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ORIGINAL ARTICLE

Low Anterior Resection Syndrome in Adults with Rectal Cancer in China: a Case Series Analysis

Yuan Qiu [1] · Yu Pu [1] · Haidi Guan [1] · Weijie Fan [2] · Shuai Wang [1] · Guangsheng Du [1] · Hua Yang [1] · Weidong Xiao [1]

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Abstract

Low anterior resection syndrome (LARS) comprises a collection of symptoms affecting patients' defecation after restorative surgery for rectal cancer. The aim of this work was to study the incidence and risk factors for LARS in China. Rectal cancer patients undergoing total mesorectal excision and colorectal anastomosis between May 2012 and January 2015 were identified from a single center. The patients completed the LARS score questionnaire through telephone. The clinical and pathological factors that may influence the occurrence of LARS were analyzed using univariate and multivariate logistic regression analysis. The influence of postoperative recovery time and pelvic dimensions on the occurrence of LARS was also analyzed. This study included 337 patients, at an average age of 61.03 SD11.32. The mean LARS score of the patients was 14.08 (range 0–41). A total of 126 patients (37.4%) developed LARS after surgery, including 63 (18.7%) severe cases. Compared with the scores within the initial 6 postoperative months, the LARS scores of the patients in 6~18 months after the surgery showed significant reductions ($p < 0.01$). In multivariate analysis, lower locations of anastomosis, pre-surgery radiotherapy, and shorter postoperative recovery time were significant predisposing factors for LARS. A subgroup analysis revealed that patients suffering from LARS over 18 months after surgery were found to have a significantly shorter interspinous distance than those without LARS ($p < 0.05$). LARS could improve over time after surgery. Lower anastomotic level and pre-surgery radiotherapy are risk factors for LARS.

Keywords LARS · Rectal cancer · Surgery · Pathological analysis

Introduction

As a significant cause of cancer death worldwide, colorectal cancer (CRC) is still one of the most common cancers in the world. The annual incidence of rectal cancer in China exceeds 200,000 cases [1]. The combination of advances in surgical technique and neoadjuvant therapy have led to an increase in sphincter preservation. Low anterior resection (LAR) with total mesorectal excision (TME) is currently regarded as the optimal procedure for the majority of patients with rectal cancer. However, many patients undergoing LAR suffer from bowel dysfunction. The complex of symptoms consisting of incontinence for flatus and/or feces, urgency, constipation, fragmentation, and frequent bowel movements is referred to as the low anterior resection syndrome (LARS) [2]. Even though recognized for a long time, this disorder has not been systematically studied. Therefore, anorectal function after sphincter-preserving surgery has not received enough attention in both research and clinical practice.

The broad definition of LARS has made it difficult to assess the quality of life of patients, and comparison of outcomes between patients has been challenging. A score has been developed on the basis of patient-reported symptoms, which is called the LARS score [2]. This score is a quick simple and valid questionnaire for measuring the severity of postoperative bowel dysfunction. In this survey, five issues that most bothered the patients were selected: incontinence for flatus, incontinence for liquid stool, frequency, clustering, and urgency. It is a summative scale, and each item is individually weighted. Developed in Danish, the LARS score has been validated and translated into several languages, including Chinese [3–5]. Although numerous studies have focused on

Yuan Qiu and Yu Pu contributed equally.

✉ Weidong Xiao
weidongxiao2@163.com

1 Department of General Surgery of Xinqiao Hospital, the Army Medical University, Shapingba, Chongqing 400037, China

2 Department of Radiology of Xinqiao Hospital, the Army Medical University, Shapingba, Chongqing 400037, China

the association between quality of life and LARS score, very few studies have used the LARS score to predict risk factors for postoperative bowel dysfunction, especially in China [6].

The incidence of LARS after LAR greatly varies in the literature [7]. The symptoms were previously thought to be transient. Recent study reported that up to 30% of LAR patients have ongoing symptoms for more than 1 year [8]. Like the symptom profile, the etiology of LARS is difficult to define and is likely related to multifactorial mechanisms: sphincter injury during anastomosis, alterations in anorectal physiology, disappearance of the rectoanal inhibitory reflex, and reduction in rectal reservoir capacity and compliance [9]. Therefore, it is important to identify the patient's factors that predispose to LARS. Moreover, detection of these factors associated with LARS should have a great value in helping doctors, and their patients make better decisions about choice of the kind of surgery. The main aims of this study were to investigate the prevalence of LARS as well as to evaluate the predictive factors of LARS using a validated scoring system.

