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

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# Chapter 5

## Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: report of a multicentre randomised trial

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## Abstract

*Background*
We investigated very long-term bowel function after total mesorectal excision (TME) with or without preoperative short-course radiotherapy (PRT) for rectal cancer, the risk factors for bowel dysfunction, and the association of bowel dysfunction with health-related quality of life (HRQL).

*Methods*
In the TME trial (1996-1999), 1530 Dutch rectal cancer patients were randomised to TME preceded by 5x5 Gy PRT, or TME alone. A set of questionnaires was sent to surviving patients (n=583) in 2012. The questionnaires included the Low Anterior Resection Syndrome Score (LARS score), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) and colorectal module (QLQ-CR29). The LARS score range is divided into 'no LARS', 'minor LARS', and 'major LARS' categories in ascending severity of bowel dysfunction. Potential risk factors for Major LARS were tested on multivariable analysis. HRQL was compared between LARS score categories.

*Results*
Of 478 respondents, 242 non-stoma patients were included in the present analysis. Median time since treatment was 14.6 years, and median age at follow-up was 75 years. Major LARS was reported by 46% of all patients (56% PRT+TME vs. 35% TME). PRT (odds ratio (OR) 3.0, 99% CI 1.3-6.9) and age ≤75 at follow-up (OR 2.4, 99% CI 1.1-5.5) increased the risk of major LARS. Gender, tumour height, anastomotic leakage, type of anastomosis, interval since treatment, and comorbid diabetes were not significant. Patients with major LARS fared worse in many HRQL domains ($P$<0.01, score difference >5% of score range).

*Conclusions*
A considerable proportion of non-stoma patients endure major LARS years after TME. PRT and age ≤75 at follow-up pose further risks of Major LARS in addition to surgery. Major LARS is associated with reduced HRQL.






## Introduction

The introduction of total mesorectal excision (TME) was a major breakthrough in the treatment of rectal cancer, leading to substantially improved local control and survival.[1,2] The additional benefit of preoperative short-course radiotherapy (PRT) has been confirmed in the TME and Medical Research Council CR07 trials: PRT greatly reduces local recurrence when used in addition to TME, but does not change overall survival.[3-6]

Unfortunately, both TME and PRT result in side effects, of which bowel dysfunction is the most common and serious, especially given the emphasis on sphincter preservation in rectal cancer treatment. Although numerous studies have explored the impact of rectal cancer surgery and radiotherapy (RT) on bowel function,[7,8] they have often been limited by the instrument used to measure bowel function. Many of the studies used non-validated questionnaires,[7,8] including the five-year follow-up of the TME trial, in which irradiated patients reported poorer bowel function.[9] Even when validated questionnaires were used, most were faecal incontinence instruments,[7] which only assess the continence aspect of bowel function. However, bowel dysfunction after rectal resection (with or without RT), referred to as anterior resection syndrome or low anterior resection syndrome (LARS), can manifest itself in various symptoms other than incontinence, including frequent bowel movements, urgency and clustering.[10]

A small number of studies have not been bound by these limitations, using validated instruments to examine LARS more comprehensively, beyond faecal incontinence.[11-15] The Low Anterior Resection Syndrome Score (LARS score) is one of such instruments.[16] It is a concise questionnaire designed for quick evaluation of a diverse range of LARS symptoms that patients find the most bothersome, and is suitable for routine use in clinical settings.[16] These studies found that LARS is prevalent, and identified several risk factors for severe LARS in addition to surgery, the strongest of which was PRT.[11,12,15] Nevertheless, these studies were observational, and their findings need to be verified in a randomised controlled trial. Moreover, the longest median follow-up period of these studies was around five years; however, a large proportion of the increasing number of rectal cancer survivors has been living > 1 decade after treatment. The TME trial has shown that the ten-year overall survival was 48% for the PRT+TME group and 49% for the TME group.[5] Little is known about the impact of rectal cancer treatment on bowel function after such an extended period.

