Health-related quality of life 14 years after preoperative short-term radiotherapy and total mesorectal excision for rectal cancer: Report of a multicenter randomised trial

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Abstract  Background: Preoperative short-term radiotherapy (PRT) in combination with total mesorectal excision (TME) has shown to improve local control in rectal cancer treatment, however without a survival benefit and at the cost of increased morbidity. The current study investigates the long-term health-related quality of life (HRQL) of patients 14 years after treatment in the Dutch TME trial.
Methods: In the TME trial (1996–1999) 1530 Dutch patients with rectal cancer were treated with TME and randomly assigned to PRT (5 × 5 Gy). In 2012 HRQL was evaluated in surviving patients (n = 606) using a questionnaire combining EORTC QLQ-C30, EORTC QLQ-CR29 and additional questions.
Findings: Results were obtained from 478 patients (82%), with a median follow up of 14 years. PRT + TME patients without stoma reported more faecal leakage and higher stool frequency, resulting in increased need of pads. Furthermore, irradiated males reported more erection problems. However, radiotherapy did not have negative effects on overall functioning. Compared with Dutch population, patients in both treatment arms reported a small decrease in overall functioning and males reported less sexual activity, interest and enjoyment and more
erection difficulties. Irradiated females reported more vaginal dryness and more pain at intercourse compared with Dutch population.

**Interpretation:** Long-term HRQL evaluation shows that treatment-related symptoms are still present 14 years after treatment for rectal cancer. Radiotherapy increased bowel dysfunction in patients without stoma. Compared with the Dutch population, both groups reported increased sexual dysfunction. Despite these treatment-related symptoms, there was no difference in overall functioning and global health between TME and PRT + TME.
contained items about bowel function, stoma function, urinary function, impact of bowel and urinary dysfunction, and level of satisfaction with bowel, stoma and urinary function. Questions were also asked about pain in the back, buttock, legs and hips, stiffness of the hip, walking difficulties, the use of walking aids and comorbidities [6]. In order to acquire more detailed information these additional questions were included in the current questionnaire and scores were transformed into binary outcome measures (i.e., only ‘no’ was no, all other scores were considered as yes).

2.3. Statistics

All data were analysed with IBM SPSS Statistics, version 20.0. To compare characteristics between the treatment groups the independent \( t \) test was used for continuous variables and the \( \chi^2 \) test for categorical variables. HRQL analysis and handling of missing values were done according to the guidelines provided by the EORTC Quality of Life Group [18]. Mean scores of the treatment groups were compared using the Mann–Whitney \( U \) test. For categorical items the \( \chi^2 \) test was used. Data from the Dutch norm population [19] were matched for age and gender and compared with both treatment groups by a linear regression model. Norm data were available for the EORTC QLQ-C30 and for questions about sexuality [19].

All patients who provided information about sexual symptoms were included in the sexual analyses. To guard against false-positive results due to multiple testing, a two-sided \( P \) value of .01 was considered statistically significant. Differences in mean scores were interpreted as clinically relevant but small, if the differences were between five and 10 points on a scale of 100 points. A difference between 10 and 20 points was indicated as moderate and a difference greater than 20 points was interpreted as large [20].

2.4. Role of the funding source

The funding sources did not have any role in the data collection, analysis, interpretation or writing of the manuscript.

3. Results

3.1. Study population and compliance

Of 1530 Dutch study patients, 606 were still alive in July 2012. Nineteen patients refused further participation on a previous questionnaire in 2003 and four patients were untraceable, leaving 583 patients who were sent a HRQL questionnaire (Fig. 1).

Of these, 478 returned the questionnaire, resulting in a response rate of 82%. Among the responders, one TME patient received chemoradiation and one TME patient received postoperative 30 Gy instead of 50.4 Gy, and 10 TME patients received postoperative chemotherapy. In the PRT + TME group, 14 patients received a total dose less than 25 Gy, and 11 patients received additional chemotherapy. The median follow-up time since surgery was 14 years for the responders, and 15 years for the non-responders (range 12–17 years). Patient characteristics are equally balanced between responders and non-responders (table 1).

Overall, the treatment groups did not differ significantly with regard to questionnaire response rates and missing items. Questionnaires were complete for all items of the EORTC QLQ-C30 in 82.2% of the responders,

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![ Consort diagram of study patients.](image_url)
in 76.6% for the EORTC QLQ-CR29 without sexual items and in 59.8% for all questions used in the 2003 HRQL analysis. When allowing up to two missing items, these rates were 95.1%, 92.4%, and 84.6% respectively. Sexually active women (29.9%) completed all sexual items in 84.7%, and sexually active men (40.9%) completed all sexual items in 91.3%. Non-irradiated patients were slightly younger than irradiated patients (median age 74 years in TME versus 77 years in PRT + TME; \( P = .04 \)), but all other patient characteristics were well balanced between the treatment arms (Table 1).

### 3.2. Patient functioning

No significant differences in mean scores of EORTC QLQ-C30 functioning scales and global health status were found between the treatment arms. However, compared with the Dutch population both treatment groups reported lower mean scores for emotional, cognitive, and social functioning. All differences were small in terms of clinical relevance. The PRT + TME patients also reported a small decrease in physical functioning compared with the Dutch population (difference −5.9 points, \( P < .001 \); table 2 and Fig. 2A).

