

The impact of Low-Anterior Resection Syndrome (LARS) on the Quality of Life in Rectal Cancer Survivors: a Narrative Review

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ABSTRACT

Low anterior rectal cancer is based on oncological radicality and recurrence rates, which translate to survival. Rectal dysfunction occurred in at least one-quarter of patients. This dysfunction is a myriad of symptoms referred to as low anterior resection syndrome (LARS). In this review, we analyzed the definitions, risk factors and pathophysiological mechanisms of LARS. A better understanding of this syndrome can lead to improved prevention and treatment of LARS..

Keywords: low anterior resection syndrome, LARS, colorectal, surgery, rectal cancer.

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INTRODUCTION

Despite advancement in therapy and treatment, the incidence of colorectal cancer (CRC) is increasing in individuals younger than 50 years, with CRC accounting for the second most common cause of death in the United States (1, 2). While multimodal CRC treatment has led to better oncological results, there is increasing recognition of the long-term postoperative consequences and side effects (3, 4). Rectal cancer survivors, including those with permanent ostomies, may encounter various postoperative challenges, encompassing emotional, psychological, physical and financial hardships. One of the most prevalent factors impacting the overall health-related quality of life (QoL) is the low anterior resection syndrome (LARS), which is commonly observed in patients who have undergone low anterior resection (LAR) for CRC. □

METHODOLOGY

This narrative review investigates the impact of LARS in the field of colorectal cancer surgery. A literature search of the PubMed database over the last two decades was performed using the following terms: 'LARS', 'low anterior resection syndrome', 'rectal cancer', 'QoL' and 'EORTC'. A thorough assessment of 64 relevant articles identified in the literature review was performed. Our main inclusion criteria were papers related to the LARS and its subsequent impact on QoL in rectal cancer survivors. Our objective was to offer a nuanced view of the complex pathophysiology of this syndrome and its relevance in the prevention and treatment of LARS.

Definition

Initially, LARS was defined as anterior resection syndrome, including changes in bowel habits oc-

curing after rectal cancer surgery, with a negative effect on the QoL (5). In 2012, the LARS score was introduced to measure the outcome of bowel dysfunction (6).

The pathophysiology of LARS is multifactorial and not fully understood, and it affects on fecal incontinence and evacuatory dysfunction (7). Numerous studies have aimed to identify factors associated with the development of LARS. Of these factors, tumor height and neoadjuvant radiation are important contributors to the risk of LARS, but other modifiable factors may also influence postoperative bowel function (8, 9).

A LARS score of 30 or higher defines major LARS, which is strongly associated with reduced QoL and represents a significant negative outcome of CRC treatment (7, 10). Some of the LARS symptoms may show improvement in the first six to 12 months, while some of them can persist during follow-up after 12 months. A recent study indicated no significant change in LARS scores when comparing two follow-up assessments taken five years apart (11). Also, a recent retrospective study conducted by Obleaga *et al* raise the awareness that major LARS patients can present a switch to minor LARS after six months (38.89%) (12).

Regarding incidence of LARS among patients undergoing rectal cancer surgery, studies showed increased incidence with reported rates ranging from 50 to 70% (5, 7). In a recent study on 82 patients, Homma *et al* found that the incidence of major LARS was 48%, which significantly impaired the QoL in both minor and major LARS (13). One remark is that high incidence of LARS emphasizes the importance of its identification in follow-up patients after LAR for CRC. Table 1 summarizes the accepted LARS definition according to the international consensus definition of LARS (14).

Recent studies emphasize the importance of documenting these symptoms, and reveal that

At least one of these symptoms	At least one of these consequences
Variable, unpredictable bowel function	Toilet dependence
Altered stool consistency	Preoccupation with bowel function
Increased stool frequency	Dissatisfaction with bowels
Repeated painful stools	Strategies and compromises
Emptying difficulties	Mental and emotional wellbeing
Urgency	Social and daily activities
Incontinency	Relationships and intimacy
Soiling (encopresis)	Roles, commitments and responsibilities

TABLE 1. Definition of LARS (14)

TABLE 2. LARS score (6)

APPENDIX 2. LARS Score: Scoring Instructions	
Add the scores from each 5 answers to one final score.	
Do you ever have occasions when you cannot control your flatus (wind)?	
☐ No, never	0
☐ Yes, less than once per week	4
☐ Yes, at least once per week	7
Do you ever have any accidental leakage of liquid stool?	
☐ No, never	0
☐ Yes, less than once per week	3
☐ Yes, at least once per week	3
How often do you open your bowels?	
☐ More than 7 times per day (24 hours)	4
☐ 4–7 times per day (24 hours)	2
☐ 1–3 times per day (24 hours)	0
☐ Less than once per day (24 hours)	5
Do you ever have to open your bowels again within one hour of the last bowel opening?	
☐ No, never	0
☐ Yes, less than once per week	9
☐ Yes, at least once per week	11
Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?	
☐ No, never	0
☐ Yes, less than once per week	11
☐ Yes, at least once per week	16
Total Score:	
Interpretation:	
0–20:	No LARS
21–29:	Minor LARS
30–42:	Major LARS

symptoms of ‘no LARS’ can be still associated with storage or evacuatory disfunction, which impacts the QoL (15).