Because of these evidence gaps, we performed the present follow-up study of the TME trial cohort more than 14 years after treatment. The primary aims were to rigorously investigate patients' very long-term bowel function using the LARS score, and to determine risk factors for severe LARS. The secondary aim was to examine the association of severe LARS with health-related quality of life (HRQL).

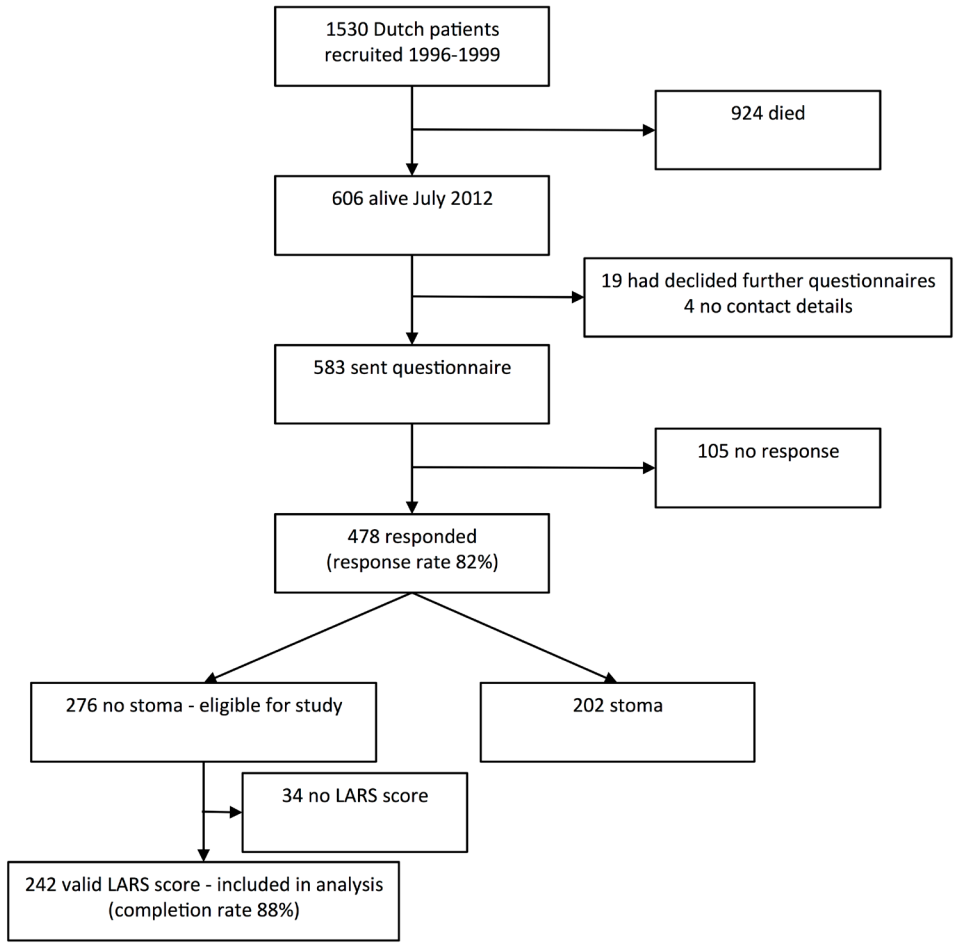


**Figure 1. Flow chart of study patients**
Abbreviations: LARS, low anterior resection syndrome.





## Patients and methods

*Data collection*
The TME trial has been previously described in detail.[3-5] In brief, from January 1996 to December 1999, 1861 patients (1530 from the Netherlands) with clinically resectable rectal adenocarcinoma without evidence of distant metastasis at time of enrolment were randomised to either 5x5 Gy PRT (delivered using a three or four-field technique over 5-7 days) followed by TME within one week, or TME alone. The inferior margin of the tumour had to be located below the level of S1/S2 and not farther than 15 cm from the anal verge.

