

Quality of Life and Bowel Dysfunction after Transanal Endoscopic Microsurgery for Rectal Cancer

Citation for published version (APA):

van Heinsbergen, M., Leijtens, J. W., Slooter, G. D., Janssen-Heijnen, M. L., & Konsten, J. L. (2020). Quality of Life and Bowel Dysfunction after Transanal Endoscopic Microsurgery for Rectal Cancer: One Third of Patients Experience Major Low Anterior Resection Syndrome. *Digestive Surgery*, 37(1), 39-46. <https://doi.org/10.1159/000496434>

Document status and date:

Published: 01/01/2020

DOI:

[10.1159/000496434](https://doi.org/10.1159/000496434)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Quality of Life and Bowel Dysfunction after Transanal Endoscopic Microsurgery for Rectal Cancer: One Third of Patients Experience Major Low Anterior Resection Syndrome

Maarten van Heinsbergen^a Jeroen W. Leijtens^b Gerrit D. Slooter^c
Maryska L. Janssen-Heijnen^{d,e} Joop L. Konsten^a

^aDepartment of Surgery, VieCuri Medical Centre, Venlo, The Netherlands; ^bDepartment of Surgery, Laurentius Medical Centre, Roermond, The Netherlands; ^cDepartment of Surgery, Maxima Medical Centre, Veldhoven, The Netherlands; ^dDepartment of Clinical Epidemiology, VieCuri Medical Centre, Venlo, The Netherlands; ^eDepartment of Epidemiology, Maastricht University Medical Centre, GROW School for Oncology and Developmental Biology, Maastricht, The Netherlands

Keywords

Colorectal cancer surgery · Transanal endoscopic microsurgery · Low anterior resection syndrome · Quality of life

Abstract

Background/Aims: The low anterior resection syndrome (LARS) severely affects quality of life (QoL) after rectal cancer surgery. Studies investigating LARS and the effect on QoL after transanal endoscopic microsurgery (TEM) for rectal cancer are scarce. The aim of our study was to assess bowel dysfunction and QoL after TEM. **Methods:** Seventy-three patients who underwent TEM for stage I rectal cancer were included in this single-centre, cross-sectional study. Bowel dysfunction was assessed by the LARS-Score, QoL by the European Organization for the Research and Treatment of Cancer QLQ-C30 and -CR29 questionnaires. **Results:** Fifty-five respondents (75.3%) could be included for the analyses. The median interval since treatment was 4.3 years, and the median age at the follow-up point was 72 years. “Major LARS” was observed in 29% of patients and “minor LARS” in 26%. Female gender (OR 4.00; 95% CI 1.20–13.36), neo-adju-

vant chemoradiotherapy (OR 3.63; 95% CI 1.08–12.17) and specimen thickness in millimetres (OR 1.10 for each mm increase in thickness; 95% CI 1.01–1.20) were associated with the development of major LARS. Patients with major LARS fared worse in most QoL domains. **Conclusion:** This is the first study demonstrating major LARS after TEM treatment for rectal cancer, with a negative effect on QoL, even years after treatment. Our data provides an adequate counselling before TEM in terms of postoperative bowel dysfunction and its effect on QoL.

© 2019 S. Karger AG, Basel

Background

The relative fraction of patients with stage I rectal cancer has increased due to screening tests for colorectal cancer [1]. The low anterior resection with total mesorectal excision (TME) is still the gold standard for treatment of rectal cancer. However, LAR can be associated with bothersome changes in bowel habits like faecal incontinence, frequent bowel movements, urgency and emptying difficulties better known as low anterior resection syndrome

(LARS), reported in 60–90% of the patients [2, 3]. A previous study has shown that major LARS is associated with decreased quality of life (QoL) [3]. Therefore, there is a growing demand for less invasive organ preserving surgery by using local excision. Recently, the GRECCAR-2 trial did not demonstrate oncological superiority of local excision over TME in a prospective randomised study, making functional outcome even more important [4]. Present guidelines only recommend local excision as a safe and effective alternative for TME in T1 tumours without lymph node invasion. With improving neo-adjuvant treatment options that lead to downstaging, a larger group of patients can be treated successfully with the rectum preserving surgery. Transanal endoscopic microsurgery (TEM), in which a full thickness excision of the residual tumour is performed, is currently the preferred rectum preserving technique. As we can offer patients both TEM and TME as therapeutic options, we should be able to perform an adequate preoperative counselling in terms of both oncological outcome and postoperative functional complaints. This might be important, since physicians are not truly aware what bothers patients the most [5]. Moreover, a recent study pointed out that patient-related outcome measurements might be more important than the oncological outcome [6]. Studies investigating LARS and the effect on QoL after TEM for rectal cancer are lacking. The aim of our study was to assess bowel dysfunction and QoL after TEM. The LARS scoring system is the only patient-related outcome measurements describing bowel dysfunction from the patient's perspective. We investigated the prevalence of LARS including associations with patient, tumour and treatment characteristics as well as the association between LARS and QoL.