The LARS score

The LARS score (Table 2) is a tool that can assess functional outcomes after low anterior cancer surgery. It is based on a validated questionnaire that includes the five inconveniences of patients: flatus incontinence, incontinence of liquid stool, frequency, clustering and urgency. The rating scale ranges from 0 to 42 points and patients are classified into three groups: “no LARS” (0–20 points), “minor LARS” (21–29 points) and “major LARS” (30–42 points) (6).

Ribas *et al* analyzed the LARS score and suggested that it was useful for screening, but not sufficiently relevant for assessing the complex bowel dysfunction occurring after low rectal cancer surgery. The authors’ recommendations include a detailed clinical evaluation and the use of multiple questionnaires such as Bristol scale,

Vaizey score, fecal incontinence quality of life (FIQL) and a bowel diary (16).

Pathophysiology and risk factors

A summary on pathophysiology of LARS is depicted in Table 3; four categories can be implied, including diagnosis, adjuvant treatment, surgical treatment and post-surgical effects.

Several symptoms, such as urgency and incontinence associated with LARS, can be partly attributed to the anatomical reduction or absence of the rectal reservoir. The diminished capacity of the remaining rectum is likely to be the primary factor contributing to these symptoms. Furthermore, research has demonstrated that radiotherapy can induce pelvic fibrosis, which negatively impacts rectal compliance and exacerbates the existing symptoms associated with a reduced rectal reservoir. Additionally, restorative proctectomy may result in increased colonic motility, potentially due to surgical disruption of the sympathetic nervous system (17, 18).

Diagnosis	Adjuvant treatment	Surgical treatment	Post-surgical effects
Tumor height (distance from anal verge)	Radiotherapy	Diverting stoma	Loss of RAIR
	Chemotherapy	Anastomosis height	Loss of rectal reservoir
	Total neoadjuvant therapy	Surgical technique: LAR-TME <i>versus</i> Ta-TME	IAS injury
	Local excision – NOM	Extent of resection	Anastomotic leak occurrence
		Technically difficult resection	

TABLE 3. Pathophysiology of LARS – summary. RAIR=rectal inhibitory reflex; NOM=non-operative management; IAS=internal anal sphincter; LAR-TME=low anterior resection total mesorectal excision; Ta-TME=transanal total mesorectal excision

Increased gastrocolic reflex
Loss of rectal reservoir
Diverting stoma – negative impact
Radiotherapy
Anastomotic leak
Tumor height and anastomosis height
Surgical technique choice

TABLE 4. Risk factors in LARS

Also, this denervation can remove the negative feedback that regulates the defecation reflex (19). Interestingly, incomplete evacuation can lead to increased frequency, which is another important symptom of LARS (20).

Surgical denervation can occur at the colonic level as well as in the rectum; using an endoanal stapling device can cause sphincter damage and nervous denervation (19).

Consistent risk factors for LARS include low-lying rectal tumors (which require low anastomosis and complete rectal resection) and neoadjuvant radiation therapy. A summary of these factors is presented in Table 3.

A. Loss of recto-anal inhibitory reflex (RAIR)

Defecation begins with high-amplitude propagated contraction (HAPC) in the colon, and as the rectum fills, wall distension is sensed via afferent fibers, leading to the urge to defecate. This is followed by continuation of distension and relaxation of the internal anal sphincter (IAS), allowing for antegrade movement of the intraluminal contents. This is known as the recto-anal inhibitory reflex (RAIR), which is mediated by the enteric nervous system and independent of the spinal reflex pathway (21). Therefore, RAIR is associated with proximal IAS relaxation and contraction of the external anal sphincter (EAS) contraction. Internal anal sphincter relaxation allows for the addition of anal canal accommodation depending on the consistency of the intraluminal contents; at this time, the rectum acts primarily

as a reservoir, and the continuation of the defecation process depends on conscious and voluntary processes. If defecation does not occur, the pubic diaphragm and external anal sphincter hypercontract to prevent accidental incontinence and to move the stool away from the distal rectum. The coloanal reflex is associated with relaxation of both anal sphincters (22).