Because of logistic feasibility, only Dutch patients were followed up in the present study (figure 1). In July to August 2012, at which time the median follow-up duration was 14.4 years, a set of questionnaires was sent by mail to surviving patients who had previously consented to further questionnaire follow-up. Information on vital status was provided by the Central Bureau for Genealogy and patients' general practitioners. Those who did not respond initially were sent a second questionnaire set in September 2012.

Only patients without a stoma were eligible for the study (figure 1). Stoma status was ascertained in the questionnaire set.

### Measures

The questionnaire set contained the following instruments.

*LARS score*
The LARS score was developed from and validated on a large, nationwide cohort of 961 Danish patients.[16] It has subsequently been translated into other languages, including Swedish, Spanish, German, English and Dutch. Through the standardised validation of the former three translated versions (Swedish, Spanish and German), it was found that the LARS score performs equally well in several different European countries, and that as long as the proper translation procedure is followed, validation of a newly translated version would only be necessary if the score is intended for use in cultures dissimilar to the European culture.[17] Despite this, the latter two versions (English and Dutch) are being validated to fully confirm the validity and reliability of the LARS score for these populations. The items and scoring algorithm of the LARS score are shown in Figure 2. All items must be completed for a valid score to be generated. Only patients with a valid LARS score were included in the present analysis (figure 1).

## LARS-score - Scoring Instructions

**Add the scores from each 5 answers to one final score.**

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**Do you ever have occasions when you cannot control your flatus (wind)?**

| | |
|---|---|
| ☐ No, never | **0** |
| ☐ Yes, less than once per week | **4** |
| ☐ Yes, at least once per week | **7** |

**Do you ever have any accidental leakage of liquid stool?**

| | |
|---|---|
| ☐ No, never | **0** |
| ☐ Yes, less than once per week | **3** |
| ☐ Yes, at least once per week | **3** |

**How often do you open your bowels?**

| | |
|---|---|
| ☐ More than 7 times per day (24 hours) | **4** |
| ☐ 4-7 times per day (24 hours) | **2** |
| ☐ 1-3 times per day (24 hours) | **0** |
| ☐ Less than once per day (24 hours) | **5** |

**Do you ever have to open your bowels again within one hour of the last bowel opening?**

| | |
|---|---|
| ☐ No, never | **0** |
| ☐ Yes, less than once per week | **9** |
| ☐ Yes, at least once per week | **11** |

**Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?**

| | |
|---|---|
| ☐ No, never | **0** |
| ☐ Yes, less than once per week | **11** |
| ☐ Yes, at least once per week | **16** |

**Total Score:** _____

**Interpretation:**

**0-20:** **No LARS**
**21-29:** **Minor LARS**
**30-42:** **Major LARS**

**Figure 2. The Low Anterior Resection Syndrome (LARS) Score**



*EORTC QLQ-C30 and EORTC QLQ-CR29*

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) and Colorectal Module (EORTC QLQ-CR29) are well-established HRQL instruments.[18,19] All 15 scales of the EORTC QLQ-C30, and 22 of the 28 EORTC QLQ-CR29 scales (stoma-related scales were excluded) were analysed.

*Statistical analysis*

The proportion of patients in each LARS score severity category was compared between treatment arms (PRT+TME *versus* TME) using the $\chi^2$ test. Also, the proportion of patients choosing each response option in the individual LARS score items was similarly compared. Using clinical judgement and research to date, potential risk factors for severe LARS (major LARS *versus* minor/no LARS) were tested by multiple logistic regression analysis: PRT (yes *versus* no), age (≤median age *versus* >median age), gender (female *versus* male), distance of tumour from the anal verge (<5cm, 5-9.9cm, and ≥10cm), anastomotic leakage (yes *versus* no), type of anastomosis (end-side, end-end, and pouch), time since treatment (years), and the presence of comorbid diabetes (yes *versus* no).

The EORTC HRQL instruments were scored according to guidelines. These scores were compared between the LARS score categories (major LARS *versus* minor or no LARS) using the Mann-Whitney U test.

