Original article

Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer

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Background: **Bowel dysfunction after sphincter-preserving surgery for rectal cancer is a common complication, with the potential to affect quality of life (QoL) strongly. The aim of this study was to examine the extent of bowel dysfunction and impact on health-related QoL after curative sphincter-preserving resection for rectal cancer.**

Methods: **QoL was assessed using the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire, and bowel function using a validated questionnaire, including the recently developed low anterior resection syndrome (LARS) score. Assessments were carried out at the time of diagnosis, and at 3 and 12 months after surgery.**

Results: **A total of 260 patients were included in the study. At 3 months, 58·0 per cent of patients had a LARS score of 30 or more (major LARS), which declined to 45·9 per cent at 12 months ($P < 0·001$). The risk of major LARS was significantly increased in patients who received neoadjuvant therapy (odds ratio 2·41, 95 per cent confidence interval 1·00 to 5·83), and after total *versus* partial mesorectal excision (odds ratio 2·81, 1·35 to 5·88). Global health status was closely associated with LARS, and significant differences in global health status, functional and symptom scales of QoL were found between patients without LARS and those with major LARS.**

Conclusion: **Bowel dysfunction is a major problem with an immense impact on QoL following sphincter-preserving resection. The risk of major LARS was significantly increased after neoadjuvant therapy and total mesorectal excision.**

*Members of the Rectal Cancer Function Study Group are co-authors of this study and can be found under the heading Collaborators

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Introduction

Rectal cancer is a common disease in Western populations, with an incidence of approximately 220 new cases per million individuals per year; there are 1350 new cases in Denmark per year. Both surgical and oncological treatments have undergone major improvements in recent decades resulting in a markedly increased 5-year survival rate.

For lesions in the middle and upper third of the rectum, restoration of bowel continuity by sphincter-preserving resection is the standard surgical approach. Many patients, however, develop severe bowel dysfunction following the procedure. The combination of increased stool frequency, urgency, clustering and incontinence after resection with anastomosis is often referred to as low anterior resection syndrome (LARS), named after the low anterior resection (LAR) procedure[1]. These symptoms often arise immediately after surgery and may decrease after a few months, reaching a plateau within the first 2 years. Some patients recover almost normal bowel function, but others suffer lifelong severe disability with a major impact on quality of life (QoL)[1,2].

The authors have recently developed and validated a simple scoring system to grade LARS, based on impact on QoL[3,4]. It divides patients into groups with no, minor and major LARS, and is applicable in all patients following rectal resection with maintained bowel continuity.

Chemotherapy and radiotherapy have major effects on bowel function, with a high frequency of similar symptoms

but with gradual progression over time[5–7]. Combining surgery with radiotherapy decreases the risk of local recurrence, but has no significant effect on survival. Unfortunately, the combination markedly increases the risk and severity of long-term symptoms[6].

The aims of the present study were to examine the extent of bowel dysfunction and its impact on health-related QoL after curative sphincter-preserving resection for rectal cancer, with a focus on changes in bowel dysfunction over the first year after surgery assessed using the new LARS score, and to investigate the potential risk factors for LARS.

Methods

A multicentre cohort of patients diagnosed with histopathologically confirmed adenocarcinoma of the rectum, defined as tumour within 15 cm of the anal verge, was established. Exclusion criteria were: metastatic cancer; previous cancer (excluding spinocellular/basocellular carcinoma); dementia or other psychiatric disorder that would prevent the patient from answering the questionnaires; inability to speak, read and understand the Danish language; and severe physical derangement. Patients undergoing only local excision or operations other than LAR, or whose lesions could not be resected, were subsequently excluded.

Patients were included prospectively at university hospitals in Aalborg, Aarhus, Herning and Randers, covering the population of the northern and central regions of Denmark, which have approximately 1·9 million inhabitants. The university hospitals of Hilleroed, Hvidovre and Svendborg all have specific geographical catchment areas, making the total inclusion population approximately 2·5 million inhabitants, representing nearly half of the Danish population.

All patients were informed verbally and in writing about the project, and provided informed consent. The project was reviewed by the Regional Ethical Committee of the Central Denmark Region. The project was classified as a quality assurance project, and no approval was needed according to national law.

Study protocol

Patients were asked to fill out questionnaires concerning bowel function and QoL at the time of diagnosis, before starting treatment. Patients who underwent non-radical surgery were excluded after the operation. For all other patients, details regarding the dates of surgery, neoadjuvant therapy use and follow-up, as well as information on the type of anastomosis, date of reversal of any diverting stoma, and status of the distribution and collection of the questionnaires, were registered in an online database designed for the project. Most of the demographic and treatment-related data were obtained through a national database (the Colorectal Cancer Database within the Danish Colorectal Cancer Group (http://www.dccg.dk)) at the end of the study period. Data on the type of anastomosis and type of mesorectal excision (total, TME; partial, PME) are currently not registered in the national database, and were therefore retrieved from patient charts and pathology reports. Patients were reported as having a neoreservoir if they had either a colonic J-pouch or a side-to-end anastomosis. None of the patients underwent coloplasty. The patients were asked to fill out the same questionnaires at 3 and 12 months after stoma closure, or 3 and 12 months after the primary resection if there was no diverting stoma.

