Long-term effects and quality of life after treatment for rectal cancer

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Summary

Chapter 1
This chapter provides a general introduction into the background and treatment of rectal cancer. Unfortunately, all curative treatment options for rectal cancer come at a price. Different classification systems have been developed to report side effects. During the last decade the value of patient reported symptoms and health-related quality of life (HRQL) is recognized and several questionnaires are developed to study these.

There are several known long-term adverse events after treatment for rectal cancer. For surgery, these include urinary dysfunction and sexual dysfunction, which are mainly caused by nerve damage. The Low Anterior Resection Syndrome is a known adverse event after surgery as well. Furthermore, radiation of the rectum is also an important risk factor for developing this syndrome and for the development of sexual dysfunctioning. Another long-term concern after treatment with radiotherapy, especially for patients with a young age at diagnosis, is the development of a second cancer. The existing literature is conflicting about the relation of radiotherapy for the treatment of rectal cancer and the development of second cancers.

The aims of this thesis were to address and investigate several late effects of radiotherapy in rectal cancer survivors:

1. To evaluate very long-term adverse events and health-related quality of life after preoperative short-course radiotherapy for rectal cancer.
2. To compare the long-term health-related quality of life of rectal cancer patients treated with short-course radiotherapy, with the general Dutch population, and to patients who were treated with chemoradiation.
3. To investigate the long-term probability of developing a second cancer after a primary rectal (or endometrial) cancer in patients treated with or without pelvic radiotherapy.

Chapter 2
In this thesis, long-term effects after rectal cancer treatment were studied using data from the Dutch TME trial. All Dutch patients alive in the trial received HRQL questionnaires at a median follow-up time of 14 years; 478 (82%) patients returned the questionnaire. The HRQL questionnaire consisted of the EORTC QLQ-C30, QLQ-CR29, Low Anterior Resection Syndrome score and additional questions from previous questionnaires used in trial.
Fourteen years after treatment, irradiated patients without stoma reported a higher stool frequency, more faecal incontinence and more use of incontinence pads compared to non-irradiated patients. In addition, more erection difficulties were reported after radiation as well. However, compared to the Dutch population, after correction for age and gender, both the irradiated and the surgery only group reported more sexual dysfunction in males and females. Furthermore, TME trial patients reported a small decrease in general functioning compared to the Dutch population, whereas this difference was not found in the comparison of the two treatment arms in the trial.

Chapter 3
To gain more insight into the development of these symptoms over time a comprehensive longitudinal analysis was performed, from baseline (before surgery or radiotherapy) until 14 years after treatment. To facilitate interpretation symptoms were categorized into: symptoms related to the diagnosis of rectal cancer, surgery, radiotherapy or ageing. Compared to baseline, patients reported a decrease of several symptoms during follow-up, such as difficulty sleeping, tension and difficulty concentrating. From three months onwards, less faecal incontinence was reported; however, irradiated patients reported a continuously higher level of this symptom compared to surgery only patients. In contrast, the level of urinary incontinence increased in all patients over time, with the largest increase observed within the first year, without a difference between both treatment groups.

Chapter 4
The TME trial evaluated two rectal cancer treatments: preoperative short-course radiotherapy followed by TME surgery and TME surgery alone. However, another commonly used treatment strategy that has developed since is preoperative long-course (chemo)radiation. This treatment strategy also led to decreased local recurrence rates, without an effect on overall survival. In the Netherlands, this treatment is currently recommended for patients with locally advanced disease (suspicion of involvement of the mesorectal fascia and/or N2) in whom the objective is to achieve downsizing and down staging. Long-term HRQL after this treatment was assessed in this thesis and compared to results from patients who underwent preoperative short-course radiation in the TME trial. This analysis revealed a comparable impact of both treatment schedules on long-term HRQL up to 5 years after treatment.

Chapter 5
As described above, the Low Anterior Resection Syndrome (LARS) score was also included in the long-term HRQL questionnaire to assess risk factors for bowel dysfunction after treatment. This relatively new and compact questionnaire showed that 56% of the irradiated patients and 35% of the surgery only patients experienced major LARS. Risk factors for developing a major grade of LARS were radiotherapy and age younger than 75 years at follow-up, corresponding to an age of approximately 60 years at time of treatment.