Statistical significance was set at $P<0.01$ to correct for multiple testing. In line with current evidence, a HRQL score difference of >5% of the score range was considered clinically significant.[20,21] A difference in HRQL had to be both statistically and clinically significant to be deemed significant. The analyses were conducted using SPSS Statistics, version 21 (IBM Corp, Armonk, NY)

## Results

*Patients*

A total of 242 patients were included in the present analysis (figure 1). The median time since treatment was 14.6 years (range 12.6-16.6), and the median age at the follow-up point was 75 years (range 39-95). The patients were equally distributed between the two treatment arms (table 1).

*LARS score*

Overall, major LARS was experienced by 110 of the 242 (46%) of patients, while 54 (22%) had minor LARS, and 78 (32%) reported no LARS. A higher proportion of irradiated patients experienced major LARS (56% vs. 35%, figure 3A). Irradiated patients also fared worse in all individual LARS score items, apart from incontinence for flatus (figure 3B).

*Risk factors for major LARS*

Of all the factors tested in the multivariable analysis, PRT [odds ratio (OR) 3.0, 99% confidence interval (CI) 1.3-6.9] and age ≤75 years at follow-up point (OR 2.4, 99% CI 1.1-5.5) were found to increase the likelihood of major LARS (table 2).

**Table 1. Patient characteristics in each treatment arm**

| | PRT+TME (*N* = 118) | | TME (*N* = 124) | | |
|---|---|---|---|---|---|
| | No. of patients | % | No. of patients | % | *P* |
| **Age, years** | | | | | 0.12 |
| Median | 77.0 | | 73.5 | | |
| Range | 43-95 | | 39-93 | | |
| **Gender** | | | | | 0.83 |
| Male | 64 | 54.2 | 69 | 55.6 | |
| Female | 54 | 45.8 | 55 | 44.4 | |
| **TNM stage**[a] | | | | | 0.29 |
| 0 | 1 | 0.9 | 6 | 4.9 | |
| I | 48 | 41.0 | 48 | 38.7 | |
| II | 30 | 25.6 | 35 | 28.2 | |
| III | 38 | 32.5 | 35 | 28.2 | |
| **Tumour distance from anal verge**[b] | | | | | 0.02 |
| <5cm | 3 | 2.5 | 14 | 11.4 | |
| 5-9.9cm | 58 | 49.2 | 60 | 48.8 | |
| >10cm | 57 | 48.3 | 49 | 39.8 | |
| **Time since treatment, years** | | | | | 0.21 |
| Median | 14.4 | | 14.7 | | |
| Range | 12.6-16.6 | | 12.6-16.5 | | |

Abbreviations: PRT, preoperative short-course radiotherapy; TME, total mesorectal excision; TNM, tumour node metastasis.
[a] For one irradiated patient, TNM stage could not be determined.
[b]For one surgery only patient, tumour distance from anal verge could not be determined.





*HRQL and LARS score*

Patients with major LARS had worse scores than those of patients with minor or no LARS in many of the HRQL domains measured using the EORTC QLQ-C30 and EORTC QLQ-CR29 (table 3).

**Table 2. Potential risk factors for Major LARS**

| | | *N* | OR (99% CI) |
|---|---|---|---|
| **PRT** | | | |
| | Yes | 118 | 3.0 (1.3-6.9) |
| | No | 124 | Reference |
| **Age at follow-up** | | | |
| | ≤ 75 years | 127 | 2.4 (1.1-5.5) |
| | > 75 years | 115 | Reference |
| **Gender** | | | |
| | Female | 109 | 1.7 (0.8-3.7) |
| | Male | 133 | Reference |
| **Tumour distance from anal verge**[a] | | | |
| | < 5cm | 17 | 3.6 (0.7-18.2) |
| | 5-9.9cm | 118 | 1.4 (0.6-3.1) |
| | ≥ 10cm | 106 | Reference |
| **Anastomotic leakage** | | | |
| | Yes | 16 | 1.6 (0.3-8.3) |
| | No | 226 | Reference |
| **Type of anastomosis**[b] | | | |
| | End-side | 145 | 2.5 (1.0-6.6) |
| | End-end | 26 | 2.7 (0.6-11.2) |
| | Pouch | 68 | Reference |
| **Time since treatment** (years) | | 242 | 1.0 (0.7-1.5) |
| **Comorbid diabetes**[c] | | | |
| | Yes | 34 | OR 1.8 (0.6-5.6) |
| | No | 197 | Reference |