Questionnaires

The questionnaires used in the study relate to bowel function and QoL. A detailed questionnaire including the LARS score was used to investigate bowel function[3,4]. The LARS score is based on five questions with a corresponding scoring value weighted according to impact on QoL. The score ranges from 0 to 42 points, with classification of patients into three groups: no LARS (0–20 points), minor LARS (21–29 points) and major LARS (30–42 points)[4]. The Bowel Function Questionnaire consists of 27 questions regarding the prevalence of bowel symptoms, and many of the questions are followed by an adjunct question regarding the level of impact caused by the specific symptom. The questionnaire was developed and validated as described previously[4]. In the event of missing items in the LARS score, the patient was excluded from analyses. Missing answers to more than ten of the remaining questions resulted in exclusion from the study.

To measure QoL, the validated Danish version of the European Organization for Research and Treatment of Cancer (EORTC) generic questionnaire QLQ-C30 (version 3.0)[8,9] was used. It is a self-administered questionnaire with 30 questions corresponding to global health status, five functional scales and nine symptom scales/items. Scoring of the QoL data was performed according to the EORTC QLQ-C30 scoring manual, and missing answers were dealt with according to this manual; if at least half of the items in a scale had been completed, it was assumed that the missing item(s) would have had values equal to the average of the items present[10]. All of the scores were linearly transformed to a scale of 0 to 100 points. A mean difference of ±5–10 points represented a small,

but relevant clinical difference, whereas a difference of ±10–20 points represented a moderate clinically relevant difference[11]. A high functional score represented a high level of function, and the optimal score was 100. A high symptom score represented a high level of symptoms, and the optimal score was 0.

Statistical analysis

For analysis of patient characteristics, Fisher's exact test was used to test for differences in tumour and treatment data, and the Mann–Whitney *U* test to compare age distributions. Because bowel function and QoL data were not normally distributed, non-parametric methods were used for analysis. Comparisons of bowel function between 3 and 12 months were performed using the Wilcoxon signed rank test for paired data. Adjusted odds ratios (ORs) for major LARS were calculated using multiple logistic regression analyses to estimate the impact of sex, use of neoadjuvant therapy, surgical technique (PME/TME), occurrence of symptomatic anastomotic leakage, and presence of a neoreservoir (categorized as colonic J-pouch/side-to-end anastomosis or straight colorectal anastomosis). Despite the skewed distribution, QoL data are expressed as mean(s.d.) owing to convention within EORTC data handling[8]. Differences between groups in QoL were calculated using the Kruskal–Wallis test and the Mann–Whitney *U* test when appropriate because of the potentially skewed data. Differences in QoL between 3 and 12 months were analysed using the Wilcoxon signed rank test for paired data. A global level of $P < 0{\cdot}050$ was considered statistically significant. All statistical analyses were carried out using Stata® 10 (StataCorp LP, College Station, Texas, USA).

Results

Inclusion of patients started in February 2008, with stepwise addition of hospitals until June 2009. Inclusion was ended as planned on 1 September 2009. In total, 1172 patients were diagnosed with adenocarcinoma of the rectum at the participating centres during the study period. Of these, 591 were eligible for participation: 265 had a procedure other than LAR or did not undergo surgery at all, 66 declined participation and 260 agreed to participate in the study (*Fig. 1*). In total, 170 patients had a temporary diverting stoma which was closed approximately 3 months after resection. The only difference between the participating and non-participating patients was in age (median 66 *versus* 71 years respectively; $P < 0{\cdot}001$). The demographic and treatment characteristics of the participants are shown in *Table 1*.

Table 1 Patient and treatment characteristics

	No. of patients ($n = 260$)
Age (years)*	66 (37–87)
Sex ratio (M : F)	156 : 104
Tumour height from anal verge (cm)	
≤ 5	17 (6·5)
> 5–10	118 (45·4)
> 10	125 (48·1)
Tumour stage (UICC)	
I	76 (29·2)
II	91 (35·0)
III	93 (35·8)
Neoadjuvant radio(chemo)therapy	
Yes	51 (19·6)
No	209 (80·4)
Surgical technique	
Total mesorectal excision	170 (65·4)
Partial mesorectal excision	90 (34·6)
Surgical approach	
Laparotomy	173 (66·5)
Laparoscopy	87 (33·5)
Anastomosis	
Colonic J pouch	17 (6·5)
Side-to-end	128 (49·2)
End-to-end	115 (44·2)
Temporary diverting stoma	170 (65·4)
ASA fitness grade	
I–II	235 (90·4)
III–IV	19 (7·3)
Not known	6 (2·3)
Hospital	
Aalborg	31 (11·9)
Aarhus	75 (28·8)
Herning	27 (10·4)
Hilleroed	45 (17·3)
Hvidovre	20 (7·7)
Randers	22 (8·5)
Svendborg	40 (15·4)

Values in parentheses are percentages unless indicated otherwise; *values are median (range). UICC, International Union Against Cancer; ASA, American Society of Anesthesiologists.