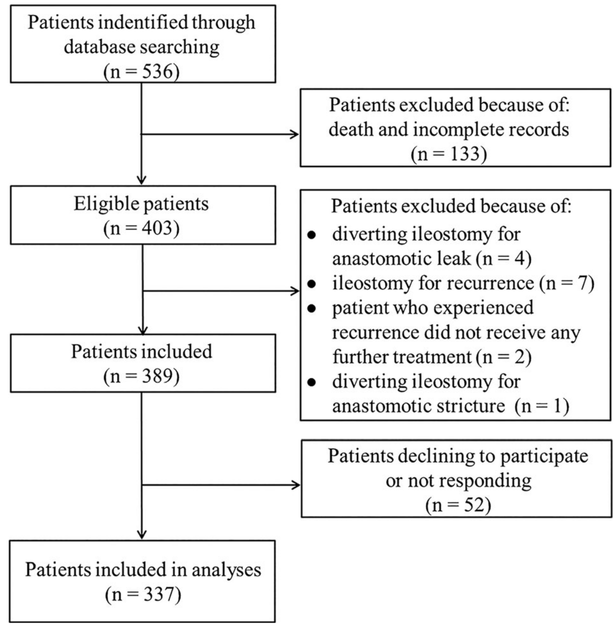

Fig. 1 Flow chart of patient selection

Patients and Methods

Study Population

This study was approved by the Research and Ethics Committee of Xinqiao Hospital, the Army Medical University (2015-YD037-02). Patients were identified from a rectal cancer database at our single center. Patient details were retrieved from a maintained departmental database in our center (from May 2012 to January 2015). All participants gave their written informed consent. Inclusion criteria included the following: (1) patients who were diagnosed with rectal cancer and had undergone sphincter-preserving low anterior resection with curative intent and (2) age 18 years or older. Exclusion criteria were intestinal stoma, intestinal obstruction, recurrence, other cancers, intellectual disability/dementia, and metastatic disease. Demographic and clinical information was obtained from databases. In total, 536 eligible patients were identified, of whom 199 were excluded (Fig. 1). Patient's age, gender, preoperative chemoradiotherapy, surgical procedure, morbidity, anastomosis level, and pathological features were retrieved from case records. Pelvic dimensions, including interspinous distance, transverse outlet, sagittal inlet, posterior sagittal diameter of pelvic outlet, and sacrum-coccyx distance, were blindly measured on three-dimensional medical CT image reconstruction by a radiologist (W.F.).

Follow-Up

We conducted this descriptive and exploratory study using a telephone-based survey with LARS questionnaire. Also, questionnaire survey was conducted during outpatient follow-up. There was no statistical difference in the survey results whether based on the outpatient follow-up or on the telephone. The surveys were conducted at least 30 days past surgery, and, hence, their bowel function was expected to have regained stability. Each question received a score based on the reply, and the scores for each question are then added together to give a final score range of 0–42. The LARS score was categorized into 3 groups: no LARS (0–20 points), minor LARS (21–29 points), or major LARS (30–42 points).

Statistical Analysis

Data on quantitative variables are presented as mean and standard deviation, and frequencies for qualitative variables. The patients selected were grouped into two groups: group I consists of patients with major/mild LARS and group II consists of patients with no LARS. A Chi-square test was applied to assess differences between the study groups for qualitative parameters. We used the Mann-Whitney *U*-test for continuous data and the χ^2 test or Fisher's exact test for categorical data. Univariate analysis was carried out and compared the presence or absence of LARS (yes/no) with patient and tumor-related variables. Multivariate analysis was performed of those variables which showed a statistically significant association on univariate analysis of $p < 0.05$.

