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The low anterior resection syndrome in a reference population: prevalence and predictive factors in the Netherlands

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Abstract

Aim The low anterior resection syndrome (LARS) severely affects quality of life (QoL) after colorectal cancer surgery. There are no data about these complaints and the association with QoL in a reference population. The aim of this study was to assess LARS and the association with QoL in a reference population.

Methods Six hundred patients who visited the outpatient clinic because of general or trauma surgical indications were asked to participate in this study. They received an invitation letter containing three validated questionnaires to assess LARS (assessed with the LARS score) and both general [European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30] and colorectal-specific (EORTC QLQ-CR29) QoL.

Results Five hundred and one respondents could be included for the analyses. The median age at inclusion was 68 years and 47.3% were men. Major LARS was observed in 15% of patients (11.4% in men and 18.9% in women, $P = 0.021$). Women reported more urgency ($P = 0.070$) and incontinence for both flatus ($P < 0.001$) and stool ($P = 0.063$) compared to men. In univariate analyses,

women reported major LARS significantly more often than men (OR 1.82; 95% CI 1.10–3.01). Patients with major LARS scored significantly worse in most QoL domains compared to patients with no/minor LARS.

Conclusion This is the first study demonstrating major LARS and the association with QoL in a reference population of patients without colorectal cancer. Our data can assist in the interpretation of LARS in past and future research about abdominal complaints after colorectal cancer surgery.

Keywords health-related quality of life, bowel dysfunction, low anterior resection syndrome, normative data

What does this paper add to the literature?

Low anterior resection syndrome (LARS) severely affects quality of life after total mesorectal excision for rectal cancer. This is the first study demonstrating major LARS and the association with quality of life in patients without colorectal cancer. Our data can assist in the interpretation of LARS in past and future research about abdominal complaints after colorectal cancer surgery.

Introduction

Colorectal cancer is the third most common cancer worldwide [1]. Due to overall ageing of the population, a further

increase is predicted [2]. Fortunately, treatment of colorectal cancer has also advanced over the last decades resulting in a significant decrease in morbidity and mortality [3]. With the growing number of colorectal cancer survivors, quality of life (QoL) has also become more important during the last decade. Previous studies have shown that colorectal cancer survivors often experience long-term side effects of the cancer and/or its treatment [4,5]. These problems can cause a persistent impact on QoL even years after surgery [6,7].

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Postoperative complaints after colorectal cancer surgery and more particularly functional bowel complaints after rectal cancer surgery have been extensively studied over the past years [8,9]. A cluster of bothersome abdominal complaints after colorectal cancer treatment was identified and is referred to as low anterior resection syndrome (LARS), with a prevalence of up to 60%–90% [10]. A previous study demonstrated that symptoms of major LARS also occur in more than 20% of patients treated for tumours above the rectum, with a significant negative effect on patients' QoL [11].

In addition, a recent study demonstrated major LARS in 29% of patients 5 years after transanal endoscopic microsurgical resection for early-stage rectal tumours [12]. The latter was an unexpected finding since transanal endoscopic microsurgical resection is considered a much less invasive procedure, with less damage to the anatomical structures compared to segmental colorectal resection for rectal cancer. Another recent study showed major LARS in 35% of patients following even a watch and wait policy for rectal cancer [13].

Apparently, functional bowel complaints that resemble LARS may also occur in colorectal cancer patients even without surgical intervention. Numerous research papers investigating the pathophysiology of functional abdominal complaints after rectal tumour resections are available but research into the prevalence of LARS in a population without colorectal carcinoma is still lacking. Since 30%–40% of patients with colorectal cancer experience severe functional abdominal complaints without major surgery, it is valuable to investigate what the prevalence of LARS and its effect on QoL is in a reference population of the same age group and gender. These data are indispensable for the interpretation of the prevalence of LARS in both past and future studies of patients after treatment for colorectal cancer. It will also enable better counselling of future colorectal cancer patients.

Aim

The aim of our study was to investigate the presence of the LARS and its potential association with QoL and patients' characteristics in a reference population that underwent medical consultation at the surgical outpatient clinic for any pathology other than abdominal disease.