Chapter 6
Another possible long-term effect after rectal cancer treatment is the development of second cancers. To assess the risk of second cancers after pelvic radiotherapy data of the TME trial were combined with data of the randomized Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) 1 and PORTEC-2 trials. In this pooled trial cohort no higher probability of developing a second cancer was found in patients treated with pelvic radiotherapy compared to patients who underwent surgery alone. However, a 2.98 times higher risk of developing a second cancer was found in patients treated for rectal or endometrial cancer compared to the general population. This risk was even 5.5 times higher for patients aged under 60 years at diagnosis, again without a higher risk after radiotherapy.

Chapter 7
In chapter 7 the use, presentation and interpretation of health-related quality of life questionnaires in trials is discussed. All very long-term rectal cancer studies found similar results concerning HRQL and adverse effects, as in studies with a shorter follow-up time. This implies that after five years, or even after two years, besides natural ageing, no large or moderate alterations in HRQL of rectal cancer survivors is expected. Therefore, it is recommended to limit longitudinal HRQL analysis in newly initiated rectal cancer trials to the first two years after treatment. Furthermore, the core of a HRQL survey should be composed of a general cancer questionnaire, measuring general HRQL, with in addition more specific rectal cancer questionnaires. Since a HRQL questionnaire improves physician-patient communication, the continuity of information and the inter-personal relationship supporting the discussion of personal issues, it would be useful to use the HRQL questionnaires in every day clinic. Furthermore, the HRQL findings in this thesis should be used to facilitate shared decision making.

During the recent years rectal cancer treatments are evolved, mainly due to technical advances both in the field of surgery and radiotherapy, resulting in lower side effects and better quality of life. Organ-sparing might be a solution for patients to preserve a large part of their rectum and to avoid having a stoma. The organ preserving could also prevent or decrease the Low Anterior Resection Syndrome. Several organ-sparing strategies have been proposed such as local excision in T1 tumours and chemoradiotherapy followed by a local excision for larger tumours. The comparison in chapter 4 revealed a comparable impact of long-term HRQL after short-course radiotherapy and chemoradiation. Although this was not a randomised comparison, other studies found no advantage of one of these treatment schedules based on acute toxicity, local control and survival as well. However, after short-course radiotherapy with delayed surgery an improved overall survival and less acute toxicity were found compared to long-course chemoradiotherapy. Besides treatment schedules also radiotherapy techniques have evolved. These techniques decrease the irradiated volume, leading to a favourable toxicity pattern compared to conventional radiotherapy. However, it is unlikely that these new techniques lead to a lower prevalence of the major low anterior resection syndrome, since in principal the same length of rectum and sphincter will receive the total radiation dose. Moreover, using these new techniques a larger volume of healthy tissue receives a low radiation dose and one of the concerns that has been raised is that these low radiation doses increase the risk for second cancers. In this thesis no higher probability of developing a second cancer was found in patients treated with pelvic external beam radiotherapy compared to patients who underwent surgery alone.

However, patients included in the pooled trial cohort, described in chapter 6, have a three times higher probability to develop a second primary cancer as could be expected based on the incidence of cancer in the general Dutch population corrected for age and gender, regardless of having been treated with radiotherapy. This indicates that the etiologic factors of the first primary cancer are most likely also involved in the development of the second cancer. These are factors such as lifestyle, environment and host factors. Therefore, it is important to counsel the modifiable behavioural and lifestyle factors of patients. This may decrease both the second cancer risk as well as risks related to the development of co-morbidities. Moreover, in this thesis long-term bowel en sexual dysfunctioning was found after rectal cancer treatment. Unfortunately, most patients who developed these symptoms after treatment are not referred for these. Therefore, more awareness about these treatment-related symptoms

should be created, especially since these symptoms can be treated or reduced in the majority of patients. Since the population of rectal cancer survivors is increasing, a specialised clinic focussing on managing long-term effects after rectal cancer could be valuable. Such a clinic could provide more direct referral to relevant specialists and coordinate care for sexual and bowel dysfunction or to support lifestyle changes.