Results

We identified 536 patient records. Of these, we excluded 199 for the following reasons: incomplete or missing records or death

($n = 133$), enterostomies due to anastomotic leakage ($n = 4$), cancer recurrence ($n = 9$), ileostomy due to anastomotic stricture ($n = 1$), and loss of follow-up ($n = 52$) (Fig. 1). Therefore, this study population included 337 patients, 208 men and 129 women. At the time of the surgery, the mean age of all patients was 61.03 SD11.32 years. The mean LARS score from all participants was 14.08 (range, 0–41). There were 211 (62.6%) patients with no LARS, 63 (18.7%) with minor LARS and 63 (18.7%) with major LARS. LARS was significantly more frequent in patients with lower locations of anastomosis (58.8% vs. 23.8%, $p < 0.05$), in those with preoperative radiotherapy (83.3% vs. 35.7%, $p < 0.05$), and those who had shorter postoperative recovery time ($p < 0.05$) (Table 1). The patients were divided into 4 groups according to the time to complete the questionnaire: 1~3 months ($n = 42$); 3~6 months ($n = 61$); 6~18 months ($n = 132$); and more than 18 months ($n = 102$). The analysis about the relationship between the postoperative recovery time and LARS score revealed that compared with the patients in the first 6 postoperative months, the LARS score of the patients in the period of 6–18 postoperative months displayed a significant gradual decrease trend ($p < 0.01$) (Fig. 2). In comparing the LARS scores between the 1~3 months and 3~6 months, there is no significant difference.

The multivariate analysis model, including lower locations of anastomosis, pre-surgery radiotherapy, and shorter postoperative recovery time, was significantly associated with LARS. Statistical analysis showed that patients of pre-surgery radiotherapy had nearly 13-fold of increased risk of developing LARS ($p < 0.01$) and patients of lower locations of anastomosis had nearly 5.3-fold of increased risk of developing LARS ($p = 0.03$) (Table 2). Moreover, shorter postoperative recovery time independently associated with LARS.

Based on above data, as many as 22.5% of patients still have LARS for more than 18 months after surgery. Thus, we investigate the clinical characteristics of patients who underwent previous surgery more than 18 months. Low rectal cancer patients (with an anastomotic level < 5 cm) had a higher incidence of LARS ($p < 0.05$).

To further study the relationship between surgical difficulty and LARS, pelvic dimensions from patients who had an anastomotic level < 5 cm and underwent surgery more than 18 months were utilized to analysis. Interspinous diameters of LARS group were significantly lower than No LARS group ($p < 0.05$) (Table 3). However, other variables such as transverse outlet, sagittal inlet, posterior sagittal diameter of pelvic outlet, and sacrum-coccyx distance were not found to be statistically significant.

Discussion

The present study is the first attempt in China to investigate the prevalence and risk factors for LARS using a scoring system. This study revealed that 22.5% of patients still have some degree of LARS for more than 18 months after surgery. Moreover, our study highlighted that lower locations of anastomosis, pre-surgery radiotherapy, and shorter postoperative recovery time are the independent risk factors of LARS occurrence. The interspinous diameter may be a potential predicating factor in LARS recovery of the patients with low rectal cancer.

It is undeniable that most rectal cancer patients will experience daily bowel dysfunction after LAR. Patients may have a combination of symptoms including frequency, urgency, incontinence, and constipation. This important realization has led to the development of a simple self-administered scoring system assessing the severity of LARS—the LARS score [2]. Prevalence of LARS assessed by this system varies in the literature between 40 and 60%, including studies with short follow-up (12 months) and longer follow-up (up to 14 years) [10, 11]. For the majority of patients, symptoms of LARS will decrease over time. In this study, 37.4% of patients developed LARS after the surgery, and as time went by, 22.5% of patients still experienced LARS symptoms for up to 18 months following surgery. The incidence of LARS in this study was slightly lower than in other studies. One possible explanation for this was that the proportion of preoperative radiotherapy in this study was lower than that published by other studies. It is recognized that preoperative radiotherapy had an influence on the anorectal function. Notably, only about 3.6% (12 of 337) of patients received preoperative radiotherapy in our study. Other studies about LARS have demonstrated that up to 20 to 70% of patients received pre-surgery radiotherapy [12, 13]. There are a lot of reasons for such a low rate of pre-surgery radiation therapy in our center. One reason is that the level of understanding and acceptance of pre-surgery radiation among Chinese people is relatively low, especially in economically backward west areas.