When defecation continued, a combination of colonic high-amplitude propagated contractions (HAPCs), recto-anal conjoint longitudinal muscle contractions (shortening and opening of the canal, flattening of the anal cushions), intra-abdominal increase in pressure from bearing down, and relaxation of the pelvic floor and anal sphincter complex led to the successful evacuation of intraluminal contents. Following defecation, the closing reflex leads to contraction of the EAS and reactivation of the IAS as the recto-anal distention is relieved (23). After surgery, mass movement disorders appear when there are discontinuities in the muscular layer and intramural nerve plexuses. In addition, denervation of the neorectum causes increased gastrocolic reflex.

a. Loss of rectal reservoir

As stated before, there is a relationship between RAIR and the rectal reservoir as well as with the coloanal reflex; continence is an intrication of these mechanisms. Therefore, the loss of rectal capacity influences the defecatory function and increases incontinence (21).

b. IAS injury – impaired function

There are several occurrences of this injury, including stapled mucosectomy, rectal transection and radiotherapy. Impaired function that leads to bowel dysfunction can impact the QoL, and patients with ‘major LARS’ have similar QoL im-

pairment as those following abdominoperineal resection (APR), as Koneru *et al* stated (23).

B. Diverting stoma

A defunctioning stoma can reduce the AL rate and the severity of anastomotic leakage, the mechanical stimulation of the feces to the anastomosis and the infection around the anastomosis. In addition, it can improve the postoperative anal function (23-25).

Whether a diverting stoma is related to LARS is still debatable. In locally advanced rectal cancer, the LARS score should be interpreted with caution. Interestingly, Vogel *et al* suggested that the risk of developing major LARS seemed higher with a defunctioning ileostomy; therefore, early reversal should be an important part of the patient pathway (27). In contrast, a study of 150 patients divided into two groups, with or without a diverting stoma, showed that the presence of ileostomy or time to ileostomy closure was not associated with LARS occurrence (28). There was a negative impact on the QoL of these patients, who reported stoma-related deterioration of social functioning as well as physiological and sexual problems.

A review of 14 studies shows that colostomy negatively influences the QoL; stomas can also affect functional bowel activity (29). In a meta-analysis, Tan *et al* concluded that a defunctioning stoma decreased AL and reoperation rates (30). However, further surgery is required for closure, with associated morbidity and mortality (31) and increased treatment costs.

A stoma can be selectively and judiciously performed, as suggested by Shetty *et al* (32). Similarly, Hanna *et al* emphasize that a diverting stoma is beneficial when used selectively in high-risk patients with low pelvic anastomoses. The risk factors included low colorectal anastomoses (<10 cm from the anal verge) and implicit coloanal anastomoses, technically difficult resections, malnutrition and male sex (33).

In a multicenter Japanese study, the recommendation of diverting stoma is attributed to the height of the anastomosis: recommendation for anastomoses within 5 cm of the anal verge and strong recommendation for low anastomosis within 2 cm (34).

Wong *et al* conducted a comparative study with ten-year duration on 1 078 patients subjected to elective low/ultralow anterior resec-

tions, of whom 324 patients with a stoma were compared with 742 patients who were diverted. These results were similar in regards to those for AL (4% vs. 3.8%). Diverting the stoma does not lead to a lower rate of AL, but can reduce feared complications such as peritonitis and septicemia. Hence, diverting should be selectively performed in patients with poorly prepared comorbid bowel (35).

Nurkin *et al* carried on an observational study on 525 patients with coloanal anastomosis and found that, in those without stoma, there was a significant incidence of sepsis, septic shock and need for reoperation; however, the authors concluded that defunctioning stoma was likely to be overused in rectal cancer surgery (36).

A randomized controlled trial analyzed 256 patients who underwent elective low anterior resection and stapler anastomosis, and divided them into two groups: those who underwent ileostomy and those who did not. In the first group, there were 12 patients (10%) with AL and two deaths (1.67%), while in the second group, three leaks (2.21%) with no additional morbidity or mortality were observed. The authors recommended diverting loop ileostomy as a routine procedure for low rectal cancer surgery (37). Instead, in a study of 96 preoperative radiation patients, the anastomotic complication rate was 6.1% when a handsewn coloanal anastomosis was performed without a diverting stoma. The authors suggested that in this instance (handsewn anastomosis), a diverting stoma was not necessary (38).