Patients and methods

Data collection

Six hundred patients aged 55 years and older who visited the outpatient clinic because of general or trauma surgical indications in two general hospitals in the

Netherlands were asked to participate in this study. The age of 55 is the age at which patients in the Netherlands are invited for the population-based screening programme for colorectal cancer. Exclusion criteria were as follows: a medical history of gastrointestinal (GI) malignancy, inflammatory bowel disease or irritable bowel syndrome, previous GI surgery, presence of a stoma, chemotherapy within 2 years before inclusion, abdominal or pelvic radiation therapy in the past, ongoing hospital treatment for obstipation or faecal incontinence, immobility as a result of a recent trauma, the use of opiates and intellectual disability or dementia. Demographic and clinical information was obtained from patients' records at each of the participating centres. Participants were given an invitation letter explaining the aim of the study together with the questionnaires, an informed consent form and a prepaid return envelope. Participation was completely voluntary and no reminders were sent.

Measures

The LARS score, an internationally validated tool for the assessment of bowel dysfunction after rectal cancer surgery, was used to assess bowel dysfunction in this reference population [14,15]. It consists of five questions with a score that ranges from 0 to 42 points, with classification of patients into no LARS (0–20 points), minor LARS (21–29 points) or major LARS (30–42 points) [16]. Additionally, the EORTC QLQ-C30 and EORTC QLQ-CR29 questionnaires were used. These modules were designed by the European Organization for the Research and Treatment of Cancer (EORTC). The EORTC QLQ-C30 questionnaire consists of 30 questions on functional scales, a global QoL measure and symptom assessment [17]. The EORTC QLQ-CR29 questionnaire is designed specifically for colorectal cancer and consists of 29 items addressing GI symptoms, chemotherapy side effects, defaecation problems, pain and problems with micturition, and separate items addressing sexual function for men and women [9]. For both EORTC questionnaires, a high functional score represented a high level of function while a high symptom score represented a high level of symptoms.

Statistical analyses

Comparisons of patient characteristics between LARS groups (no/minor *vs* major) were performed using the chi-squared test or Fisher's exact test for categorical data and the Mann–Whitney *U* test for continuous data. The following factors with a possible association with major LARS were first tested in univariable analysis: gender

(women *vs* men), marital status (married *vs* unmarried), age (≤ 68 *vs* > 68 years), non-GI abdominal surgery in the past (yes *vs* no), smoking (yes *vs* no), number of vaginal births in women (0 *vs* ≥ 1), reason for hospital visit (general *vs* trauma surgical). Associated factors were estimated by odds ratios as calculated with logistic regression analyses. Comparisons of LARS subscales between men and women were performed using the chi-squared test. The EORTC QoL questionnaires were scored according to the guidelines. Both general and colorectal-specific QoL was compared between the no/minor and major LARS groups using the Student *t* test (in the case of normal distribution) or Mann–Whitney *U* test (in the case of abnormal distribution). For all analyses, $P < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. (IBM Corp., Armonk, NY, USA).

Results

Five hundred and nine of the 600 invited patients (84.8%) returned the questionnaire, of whom eight patients returned a blank or incomplete questionnaire. A total of 501 patients (83.5%) with completed questionnaires were included for analyses. Patient characteristics are described in Table 1. 47.3% of the study patients were men. Median age was 68 years (range 55–93). 39.8% visited the outpatient clinic for a trauma

surgical reason (e.g. radial fracture, clavicular fracture) while 60.2% visited the outpatient clinic for general surgical reasons (e.g. inguinal hernia, lipoma) (Table 1).

Bowel dysfunction

Major LARS was observed in 15% of patients while minor LARS was observed in 14% of patients and no LARS was observed in 71%. Major LARS was reported in 11.4% of men and 18.9% of women ($P = 0.021$) (Fig. 1). The median LARS score was 11 (0–38) among men and 15 (0–42) among women ($P < 0.001$). In univariate analyses, female gender (OR 1.82; 95% CI 1.10–3.01) was significantly associated with major LARS. For the other patient characteristics, no significant association with the occurrence of major LARS was found. Therefore, no multivariate analysis was performed (Table 1). Concerning the subscales of LARS, women reported more urgency ($P = 0.070$) and incontinence for both flatus ($P < 0.001$) and stool ($P = 0.063$) compared to the men participating in our study, although only the association between gender and incontinence for flatus reached significance at the $P < 0.05$ level (Table 2).

