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

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Chapter 7

Discussion and future perspectives

Health-related Quality of Life

The World Health Organization defined health as "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[1] This definition underlines that health is strongly related to the perception of the individual patient and consequently supports the use of patient reported health-related quality of life. Only patients themselves are able to indicate the impact of their symptoms, since all patients experience HRQL differently. This is demonstrated in the TME trial, where at 14 years after treatment more bowel and sexual dysfunction was found in irradiated patients. However, these dysfunctions did not lead to a lower overall functioning or global health status in irradiated patients as measured with the QLQ-C30.

Presentation

A large variation exists in how patient reported symptoms are presented, and this can have implications for a comprehensive interpretation and limit comparison to other study populations.[2] Outcomes can be shown as single response items, but also in a summated scale based on a few single items. To calculate a summated scale a simple linear scoring system is used, which is found to be robust[3] and likely to be enough for many purposes[4]. Due to this linear scoring system, one altered single item can alter the outcome of the whole scale. If a HRQL scale is de- or increased, the scale provides no information about the cause of this change. Therefore, scales should be interpreted with caution and single items should be used for the interpretation of HRQL as well. Scales are also used to handle missing data. Most often the "imputing" system is applied. If more than half of the items in het scale are reported, the mean value of these items is substituted for the missing item.[5,6] The value of both single items and scales can be presented either as a mean score or dichotomous with categories such as "not at all" versus "to any extent". The dichotomous presentation leads to a loss of data since each category "to any extent" consists of a group of patients that reported a low, intermediate or high level of the symptom. Mean scores take this varying degree of the level of the symptoms into account, but a mean score is more difficult to explain to an individual patient.

Interpretation

When measuring HRQL, it is important to include a general quality of life questionnaire, such as the QLQ-C30,[7] SF-36[8] or the EQ-5D,[9] to put reported symptoms of patients in perspective of their daily life. As shown in the long-term HRQL analysis of the TME trial, specific dysfunctions did not lead to a lower overall functioning. One explanation may be that treatment-related symptoms are too small to have an effect on the functioning scales. Another could be that patients psychologically adapt to their symptoms, a well known phenomenon.[10]

However, it must be noted that five years after treatment more irradiated patients in the TME trial reported impact of their bowel function on daily activities like work or household activities and activities outside the house compared to surgery only patients.[11] Alteration of overall functioning in the trial population can also be determined by comparing HRQL scores of the trial patients to age and gender matched scores of a general population. In the TME trial, at 14 years after treatment, patients in both treatment arms reported a small decrease of maximal 5 points in general health and functioning compared to the Dutch general population. However, patients do not necessarily notice small differences in mean scores, for example if the mean symptom score is only increased by 1 or 2 points out of 100 points. Several studies tried to define a cut off value for what constitutes a minimal clinical relevant difference. Osoba et al. studied changes in the perception of health of patients and the effect on scores of the QLQ-C30 and found that a difference of 5 until 10 points on a scale of 100 points had a clinically small relevance for patients, whereas a difference between 10 and 20 points had a moderate and an alternation greater than 20 points a large effect on the perception of their health.[12] In addition, a study by Ringash et al. reported that patients noticed a positive change in the perception of their health, if the change was about 5% of the maximal instrument score, whereas a negative alteration was only noticed if the change was at least 10% of the maximal instrument score.[13] An alternative and more statistical approach that has been proposed to interpret differences in HRQL scores is the use of the half-standard deviation as a minimum change to detect a clinical relevant difference.[14] Although much research is performed to define a cut off point for clinically relevance, it is still a difficult issue since a clinical cut of point in one population at a specific questionnaire or scale cannot be applied universally. Furthermore, a universal rule for all populations could lead to missing clinically relevant differences to an under- or overestimation of the HRQL.[15]

Recommendations

Apart from our study, only a few studies assessed very long-term HRQL; the Stockholm trials (follow-up time up to 15 years)[16], the Swedish Rectal Cancer

trial (follow-up time up to 10 years)[17] and a study on rectal cancer survivors in the Eindhoven Cancer Registry (follow-up time up to 10 years).[18] In all these studies similar results are found 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 aging, no large or moderate alterations in HRQL of rectal cancer survivors are expected. This knowledge leads to the recommendation to limit longitudinal HRQL analysis in newly initiated rectal cancer trials to the first two years after treatment. Moreover, based on the experience of this thesis, it would ease the extrapolation of findings from one study population to another if similar questionnaires would be used. Furthermore, it is highly recommended to use the same validated questionnaire at each time point for a longitudinal analysis and to include a baseline assessment to show whether symptoms were present before treatment and thus no adverse event of this treatment.[5] Preferably, the core of a HRQL survey should be composed of a general cancer questionnaire with additionally a more specific rectal cancer questionnaire, like the QLQ-CR29 and/or the LARS score. Moreover, since treatment develops and new drugs and therapy options are introduced in the clinic, flexibility should remain to add additional questions anticipating other toxicities.