### 3.3. Symptoms

While there were no differences in bowel symptoms between treatment groups in patients with a stoma, more PRT + TME patients without stoma had an increase in stool frequency (mean PRT + TME 26.3 versus TME 19.4); this difference is mainly explained by more PRT + TME patients reporting the response option a little (during the day, PRT + TME 41.4% versus TME 28.6%). Furthermore, TME patients had less faecal leakage (72.6% not at all after TME compared to 54.3% after PRT + TME, Table 3) and less urge for defecation, less defecation within 1 h of the last bowel opening, and less anal mucus loss, leading to lower frequency of use of pads for faecal leakage (Table 4). No significant differences were found in urinary function between the treatment arms (Table 4). Furthermore, no differences were reported in pain in the back, buttock, legs and hips, and in use of walking aids between the treatment arms. However, a trend was shown towards an increase in walking difficulties after...
Higher scores for functioning indicate better functioning. For the symptom items, a higher score reflects a higher level of symptoms and decreased HRQL. A negative difference in functioning indicates worse functioning in the treatment arms and a positive difference for symptoms indicates a higher level of symptoms in the treatment arms compared to Norm.

**Abbreviations:** PRT, preoperative short-term radiotherapy; TME, total mesorectal excision; Norm, age and gender matched Dutch population.

* Difference between PRT + TME and TME.
\(^1\) Difference between PRT + TME and Norm.
* Difference between TME and Norm.

PRT + TME (53.9% after PRT + TME compared to 40.5% after TME, \(P = .02\)). Compared with the Dutch population, differences in mean scores of EORTC QLQ-C30 symptoms were found. Patients in both treatment arms indicated more fatigue, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea, while indicating less pain. However, all these differences were small in terms of clinical relevance (Table 2, Fig. 2B and C).

### 3.4. Sexual functioning

Of all males, 40.9% reported to be sexually active. A significant increase was found in erection difficulties in the irradiated group (50.5% very much after PRT + TME compared to 29.8% very much after TME). Compared with the Dutch population, both males treated with PRT + TME or TME alone reported significantly less interest in sex, less sexual activity, less enjoyment of sex, and more erection difficulties: the difference in erection difficulties is large, whereas the difference in sexual interest is moderate in terms of clinical relevance (Table 2, Fig. 2B and C).

Of all females, 29.9% reported to be sexually active. Irradiated females reported a trend towards more pain during intercourse (7.5% quite a bit and 12.5% very much after PRT + TME compared to 0% and 5.4% respectively after TME), and decreased extent to which sex was enjoyable. Compared with the Dutch population, irradiated females reported a significant, clinically large difference in enjoyment of sex and pain during intercourse, and a clinically moderate difference in vaginal dryness, whereas this was not found in non-irradiated females. In addition, irradiated females reported a clinically large decrease in extent of enjoyment of sex, and non-irradiated females a small decrease compared with the Dutch population (Table 5, Fig. 2D and E).

### 4. Discussion

This analysis of patient-reported HRQL in the Dutch TME trial shows that treatment-related symptoms are still present at 14 years after treatment for rectal cancer, while overall patient functioning and global health are similar between the treatment groups. After PRT + TME, patients without stoma reported increased bowel dysfunction compared with TME. Compared with the Dutch population, both treatment groups reported increased sexual dysfunction and a small decrease in quality of life.

Our results provide unique information about the very long-term HRQL of patients treated for rectal cancer using validated questionnaires with a high response rate (82%). To our knowledge, only one study reported HRQL of rectal cancer survivors after more than 10 years [12] and three observational studies reported long-term anorectal and colorectal function after 10 years [9,21,22]. However, patients included in these studies did not undergo surgery according to the TME technique and in two studies patients underwent postoperative radiotherapy instead of preoperative radiotherapy [21,22]. Moreover, HRQL of both treatment arms...
in our study was compared to age and sex matched Dutch population data.

Our present findings are consistent with the previous reported findings of increased bowel dysfunction after PRT + TME at 2 and 5 years after treatment in this trial [6,23]. The data are also in line with other studies that reported long-term bowel dysfunction [9,10]. In a study that included 340 patients of the Eindhoven Cancer Registry up to 10 years after treatment, more gastrointestinal and defecation problems (EORTC QLQ-CR38) were found after PRT + TME compared with patients who only underwent surgery [11]. In the Stockholm trials, patients who underwent PRT and anterior resection, reported more faecal incontinence compared to the surgery only patients (57.1% after PRT + surgery versus 26.2% after surgery alone) [12]. Bowel dysfunction can be caused by different mechanisms. First, muscles of the pelvic floor can be impaired by fibrosis caused by radiotherapy, resulting in a weaker pelvic floor and a weakening of the anal sphincter and therefore in more faecal leakage. Second, the myenteric plexus in the internal anal sphincter can be damaged due to PRT, which impairs impulse conduction in sacral and pudendal nerves [9]. The combination of the muscle and nerve impairment is suggested to cause a stiffer and smaller neorectum after radiotherapy [24], which can lead to a higher pressure in the neorectum even when just small

Fig. 2. Mean scores of treatment arms compared to the mean scores of the Dutch population. Abbreviations: PRT, preoperative short-term radiotherapy; TME, total mesorectal excision; Norm, age and gender matched Dutch population. Higher scores for functioning indicate better functioning. For the symptom items, a higher score reflects a higher level of symptoms and decreased HRQL.
faecal volumes are involved. This results in a decreased capacity for the neorectum to act as a reservoir and consequently leads to more frequent defecation within 1 h and a higher stool frequency.