Regarding the type of diverting stoma, it is not known which surgical approach – loop ileostomy (LI) or loop colostomy (LC) – is more advantageous. A meta-analysis showed that LI might be superior to LC (39). Another recent meta-analysis strongly recommends preventive LI for anterior resections against LC, but emphasizes the problems related to it, including dehydration, renal insufficiency and intestinal obstruction (40). More reviews have shown similar outcomes (41-43), but the controversy has not been resolved, as other studies have emphasized (39, 44-46). Large-scale randomized controlled trials can provide better evidence in this regard.

c. Radiotherapy (RT)

Radiotherapy is one of the pillars of treatment in patients with low rectal cancer. Short- or

long-term RT influences all aspects related to surgery and the postoperative course.

There are well known benefits of RT on tumor development, including downstaging effect, reducing the volume of nodules and TEM and creating the premises of R0 surgical resection.

Moreover, total neoadjuvant therapy (RT combined with chemotherapy) significantly reduces distant metastases and increases disease-free and overall survival (47). On the other hand, RT creates grades of fibrosis and tissue edema, increasing the difficulty of surgery and prolonging the operative time. For the surgeon, this translates to difficulties in delineating the anatomy, which can also influence the course of surgery and intraoperative decisions. During the postoperative course, RT affects the rate of healing and impairs anorectal and sacral functions. In addition, it has a proven effect on the anastomotic leakage rate (ALR). Moreover, in the long run, there is a risk of strictures, and some authors have shown impairment in urinary function. In addition, RT can contribute to a higher defecation frequency and reduced compliance (48).

Pelvic irradiation causes genitourinary toxicity, and this mechanism can be explained by inflammation and fibrosis (49). A similar inference can be applied to fecal incontinence.

An interesting study by Iwamoto *et al* regarding the effects of pelvic radiation on defecation concluded that radiation reduced the capacity of the rectal reservoir, even in asymptomatic patients; these were developing during radiotherapy and progress over time (50). The patients reported disturbed gas-stool discrimination, urgency, sense of residual stool and soiling.

Similarly, Krol *et al* analyzed 32 patients who were irradiated for localized prostate carcinoma and inferred that irradiation for prostate cancer could lead to reduced rectal distensibility, patient-accused urgency and impairment of anal sphincter function (51). These considerations suggest that neoadjuvant radiotherapy can be a risk factor for LARS. Rodriguez *et al* also conclude that preoperative radiotherapy and male sex are risk factors for LARS (28).

d. Anastomotic leak

Anastomotic leakage is a major problem in low rectal resection, leading to abscesses, recurrence, peritonitis and septicemia. McGiffin *et al* suggest that the occurrence of LARS is depen-

dent on the extent of resection rather than the occurrence of anastomotic leak (52).

e. Tumor height and anastomosis height

There is a correlation between the anastomosis distance from the anal verge and LARS severity (53).

f. Surgical technique choice – sphincter-preserving surgery

If we think about preventing LARS, one possible way is the organ preservation, that can avoid stomas and improve perioperative morbidity. Non-operative management (NOM), including complex treatment with neoadjuvant treatment and local excision, has yielded good results, as reported by Flemming *et al* (54). Same authors also found a QoL-related benefit, maintaining bowel function and not compromising oncological outcomes. A study conducted by the Dutch Watch-and-Wait Consortium investigated the bowel function of 221 patients who underwent a NOM approach and found that 25% of subjects experienced severe LARS, while 22% reported significant incontinence according to the Vaizey score (55). The results are promising when compared to patients who undergo low anterior resection (56, 57). Laparoscopic or open – low anterior resection, total mesorectal excision (LAR-TME) versus transanal TME (TaTME) functional outcomes and QoL were similar for rectal cancer patients who underwent taTME or LaTME (58). Filips *et al* reported a lower LARS for the TaTME technique than for the LAR-TME one (59). In contrast, a multicenter study that compared the two techniques revealed that TaTME may be associated with more severe bowel dysfunction and worse results in QoL scales than LAR-TME (60). Alimova *et al* emphasized the same outcome; further randomized controlled trials are needed to draw conclusions applicable to our current practice (61-63). ■

CONCLUSION

Low anterior resection syndrome is characterized by a series of symptoms that affect the QoL of patients with rectal cancer. It is a multifactorial pathology that follows low and very low anterior resection for rectal cancer and is represented by the effects on anal sphincters and the neorectum. An important factor is adjuvant and

neoadjuvant therapy; other factors include the presence of a diverting stoma, injury to the internal anal sphincter and choice of surgical sphincter-preserving approach (either open or laparoscopic).

There is currently a gap in reporting LARS, which can be solved by better informing and educating patients about this condition. Future research should focus on potential strategies for the prevention and treatment of LARS. $\square$

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