Methods

Data Collection

All patients >18 years who underwent a TEM for a clinical stage I (T1N0M0 & T2N0M0) [7] rectal cancer in Laurentius Medical Centre Roermond, a referral centre for TEM in the Southern part of the Netherlands between January 2008 and December 2013 were included. Staging was based on both MRI and colonoscopic biopsy. Exclusion criteria were as follows: presence of a stoma; the necessity of a completion TME within the follow-up period; recurrent disease; inadequate Dutch language skills; and intellectual disability or dementia. Also, patients who underwent other operations than TEM for rectal cancer or whose lesions could not be resected were excluded. The following patient, tumour and treatment characteristics were obtained from patient records: gender, age at surgery (categorized as ≤ 75 vs. > 75 years), marital status (married vs. single/widowed), time since operation (registered in days and classified in years), tumour

height measured by MRI (lower rectum: < 5 cm, mid rectum 5–9.9 cm, high rectum: 10–14.9 cm), clinical tumour stage (TNM: T0N0, T1N0, T2N0), neo-adjuvant (chemo) radiotherapy (5×5 or 25×2 Gy with Capecitabine monotherapy), operative complications (Clavien-Dindo scale) and ASA- classification (1–6). Specific data on the type of procedure was obtained from surgical reports. Participants were contacted through a letter explaining the aim of the study together with the questionnaires and a prepaid return envelope. The letters were sent between September 2015 and April 2016 to allow their bowel function to have regained stability [8–10]. The study was approved by the hospitals' Ethical Committee.

Surgical Technique

All surgical procedures were performed by the same team of 2 surgeons using a TEM equipment (Richard Wolf GmbH, Knittlingen, Germany) under general anaesthesia. Patients were positioned in lithotomy, prone, or lateral decubitus position depending on the location of the lesion. Operation was started by diathermic marking of the resection margins 1 cm around the lesion, followed by a full thickness removal of the specimen with the Harmonic energy device. Rectal wall defect was closed with a running suture if possible. Removed lesions were pinned on a board, measured, and sent for pathology examination.

Measures

The LARS score, an internationally validated tool, was used to assess bowel dysfunction [11]. It consists of 5 questions that have a high convergent validity between LARS and QoL [12]. The LARS score has recently been validated for use in Dutch [13]. The score ranges from 0 to 42 points, with classification of patients into No LARS (0–20 points), Minor LARS (21–29 points), and Major LARS (30–42 points). Additionally, the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and -CR29 questionnaires were used for measuring QoL. These modules were designed by the EORTC. The EORTC QLQ-C30 questionnaire consists of 30 questions on functional scales, a global QoL measure and symptom assessment [14]. The EORTC QLQ-CR29 questionnaire is designed specifically for colorectal cancer, and consists of 29 items addressing gastrointestinal symptoms, chemotherapy side effects, defecation problems, pain and problems with micturition, and separate items addressing sexual function for men and women [15]. We analysed 28 of the 29 EORTC QLQ-CR29 scales, as the stoma-related items were not relevant. For both questionnaires a high functional score represented a high level of function, while a high symptom score represented a high level of symptoms.

Statistical Analyses

The EORTC HRQL instrument was scored according to the guidelines. Mean scores were compared between LARS score categories using the Mann-Whitney U test. A recent study showed both clinical and significant differences in QoL 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 [16]. Based on these findings, we compared QoL scores for patients with "major LARS" versus "no or minor LARS".

Patient, tumour and treatment characteristics with a possible association with major LARS were first tested in univariate analyses