Measuring HRQL is a valuable addition in cancer treatment, since it improves physician-patient communication, the continuity of information and the inter-personal relationship, which supports discussing personal issues.[19] For these reasons it would be useful to use of HRQL questionnaires in the routine of every day clinic, and not only in trial patients. Individual patient scores can be compared to those of patients who underwent similar treatment or the general population and differences could stimulate patient – physician interaction and direct interventions.[20] This seems to be increasingly feasible, especially since electronic methods for patient reporting are acceptable to patients and provide better quality data than paper methods.[20] Patients are willing to respond to HRQL questionnaires using home internet, mobile devices or at touch screen computers or tablets in the waiting room.[20]

Facilitation of shared decision making

Adverse events found in HRQL analyses should be discussed prior to treatment to facilitate shared decision making. Research demonstrated a considerable inconsistency of the provided information between and within oncologists.[21] With a four-round Delphi-study among patients and oncologists consensus was found which topics should be discussed to support the shared decision making process concerning preoperative radiotherapy. These topics are local recurrences, survival, long term defecation pattern, faecal incontinence, wound healing problems and advice to avoid pregnancy. For male patients erectile dysfunction, ejaculation problems and infertility and for females vaginal dryness, pain during intercourse, menopause and infertility should also be discussed prior to the treatment decision.[22] After providing treatment information, the patient's preferences should be clarified to support decision making, which leads to an increased perceived involvement of patients.[23]

New Developments

In this thesis it has become apparent that all curative treatment options for rectal cancer come at a price. During recent years treatments have evolved, mainly due to technical advances both in the field of surgery and radiation therapy, resulting in lower side effects and better quality of life.

Organ-sparing surgery

Organ-sparing surgery might be a solution for patients to preserve a large part of their rectum and to avoid having a stoma. Furthermore, as shown in chapter 5, a low anterior resection is the main cause of the Low Anterior Resection Syndrome, which consists of a broad spectrum of symptoms related to bowel dysfunction, like clustering, frequent bowel movements and urgency. Organ-sparing surgery could prevent or decrease LARS, since it treats rectal cancer without removing the rectum. Several organ-preservation strategies have been proposed, such as local excision for which acceptable outcomes are found in selected T1 tumours, but, not for high-risk T1 or T2-3 tumours.[24,25] Transanal endoscopic microsurgery is found to be the best surgical technique to facilitate a local excision, mostly due to the superior accessibility, visualisation and precision of resection in comparison to the conventional local excisions like a mucosectomy or an extensive local excision.[26] Another option for organ sparing is chemoradiotherapy followed by a local excision or watchful waiting. Habr-Gama et al. showed that for patients with T2-3 tumours and a clinical complete response after chemoradiotherapy, the wait and watch strategy resulted in acceptable outcomes.[27,28] Since population screening facilitates more early detection of early stage rectal cancer,[29] these results are promising for treatment in this patient category. However, these results could not be reproduced in all

other comparable studies and results of patients with small low rectal cancers cannot be extrapolated to patients with more advanced cancers.[30] For patients with larger T3-T4 tumours it is more likely that residual disease is still present after chemoradiotherapy and consequently organ preservation should not be advised. Also, whereas conventional fluorourarcil-based chemoradiation seems the most suitable regimen for organ preservation, no consensus exists for the optimal radiotherapy schedule yet.[26]

In the ACOSOG trial patients with T2N0 rectal cancer reported a comparable level of leakage of gas, mucus, liquid and solid stools before and one year after chemoradiation followed by a local excision, whereas a higher level of these leakages is reported after TME alone, demonstrating the beneficial effect on HRQL of organ preserving strategies.[31] Currently, HRQL data after organ preservation are scarce, so there is a need for prospective studies.

