term Chemoradiotherapy in Locally Advanced Rectal Cancer (STELLAR). J Clin Oncol 2022; 40(15): 1681-92.
24. Andre T, Meyerhardt J, Iveson T, et al. Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results from a prospective, pooled analysis of six randomised, phase 3 trials. Lancet Oncol 2020; 21(12): 1620-9.
25. Garcia-Aguilar J, Chow OS, Smith DD, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol 2015;

16(8): 957-66.
26. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 1990; 322(6): 352-8.
27. Babaei M, Balavarca Y, Jansen L, et al. Administration of adjuvant chemotherapy for stage II-III colon cancer patients: An European population-based study. Int J Cancer 2018; 142(7): 1480-9.
28. Leijssen LGJ, Dinaux AM, Amri R, Kunitake H, Bordeianou LG, Berger DL. The Impact of a Multivisceral Resection and Adjuvant Therapy in Locally Advanced Colon Cancer. J Gastrointest Surg 2019; 23(2): 357-66.
29. Gosavi R, Chia C, Michael M, Heriot AG, Warrier SK, Kong JC. Neoadjuvant chemotherapy in locally advanced colon cancer: a systematic review and meta-analysis. Int J Colorectal Dis 2021; 36(10): 2063-70.
30. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010; 11(9): 835-44.
31. Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 2011; 29(35): 4633-40.
32. Renehan AG, Malcomson L, Emsley R, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol 2016; 17(2): 174-83.
33. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004; 240(4): 711-7; discussion 7-8.
34. van der Valk MJM, Hilling DE, Bastiaannet E, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet 2018; 391(10139): 2537-45.
35. Maas M, Lambregts DM, Nelemans PJ, et al. Assessment of Clinical Complete Response After Chemoradiation for Rectal Cancer with Digital Rectal Examination, Endoscopy, and MRI: Selection for Organ-Saving Treatment. Ann Surg Oncol 2015; 22(12): 3873-80.
36. van der Sande ME, Beets GL, Hupkens BJ, et al. Response assessment after (chemo)radiotherapy for rectal cancer: Why are we missing complete responses with MRI and endoscopy? Eur J Surg Oncol 2019; 45(6): 1011-7.
37. Tjalma JJJ, Koller M, Linssen MD, et al. Quantitative fluorescence endoscopy: an innovative endoscopy approach to evaluate neoadjuvant treatment response in locally advanced rectal cancer. Gut 2020; 69(3): 406-10.
38. Fokas E, Appelt A, Glynne-Jones R, et al. International consensus recommendations on key outcome measures for organ preservation after (chemo)radiotherapy in patients with rectal cancer.

Nat Rev Clin Oncol 2021; 18(12): 805-16.
39. Habr-Gama A, Sao Juliao GP, Fernandez LM, et al. Achieving a Complete Clinical Response After Neoadjuvant Chemoradiation That Does Not Require Surgical Resection: It May Take Longer Than You Think! Dis Colon Rectum 2019; 62(7): 802-8.
40. https://www.opaxx.nl/. Accessed on 11th Nov 2022.
41. Fernandez LM, Sao Juliao GP, Figueiredo NL, et al. Conditional recurrence-free survival of clinical complete responders managed by watch and wait after neoadjuvant chemoradiotherapy for rectal cancer in the International Watch & Wait Database: a retrospective, international, multicentre registry study. Lancet Oncol 2020.
42. Bai J, Chen H, Bai X. Relationship between microsatellite status and immune microenvironment of colorectal cancer and its application to diagnosis and treatment. J Clin Lab Anal 2021; 35(6): e23810.
43. Kloor M, von Knebel Doeberitz M. The Immune Biology of Microsatellite-Unstable Cancer. Trends Cancer 2016; 2(3): 121-33.
44. Gelsomino F, Barbolini M, Spallanzani A, Pugliese G, Cascinu S. The evolving role of microsatellite instability in colorectal cancer: A review. Cancer Treat Rev 2016; 51: 19-26.
45. Tomasello G, Ghidini M, Galassi B, Grossi F, Luciani A, Petrelli F. Survival benefit with adjuvant chemotherapy in stage III microsatellite-high/deficient mismatch repair colon cancer: a systematic review and meta-analysis. Sci Rep 2022; 12(1): 1055.
46. Cercek A, Lumish M, Sinopoli J, et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. N Engl J Med 2022; 386(25): 2363-76.
47. Chalabi M, Fanchi LF, Dijkstra KK, et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. Nat Med 2020; 26(4): 566-76.
48. Zelenay S, van der Veen AG, Bottcher JP, et al. Cyclooxygenase-Dependent Tumor Growth through Evasion of Immunity. Cell 2015; 162(6): 1257-70.
49. Emambux S, Tachon G, Junca A, Tougeron D. Results and challenges of immune checkpoint inhibitors in colorectal cancer. Expert Opin Biol Ther 2018; 18(5): 561-73.
50. Tang C, Wang X, Soh H, et al. Combining radiation and immunotherapy: a new systemic therapy for solid tumors? Cancer Immunol Res 2014; 2(9): 831-8.
51. Wang Y, Shen L, Wan J, et al. Short-course radiotherapy combined with CAPOX and Toripalimab for the total neoadjuvant therapy of locally advanced rectal cancer: a randomized, prospective, multicentre, double-arm, phase II trial (TORCH). BMC Cancer 2022; 22(1): 274.
52. Navarro M, Nicolas A, Ferrandez A, Lanas A. Colorectal cancer population screening programs worldwide in 2016: An update. World J Gastroenterol 2017; 23(20): 3632-42.
53. https://iknl.nl/getmedia/a1826b9e-7705-42fe-8e3c-56690c045b57/Monitor_