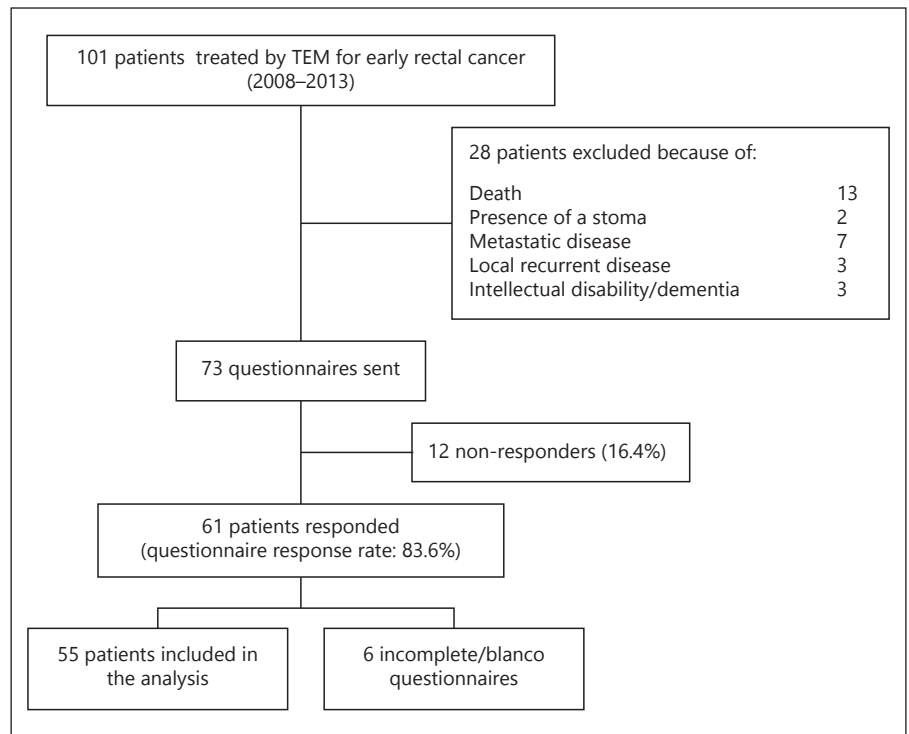


Fig. 1. Flowchart of included patients. TEM, transanal endoscopic microsurgery.

by using a logistic regression model. The independent association of these characteristics with major LARS was tested using a multiple logistic regression analysis. Only the variables that were significantly associated with major LARS in univariate analyses ($p < 0.10$) and were significantly associated with at least one of the other selected variables (confounding) were included in a stepwise multivariate analysis to derive a final model of the variables that had a significant relationship with major LARS. To add or remove a variable from the model, the corresponding p value had to be respectively < 0.05 and > 0.10 . All statistical analyses were performed using IBM® SPSS® Statistics, version 22.

Results

A total of 101 patients underwent TEM surgery for rectal cancer between January 2008 and December 2013. In all, 28 patients were excluded: died prior to the start of study ($n = 13$), presence of a stoma ($n = 2$), metastatic ($n = 7$) or local recurrent ($n = 3$) disease, intellectual disability/dementia ($n = 3$). Finally, 73 patients were eligible for inclusion. Sixty-one patients (83.6%) returned the questionnaire, of whom 6 patients returned a blank or incomplete questionnaire. A total of 55 patients with completed questionnaires were included for analyses (Fig. 1). Patient, tumour and treatment characteristics are described in Table 1. The median interval since treatment

was 4.3 years (range 2.5–8.0). The median age was 72 years (range 49–86).

Bowel Dysfunction

“Major LARS” was observed in 29% patients after TEM for rectal cancer. “Minor LARS” was observed in 26% of patients, while “No LARS” was observed in 45%. In the group of patients who received neo-adjuvant chemoradiotherapy, 50% of patients declared major LARS, while major LARS was observed in only 22% of patients in the group who did not receive neo-adjuvant treatment. This was a statistical significant difference ($p = 0.037$). In univariate analyses, female gender (OR 4.00; 95% CI 1.20–13.36), neo-adjuvant chemoradiotherapy (OR 3.63; 95% CI 1.08–12.17) and specimen thickness in millimetres (OR 1.10 for each mm increase in thickness; 95% CI 1.01–1.20) were significantly associated with major LARS. Confounding was not an issue among selected variables, since none of the variables was significantly associated with at least one of the other selected variables. Therefore, no multivariate analysis was performed (Table 1).

LARS and QoL

After TEM, patients with major LARS fared worse compared with patients with no/minor LARS in almost all “general” (QLQ-C30 questionnaire; Fig. 2) and

Table 1. Patient characteristics and univariate analyses of associations between patient, tumour and treatment characteristics, on the one hand, and major LARS, on the other hand, in patients who underwent TEM