LARS and quality of life

Patients with major LARS fared significantly worse compared to patients with no/minor LARS in all

Table 1 Patient characteristics and univariate analyses of associations between patient characteristics on the one hand and major LARS on the other hand

Characteristic	Patients <i>N</i> = 501 (%)	Major LARS (%)	Unadjusted OR (95% CI)	<i>P</i> value
Age (years)				
< 68	260 (52.8%)	14.2%	Reference	0.451
≥ 68	232 (47.2%)	16.7%	1.21 (0.74–1.96)	
Gender				
Male	237 (47.3%)	11.4%	Reference	0.021
Female	264 (52.7%)	18.9%	1.82 (1.10–3.01)	
Marital status				
Married	395 (78.8%)	14.7%	Reference	0.412
Single/widowed	106 (21.2%)	17.9%	1.27 (0.72–2.24)	
Reason for hospital visit				
Trauma surgical	196 (39.8%)	14.3%	Reference	0.579
General surgical	296 (60.2%)	16.1%	1.15 (0.70–1.90)	
Smoking				
No	431 (86.0%)	14.8%	Reference	0.424
Yes	70 (14.0%)	18.6%	1.31 (0.68–2.53)	
Partus if female				
0	38 (14.4%)	15.8%	Reference	
1	27 (10.2%)	18.5%	1.80 (0.54–6.00)	0.340
2	121 (45.8%)	16.5%	1.23 (0.46–3.33)	0.679
≥ 3	78 (29.6%)	24.4%	1.91 (0.70–5.26)	0.209

Figure 1 LARS score severity categories among men and women.

‘general’ QoL domains (QLQ-C30 questionnaire). The highest mean differences in general QoL domains between major and no/minor LARS were found for global health status ($P < 0.001$), emotional functioning ($P < 0.001$), diarrhoea ($P < 0.001$) and constipation ($P < 0.001$) (Fig. 2). Also for colorectal-cancer-specific QoL (QLQ-CR29 questionnaire), patients with major LARS scored significantly worse in all QoL domains except for sexual interest among men and dyspareunia among women where significance at $P < 0.05$ could not be reached (Fig. 3). The highest mean differences in colorectal-specific QoL domains between major and no/minor LARS were found for stool frequency

($P < 0.001$), bloating ($P < 0.001$), flatulence ($P < 0.001$), faecal incontinence ($P < 0.001$) and embarrassment ($P < 0.001$). No significant differences in QoL between male and female patients with major LARS were found.

Discussion

This, to the best of our knowledge, is the first study demonstrating major LARS and its detailed association with QoL in a reference population. We found 15% major LARS in patients aged between 55 and 93 years, which is a relevant age for the vast majority of colorectal cancer studies. Together with 14% of patients declaring minor LARS, almost one-third of the reference population experiences functional abdominal complaints without any history of GI surgery. In line with the findings among surgically treated rectal cancer patients, the LARS subscales that scored for incontinence for flatus, clustering and urgency were the most common complaints [9]. Comparing the gender groups, women reported significantly more major LARS (OR 1.82; 95% CI 1.10–3.01). These data are in line with a recent study that investigated the prevalence of LARS in the general Danish population. This study showed, respectively, 10% and 19% major LARS among men and women in the age group 50–79 years [18]. However, QoL was not extensively measured in that study and no

Table 2 LARS score items among men and women

Response (score value)	Men, <i>n</i> (%)	Women, <i>n</i> (%)	<i>P</i> value
1. Do you ever have occasions when you cannot control your flatus?			
No, never (0)	138 (58.2%)	106 (40.1%)	< 0.001
< once per week (4)	46 (19.4%)	63 (23.9%)	
> once per week (7)	53 (22.4%)	95 (36.0%)	
2. Do you ever have any accidental leakage of liquid stool?			
No, never (0)	205 (86.9%)	215 (81.4%)	0.063
< once per week (3)	23 (9.7%)	35 (13.3%)	
> once per week (3)	8 (3.4%)	14 (5.3%)	
3. How often do you open your bowels?			
> 7 per day (4)	3 (1.3%)	5 (1.9%)	0.210
4–7 per day (2)	16 (6.7%)	16 (6.8%)	
1–3 per day (0)	181 (76.4%)	183 (69.3%)	
< once per 5 days (5)	37 (15.6%)	60 (22.7%)	
4. Do you ever have to open your bowels again within 1 h of the last bowel opening?			
No, never (0)	162 (68.4%)	163 (61.7%)	0.106
< once per week (9)	44 (18.6%)	48 (18.2%)	
> once per week (11)	31 (13.0%)	53 (20.1%)	
5. Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?			
No, never (0)	130 (54.9%)	130 (49.2%)	0.070
< once per week (11)	76 (32.1%)	79 (29.9%)	
> once per week (16)	31 (13.1%)	55 (20.8%)

