

Prevalence of low anterior resection syndrome and impact on quality of life after rectal cancer surgery: population-based study

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Background: The prevalence of major low anterior resection syndrome (LARS) after rectal cancer surgery varies from 17.8 to 56.0 per cent, but data from high-quality studies are sparse. The aim of this study was to determine the prevalence of LARS and its association with quality of life (QoL) in a large, well defined, population-based cohort.

Methods: This was a population-based study that included all patients who had curative rectal cancer surgery with total or partial mesorectal excision in Stockholm County in Sweden between 2007 and 2013. Patients without a remaining stoma, free from cancer and alive in April 2017 were eligible for the study. The LARS score questionnaire, EORTC QLQ-C30 and Cleveland Clinic Florida Fecal Incontinence score were used as outcome measures. Adjusted mean scores (and differences) of EORTC QLQ-C30 for LARS groups were calculated using repeated measures ANCOVA regression models while adjusting for predefined confounders.

Results: In total, 481 patients (82.6 per cent response rate) were included in the analysis. Mean follow-up time was 6.7 (range 3.4–11.0) years after surgery. The prevalence of LARS was 77.4 per cent (370 of 478 patients), with 53.1 per cent (254 of 478) experiencing major LARS. Patients with major LARS reported worse on all EORTC QLQ-C30 subscales (except for financial difficulties) than patients without LARS. A higher mean LARS score was associated with a greater impact on bowel-related QoL.

Conclusion: After anterior resection for rectal cancer, the majority of patients suffer from major LARS with a negative impact on QoL.

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Introduction

After sphincter-preserving rectal cancer surgery, 70–90 per cent of the patients suffer from bowel dysfunction of varying degree, commonly known as low anterior resection syndrome (LARS)^{1–3}. Symptoms include incontinence for flatus and/or faeces, urgency, clustering, emptying difficulties and frequent bowel movements, and can be recognized with a validated self-administered questionnaire, the LARS score questionnaire^{1,4}. The development of LARS is thought to be multifactorial, including colonic

dysmotility, impaired capacity and compliance of the neorectum, and sphincter dysfunction⁵. In addition, LARS has a significant impact on patients' quality of life (QoL)^{3,6–8}.

Several earlier studies⁹ have reported on functional outcome after rectal cancer surgery. There has been substantial variation in the outcome measures used, making it difficult to compare results⁹. The LARS score questionnaire is a short and easy instrument for measuring bowel dysfunction, and it enables comparison of results from other studies. Before development of the LARS score, the most commonly used instrument to

evaluate bowel function after rectal cancer surgery was the Cleveland Clinic Florida Fecal Incontinence Score (CCFIS), also known as the Wexner score, which evaluated only symptoms related to incontinence⁹.

The reported prevalence of major LARS, the most severe bowel dysfunction according to the LARS score, varies between 17.8 and 56.0 per cent^{7,10–13}. A summary of the prevalence of LARS in previously reported studies^{3,7,10,11,13–18} is presented in *Table S1* (supporting information). Recently, the prevalence of LARS was investigated in a meta-analysis¹² using the validated LARS score questionnaire, and the prevalence of major LARS was estimated to be 41 per cent based on 11 studies. A limitation mentioned was that the majority of the larger and more reliable studies included were from Denmark and the UK. Studies from other countries frequently involved a limited number of patients, resulting in more uncertain results, and it was concluded that further prevalence studies from other countries were needed¹².

The primary aim of the present study was to investigate the prevalence of LARS in a large population-based Swedish cohort of patients who underwent surgery during 2007–2013. The secondary aim was to assess the association between symptoms of LARS and QoL. The CCFIS was included to obtain a more detailed evaluation of incontinence symptoms.