Associated factor	Patients, <i>n</i> (%)	Unadjusted OR (95% CI)	<i>p</i> value
Age at follow-up, years, median (range)	72 (49–86)	1.03 (0.96–1.10)	0.401
Gender, <i>n</i> (%)			
Male	35 (63.6)	Reference	
Female	20 (36.4)	4.00 (1.20–13.36)	0.024
Marital status			
Married	40 (72.7)	Reference	
Single/widowed	15 (27.3)	1.76 (0.51–6.10)	0.374
TNM stage			
T0N0	7 (12.7)	1.67 (0.23–12.22)	0.615
T1N0	39 (70.9)	0.38 (0.83–1.70)	0.203
T2N0	9 (16.4)	Reference	
Tumour height (distance from anal verge)			
High rectum (10–14.9 cm)	15 (27.3)	Reference	
Mid rectum (5–9.9 cm)	21 (38.2)	1.10 (0.25–4.86)	0.900
Low rectum (<5 cm)	19 (34.5)	1.60 (0.37–7.02)	0.530
Tumour location			
Anterior	17 (23.0)	2.67 (0.36–19.71)	0.337
Left Lateral	15 (20.3)	2.00 (0.28–14.20)	0.488
Posterior	19 (25.7)	2.00 (0.30–13.17)	0.471
Right Lateral	10 (13.5)	Reference	
Specimen size (cm ²), median (range)	8.60 (1.70–38.50)	1.01 (0.95–1.07)	0.815
Specimen thickness, mm, median (range)	8 (2–30)	1.10 (1.01–1.20)	0.023
Interval since treatment, years, median (range)	4.3 (2.5–8.0)	1.01 (0.97–1.04)	0.912
Neo-adjuvant therapy			
No neo-adjuvant therapy	38 (69.1)	Reference	0.037
(Chemo) radiotherapy	17 (30.9)	3.63 (1.08–12.17)	
ASA grade			
Grade I–II	45 (81.8)	Reference	
Grade III–VI	10 (18.2)	0.95 (0.21–4.22)	0.945
Complication (Clavien-Dindo)			
Grade 0 (no complication)	47 (85.5)	Reference	
Grade I–II	4 (7.3)	0.79 (0.08–8.22)	0.840
Grade III–IV	4 (7.3)	2.36 (0.30–18.44)	0.414

LARS, low anterior resection syndrome; TEM, transanal endoscopic microsurgery.

colorectal cancer specific (QLQ-CR29 questionnaire; Fig. 3) QoL domains, except for constipation and sexual interest for both men and women. However, a statistically significant difference in QoL between no/minor and major LARS groups could not be reached for all subscales.

Discussion

This study has shown an unknown problem after TEM for stage I rectal tumours as severe bowel dysfunction (major LARS) was present in 29% of these patients. Together with 26% of patients experiencing minor LARS, more than half (55%) of the patients treated with TEM

do experience functional abdominal complaints even years after treatment. Major LARS occurred significantly more often among women, those who underwent neoadjuvant chemoradiotherapy and those with a thicker specimen. In addition, patients with major LARS fared worse in almost all general and colorectal-specific QoL domains.

The prevalence of major LARS as reported in the current study is similar to that in a recent publication of Hupkens and Stoot [17] reporting major LARS in one third of rectal cancer patients who were treated by neo-adjuvant chemoradiotherapy only, in terms of the “watch and wait” policy. Also a recent study investigating faecal incontinence after TEM for rectal cancer by using the