Abbreviations: CI, confidence interval; LARS, low anterior resection syndrome; OR, odds ratio; PRT, preoperative short-course radiotherapy.
[a]Tumour distance from anal verge could not be determined for one patient.
[b]Type of anastomosis could not be determined for three patients.
[c]Comorbid diabetes could not be determined for 11 patients.

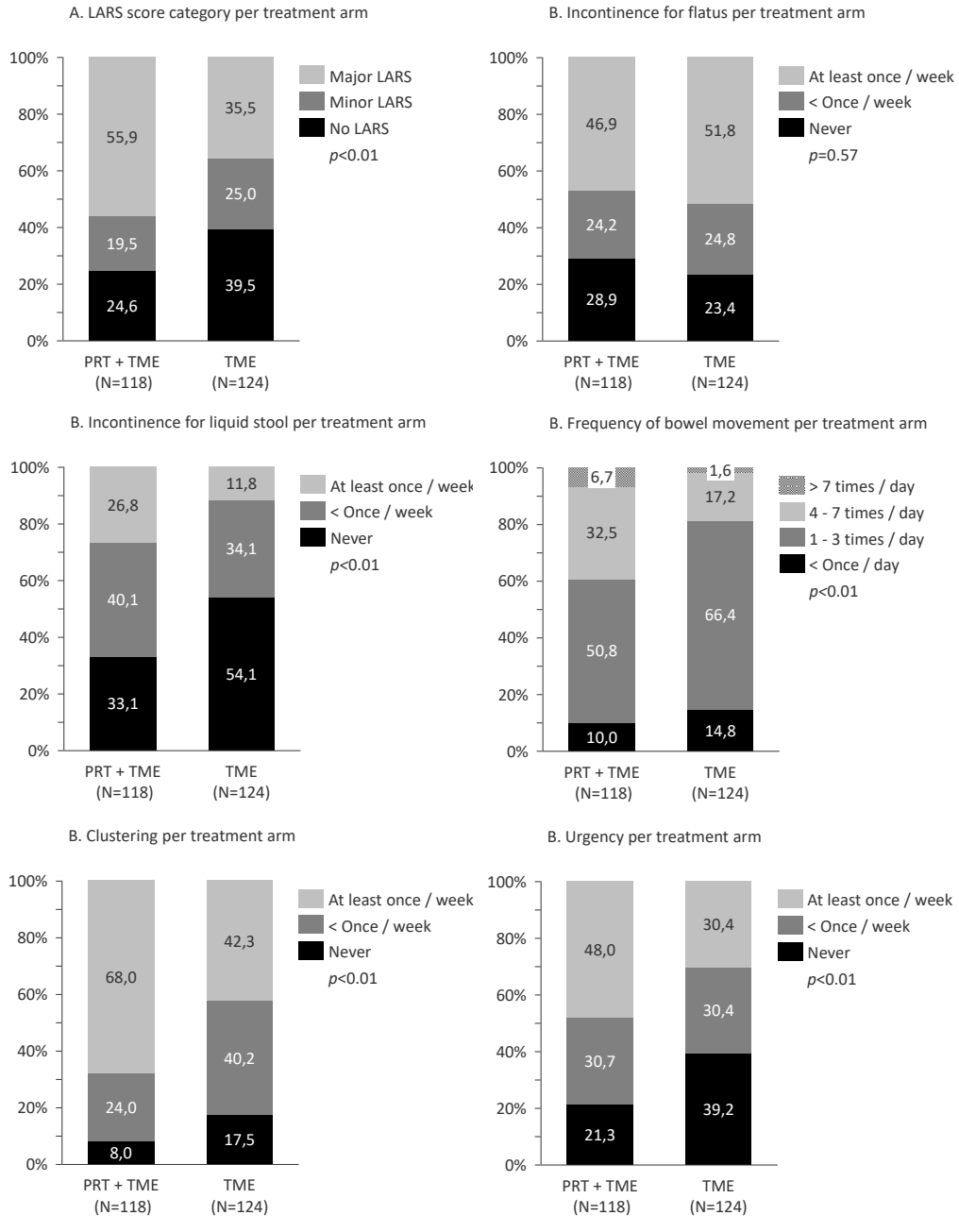


**Figure 3(A) Patient distribution across the LARS score severity categories in each treatment arm (B) Patient distribution across the response options of the individual LARS score items in each treatment arm**

Abbreviations: LARS, low anterior resection syndrome; PRT, preoperative short-course radiotherapy; TME, total mesorectal excision.

**Table 3. Comparison of the QLQ-C30 and QLQ-CR29 scores between the LARS score severity categories**

| | Mean score Major LARS | Mean score Minor/No LARS | *P* | CS |
|---|---|---|---|---|
| **QLQ-C30** | | | | |
| Global health status/QOL* | 73.4 | 80.3 | < 0.01 | Yes |
| Physical functioning* | 80.1 | 82.0 | 0.35 | No |
| Role functioning* | 79.0 | 85.5 | 0.03 | Yes |
| Emotional functioning* | 81.8 | 87.5 | 0.02 | Yes |
| Cognitive functioning* | 80.9 | 87.7 | < 0.01 | Yes |
| Social functioning* | 83.3 | 91.2 | < 0.01 | Yes |
| Fatigue | 27.0 | 18.6 | < 0.01 | Yes |
| Nausea and vomiting | 2.1 | 2.3 | 0.99 | No |
| Pain | 14.5 | 9.7 | 0.04 | No |