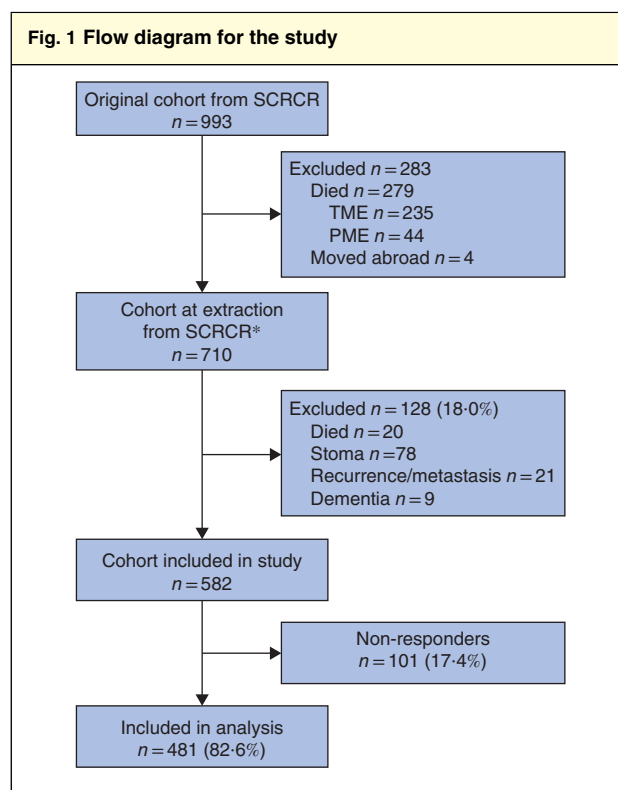
Methods

This was a population-based cohort study of all patients who had curative rectal cancer surgery with total (TME) or partial (PME) mesorectal excision between January 2007 and December 2013 in Stockholm County, Sweden. For healthcare, the island of Gotland is also included, and according to Statistics Sweden¹⁹ around 2.1 million inhabitants lived in Stockholm County in 2013.

Patients aged 18 years or more were identified through the Swedish Colorectal Cancer Registry (SCRCR)²⁰. A combination of data obtained from the SCRCR and a review of patients' medical records provided demographic information and data concerning surgery, neoadjuvant treatment, presence of dementia, and information on recurrent and/or disseminated disease. Patients without metastasis and/or recurrence at follow-up (irrespective of primary stage and neoadjuvant/adjuvant treatment), alive on 4 April 2017, were included. Patients with a stoma, diagnosis of dementia or recurrent disease, and those who died, were excluded.

All patients who met the inclusion criteria were invited to participate in the study. A letter was sent to each patient with questionnaires for the LARS score, CCFIS, European

Fig. 1 Flow diagram for the study



*Number of patients operated on for rectal cancer eligible for the study at the time of data extraction from the Swedish Colorectal Cancer Registry (SCRCR). TME, total mesorectal excision; PME, partial mesorectal excision.

Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0, and a study-specific questionnaire concerning presence of a stoma or not.

Medical records of patients who did not respond were reviewed to ascertain the presence of a stoma or other exclusion criteria.

The study was approved by the local ethics committee of Stockholm (2016/1604-31/2 and 2017/605-32). Patients had given their informed consent.