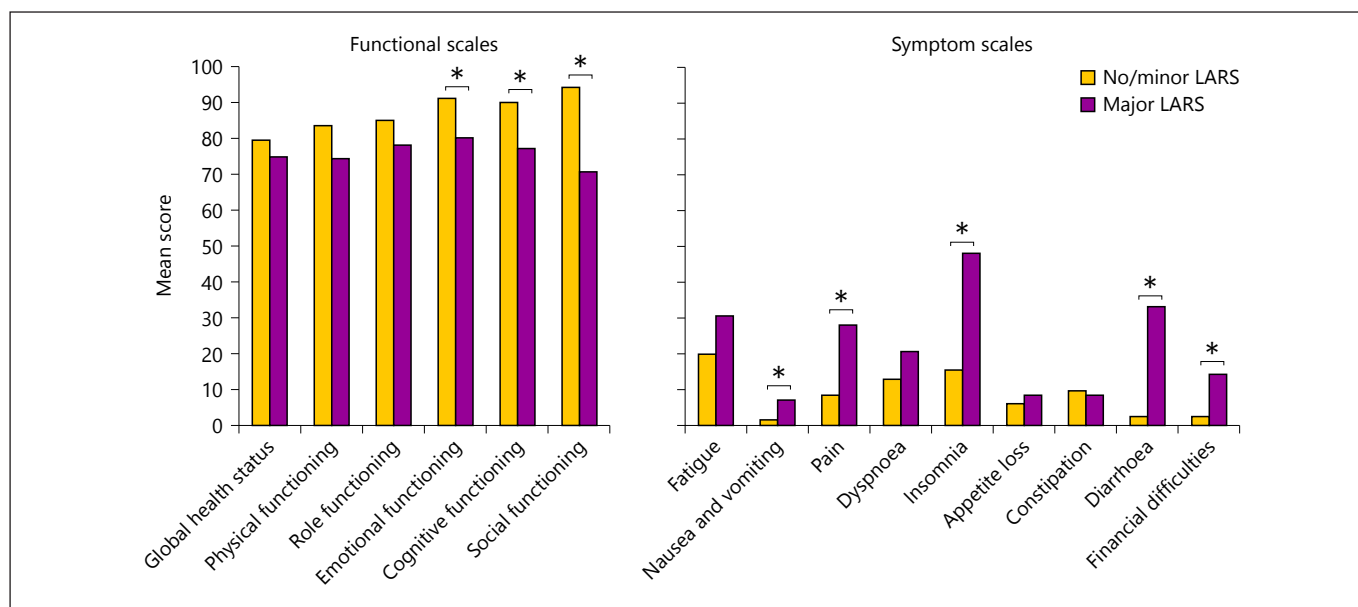


Fig. 2. Mean scores of EORTC QLQ-C30 subscales by LARS groups in TEM-treated patients. Functional scales: a higher score represents a better level of functioning. * $p < 0.05$ between major LARS and no/minor LARS. Symptom scales: a higher score repre-

sents a higher level of symptom. * $p < 0.05$ between major LARS and no/minor LARS. EORTC, European Organization for the Research and Treatment of Cancer; LARS, low anterior resection syndrome; TEM, transanal endoscopic microsurgery.

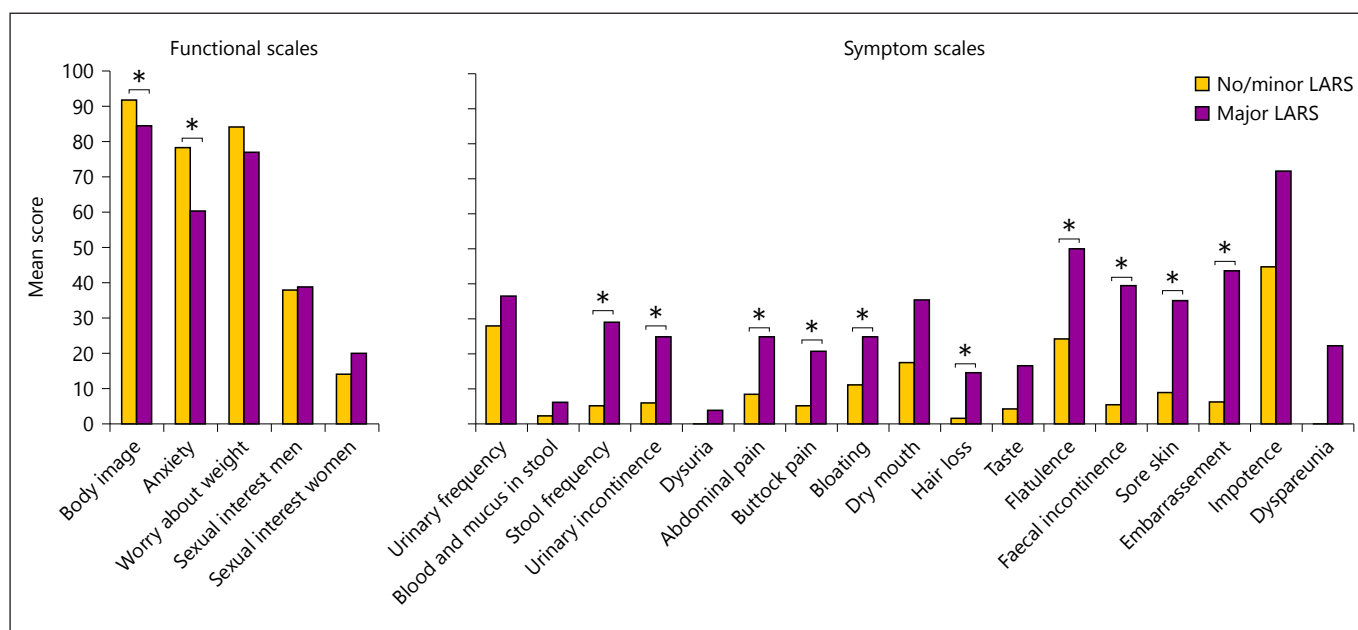


Fig. 3. Mean scores of EORTC QLQ-CR29 subscales by LARS groups in TEM treated patients. Functional scales: a higher score represents a better level of functioning. * $p < 0.05$ between major LARS and no/minor LARS. Symptom scales: a higher score repre-

sents a higher level of symptom. * $p < 0.05$ between major LARS and no/minor LARS. EORTC, European Organization for the Research and Treatment of Cancer; LARS, low anterior resection syndrome; TEM, transanal endoscopic microsurgery.