Of the 260 patients included in the study, 246 answered the inclusion questionnaire, whereas 14 patients who agreed to participate did not answer the first questionnaire. In total, 213 patients were still included at the time of first follow-up. Of these patients, 203 answered the questionnaire, but ten did not; however, the ten patients did agree to participate in the 12-month follow-up. A total of 193 patients participated in the 12-month follow-up (59·2 per cent of the 326 eligible patients who had LAR, 74·2 per cent of the 260 patients included) (*Fig. 1*). All patients included in the analyses completed at least two questionnaires.

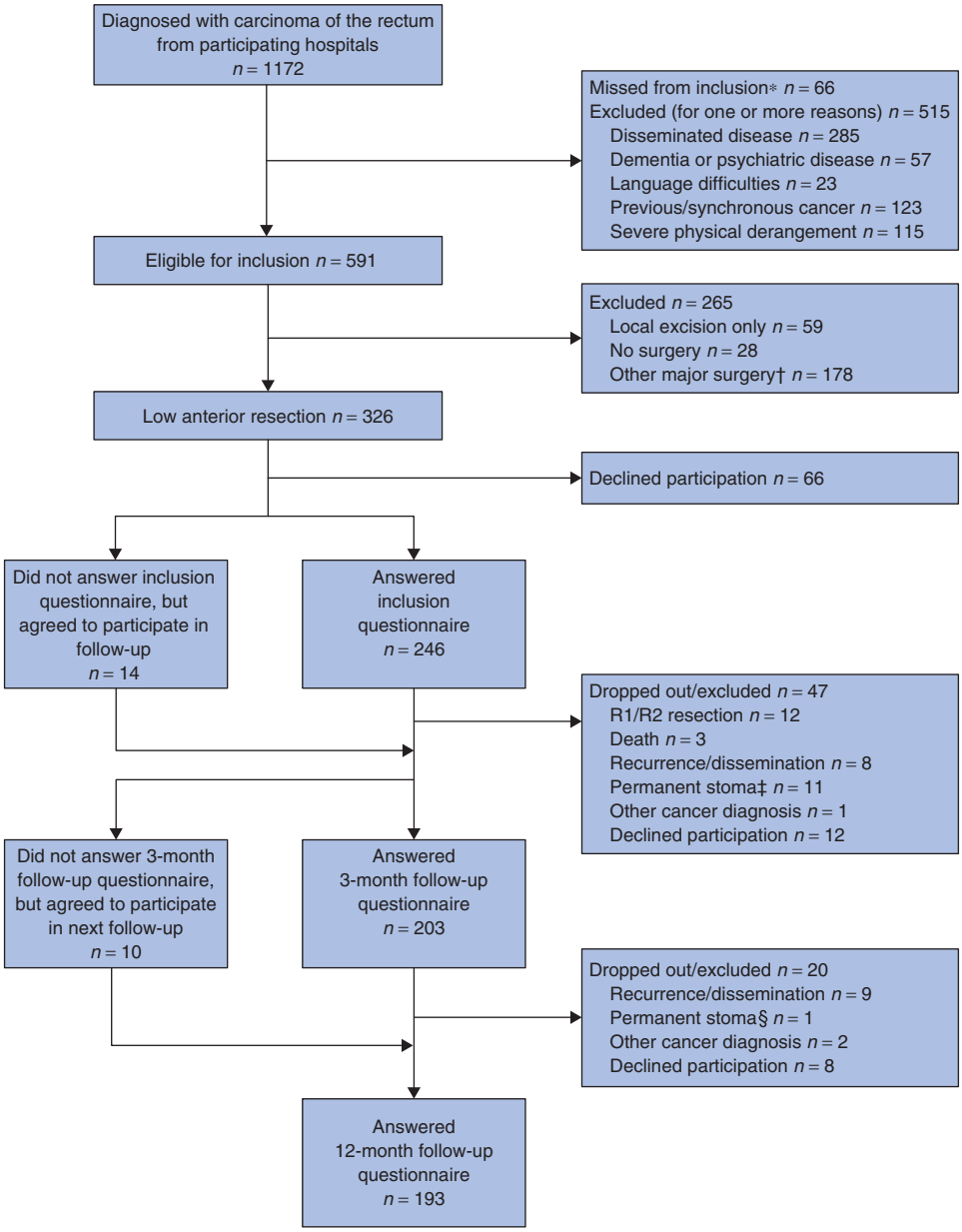

Fig. 1 Flow diagram showing patient selection. *Project nurse not available, patient diagnosed or treated acutely, patient overlooked for some other reason. †Abdominoperineal resection, proctocolectomy, pelvic exenteration, etc. ‡Reoperation because of complications at primary surgery or at reversal of ileostomy. §One patient who experienced 25 daily bowel movements received a permanent colostomy

Bowel function

Bowel Function Questionnaire

At inclusion many patients experienced bowel dysfunction (*Table 2*). The most frequent symptoms (occurring once or more each week) were blood and mucus in the stool (45·9 and 32·7 per cent respectively), incomplete evacuation (38·5 per cent), obstructive sensation (36·2 per cent), clustering (40·2 per cent), inability to defer defaecation for more than 15 min (56·0 per cent) and urgency (37·7 per cent), with moderate to severe impact in most patients.