Questionnaires

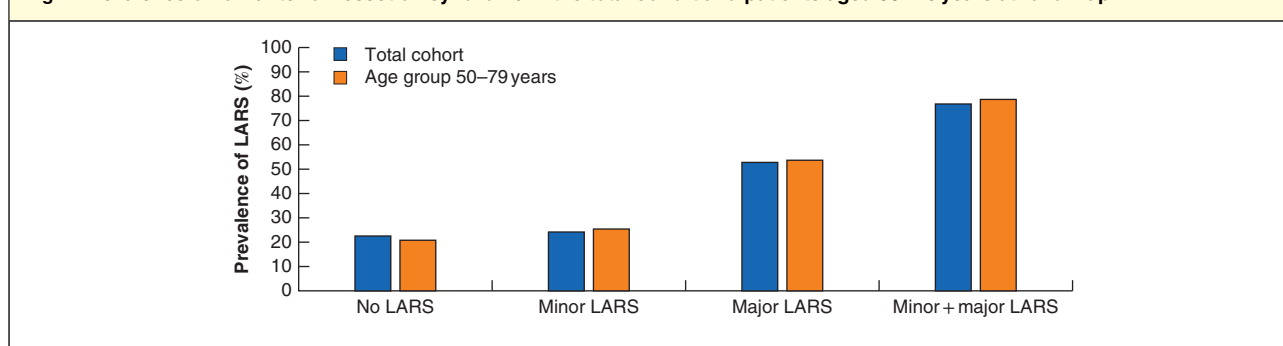
The LARS score questionnaire consists of five questions; each question has response alternatives with a weighted score¹ and the total maximum score is 42 points. Patients are divided into three groups: no LARS (0–20 points), minor LARS (21–29 points) and major LARS (30–42 points)^{1,4}.

The question, ‘Overall, how much does your bowel function affect your quality of life?’ was added to the questionnaire. This question has been validated through test–retest reliability and is commonly used in combination

Table 1 Patient characteristics

	No LARS (n = 108)	Minor LARS (n = 116)	Major LARS (n = 254)	P†
Age at follow-up (years)*	74.4(11.5)	72.3(8.7)	70.2(9.5)	<0.001‡
Male sex	55 (50.9)	72 (62.1)	146 (57.5)	0.239
Length of follow-up after surgery (years)*	6.6(2.2)	6.8(2.0)	6.6(2.1)	0.863‡
Level of tumour from anal verge (cm)*	11.3(2.7)	11.0(2.7)	10.1(2.6)	<0.001‡
Preoperative T category 3–4	56 of 107 (52.3)	73 (62.9)	177 of 253 (70.0)	0.025
TME	82 (75.9)	91 of 115 (79.1)	230 of 252 (91.3)	<0.001
Preoperative radiotherapy	46 (42.6)	74 (63.8)	198 (78.0)	<0.001
Preoperative chemotherapy†	11 (10.2)	20 (17.2)	56 (22.0)	0.027

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.) †Includes preoperative chemoradiotherapy. LARS, low anterior resection syndrome; TME, total mesorectal excision. ‡ χ^2 test, except ‡ANOVA.

Fig. 2 Prevalence of low anterior resection syndrome in the total cohort and patients aged 50–79 years at follow-up

LARS, low anterior resection syndrome.

with the LARS score questionnaire^{1,4}. The available response alternatives were ‘not at all’, ‘a little’, ‘some’ and ‘a lot’. The response alternatives ‘some’ and ‘a lot’ indicate a significant impact on QoL, and were grouped in analysis.

The CCFIS consists of five separate questions²¹. Three questions concern incontinence for flatus and/or faeces, one concerns the use of pads, and one concerns lifestyle alteration owing to bowel dysfunction. Each question has five different response alternatives (range 0–4 points), resulting in a maximum of 20 points²¹.

The study-specific questionnaire concerning presence of a stoma was developed for this study. It contains two questions: ‘Do you have a stoma?’ (yes or no); and ‘If yes, what is the reason for you having a stoma?’ (‘No stoma reversal was attempted after my primary rectal cancer operation’ or ‘I got a stoma later because of severe bowel dysfunction’ or ‘None of the above response alternatives’).

The EORTC QLQ-C30 contains 30 items that generate nine multi-item scales (1 global health status/QoL scale, 5 functional scales and 3 symptom scales) and six single

Table 2 Prevalence of low anterior resection syndrome in the total cohort and patients aged 50–79 years

LARS group	Total cohort (n = 478)*	Patients aged 50–79 years (n = 412)
No LARS	108 (22.6)	85 (20.6)
Minor LARS	116 (24.3)	104 (25.2)
Major LARS	254 (53.1)	223 (54.1)
Minor + major LARS	370 (77.4)	327 (79.4)