Treatment schedules in radiotherapy

Currently, surgery remains the most important part of curative rectal cancer treatment. To facilitate surgery of locally advanced tumours with negative resection margins, down sizing and staging of the tumour is necessary. Tumour down staging has been studied both after preoperative chemoradiotherapy and after preoperative short-course radiotherapy. In the TROG trial 326 patients were randomised for either preoperative short-course radiotherapy (5x5 Gy) followed by immediate surgery and 6 courses chemotherapy, or long course preoperative chemoradiotherapy (50.4 Gy and 5-FU), followed by surgery after 4 to 6 weeks and 4 courses of chemotherapy. More downstaging and downsizing of the tumour after chemoradiotherapy was found, but this did not lead to a lower recurrence rate or improved overall survival.[32] Similar results were found in the Polish trial, where the same treatment arms were compared in 312 patients.[33] Most likely, preoperative short-course radiation followed by immediate surgery does not allow enough time for the tumour to regress. Therefore other studies are initiated to investigate downsizing and downstaging after short-course radiation and delayed surgery. In the Stockholm III trial patients who underwent this treatment strategy had a lower tumour stage, a higher rate of complete pathological response and a greater degree of tumour regression than patient treated with short-course radiotherapy followed by immediate surgery.[34] Bujko et al. compared 261 patients receiving 5x5 Gy followed by chemotherapy and delayed surgery versus 254 patients receiving long-course chemoradiotherapy. The overall survival was improved (73% vs. 65%, p=0.046) and less acute toxicity was found after short-course radiotherapy.[35] Currently, the RAPIDO trial investigates if the disease free survival is improved in a study with a similar design. Inclusion of 920 patients was recently achieved and [36] results of this trial have to be awaited. 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. Therefore, long-term oncological outcomes of these new trials should be awaited to provide evidence based information about the optimal treatment schedule.

Radiotherapy techniques

At 14 years after treatment irradiated patients without stoma still reported more faecal incontinence, a higher stool frequency and more use of pads. In addition, males still reported more erection difficulties. The main aetiology of these persisting treatment related symptoms is organ dysfunction caused by the formation of fibrosis and damage to the microvasculature in irradiated tissues. Fibrosis impairs the functioning of the specific organ and supporting nerves, blood and lymph vessels. Most likely, a reduction of the irradiated volumes leads to a reduction of the adverse effects as well. This was already demonstrated for cardiac death and urinary symptoms by comparing the TME trial with the Stockholm I trial. In the TME trial a three or four-field technique was used instead of the two-field technique that was used in the Stockholm I trial. This resulted in a smaller irradiated volume and more bladder sparing in the TME trial leading to no increased urinary incontinence in irradiated patients, whereas increased incontinence was found after radiation in the Stockholm I trial.[37]

Several alternative radiotherapy techniques have been introduced that decrease the irradiated volume. Endorectal brachytherapy, with its characteristic steep dose gradient and different target volume, results in the smallest irradiated volume and might decrease long-term dysfunction. Since this local treatment spares normal tissues even further, it has a favourable toxicity pattern compared to external beam radiation. Despite the smaller target volume after brachytherapy, also an acceptable local control is found: at a median follow-up time of 63 months a local recurrence rate of 4.8% and a disease-free survival of 65.5% were found, which are promising results.[38] At this moment there is a lack of HRQL data after rectal brachytherapy, therefore prospective HRQL studies should be encouraged.

Currently, 3D-conformal radiotherapy, intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) are used, resulting in a more conformal dose delivery and a smaller volume of healthy tissue receiving a high radiation dose. IMRT has already been associated with a significant reduction in acute lower gastro-intestinal tract toxicity compared to conventional techniques.[39] It is not yet known if IMRT contributes to a reduction of long-term side effects as well.