The rate of bowel symptoms was high at both the 3- and 12-month follow-up. The most frequent symptoms were the typical LARS symptoms: clustering, urgency, frequent bowel movements and incontinence to flatus.

Table 2 Prevalence and degree of impact of bowel symptoms at inclusion, and at 3 and 12 months of follow-up

	Inclusion ($n = 246$)		3 months ($n = 203$)		12 months ($n = 193$)		
	n	Impact (%)*	*n*	Impact (%)*	*n*	Impact (%)*	*P*#
Incontinence‡							
Solid stool	8 of 244 (3·3)	75	18 of 200 (9·0)	94	8 of 191 (4·2)	71	0·046
Liquid stool†	32 of 244 (13·1)	88	39 of 202 (19·3)	92	25 of 191 (13·1)	96	0·029
Flatus†	69 of 245 (28·2)	49	117 of 202 (57·9)	58·6	102 of 192 (53·1)	57·6	0·105
Soiling‡	47 of 243 (19·3)	65	73 of 197 (37·1)	76	55 of 188 (29·3)	75	0·077
Use of pads‡	32 of 243 (13·2)	37	64 of 201 (31·8)	47	51 of 192 (26·6)	30	0·414
Antidiarrhoeal agents§	4 of 245 (1·6)	25	28 of 199 (14·1)	18	25 of 191 (13·1)	24	0·808
≥ 4 daily bowel movements†	70 of 243 (28·8)	63	112 of 199 (56·3)	63·6	74 of 188 (39·4)	57	< 0·001
Nocturnal bowel movements‡	38 of 243 (15·6)	68	64 of 199 (32·2)	65	41 of 191 (21·5)	48	< 0·001
Urgency†‡	92 of 244 (37·7)	81	100 of 199 (50·3)	77·9	59 of 191 (30·9)	69	< 0·001
Ability to defer defaecation < 15 min	135 of 241 (56·0)	49·2	136 of 201 (67·7)	61·6	103 of 190 (54·2)	50·5	0·003
Clustering†‡	98 of 244 (40·2)	66	119 of 198 (60·1)	66·7	85 of 190 (44·7)	73	< 0·001
Incomplete evacuation‡	94 of 244 (38·5)	68	115 of 197 (58·4)	73·9	88 of 189 (46·6)	75	0·013
Obstructive sensation§	89 of 246 (36·2)	56	56 of 198 (28·3)	53	58 of 189 (30·7)	49	0·586
Strain to defaecate‡	31 of 246 (12·6)	73	62 of 201 (30·8)	57	57 of 190 (30·0)	53	0·866
Pain at defaecation‡	28 of 245 (11·4)	75	30 of 199 (15·1)	87	18 of 190 (9·5)	82	0·008
Abdominal pain‡	43 of 245 (17·6)	79	23 of 199 (11·6)	73	19 of 191 (9·9)	72	0·532
> 5 min per attempt to defaecate	59 of 244 (24·2)	26	91 of 202 (45·0)	38	81 of 192 (42·2)	29	0·366
Defaecational assistance§	20 of 245 (8·2)	44	39 of 201 (19·4)	35	38 of 192 (19·8)	27	0·715
Unproductive call to stool§	106 of 245 (43·3)	36·4	99 of 201 (49·3)	35	77 of 191 (40·3)	30	0·003
Stool consistency							
Hard/lumpy	9 of 244 (3·7)	–	8 of 199 (4·0)	–	13 of 190 (6·8)	–	
Soft/formed	105 of 244 (43·0)	–	126 of 199 (63·3)	–	120 of 190 (63·2)	–	
Loose	29 of 244 (11·9)	–	13 of 199 (6·5)	–	14 of 190 (7·4)	–	
Liquid	27 of 244 (11·1)	–	9 of 199 (4·5)	–	3 of 190 (1·6)	–	
Alternating	74 of 244 (30·3)	–	42 of 199 (21·1)	–	40 of 190 (21·1)	–	
Stool content‡							
Mucus in stool	80 of 245 (32·7)	56	19 of 201 (9·4)	50	17 of 189 (9·0)	38	1·000
Blood in stool	113 of 246 (45·9)	58·7	1 of 201 (0·5)	100	1 of 190 (0·5)	–	1·000
Quality of life¶	113 of 246 45·9)	–	92 of 199 (46·2)	–	71 of 189 (37·6)	–	0·101

Values in parentheses are percentages. *Prevalence of subjects experiencing moderate or severe impact among subjects reporting to have the specific symptom/condition at least once a week. †Symptoms included in low anterior resection syndrome (LARS) score. ‡At least one episode weekly. §The specific symptom/condition/treatment being present or used. ¶Moderate or severe impact of bowel dysfunction on quality of life. #Wilcoxon signed rank test of differences between 3 and 12 months.

All of these had a moderate or severe impact in most patients. At 12 months, the prevalence of these symptoms (except incontinence to flatus) had decreased significantly (*Table 2*).