Values in parentheses are percentages. *Three of the 481 patients in the study did not complete the LARS score questionnaire and so are not included here. LARS, low anterior resection syndrome.

items measuring dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties²². The generated score for each scale and single item ranges from 0 to 100. A high score on the global health status/QoL and functional scales represents a high level of QoL and functioning. Conversely, a high score on the symptom scales and single items is equivalent to a high grade of symptoms^{22,23}. To interpret the clinical relevance of observed mean differences in EORTC scores, the guidelines published by Cocks *et al.*²⁴ were used. These guidelines, however, do not provide any

Table 3 LARS score and Cleveland Clinic Florida Fecal Incontinence Score comparisons

LARS group	LARS score	CCFIS	Comparison of CCFIS between groups		
			Groups	Score difference	P*
No LARS	9.9 (8.6, 11.1)	3.2 (2.1, 4.3)	Minor <i>versus</i> no LARS	2.0 (0.9, 3.1)	<0.001
Minor LARS	26.1 (25.6, 26.7)	5.2 (4.1, 6.3)	Major <i>versus</i> minor LARS	5.3 (4.4, 6.3)	<0.0001
Major LARS	35.6 (35.2, 36.1)	10.5 (9.6, 11.5)	Major <i>versus</i> no LARS	7.3 (6.3, 8.3)	<0.0001

Values are mean (95 per cent c.i.). LARS, low anterior resection syndrome; CCFIS, Cleveland Clinic Florida Fecal Incontinence Score. *ANCOVA regression model, adjusted for age, sex, tumour level, preoperative T category, type of operation, preoperative radiotherapy and preoperative chemotherapy.

Table 4 EORTC QLQ-C30 scores in the three low anterior resection syndrome groups

	No LARS	Minor LARS	Major LARS
Summary score	89.9 (85.9, 93.8)	87.5 (83.8, 91.3)	78.0 (74.6, 81.5)
Global health status/QoL	79.6 (73.6, 85.6)	75.1 (69.3, 80.8)	62.6 (57.4, 67.9)
Functional scales			
Physical functioning	92.0 (86.9, 97.1)	88.0 (83.2, 92.9)	82.8 (78.4, 87.3)
Role functioning	90.4 (83.4, 97.5)	85.6 (78.9, 92.3)	76.0 (69.9, 82.1)
Emotional functioning	88.6 (81.9, 95.4)	85.6 (79.2, 92.1)	75.9 (70.0, 81.8)
Cognitive functioning	90.3 (84.7, 95.9)	90.8 (85.4, 96.1)	83.3 (78.3, 88.2)
Social functioning	84.7 (77.7, 91.7)	82.8 (76.1, 89.5)	65.5 (59.4, 71.6)
Symptom scales			
Fatigue	10.3 (4.1, 16.6)	17.1 (11.2, 23.0)	27.3 (21.9, 32.8)
Nausea and vomiting	1.6 (-1.1, 4.3)	1.5 (-1.1, 4.1)	5.8 (3.4, 8.1)
Pain	7.7 (1.6, 13.8)	12.9 (7.2, 18.7)	16.6 (11.3, 21.8)
Single items			
Dyspnoea	8.5 (1.2, 15.7)	11.9 (5.0, 18.8)	17.8 (11.6, 24.1)
Insomnia	17.0 (9.3, 24.8)	21.1 (13.7, 28.5)	32.3 (25.7, 39.1)
Appetite loss	5.1 (-0.3, 10.5)	4.3 (-0.8, 9.5)	10.6 (5.9, 15.2)
Constipation	20.8 (13.4, 28.2)	18.3 (11.3, 25.3)	29.4 (23.0, 35.8)
Diarrhoea	9.3 (2.2, 16.5)	19.8 (13.0, 26.7)	39.9 (33.6, 46.2)
Financial difficulties	7.4 (1.7, 13.1)	9.7 (4.3, 15.2)	12.1 (7.2, 17.1)

Values are mean (95 per cent c.i.). LARS, low anterior resection syndrome; QoL, quality of life.

guidance on the summary score and emotional functioning, and in these subscales a difference of 10 points or more was considered clinically relevant.