It is unlikely that these new external beam 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. Furthermore, the role of the lateral lymph nodes in the occurrence of local recurrences remains unclear. With the more conformal radiotherapy the dose in this lateral lymph nodes is significantly lower, since they are no part of the classical target volume. Whether this will result in more local recurrences remains to be seen. 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.[40]

Second cancers

In this thesis the risk of developing a second cancer was studied in a pooled trial cohort including over 2500 patients treated with similar radiotherapy techniques to the pelvic area. No higher probability of developing a second cancer was found in patients treated with pelvic radiotherapy compared to patients who underwent surgery alone. A large Surveillance, Epidemiology and End Results (SEER) Registry study evaluated second cancer risk in 647 672 patients with different primary cancers. It was estimated that only 8% of the second cancers in irradiated patients might have been related to radiotherapy, while the majority were related to lifestyle or genetic factors.[41] Studies that investigated the risk of second cancers in Hodgkin survivors found an increasing risk with longer follow-up, especially after 20 years.[42] Although there are probably inherent genetical differences in Hodgkin survivors compared to rectal cancer patients, there is a possibility that more second cancers are found after an even longer follow-up time. The longest follow-up time in this study was 20 years after diagnosis. However, when considering the median age of patients at diagnosis (66 years) it is questionable if a longer follow-up time will provide more clinically relevant information.

Balancing the profits and costs of radiotherapy

Thus, is the benefit of radiotherapy larger than the costs of experiencing long-term side effects? This question will lead to different answers at the individual level. However, the benefit of radiotherapy concerning local control is solid, which reassures use of this treatment. Nevertheless, a strict patient selection for radiotherapy is required to ensure that only patients, who are likely to benefit from it, take the involved risks and receive this treatment. Moreover, both research into new (radiation) techniques, which minimize long-term side effects and research into the prevention and management of these long-term side effects should be encouraged.

Managing long-term treatment-related effects

As described in this thesis, bowel dysfunction is a major problem in many patients after rectal cancer treatment. Clinical management of these long-term symptoms is currently studied and results so far show several treatment options for these symptoms. In the ORBIT trial patients with chronic gastrointestinal symptoms after pelvic radiotherapy were randomised between follow-up by a gastroenterologist-led algorithm-based treatment, follow-up by a nurse-led algorithm-based treatment or they received a detailed self-help booklet. It demonstrated that a gasteroenterologist- or nurse-led algorithm-based treatment resulted in better improvement of the bowel symptoms compared to a self-help booklet.[43] However, unfortunately, most patients who developed gastrointestinal symptoms after treatment are not referred for these symptoms.[44] 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. A key factor in managing this bowel dysfunction is the identification and correction of physiological deficits, which are results of pathological changes. This identification is very important, because one symptom can be triggered by different mechanisms in different parts of the small and large bowel.[44,45] Frequent causes of the gastrointestinal symptoms are small intestinal bacterial overgrowth, bile acid malabsorption, insufficiency of the pancreas and rectal bleeding.[46]

Sexual dysfunction after pelvic radiotherapy could be subdivided into desire and arousal difficulties, sexual pain, and orgasmic difficulties. For all categories specific treatments are available ranging from hormone replacement, vaginal

moisturisers, phosphodiesterase type 5 inhibitors and vaginal dilator therapy to psychosexual therapies (such as scheduled intimacy), psychological therapies (like mindfulness and cognitive behavioural therapy), and couple therapy. However, also long-term sexual difficulties are not always routinely discussed in busy oncology clinics. It was found that use of patient reported outcomes, like HRQL questionnaires, helped to structure a patient-focused conversation with regard to sexual dysfunctionig.[47] In addition, discussing the HRQL questionnaires facilitates improvement of the inter-personal relationship between physician and patient, which enhances the dialogue about personal issues like sexuality.[19] Moreover, in the majority of patients, sexual dysfunctioning is multifactorial, and a multidisciplinary approach of these problems should be encouraged.

Another concern for which more awareness should be created is the increased risk of rectal cancer patients to develop a second cancer. 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. For patients aged under 60 years at diagnosis, this risk was even increased to a 5.5 times higher probability. 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 (e.g. genetic predisposition).[48] 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. Patients should be actively referred to for instance exercise trainers and dieticians to support lifestyle interventions.[49]

For survivors of the Hodgkin lymphoma a late effects outpatient clinic, called 'Better', has been established, reflecting the need of patients for long-term care and counselling. Since the population of rectal cancer survivors is increasing, a specialised clinic focussing on managing long-term effects after rectal cancer could be valuable as well. Such a clinic could provide more direct referral to relevant specialists and coordinate care for sexual and bowel dysfunction or to support lifestyle changes. Preferably, all rectal cancer patients should be once invited to this clinic to evaluate their health status after treatment. Obviously, after this first evaluation, more consultations should be arranged if necessary.

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