Low anterior resection syndrome score

At both 3 and 12 months, missing answers made calculation of the LARS score impossible for ten patients, leaving a total of 193 and 183 patients available for analysis respectively (*Table 3*). At the 3-month follow-up, the prevalence of LARS was high, with a total of 112 (58·0 per cent) of the 193 patients experiencing major LARS; by 12 months, the prevalence had declined significantly to 84 (45·9 per cent) of 183 patients ($P < 0·001$).

Risk factors

Patients receiving neoadjuvant therapy had a significantly higher risk of developing major LARS compared with non-irradiated patients (OR 2·41, 95 per cent confidence interval 1·00 to 5·83) at 12 months (*Table 4*). Patients who underwent TME had a significantly higher risk of major LARS than those who had PME (OR 2·81, 1·35 to 5·88). Among patients still included at 12 months, of 94 with a high tumour (10–15 cm from the anal verge), 28 per cent underwent TME despite the tumour location. Patients in this group had a higher risk of developing major LARS compared with patients who underwent PME (OR 3·10, 1·10 to 8·79).

The risk of major LARS at 12 months was significantly greater in patients with a temporary stoma (crude OR 4·51, 2·28 to 8·93), but this effect disappeared when the analysis was adjusted for tumour height (OR 1·73, 0·44 to 6·91). The risk of developing major LARS was not associated with sex, anastomotic leakage, surgical approach (laparoscopy *versus* laparotomy) or the presence of a neoreservoir, but the confidence intervals were wide.

Table 3 Low anterior resection syndrome score at 3 and 12 months according to risk factors

	3 months ($n = 193$*)			12 months ($n = 183$*)			
	No LARS	Minor LARS	Major LARS	No LARS	Minor LARS	Major LARS	P†
All patients	35 (18·1)	46 (23·8)	112 (58·0)	53 (29·0)	46 (25·1)	84 (45·9)	< 0·001
Neoadjuvant therapy							
Yes	3 (9)	2 (6)	28 (85)	5 (16)	4 (13)	22 (71)	0·026
No	32 (20·0)	44 (27·5)	84 (52·5)	48 (31·6)	42 (27·6)	62 (40·8)	0·001
Reservoir							
Straight anastomosis	18 (21)	22 (26)	45 (53)	29 (35)	24 (29)	31 (37)	0·013
Colonic J-pouch or side-to-end anastomosis	17 (15·7)	24 (22·2)	67 (62·0)	24 (24)	22 (22)	53 (54)	0·005
Surgical technique							
Total mesorectal excision	18 (14·1)	20 (15·6)	90 (70·3)	20 (16·8)	32 (26·9)	67 (56·3)	0·009
Partial mesorectal excision	17 (26)	26 (40)	22 (34)	33 (52)	14 (22)	17 (27)	0·008

Values in parentheses are percentages. *At both 3 and 12 months, missing answers made calculation of a low anterior resection syndrome (LARS) score impossible in ten patients. †Differences between 3 and 12 months (Wilcoxon signed-rank test).

Table 4 Odds ratios for major low anterior resection syndrome score among 193 patients included at 12 months of follow-up

	Major LARS* ($n = 84$)	Crude OR for major LARS†	Adjusted OR for major LARS†
Sex			
M	51 (61)	1·00 (reference)	1·00 (reference)
F	33 (39)	0·81 (0·45, 1·46)	0·73 (0·39, 1·38)
Neoadjuvant therapy			
No	62 (74)	1·00 (reference)	1·00 (reference)
Yes	22 (26)	3·55 (1·53, 8·22)	2·41 (1·00, 5·83)
Surgical technique			
Partial mesorectal excision	17 (20)	1·00 (reference)	1·00 (reference)
Total mesorectal excision	67 (80)	3·56 (1·84, 6·91)	2·81 (1·35, 5·88)
Anastomotic leakage			
No	81 (96)	1·00 (reference)	1·00 (reference)
Yes	3 (4)	0·42 (0·11, 1·64)	0·43 (0·10, 1·81)
Neorectal reservoir			
Straight (end-to-end) anastomosis	31 (37)	1·00 (reference)	1·00 (reference)
Colonic J-pouch/side-to-end anastomosis	53 (63)	1·97 (1·09, 3·57)	1·17 (0·59, 2·30)

Values in parentheses are *percentages and †95 per cent confidence intervals. LARS, low anterior resection syndrome. The Mantel–Haenszel estimate with the Woolf approximation was used to calculate crude odds ratios (ORs); adjusted ORs were calculated by multiple logistic regression analysis.

Quality of life

QoL was affected at the time of inclusion. Patients had low functional scores for overall global health status and emotional functioning, and high symptom scores for insomnia, appetite loss and diarrhoea (*Fig. 2*). No statistical comparison was made between QoL scores at inclusion and follow-up.