Endpoints

The primary endpoint of interest was the prevalence of LARS. Secondary endpoints were the association between the presence of LARS and QoL, and a more detailed evaluation of incontinence symptoms using the CCFIS.

Statistical analysis

The LARS and EORTC QLQ-C30 questionnaires were scored using the prescribed manuals, and missing data were handled according to the guidelines provided^{1,22,25}.

Descriptive statistics for patient characteristics are presented as frequencies and percentages for categorical variables and as mean(s.d.) values for continuous variables. The χ^2 test and ANOVA were used to test patient characteristics between LARS groups, and χ^2 and Student's *t* test to test responders *versus* non-responders, and excluded *versus* included patients.

Adjusted mean scores of EORTC QLQ-C30 (difference and summary scores^{22,25}) and CCFIS for LARS groups (no LARS, minor LARS and major LARS) were calculated using ANCOVA regression models with adjustment for predefined confounders. The adjusting model included age (per year), tumour level (per cm), T category, sex, surgical approach (TME or PME), radiotherapy (yes or no) and chemotherapy (yes or no). Statistically significant differences were defined as $P < 0.050$. The adjusted mean

Table 5 Pairwise comparisons of EORTC QLQ-C30 scores in the three low anterior resection syndrome groups

	No LARS – minor LARS		Minor LARS – major LARS		No LARS – major LARS	
	Score difference	P**	Score difference	P**	Score difference	P**
Summary score	2.3 (-1.6, 6.3)	0.246	9.5 (6.1, 12.9)	<0.001	11.8 (8.2, 15.4)¶	<0.001
Global health status/QoL	4.5 (4.5, 10.6)*	0.140	12.4 (7.3, 17.6)‡¶	<0.001	17.0 (11.5, 22.4)‡¶	<0.001
Functional scales						
Physical functioning	3.9 (-1.2, 9.1)§	0.136	5.2 (0.8, 9.6)*¶	0.021	9.1 (4.4, 13.8)*¶	0.001
Role functioning	4.8 (-2.3, 12.0)§	0.182	9.6 (3.5, 15.7)*¶	0.002	14.4 (8.0, 20.9)*¶	<0.001
Emotional functioning	3.0 (-3.8, 9.8)	0.383	9.7 (3.9, 15.5)	0.001	12.8 (6.6, 18.9)¶	<0.001
Cognitive functioning	-0.5 (-6.1, 5.1)§	0.860	7.5 (2.7, 12.3)*¶	0.002	7.0 (1.8, 12.1)*¶	0.008
Social functioning	1.9 (-5.1, 8.9)§	0.589	17.3 (11.3, 23.3)‡¶	<0.001	19.2 (12.8, 25.6)‡¶	<0.001
Symptom scales						
Fatigue	-6.8 (-13.1, -0.5)*¶	0.034	-10.2 (-15.6, -4.9)*¶	<0.001	-17.0 (-11.3, -22.7)‡¶	<0.001
Nausea and vomiting	0.10 (-2.6, 2.9)§	0.944	-4.3 (-6.6, -1.9)*¶	<0.001	-4.2 (-6.6, -1.7)*¶	0.001
Pain	-5.2 (-11.3, 0.9)§	0.092	-3.6 (-8.8, 1.5)§	0.168	-8.8 (3.3, 14.4)*¶	0.002
Single items						
Dyspnoea	-3.4 (-10.8, 3.9)§	0.355	-5.9 (-12.1, 0.3)*	0.063	-9.4 (-15.9, -2.8)‡¶	0.006
Insomnia	-4.1 (-11.9, 3.7)*	0.304	-11.2 (-17.9, -4.6)*¶	0.001	-15.3 (-22.4, -8.3)‡¶	<0.001
Appetite loss	0.8 (-4.6, 6.3)§	0.771	-6.2 (-1.6, -10.9)*¶	0.009	-5.4 (-10.4, -0.5)*¶	0.031
Constipation	2.5 (-5.0, 10.0)§	0.510	-11.1 (-4.8, -17.5)*¶	<0.001	-8.6 (-15.3, -1.9)*¶	0.012
Diarrhoea#	-10.5 (-17.6, -3.3)‡¶	0.004	-20.1 (-26.2, -14.0)‡¶	<0.001	-30.6 (-37.1, -24.1)‡¶	<0.001
Financial difficulties#	-2.3 (-8.0, 3.4)§	0.424	-2.4 (-7.3, 2.5)§	0.330	-4.7 (-9.9, 0.4)*	0.073