Figure 2 Mean scores of EORTC QLQ-C30 subscales by LARS groups. 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 represents a higher level of symptoms. * $P < 0.05$ between major LARS and no/minor LARS.

conclusions regarding the impact of bowel dysfunction on QoL in the general population could be drawn. Also for the LARS subscales of the current study, a significantly higher prevalence of urgency and incontinence for stool and flatus among women compared to men was reported. Several causes such as a difference in pelvic anatomy, pelvic floor dysfunction and potential obstetric trauma were hypothesized previously [9,19]. Nevertheless, in the present study no significant association between the occurrence of major LARS and obstetric history in female participants was found. In our study, major

LARS was also not significantly associated with lower age, in contrast to previous studies in which a higher prevalence of major LARS among younger patients who underwent colorectal cancer surgery was reported [9,11,20]. A possible explanation could be the fact that elderly people often receive less aggressive treatment after diagnosis of colorectal cancer and are therefore less likely to experience abdominal complaints as an adverse effect of their treatment [21]. Because of the absence of these age-dependent differences in therapy, no age-related bowel dysfunction is expected in a reference population.

Figure 3 Mean scores of EORTC QLQ-CR29 subscales by LARS groups. 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 represents a higher level of symptoms. * $P < 0.05$ between major LARS and no/minor LARS.

The association between major LARS and patients' QoL in a reference population has not been extensively described previously. In line with previous studies among rectal cancer patients, our study identified similar differences in QoL between major and no/minor LARS groups [22]. The QoL subscales with the highest association with LARS score items, such as 'stool frequency', 'flatulence', 'diarrhoea' and 'constipation', reached the highest level of statistical significance with a $P < 0.01$. These findings contribute to our presumption that there is also a high level of correlation between major LARS and poor QoL in patients without any history of GI surgery or colorectal cancer.

Previous studies that looked into the pathophysiology of developing LARS after surgery found that, besides treatment-associated factors such as tumour height, neo-adjuvant chemo-radiotherapy and a temporary stoma, also non-treatment-related factors such as age and sex were associated with the prevalence of major LARS [9,13,20,23–26]. These observations, combined with the 30% major LARS that was reported after a watch and wait policy for rectal cancer, suggest that the aetiology of LARS is multifactorial [9,13,20,23–26]. Data from these previous studies add weight to the hypothesis that not surgery on its own but the combination of certain patient- and treatment-related factors contributes to the risk of developing LARS after colorectal cancer treatment. In fact, part of the observed major LARS after rectal surgery might not be induced by surgery but might be pre-existent.

The strength of this study lies in the high response rate together with the use of comprehensive validated questionnaires in a large patient cohort of relevant age for comparison with colorectal cancer patients. Nevertheless, selection bias may have occurred due to recruitment of patients who visited the outpatient clinic for general or trauma surgical care. Since the presence of a physical disease was found to be a risk factor for the development of LARS in a normal population, the prevalence of LARS and the concomitant QoL as reported in our study could be positively influenced and thereby it may have resulted in an underestimation of LARS in the general population [18]. However, the effect of a physical disease on the prevalence of abdominal complaints in our study could have been decreased by the fact that people with a history of GI pathology were excluded.

The use of the LARS score may be a potential limitation. Knowing that the LARS score is specifically designed and validated to evaluate bowel symptoms after surgery for rectal cancer, it may sound contradictory to use this in a reference population. However, as a considerable number of patients in the reference group

reported LARS-like complaints, functional problems as described in the LARS score also seem to be of clinical relevance in these patients.

The results of this study demonstrate that a considerable number of patients without abdominal disease experience functional abdominal complaints, as defined by the LARS score, even without surgical treatment for colorectal cancer. Assessment of these bothersome symptoms in patients in advance of colorectal cancer treatment may be useful when considering certain treatment options that can further degrade these pre-existing functional abdominal complaints. Until now researchers investigating LARS and QoL in colorectal cancer patients had no normal data to substantiate their findings. With the presence of our data future studies can assess, in a more substantiated way, the additional effect of colorectal cancer treatment on pre-existing or expected functional abdominal complaints and their impact on QoL.

Conclusion

This is the first study demonstrating that major LARS occurs in 15% of patients without abdominal disease and is associated with poorer QoL. These data should be considered as normative data when interpreting LARS in future research concerning functional abdominal complaints and QoL after colorectal cancer surgery.

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