Comparing QoL at 3 and 12 months in the total cohort, only role functioning showed an overall clinically and statistically significant change of 6·3 points (mean 84·2 *versus* 90·5 respectively; $P = 0·007$) (*Fig. 2*). Focusing on subgroups of patients, the 11 patients who had major LARS at 3 months, but whose functional status improved no LARS at 12 months, showed major improvements in QoL for global health status (82·6 *versus* 92·7; $P = 0·080$), role functioning (90 *versus* 100; $P = 0·084$), emotional functioning (86·7 *versus* 95·5; $P = 0·047$), cognitive functioning (86·4 *versus* 97·0; $P = 0·084$) and social functioning (87·9 *versus* 95·5; $P = 0·084$). Most of these differences did not reach statistical significance most probably because of the small number of subjects. Among 67 patients with unchanged bowel function (major LARS at both 3 and 12 months), there was a significant improvement in role functioning between 3 and 12 months (78·1 *versus* 86·4; $P = 0·047$).

Association between quality of life and low anterior resection syndrome score

At both 3 and 12 months, QoL was closely associated with LARS; significant differences were found in QoL between patients without LARS and those with major LARS for all functional scales, except cognitive functioning at 3 months (*Table 5*). Major differences were found in global health status (88·8 *versus* 73·3 for no LARS *versus* major LARS;

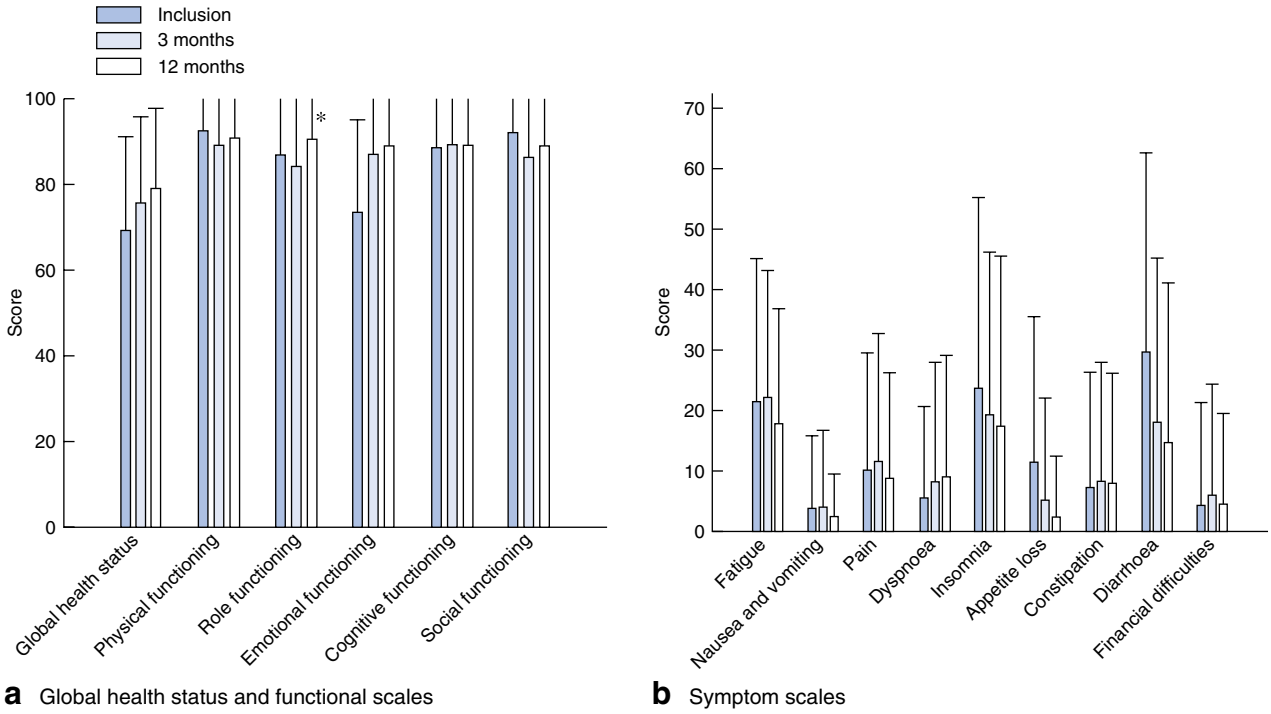

Fig. 2 Quality of life, measured by the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire, at inclusion, and after 3 and 12 months. Mean(s.d.) scores are shown. Significant difference between 3 and 12 months. *$P = 0{\cdot}007$ (Wilcoxon signed rank test)

Table 5 Differences between low anterior resection syndrome groups in quality of life at 3 and 12 months, measured on European Organization for Research and Treatment of Cancer QLQ-C30 functional scales