Differences in scale/item means are shown with 95 per cent confidence intervals. *Small, †medium and ‡large clinically relevant difference; §trivial mean difference, not considered clinically relevant. ¶Difference was both clinically relevant and statistically significant ($P < 0.050$). #For diarrhoea and financial difficulties, no guidelines for large differences were provided; medium difference was the highest grade of difference for these items. No guidelines were provided for summary score and emotional functioning, and in these subscales ≥ 10 (or more points) were considered clinically relevant. **ANCOVA regression model, adjusted for age, sex, tumour level, preoperative T category, type of operation, preoperative radiotherapy and preoperative chemotherapy.

LARS score for response groups on the question of the impact of LARS on QoL in the LARS questionnaire was analysed by ANCOVA regression models, with adjustment for the above-mentioned predefined confounders. To be able to compare with existing relevant normative data, prevalence in the subgroup of patients aged 50–79 years is presented in the results²⁶.

Statistical analysis was conducted using SAS[®] V.9.4 (SAS Institute, Cary, North Carolina, USA).

Results

In total, 993 patients had undergone surgery for rectal cancer (with an anastomosis) between January 2007 and December 2013 (Fig. 1). Of these, 481 patients were included in the final analysis (response rate 82.6 per cent, 481 of 582). Three patients (who responded) did not complete the LARS score questionnaire and were excluded.

Non-responders and excluded patients

There were no statistically significant differences in patient characteristics between included and excluded patients (data not shown).

Non-responders had a lower tumour level (10.0 cm *versus* 10.6 cm in responders; $P = 0.048$), but no other differences were observed between the groups.

Prevalence of low anterior resection syndrome

The characteristics of included patients are presented in Table 1, stratified by the presence of LARS. The mean duration of follow-up after surgery was 6.7 (range 3.4–11.0) years. The prevalence of some degree of LARS was 77.4 per cent (370 of 478) (Fig. 2 and Table 2). In an analysis restricted to patients aged 50–79 years, the distribution of patients in the different LARS categories was similar. Of the 78 patients who were excluded owing to the presence of a stoma, 25 (32 per cent) responded 'I got a stoma later because of severe bowel dysfunction' as the reason for the stoma.

CCFIS in patients with low anterior resection syndrome

Patients with major LARS had a higher CCFIS than those in the minor and no LARS groups. The mean CCFIS was

Table 6 LARS score and pairwise comparison of response groups to question concerning the impact of bowel function on quality of life

Response to question	No. of patients (n = 478)*	LARS score†	Comparison of LARS scores		
			Groups	Score difference†	P‡
'Not at all' (group 1)	52 (10.9)	11.4 (8.6, 14.1)	2 versus 3	8.8 (7.2, 10.4)	< 0.001
'A little' (group 2)	204 (42.7)	24.3 (22.4, 26.2)	1 versus 2	12.9 (10.3, 15.5)	< 0.001
'Some' or 'a lot' (group 3)	222 (46.4)	33.1 (31.2, 34.9)	1 versus 3	21.7 (19.1, 24.3)	< 0.001

*Values in parentheses are percentages; †values are mean (95 per cent c.i.). LARS, low anterior resection syndrome. ‡ANCOVA regression model, adjusted for age, sex, tumour level, preoperative T category, type of operation, preoperative radiotherapy and preoperative chemotherapy.