| Dyspnoea | 15.0 | 13.6 | 0.89 | No |
| Insomnia | 26.0 | 19.8 | 0.05 | Yes |
| Appetite loss | 5.6 | 6.9 | 0.92 | No |
| Constipation | 20.8 | 12.1 | 0.02 | Yes |
| Diarrhoea | 24.8 | 4.6 | < 0.01 | Yes |
| Financial difficulties | 6.1 | 3.6 | 0.20 | No |
| **QLQ-CR29** | | | | |
| Body image* | 85.2 | 94.4 | < 0.01 | Yes |
| Anxiety* | 77.0 | 85.9 | < 0.01 | Yes |
| Weight* | 85.6 | 88.5 | 0.26 | No |
| Sexual interest (men)* | 68.0 | 70.6 | 0.81 | No |
| Sexual interest (women)* | 80.6 | 78.4 | 0.82 | No |
| Urinary frequency | 33.3 | 25.3 | 0.01 | Yes |
| Blood and mucus in stool | 5.7 | 0.6 | < 0.01 | Yes |
| Stool frequency | 34.1 | 13.8 | < 0.01 | Yes |
| Urinary incontinence | 17.1 | 10.1 | < 0.01 | Yes |
| Dysuria | 2.2 | 1.3 | 0.51 | No |
| Abdominal pain | 13.3 | 3.4 | < 0.01 | Yes |
| Buttock pain | 13.3 | 3.9 | < 0.01 | Yes |
| Bloating | 19.1 | 7.6 | < 0.01 | Yes |
| Dry mouth | 26.0 | 17.2 | 0.03 | Yes |
| Hair loss | 3.2 | 2.8 | 0.98 | No |
| Taste | 4.8 | 2.8 | 0.45 | No |
| Flatulence | 46.3 | 23.2 | < 0.01 | Yes |
| Faecal incontinence | 27.5 | 7.6 | < 0.01 | Yes |
| Sore skin | 17.5 | 3.9 | < 0.01 | Yes |
| Embarrassment | 36.6 | 11.1 | < 0.01 | Yes |
| Impotence | 66.7 | 62.2 | 0.39 | No |
| Dyspareunia | 22.2 | 6.1 | 0.21 | Yes |

Abbreviations: CS, clinically significant; LARS, low anterior resection syndrome; QOL, quality of life.