	Mean(s.d.) QLQ-C30 functional score				No *versus* major LARS		
	No LARS	Minor LARS	Major LARS	*P**	Score difference	*P*†	Clinical relevance of difference
Global health status							
3 months	81·7(21·3)	81·7(15·0)	71·0(20·6)	0·001	10·6	0·002	Moderate
12 months	88·8(15·4)	79·4(20·5)	73·3(18·0)	< 0·001	15·5	< 0·001	Moderate
Physical functioning							
3 months	95·1(10·2)	90·1(13·8)	86·9(15·1)	0·001	8·2	< 0·001	Minor
12 months	95·1(9·9)	93·6(11·9)	87·0(16·1)	< 0·001	8·1	< 0·001	Minor
Role functioning							
3 months	91·4(23·2)	90·9(16·7)	78·6(28·5)	0·002	12·8	0·003	Moderate
12 months	96·8(12·3)	94·3(13·4)	85·2(22·7)	< 0·001	11·7	< 0·001	Moderate
Emotional functioning							
3 months	91·9(11·5)	92·0(12·4)	82·9(20·3)	0·005	9·0	0·020	Minor
12 months	96·1(7·9)	92·6(12·1)	83·3(19·9)	< 0·001	12·7	< 0·001	Moderate
Cognitive functioning							
3 months	91·7(16·5)	91·1(13·1)	88·2(16·8)	0·267	3·5	0·123	
12 months	93·4(13·6)	90·0(16·0)	86·5(15·9)	0·007	6·9	0·002	Minor
Social functioning							
3 months	94·1(11·5)	93·3(12·5)	80·6(23·0)	< 0·001	13·5	0·001	Moderate
12 months	98·1(6·3)	95·1(12·2)	80·3(25·4)	< 0·001	17·8	< 0·001	Moderate

Values in parentheses are percentages. *Difference between the three low anterior resection syndrome (LARS) groups (Kruskal–Wallis test); †Mann–Whitney *U* test

Table 6 Differences between low anterior resection syndrome groups in quality of life at 3 and 12 months, measured on European Organization for Research and Treatment of Cancer QLQ-C30 symptom scales

	Mean(s.d.) QLQ-C30 symptom score				No *versus* major LARS		
	No LARS	Minor LARS	Major LARS	*P**	Score difference	*P*†	Clinical relevance of difference
Fatigue							
3 months	13·8(16·9)	17·9(17·6)	26·6(22·8)	0·004	12·8	0·003	Moderate
12 months	12·1(14·6)	13·9(19·4)	23·0(20·0)	0·001	11·0	0·001	Moderate
Nausea and vomiting							
3 months	2·0(6·9)	1·5(6·0)	6·1(15·9)	0·103	4·0	0·195	
12 months	0·3(2·3)	2·2(6·7)	3·9(8·8)	0·013	3·6	0·004	
Pain							
3 months	6·4(18·8)	4·8(9·8)	16·4(24·5)	0·001	10·0	0·003	Moderate
12 months	5·0(13·3)	5·6(10·7)	11·9(21·4)	0·032	6·9	0·014	Minor
Dyspnoea							
3 months	6·1(15·5)	8·3(19·2)	8·8(21·0)	0·865	2·7	0·592	
12 months	4·5(13·2)	4·5(15·4)	12·3(21·4)	0·006	7·9	0·015	Minor
Insomnia							
3 months	16·2(22·2)	14·8(24·2)	23·6(29·4)	0·162	7·5	0·266	
12 months	8·2(20·6)	14·8(24·2)	25·2(32·9)	0·002	17·2	0·001	Moderate
Appetite loss							
3 months	2·0(8·1)	3·0(9·6)	6·1(18·8)	0·550	4·1	0·317	
12 months	0·6(4·6)	3·0(9·6)	2·9(10·8)	0·292	2·3	0·160	
Constipation							
3 months	2·0(8·0)	3·0(9·6)	12·9(24·3)	0·002	11·0	0·008	Moderate
12 months	3·8(10·7)	6·7(15·2)	9·9(21·2)	0·263	6·1	0·104	
Diarrhoea							
3 months	6·9(13·7)	5·9(16·3)	25·5(30·8)	< 0·001	18·7	0·001	Moderate
12 months	5·7(14·2)	6·0(19·4)	25·7(31·8)	< 0·001	20·0	< 0·001	Moderate
Financial difficulties							
3 months	3·0(12·8)	3·7(12·8)	8·2(21·7)	0·251	5·2	0·166	
12 months	1·3(6·4)	4·4(16·8)	6·8(17·9)	0·080	5·6	0·030	Minor

Values in parentheses are percentages. *Difference between the three low anterior resection syndrome (LARS) groups (Kruskal–Wallis test); †Mann–Whitney *U* test.

$P < 0·001$), social functioning (98·1 *versus* 80·3; $P < 0·001$) and role functioning (96·8 *versus* 85·2; $P < 0·001$). For the symptom scales, there were significant differences between the groups with no LARS and major LARS for fatigue, pain and diarrhoea at both 3 and 12 months (*Table 6*). For dyspnoea, insomnia and financial difficulties significant differences between these groups were detected only at 12 months; there were no differences at 3 months.

Discussion

The present study showed that bowel dysfunction is a major issue after LAR, with 58·0 per cent of the patients experiencing severe bowel dysfunction at 3 months after surgery. The frequency of the symptoms decreased over time, but even at 12 months 45·9 per cent still reported major bowel dysfunction. There was a close association between bowel function and QoL, particularly with regard to global health status, social functioning and role functioning. The LARS score reliably identified patients for whom poor bowel function impaired overall QoL.

The typical LARS symptoms of urgency, incontinence to flatus, frequent bowel movements and clustering were common, occurring more than once per week in 50·3–60·1 per cent of patients at 3 months and in 30·9–53·1 per cent at 12 months. These results are in agreement with previous findings regarding the development of bowel function during the first year after LAR[6,12–16].