Several factors have been reported to be associated with LARS including age, gender, operation method (laparotomy vs. laparoscopy), T stage, level of anastomosis, radiotherapy, and pelvic cavity. Different studies have provided different conclusions. In this study, gender was not associated with LARS. Bregendahl et al. reported that female gender was a risk factor for LARS [12], while some authors found that male was related to LARS [14]. On the other hand, LARS prevalence has been reported to be lower in older patients compared to younger patients [12, 15]. However, we did not find any statistical difference in our study. The only factors related to LARS in this study were as follows: preoperative radiotherapy, level of anastomosis, and shorter postoperative recovery time. Among these factors, preoperative radiotherapy has been the most extensively studied. It does cause tissue edema, fibrosis, extensive mist, and exudates which impede the dissection of the tissue [16]. Luis et al. reported that both preoperative radiotherapy and postoperative radiotherapy were risk

Table 1 Association analysis between clinical parameters and the occurrence of low anterior resection syndrome (LARS)

Patient demographics	No LARS	LARS (major/minor)	*p* value
All	211	126	
Sex			
Male	131	77	0.859
Female	80	49	
Age			
<60 years	82	53	0.562
≥60 years	129	73	
Surgical treatment			
Laparotomy	24	10	0.311
Laparoscopy	187	116	
T stage			
T0~T2	96	53	0.539
T3~T4	115	73	
N stage			
N0	125	70	0.507
N1~N2	86	56	
Anastomosis locations			
<5 cm	54	77	0.000
≥5 cm	157	49	
Pre-surgery radiotherapy			
No	209	116	0.002
Yes	2	10	
Follow-up duration			
1 month~3 months	18	24	0.000
3 month~6 months	30	31	
6 month~18 months	84	48	
>18 months	79	23	
Posterior sagittal diameter of pelvic outlet			
<90 mm	151	82	0.212
≥90 mm	60	44	
Transverse outlet			
<108.5 mm	108	61	0.622
≥108.5 mm	103	65	
Interspinous distance			
<96.2 mm	104	69	0.331
≥96.2 mm	107	57	
Sagittal inlet			
<104 mm	114	61	0.318
≥104 mm	97	65	
Sacrum-coccyx distance			
<119 mm	105	62	0.921
≥119 mm	106	64	

factors associated with LARS [17]. It is possible that for some of these irradiated patients with low rectal cancer, a sphincter-preserving surgery was not the optimal procedure, and the abdominoperineal resection should also be considered. These findings emphasize the need of an intricate decision-making to balance rectal cancer staging, patient beliefs, and surgeon-related factors.

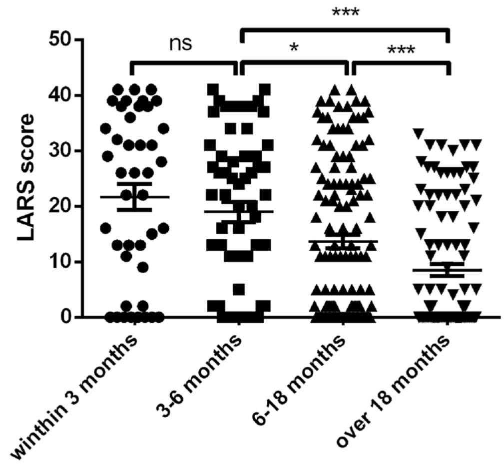

Fig. 2 Distribution of low anterior resection scores according to postoperative recovery time

Another factor found to correlate with LARS is the level of anastomosis. In other literatures, the levels of anastomosis related to LARS ranged from 2 to 12 cm [18, 19]. Recent study found that the best cut-off value for LARS was 5 cm (anastomosis level), which corresponded to a tumor level of around 7 cm from the anal verge [13, 20]. Thus, the cut-off point was set at 5 cm in this study. We found a 5.3-fold increase in the risk of LARS in patients who had lower locations of anastomosis (< 5 cm). This is consistent with the findings from the other studies, where pronounced bowel dysfunction was reported for patients with low-lying tumors. Interestingly, LARS occurred not only in rectal cancer cases who underwent low anterior resection but also in patients with a high-lying tumor (locations of anastomosis > 5 cm) who had anterior resection, although at a lower frequency (23.8%). Understanding the pathophysiology of such failures of functional recovery may help in surgical decision-making and anorectal rehabilitation for rectal cancer patients. In this respect, some studies suggest that the type of reconstruction methods, such as side-to-end anastomosis and colonic J-pouch, used for bowel anastomosis influence the functional outcome [21–23]. Unfortunately, the differences in LARS

Table 2 Univariate analysis of factors associated with the risk of developing low anterior resection syndrome