In this study, irradiated men reported to have more erection difficulties compared with non-irradiated men at 14 years after treatment, which confirms the previous analysis of this trial [23]. Sexual function of rectal cancer survivors was also assessed in a study of the Norwegian Rectal Cancer Registry (NRCR). Patients were included if they had been treated with pre- or postoperative (chemo-) radiation or with surgery only, and at 5 years after treatment a higher prevalence of erectile dysfunction after radiation was found (86% in irradiated males versus 55% in non-irradiated males) [8]. With regard to females in the NRCR study, more vaginal dryness (50% after radiation versus 24% after surgery only), dyspareunia (35% versus 11%) and reduced vaginal dimension (35% versus 6%) were found after radiotherapy [7]. In the previous analysis of the TME trial 2 years after treatment, females reported problems with lubrication and dyspareunia after PRT + TME as well [23]. However, 14 years after treatment, no difference in vaginal dryness was found between the treatment arms. When comparing patients treated for rectal cancer with the Dutch population, all treated males reported less interest in sex, less sexual activity, decreased extent to which sex was enjoyable and more erection difficulties. Treated females also reported a decreased extent to which sex was enjoyable. Furthermore, irradiated females reported more vaginal dryness, and more pain at intercourse compared with the Dutch population. In the study using data from the Eindhoven Cancer registry, sexual function of patients 4 years after treatment was compared with the Dutch population. This study found results pointing in the same direction, but did find a difference in female sexual function and no difference in sexual enjoyment of males. However, no surgery only group was included in this analysis [25].

Despite the increased bowel symptoms and erection difficulties in male patients in the irradiated group, scores for general health status and functioning scales were not different from the non-irradiated group. This was also found in two other studies in which patients were treated with surgery alone or with additional PRT [11,12]. When HRQL is compared between PRT + TME patients and patients who received preoperative (Polish trial) [26], or postoperative chemoradiation (MRC CR07/NCIC CTG C016) [27], no differences were reported either. In addition, previous analysis of the TME trial did not find differences in overall functioning and general health status between the treatment arms [23]. Possible explanations for why bowel and sexual dysfunction after PRT did not impact on general health status and functioning scores compared with TME are: firstly, patients adapt to their symptoms, especially 14 years after treatment; secondly, the impact of the symptoms is too small to have an effect on the more general functioning scales of the QLQ-C30.

In the Stockholm trials, more urinary incontinence was demonstrated in the PRT + surgery group [12], a finding that was not observed in our study. Because the Stockholm trials included a higher proportion of females (46.0%) compared to our study (41.2%), an additional analysis was performed in female patients,
which again did not find a difference between PRT + TME and TME. In the Stockholm trials, 32.4% of the patients were originally included in the Stockholm I trial. In this trial patients received preoperative radiotherapy (5 × 5 Gy) using a two-field technique. With this technique a larger part of the bladder is included in the radiation field compared to patients irradiated with a three or four-field technique. Other large randomised studies, which used the three or four-field technique, did not find major effects on the urinary function either [6,10].

As mentioned above, radiation technique is relevant for the risk of treatment-related toxicity. When irradiated volumes are reduced, adverse effects reduce as well, as can be seen when the TME trial is compared with the Stockholm I trial [28]. With the introduction of 3D-conformal radiotherapy and intensity-modulated radiotherapy, damage to adjacent healthy tissue can be minimised, which results in less acute bowel toxicity [29]. Although likely, it is not yet clear if these new radiation techniques also decrease long-term treatment-related toxicity. Therefore, optimal patient selection for radiotherapy is required, ensuring that only patients who are most likely to benefit from radiotherapy should receive this treatment. In addition, a recent trial found that bowel function could be improved with an intervention by a gastroenterologist or nurse during follow-up, compared to a self-help booklet [30]. This result shows that in the follow-up of patients treated for rectal cancer specific attention should be paid to functional outcome.

This very long-term HRQOL analysis shows that 14 years after treatment for resectable rectal cancer, patients still experience negative effects of their treatment. PRT + TME patients without stoma reported more bowel dysfunction than TME patients, and both treatment groups reported more sexual dysfunction than the norm population. Finally, both treatment arms showed a clinically small decrease in overall functioning and global health status compared to the norm population. These findings can be used to provide newly diagnosed rectal cancer patients with information about their possible long-term morbidity and health status after PRT + TME in order to make an informed decision about the risks and benefits of adjuvant radiotherapy.

Conflict of interest statement

None declared.

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References