bevolkingsonderzoek_darmkanker_2020.pdf. Accessed on 11th Nov 2022.
54. Di Lena M, Porcelli F, Altomare DF. Volatile organic compounds as new biomarkers for colorectal cancer: a review. Colorectal Dis 2016; 18(7): 654-63.
55. Amal H, Leja M, Funka K, et al. Breath testing as potential colorectal cancer screening tool. Int J Cancer 2016; 138(1): 229-36.
56. Giesen LJX, Olthof PB, Elferink MAG, et al. Changes in rectal cancer treatment after the introduction of a national screening program; Increasing use of less invasive strategies within a national cohort. Eur J Surg Oncol 2021.
57. Hupkens BJP, Breukink SO, Stoot J, et al. Oncological Outcomes and Hospital Costs of the Treatment in Patients With Rectal Cancer: Watch-and-Wait Policy and Standard Surgical Treatment. Dis Colon Rectum 2020; 63(5): 598-605.
58. Hupkens BJP, Martens MH, Stoot JH, et al. Quality of Life in Rectal Cancer Patients After Chemoradiation: Watch-and-Wait Policy Versus Standard Resection - A Matched-Controlled Study. Dis Colon Rectum 2017; 60(10): 1032-40.
59. Rullier E, Vendrely V, Asselineau J, et al. Organ preservation with chemoradiotherapy plus local excision for rectal cancer: 5-year results of the GRECCAR 2 randomised trial. Lancet Gastroenterol Hepatol 2020; 5(5): 465-74.
60. Collaborative S-T. Can we Save the rectum by watchful waiting or TransAnal surgery following (chemo)Radiotherapy versus Total mesorectal excision for early REctal Cancer (STAR-TREC)? Protocol for the international, multicentre, rolling phase II/III partially randomised patient preference trial evaluating long course concurrent chemoradiotherapy versus short course radiotherapy organ preservation approaches. Colorectal Dis 2022.
61. Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study. J Clin Oncol 2005; 23(25): 6199-206.
62. van der Sande ME, Hupkens BJP, Berbee M, et al. Impact of radiotherapy on anorectal function in patients with rectal cancer following a watch and wait programme. Radiother Oncol 2019; 132: 79-84.
63. Costa B, Estrada MF, Mendes RV, Fior R. Zebrafish Avatars towards Personalized Medicine-A Comparative Review between Avatar Models. Cells 2020; 9(2).
64. Brenner H, Chen C. The colorectal cancer epidemic: challenges and opportunities for primary, secondary and tertiary prevention. Br J Cancer 2018; 119(7): 785-92.
65. Lee IM. Physical activity and cancer prevention--data from epidemiologic studies. Med Sci Sports Exerc 2003; 35(11): 1823-7.
66. van Zutphen M, Boshuizen HC, Kenkhuis MF, et al. Lifestyle after colorectal cancer diagnosis in relation to recurrence and all-cause mortality. Am J Clin Nutr 2021; 113(6): 1447-57.

67. https://www.vtv2018.nl/zorguitgaven. Accessed on 11th Nov 2022.
68. https://connect.ichom.org/patient-centered-outcome-measures/colorectal-cancer/. Accessed on 11th Nov 2022.