Wexner score, found a similar percentage (28.8%) of patients experiencing invalidating faecal incontinence with a negative effect on QoL. The effect of neo-adjuvant chemoradiotherapy on the presence of postoperative faecal incontinence was not investigated in the latter study, as they included only patient without a past of chemoradiation therapy [18]. Until recently, LARS was only recognized as a cluster of bothersome complaints after invasive rectal surgery. The fact that LARS not only occurs after invasive surgery, but also after rectum sparing surgery or only neoadjuvant chemoradiotherapy, raises a lot of questions about the underlying pathophysiology and potential risk factors.

Although most previous studies focused on LARS after TME, our study confirmed previous results that female gender was associated with major LARS after surgery, hypothesizing that besides a different pelvic anatomy other concomitant risk factors such as obstetric trauma and pelvic floor dysfunction might play an important role in the development of major LARS [19]. Although a recent study concluded that neo-adjuvant chemoradiation therapy before TEM treatment does affect the anal function but without causing major anal incontinence, in our study, neo-adjuvant chemoradiotherapy was identified as risk factor for the occurrence of major LARS after TEM [20]. Our results are in line with previous findings of an impaired rectal function due to chemoradiotherapy-induced fibrosis and neurovascular toxicity [21–23]. The relatively high amount of patients who underwent chemoradiation before surgery for stage I rectal cancer in our study can be explained by the early implementation of the watch and wait policy in the south of the Netherlands causing a relatively high amount of incomplete responses; these patients still needed a TEM resection after all. This high amount of neo-adjuvant chemoradiotherapy, which is not the current standard-of-care regimen for stage I rectal cancer, most likely influenced the prevalence of major LARS in our study population. The implementation of watch and wait policy during our inclusion period could have led to selection bias, as frail elderly patients may have been selected for organ preservation, which reflects the relatively high median age among the patients' cohort. The association between specimen thickness and LARS after TEM as was found in our study has not been investigated previously. The higher prevalence of major LARS with increasing specimen thickness may be due to the fact that rectal wall anatomy will become more affected in full thickness specimens. This may result in a reduction of the rectal compliance through the removal of part of the rectal wall on the one hand and a diminished

recto-inhibitory reflex, by direct surgical damage to essential neurovascular structures, on the other hand [24]. Another contributory factor to the prevalence of major LARS after TEM, although not investigated in our study, could be the occurrence of sphincter damage after introduction of a 40-mm scope through the anal sphincter. It causes a temporary rise in urge-incontinence due to a reduction in anal resting and anal squeezing pressure, even 1 year postoperatively [25, 26]. In contrast to studies among patients who underwent a TME for rectal cancer, we found no association between major LARS and tumour height [27]. This can be declared by the absence of a colo-anal anastomosis, causing circumferential neurovascular damage to the colo-anal functional coordination [23]. The variety of contributing patient, tumour and treatment characteristics points to a multifactorial pathophysiological mechanism for major LARS in patients treated for rectal cancer.

In line with previous finding after LAR for rectal cancer, patients treated by TEM who were affected by major LARS scored worse in almost all "general" QoL domains (QLQ-C30 questionnaire), compared with patients reporting no or minor LARS [28]. Regarding the colorectal cancer-specific QoL (EORTC QLQ CR29), a lower QoL score was observed in patients reporting major LARS for all scales except for sexual interest in men and women. The highest level of significance was reached in the LARS-related subscales as flatulence, faecal incontinence, stool frequency, bloating, abdominal pain and embarrassment. These individual subscales reached statistical significance with a $p < 0.01$. The fact that the subscales that have the highest consistency with the LARS-score are also most significantly different in our patient population contributes to the presumption that there also is a high correlation between the EORTC QLQ-CR29 questionnaire and LARS score in a rectal cancer population treated by TEM, which had not been described previously.