3.2 in the no LARS group, 5.2 in the minor LARS group, and 10.5 in the major LARS group (Table 3).

Association between low anterior resection syndrome and quality of life

Clinically relevant (small, medium and large differences) and statistically significant differences between patients with major LARS and those with no LARS were observed for all EORTC QLQ-C30 subscales, except for the financial difficulties subscale²⁴. In 11 of 15 subscales, patients with major LARS scored worse than those with minor LARS. Patients with minor LARS scored clinically and statistically worse than patients with no LARS in two subscales (fatigue and diarrhoea) (Tables 4 and 5).

Pairwise comparison of LARS score and impact of bowel function on quality of life

A higher mean LARS score was clearly associated with response alternatives corresponding to a greater impact on bowel-related QoL (Table 6).

Discussion

In this study, the prevalence of LARS symptoms in patients treated with anterior resection surgery for rectal cancer was 77.4 per cent and the prevalence of major LARS was 53.1 per cent. There was an association between the CCFIS and LARS score for each LARS group, which helps to put the results in context with the literature published before development of the LARS score.

Of patients excluded because of the presence of a stoma, one-third responded that the reason for the stoma was severe bowel dysfunction. The authors assume that these patients also experienced major LARS before stoma surgery, although LARS scores were not available.

A multinational study⁶ reported on the prevalence of LARS in a Swedish cohort with a limited number of

patients, presented as a subgroup from a larger international multicentre cohort. That study did not have a population-based design. Included patients were treated at two of five hospitals in Stockholm County. In the study, major LARS was experienced by 60 per cent of the Swedish patients at a mean postoperative follow-up of 5.3 years. The results of the present study were fairly concordant.

The present results are comparable with those from other long-term studies focusing on LARS. Chen and colleagues⁷ reported a prevalence of 46 per cent of major LARS with a longer follow-up. Symptoms of LARS may occur directly after surgery (if no protective stoma) or after stoma reversal, and may improve during the first year and stabilize thereafter³. This finding has been supported by longitudinal data⁸. In a previous study¹⁶, no association was shown between time from surgery and the presence of major LARS (range 25–97 months).

Interestingly, a recent study²⁶ reporting normative data on LARS showed that the prevalence of LARS was 18 per cent (women 18.8 per cent and men 9.6 per cent) in people with no known previous rectal cancer surgery aged 50–79 years. As expected, the present study showed that major LARS was much more common after rectal cancer surgery in patients with an anastomosis than in normative comparators. However, it is likely that not all LARS symptoms are caused solely by rectal cancer surgery. More patients who already experienced complaints before surgery may have had creation of a definitive stoma.

The present study confirms an association between LARS and QoL. In all but one subscale (financial difficulties), a greater impact on QoL was seen in the major LARS group compared with that in the no LARS group. This association has been shown previously, but some of the previous studies^{3,6,7} had limitations owing to short duration of follow-up and selection bias of patients.

The main strength of this study is the population-based design, based on a large number of patients from Stockholm County. As patients with all stages of rectal cancer were treated in the same county, the risk of selection bias was limited. The study was based on high-quality data

and data from the SCRCR (regarding exclusion criteria) were cross-checked using patients' medical records. The response rate was high, with minimal differences in patient characteristics between responders and non-responders, and no significant differences between included and excluded patients.

A limitation of the study was the retrospective design, precluding determination of LARS at a specific time point after surgery. The design was also a limitation in terms of obtaining more detailed patient data and details of any attempted symptomatic treatment for LARS. Another limitation concerns the fact that only 481 of 993 patients were included in the final analysis. However, this reflects the reality in long-term follow-up of patients with cancer.

The fact that LARS is so common illustrates the need for every unit involved in rectal cancer surgery to have knowledge of the condition. Patients with LARS need to be recognized and offered ongoing support.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.