For the symptom items, a higher score reflects a higher level of symptoms and decreased health-related quality of life.

*Higher scores indicate better functioning and increased health-related quality of life.

## Discussion

Numerous studies have already explored the impact of rectal cancer surgery and RT on bowel function, with two systematic review and meta-analysis reports concluding that TME and PRT negatively affect long-term bowel function.[7,8] The report by Scheer et al[7] derived a 35% pooled incidence of faecal incontinence after curative anterior resection, and pinpointed that PRT was associated with higher rates of post-resection incontinence ($P$=0.006). The report by Loos et al.[8] found a higher rate of stool incontinence after preoperative radio(chemo) therapy and TME than TME alone (relative risk (RR) 1.67, 95% CI 1.36-2.05). Nevertheless, the various studies included in these 2 systematic review and meta-analysis reports adopted different definitions and severity measures of bowel dysfunction. More importantly, the quality of the vast majority of the studies was limited by the instrument used to examine bowel function. Many of the studies used non-validated questionnaires, while among the studies that did use validated questionnaires; also, among the studies that did use validated questionnaires most used a faecal incontinence instrument, such as the Wexner score or the Kirwan score.[7,8] However, LARS is a disorder with heterogeneous symptoms involving more than just incontinence, and even validated faecal incontinence instruments cannot fully capture the complexity of the problem.[16] It has been revealed that urgency and clustering are the most bothersome LARS symptoms for the patient; however, clinicians have tended to underestimate their impact, placing more emphasis on incontinence and frequent bowel movements instead.[22] Therefore, any assessment of LARS that either uses a non-validated questionnaire or a validated one that only focuses on incontinence cannot be considered a truly sound assessment.

Our study is among the few that used validated instruments to comprehensively examine the spectrum of LARS symptoms after rectal cancer treatment.[11-15] However, the other studies are observational, with the longest median follow-up period around five years. Our study stands out for the robust TME trial design and the exceptionally long follow-up. The TME trial was not only randomised and controlled, but also included treatment standardisation and quality control measures.[3] The long follow-up enabled insight into the long-lasting impairment of bowel function beyond a decade after treatment. Furthermore, our study adopts a more stringent significance level ($P$<0.01).

Although our study provides a stronger level of evidence than did the earlier studies, our results should be interpreted in light of other evidence. Two studies have previously used the LARS score to evaluate bowel function after rectal cancer treatment.[11,12] The study by Emmertsen et al. revealed that 46% of patients reported major LARS at 12 months, with neoadjuvant therapy and TME (*versus* partial mesorectal excision) being risk factors.[11] In the population-based study by Bregendahl et al, 41% of patients experienced major LARS after a median follow-up of 54 months. Neoadjuvant therapy, TME, anastomotic leakage, age ≤64 at surgery and female gender were identified as risk factors.[12] Our findings were mostly in keeping with the findings of these studies. In terms of discrepancies, our female gender OR closely resembles that reported by Bregendahl et al. (1.7 *versus* 1.35, respectively), and the narrow CIs overlapped (0.8-3.7 *versus* 1.02-1.79, respectively),[12] suggesting that our non-significant female gender result may not be definitive. Bregendahl et al. concluded that anastomotic leakage should be considered a risk factor (OR 2.06, 95% CI 0.93-4.55), with the justification that infrequent occurrences ($n$=29) accounted for the borderline non-significance.[12] The occurrence of leakage were also few in our study ($n$=16), yet it could not be deemed a risk factor owing to the wide, non-significant CI (OR 1.6, 99% CI 0.3-8.3). The same applies to tumour height. Few patients had a tumour distance <5cm in our study ($n$=17), and despite yielding the highest OR (OR 3.6, 99% CI 0.7-18.2), the CI was very broad and non-significant. Although not directly comparable, it is worth mentioning that tumour height was previously found in the TME trial to be associated with faecal incontinence at five years, but only in patients treated with PRT.[23] The role of female gender, anastomotic leakage and tumour height in major LARS require further clarification.