Our study is the first to report major LARS after TEM with a concomitant adverse effect on QoL, even years after treatment. It seems contrasting that these bothersome complaints were still present years after treatment, while previous literature pointed out that QoL returned to baseline within the first year after TEM treatment [26]. Nevertheless, a stabilization of functional bowel complaints and QoL in the first year after treatment followed by a slow deterioration has been shown before [29]. Therefore, a prospective study investigating changes in QoL over time can yield more information on the evolution of bowel dysfunction after TEM treatment for rectal cancer [9, 10]. However, the current cross-sectional study clear-

ly shows that functional abdominal complaints persist, even after the first year. Despite the relatively high prevalence of LARS that was found in our study, TEM remains the treatment of favour for stage I rectal tumours as the prevalence of major LARS after rectum-sparing TEM is only half the prevalence of major LARS after radical rectal surgery by TME [3].

The strength of our study lies in the use of comprehensive, validated questionnaires together with the high questionnaire response rate (83.6%). Knowing that the LARS score was developed to evaluate bowel dysfunction after complete rectal excision, it may sound contradictory to use this in patients who underwent local excision [11]. Nevertheless, as one third of patients after TEM resection reported major LARS, functional problems as described in the LARS-score also seem to be of clinical relevance in these patients. This appears from comments and personal reactions of patients, in which they thank us for finally showing interest in a problem that they have long been facing. Another possible limitation of our study is the cross-sectional design, which is not the most reliable way to investigate associations and risk factors for the occurrence of post-surgical complaints. A prospective research design with the inclusion of relevant control groups to investigate changes in QoL within the first year after treatment can yield more information on the evolution of bowel dysfunction. Also determining the pre-operative

LARS score of study patients would be a valuable addition, although the reliability of such preoperative measurement could already be influenced by the presence of a tumour, influencing the patients' bowel function. Besides that, the power of statistical analysis was reduced by the small number of patients in each subgroup.

In conclusion, this is the first study demonstrating the prevalence of major LARS in a considerable portion of stage I rectal cancer patients treated by TEM. The similar effect of major LARS on QoL as we know from patients who underwent TME makes it a vital issue, even years after treatment. Although the prevalence of major LARS after TEM is only half of the estimated prevalence of major LARS after TME for rectal cancer, this problem should be addressed by colorectal surgeons in order to offer adequate counselling throughout the treatment and follow-up process for patients treated with local excision for rectal cancer. LARS after TEM needs further prospective investigation to identify specific patient, tumour and treatment associated risk factors in order to develop new modalities for preventing and treating LARS.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

References

- 1 Logan RF, Patnick J, Nickerson C, Coleman L, Rutter MD, von Wagner C; English Bowel Cancer Screening Evaluation Committee. Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. *Gut*. 2012 Oct;61(10):1439–46.
- 2 Bryant CL, Lunniss PJ, Knowles CH, Thaha MA, Chan CL. Anterior resection syndrome. *Lancet Oncol*. 2012 Sep;13(9):e403–8.
- 3 Chen TY, Wiltink LM, Nout RA, Meershoek-Klein Kranenbarg E, Laurberg S, Marijnen CA, et al. Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomized trial. *Clin Colorectal Cancer*. 2015 Jun;14(2):106–14.
- 4 Rullier E, Rouanet P, Tuech JJ, Valverde A, Le-long B, Rivoire M, et al. Organ preservation for rectal cancer (GRECCAR2): a prospective, randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2017 Jul;390(10093):469–79.
- 5 Chen TY, Emmertsen KJ, Laurberg S. Bowel dysfunction after rectal cancer treatment: a study comparing the specialist's versus patient's perspective. *BMJ Open*. 2014 Jan;4(1):e003374.
- 6 Aigner F. PROMS and LARS - will functional outcomes trump cancer survival?: rectal cancer surgery has focussed on local recurrence and cancer survival. Will patient choice drive the options in the future? *Colorectal Dis*. 2018 Feb;20(2):93.
- 7 Sobin LH, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours*. John Wiley & Sons; 2009.
- 8 Emmertsen KJ, Laurberg S. Bowel dysfunction after treatment for rectal cancer. *Acta Oncol*. 2008;47(6):994–1003.
- 9 Camilleri-Brennan J, Steele RJ. Prospective analysis of quality of life and survival following mesorectal excision for rectal cancer. *Br J Surg*. 2001 Dec;88(12):1617–22.
- 10 Puts MT, Monette J, Girre V, Wolfson C, Monette M, Batist G, et al. Quality of life during the course of cancer treatment in older newly diagnosed patients. Results of a prospective pilot study. *Ann Oncol*. 2011 Apr;22(4):916–23.
- 11 Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. *Ann Surg*. 2012 May;255(5):922–8.
- 12 Juul T, Ahlberg M, Biondo S, Emmertsen KJ, Espin E, Jimenez LM, et al. International validation of the low anterior resection syndrome score. *Ann Surg*. 2014 Apr;259(4):728–34.
- 13 Hupkens BJP, Breukink SO, Olde Reuver Of Briel C, Tanis PJ, de Noo ME, van Duijvendijk P, van Westreenen HL, Dekker JWT, Chen TYT, Juul T. Dutch validation of the low anterior resection syndrome score. *Colorectal Dis*. 2018 Oct;20(10):881–7.
- 14 Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993 Mar;85(5):365–76.
- 15 Whistance RN, Conroy T, Chie W, Costantini A, Sezer O, Koller M, et al; European Organisation for the Research and Treatment of Cancer Quality of Life Group. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. *Eur J Cancer*. 2009 Nov;45(17):3017–26.