Variable	OR	95% CI	p
Location of anastomosis	5.336	3.197~8.907	0.000
Pre-surgery radiotherapy	13.216	2.597~67.260	0.002
Postoperative recovery time	3.477	2.033~5.946	0.000

Table 3 Comparison of pelvic parameters in patients with and without low anterior resection syndrome who had an anastomotic level < 5 cm and underwent surgery more than 18 months

	n	Interspinous distance	Transverse outlet	Sagittal inlet	Posterior sagittal diameter of pelvic outlet	Sacrum-coccyx distance
No LARS	29	100.97±10.28	113.37±13.48	104.67±13.74	84.88±8.08	116.90±16.19
LARS	19	94.04±8.71*	105.40±14.61	104.20±9.61	85.21±8.68	118.26±13.63

*, $P < 0.05$

score after different types of anastomotic technique have not been evaluated in this study due to incomplete records.

There is a correlation between LARS and postoperative recovery time which was confirmed in the present study. It has been reported and it is also our clinical experience that bowel dysfunction stabilizes within the first 1–2 years, although some patients experience poor anorectal function within 6 months after LAR. This study found that some patients show an improvement of anorectal function at 18 months after surgery. Moreover, long-term studies show minimal functional differences overall over a 2-year or greater follow-up [8]. The results presented above suggest that the cause of LARS is considered to be multifactorial, including damage to the anatomy or the function of the anal sphincters, neurologic impairment, and poor neorectal capacity. Among them, some deficits are considered recoverable. For example, the hypogastric nerves could be injured by the dissection of the rectum, and consequently the rectoanal inhibitory reflex (RAIR) is absent postoperatively. In this respect, O'Riordain et al. have demonstrated that the RAIR disappeared in 83% of patients with LAR, with RAIR recovery at 6 months in 21% and in 85% at 24 months [24]. Consistent with this, some investigators found that autonomic nerves regeneration occur across the anastomotic scar 6 months after surgery [25]. However, some deficits are considered unrecoverable. The most obvious mechanism potentially responsible for LARS is the distension of the sphincter muscles after the insertion of the circular stapling device. In a manometric study by Ho and colleagues, at 6 months of follow-up, patients undergoing stapled anastomoses demonstrated significantly reduced resting anal pressures with a higher incidence of endosonographically visible internal anal sphincter fragmentation when compared with patients who did not undergo trans-anal stapled anastomosis [26]. In addition to sphincter damage, neorectal capacity and compliance are central to rectal function. The neorectum, which is part of the descending colon, does not have the same elastic wall properties as the rectum [27]. Therefore, after LAR, the pressure of the anal canal decreases, while the pressure of the neorectum significantly increases even when associated with small fecal volumes.

To further study the precise description of relationship between pelvic parameters and LARS, pelvic dimensions from patients who had an anastomotic level < 5 cm and underwent surgery more than 18 months were utilized to analysis. Five indicators (based on CT images) were employed in the investigation of pelvic dimensions, including interspinous distance (the narrowest distance between the ischial spines), transverse outlet, sagittal inlet, posterior sagittal diameter of pelvic outlet, and sacrum-coccyx distance. As expected, interspinous diameter of LARS group were significantly lower than no LARS group ($p < 0.05$), while other parameters were not found to be statistically significant. According to previous studies and our own experience, the operative field for LAR is strictly limited transversely by the pelvis at the ischial spine level. In contrast, the anterior-posterior direction of the operative field is relatively more flexible. For example, the organs, such as the bladder, and the prostate or uterus, can be pushed anteriorly to a certain extent.

Our study had several limitations. Several potential risk factors for LARS, including the anastomosis type, point of ligation ("high' or "low") of the inferior mesenteric artery, and obstetric anal sphincter injury, were not prospectively recorded in this study. Due to conservative ideas or extra costs, only 3.6% of patients were willing to receive presurgery radiation therapy. Another limitation is that the majority of patients were only contacted by telephone and not visited unless they requested it. Despite these limitations, this study has yielded potentially important information about the risk factors of LARS in China.

Author's Contributions The contribution of each author is as follows: YH and XWD (design the study); QY and PY (data acquisition, analysis, and interpretation); GHD and FWJ (proofread and revise the manuscript); and WS and DGS (collect the date). All authors read and approved the final manuscript.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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