This study also showed a close relationship between LARS and QoL. Several studies have investigated QoL in patients with rectal cancer, but most focused on differences in QoL after LAR *versus* abdominoperineal resection, patients with or without neoadjuvant therapy, or different groups based on treatment or patient characteristics[2,17–19]. However, Vironen and colleagues[18] showed that both faecal incontinence and urgency had a significant effect on social functioning, whereas mental health and general health perception were associated with urgency alone. Pucciarelli and colleagues[20] reported a strong relationship between urgency and physical functioning, role functioning and social functioning in a cohort of patients undergoing LAR treated with neoadjuvant chemoradiotherapy. Strong

associations were found between all functional scales and major LARS at 12 months in the present study. The impact on social and role functioning is comparable to previous findings[18,20]. Many patients withdraw from social and regular daily activities because of fear of having an accident in public and therefore risk being socially isolated.

The only functional scale that was not strongly associated with LARS at both time points was cognitive functioning. No association between bowel function and cognitive functioning was expected because neither memory nor concentration seems to be directly affected by bowel function. However, for cognitive function, a minor but clinically relevant difference at 12 months was shown in the present study. It is speculated that, as bowel function was strongly associated with insomnia and fatigue, it may over time affect both memory and concentration.

Many of the symptom scales were associated with major LARS. In particular, diarrhoea and fatigue showed strong associations with bowel function, with differences of 11·0–20·0 points between patients without LARS and those with major LARS. Constipation showed an association only at 3 months. Diarrhoea and constipation are symptoms of bowel function, and are therefore expected to be associated with LARS. The symptoms are not clearly defined in the EORTC QLQ-C30; for example, the questions are phrased as 'Have you been constipated?' and 'Have you had diarrhoea?'. Patients' understanding of these terms might be different from the medical definitions. The mental distress of having bowel dysfunction in combination with occasional nocturnal bowel movements may disturb the sleep pattern, leading to a higher level of fatigue.

For dyspnoea, insomnia and financial difficulties, significant differences were found at 12 months but not at 3 months. Major LARS could, over time, affect the general level of health and physical activity as well as ability to work, and therefore could influence these areas.

Several studies have previously compared preoperative status with follow-up status[21–23]. This comparison must be made with caution, as at the time of inclusion patients have just received a life-threatening diagnosis which will surely influence their QoL. In addition, bowel function is usually affected by the tumour. Therefore, no comparison was made between inclusion and follow-up data here. In accordance with this understanding, a high prevalence of bowel symptoms and low functional scores for global health status and emotional functioning, and high symptom scores for insomnia, appetite loss and diarrhoea, were found at inclusion.

The present study showed a significantly higher risk of major LARS in patients who received neoadjuvant therapy than in those who did not, and after TME compared with PME. These results are in accordance with previous findings[7,17,20]. However, the oncological outcome is the primary focus of the procedure, and PME should be chosen only for patients with high tumours in whom the oncological outcome will not be jeopardized. No differences in risk were found in relation to sex, symptomatic anastomotic leakage or the presence of a neoreservoir. Previous studies have shown that the presence of a neoreservoir can reduce the severity of bowel dysfunction, although this effect might diminish over time[24–30], and anastomotic leakage can significantly impair bowel function[7,31]. This relationship could be neither confirmed nor disputed in this study, possibly owing to the relatively small number of leaks (11). There was a high risk of major LARS in patients who had a temporary diverting stoma. In Denmark, a diverting stoma is generally recommended only after low anastomosis, which is known to carry a higher risk of major LARS. After correction for tumour height, no significant differences were found.

Chronic pain has not been investigated in patients with rectal cancer. In the present study, after 12 months 9·9 per cent of patients experienced abdominal pain more than once per week, and 9·5 per cent reported pain on defaecation. This high incidence appears to be connected to LARS, there being a highly significant relationship between LARS and pain both at 3 and 12 months.

The high prevalence of severe bowel dysfunction with an immense impact on QoL clearly indicates the need to inform all patients before surgery about possible changes in bowel function resulting from LAR. As neoadjuvant therapy reduces only the local recurrence rate, but not overall survival, in patients with resectable cancers[32], patients should be informed about the increased risk of bowel dysfunction before consenting to this treatment. In a Danish national cross-sectional study of long-term survivors of rectal cancer, 41 per cent of patients had major LARS 2–9 years after surgery[7].This is only slightly lower than the proportion in the present study, suggesting that some improvement in function might be expected even after 1 year of follow-up. Several small studies have suggested a beneficial effect of transanal irrigation[33], sacral nerve stimulation[34,35] and biofeedback[36,37] in patients with LARS. Although the results are encouraging, further investigations, preferably in the form of randomized trials, are required to clarify their value.

The LARS score has a high sensitivity and specificity for identifying patients with major bowel dysfunction causing impairment of QoL after sphincter-preserving resection for rectal cancer[4]. Owing to its simplicity and ease of application, the score is optimal for regular screening for bowel dysfunction during follow-up. The results of

this study underline the strengths of the score by clearly demonstrating the relationship between LARS and health-related QoL. After this procedure, all patients should be screened routinely for LARS, and those with major LARS should be offered treatment to improve their QoL.

Collaborators

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