Only non-stoma patients were included in the present study. However, it is known that some patients will subsequently receive a colostomy, even after initial restoration of intestinal continuity, because of severe bowel dysfunction. These patients would have been excluded from the present study, and it is likely that the patients in the PRT+TME group would have been more affected by this effect, which might have reduced the difference in major LARS rates observed between the two treatment groups.

The finding of younger age increasing the risk of major LARS seems to be against the natural deterioration of bowel function with age. Selection bias could have been at play, with younger patients receiving more sphincter-preserving procedures. However, this was not the case in our study, because the age at treatment between patients undergoing low anterior resection and abdominoperineal resection, as well as age at follow-up between those with and without a stoma were no different (data not shown). One plausible explanation

is that elderly individuals have poorer bowel function at baseline, and hence would be less perceptive to changes after treatment.[12] This can be verified in future longitudinal studies by obtaining the baseline LARS score.

Our study is not the first to show the association between bowel dysfunction, measured using the LARS score, and HRQL, measured using the EORTC QLQ-C30. The study by Emmertsen et al. demonstrated a close relationship between the two, focusing on the comparison of EORTC QLQ-C30 scores between the major LARS and no LARS groups.[11] In another study by Juul et al, the EORTC QLQ-C30 scores were significantly (both statistically and clinically) different between the major LARS and no LARS groups, and between the major LARS and minor LARS groups, but not between the no LARS and minor LARS groups.[24] The findings by Juul et al. support our rationale of comparing EORTC QLQ-C30 scores for patients of major LARS versus no or minor LARS.[24] The conjoint application of the more disease-specific EORTC QLQ-CR29 adds rigour to our assessment.

The TME trial has established that PRT decreases local recurrence by more than half (10-year cumulative incidence 5% *versus* 11%).[5] The present very long-term follow-up study had demonstrated that such benefit is achieved at the expense of a threefold increase in the odds of severe bowel dysfunction that persists even more than 14 years after treatment. Local recurrence causes disabling symptoms, is challenging to treat, and treatment is associated with substantial morbidity. It would be hard to argue that LARS is more detrimental than local recurrence or that PRT should not be offered to those at higher risk of LARS. The definitive prevention and treatment of LARS is colostomy. Although the common impression is that HRQL is superior with sphincter preservation than with colostomy after rectal cancer resection, a Cochrane review could not draw firm conclusions about this,[25] and the compromised HRQL in patients with major LARS could have been the reason. It has been revealed that the presence of a stoma and faecal incontinence may be similarly troublesome for patients.[26] However, a large number of non-stoma patients who suffer from faecal incontinence still prefer this to life with a stoma.[27] Therefore, patient communication is key. Our study can be used to better inform patients of the possible long-term consequences of PRT. Ultimately, treatment decisions must be based on both patient preference and clinical judgement, after a thorough deliberation of the benefit and risks of adverse effects. Bowel function should be routinely and systematically assessed at follow-up visits, and patients should be educated about LARS. Several options for managing LARS are available before resorting to colostomy, including transanal irrigation and sacral neuromodulation, which are showing promising results, however more research is required to consolidate their effectiveness. Finally, additional research is needed to corroborate whether enhanced radiation and surgical techniques lead to less long-term bowel dysfunction.

The present study has illustrated long-term survivorship issues in rectal cancer. At 14.6 years, almost half (46%) of the Dutch TME trial patients without a stoma experienced major LARS. Although a greater proportion of irradiated patients experienced major LARS (56% *versus* 35%), the finding that one third of the non-irradiated patients had major LARS indicates that TME surgery was most probably the main contributing factor, with PRT and age ≤75 at follow-up point posing additional risks. Major LARS was associated with poorer HRQL.

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