- 16 Juul T, Ahlberg M, Biondo S, Espin E, Jimenez LM, Matzel KE, et al. Low anterior resection syndrome and quality of life: an international multicenter study. *Dis Colon Rectum*. 2014 May;57(5):585–91.
- 17 Hupkens BJ, Martens MH, Stoot JH, Berbee M, Melenhorst J, Beets-Tan RG, 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 Oct;60(10):1032–40.
- 18 Jakubauskas M, Jotautas V, Poskus E, Mikalauskas S, Valeikaite-Tauginiene G, Strupas K, et al. Fecal incontinence after transanal endoscopic microsurgery. *Int J Colorectal Dis*. 2018 Apr;33(4):467–72.
- 19 Bregendahl S, Emmertsen KJ, Lous J, Laurberg S. Bowel dysfunction after low anterior resection with and without neoadjuvant therapy for rectal cancer: a population-based cross-sectional study. *Colorectal Dis*. 2013 Sep;15(9):1130–9.
- 20 Biviano I, Balla A, Badiali D, Quaresima S, D'Ambrosio G, Lezoche E, Corazziari E, Paganini AM. Anal function after endoluminal locoregional resection by transanal endoscopic microsurgery and radiotherapy for rectal cancer. *Colorectal Dis*. 2017 Jun;19(6):O177–85.
- 21 Bregendahl S, Emmertsen KJ, Fassov J, Krogh K, Zhao J, Gregersen H, et al. Neorectal hyporesponsivity after neoadjuvant therapy for rectal cancer. *Radiother Oncol*. 2013 Aug;108(2):331–6.
- 22 Ozgen Z, Ozden S, Atasoy BM, Ozyurt H, Gencosmanoglu R, Imeryuz N. Long-term effects of neoadjuvant chemoradiotherapy followed by sphincter-preserving resection on anal sphincter function in relation to quality of life among locally advanced rectal cancer patients: a cross-sectional analysis. *Radiat Oncol*. 2015 Aug;10(1):168.
- 23 Gavaruzzi T, Lotto L, Giandomenico F, Perin A, Pucciarelli S. Patient-reported outcomes after neoadjuvant therapy for rectal cancer: a systematic review. *Expert Rev Anticancer Ther*. 2014 Aug;14(8):901–18.
- 24 Herman RM, Richter P, Walega P, Popiela T. Anorectal sphincter function and rectal barostat study in patients following transanal endoscopic microsurgery. *Int J Colorectal Dis*. 2001 Nov;16(6):370–6.
- 25 Kreis ME, Jehle EC, Haug V, Manncke K, Buess GF, Becker HD, et al. Functional results after transanal endoscopic microsurgery. *Dis Colon Rectum*. 1996 Oct;39(10):1116–21.
- 26 Hompes R, Ashraf SQ, Gosselink MP, van Dongen KW, Mortensen NJ, Lindsey I, Cunningham C. Evaluation of quality of life and function at 1 year after transanal endoscopic microsurgery. *Colorectal Dis*. 2015 Feb;17(2):O54–61.
- 27 Matzel KE, Stadelmaier U, Muehldorfer S, Hohenberger W. Continence after colorectal reconstruction following resection: impact of level of anastomosis. *Int J Colorectal Dis*. 1997;12(2):82–7.
- 28 Vironen JH, Kairaluoma M, Aalto AM, Kellokumpu IH. Impact of functional results on quality of life after rectal cancer surgery. *Dis Colon Rectum*. 2006 May;49(5):568–78.
- 29 Wiltink LM, Marijnen CA, Meershoek-Klein Kranenburg E, van de Velde CJ, Nout RA. A comprehensive longitudinal overview of health-related quality of life and symptoms after treatment for rectal cancer in the TME trial. *Acta Oncol*. 2016;55(4):502–8.