Chapter

Low Anterior Resection Syndrome (LARS)

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Abstract

Rectal cancer surgery has undergone significant advancements, with a shift towards sphincter-sparing operations due to improved surgical techniques and neoadjuvant treatments. However, this has given rise to low anterior resection syndrome (LARS), characterised by various bowel functional abnormalities adversely impacting patients' quality of life. This chapter delves into the definition, risk factors, diagnosis and current treatment recommendations for LARS. The new consensus definition of LARS incorporates a range of symptoms, and their impact on mental, emotional and social well-being. The widely accepted LARS score, a patient-reported outcome measure, aids in standardising reporting but has limitations. LARS has a multifactorial aetiology involving colonic dysmotility, iatrogenic nerve damage, neorectal reservoir dysfunction, recto-anal inhibitory reflex loss, and anal sphincter dysfunction. Various risk factors, including tumour location, anastomotic leak, diverting stoma, pelvic radiotherapy and surgical approach, all contribute to LARS development. Treatment modalities encompass conservative measures such as dietary modifications, probiotics and medications, while advanced treatments include pelvic floor rehabilitation, transanal irrigation, neuromodulation and, ultimately, surgery for refractory cases. Although research has improved our understanding of LARS, further studies are essential to increase prevention and improve treatment strategies.

Keywords: low anterior resection syndrome, colorectal surgery, ano-rectal dysfunction, rectal cancer, defecation abnormalities

1. Introduction

Surgery for rectal cancer has evolved, especially for low-lying tumours. Thanks to better surgical techniques combined with the ever-advancing neoadjuvant treatments, abdominoperineal resections have decreased in favour of sphincter-sparing operations. Although these procedures assure bowel continuity and avoid the need for a permanent stoma, they come with frequent functional disturbances that can have a detrimental impact on patients' quality of life. Low anterior resection syndrome (LARS) is the term used to describe the bowel functional abnormalities following rectal surgery and consists of a constellation of symptoms, ranging from incontinence to obstructed defecation. In this chapter, we will discuss the definition, risk factors, diagnosis and current treatment recommendations.

2. Definition

Traditionally, LARS was defined as a "disordered bowel function after rectal resection, leading to a detriment in quality of life" [1]. Although this definition accurately describes the clinical picture, it makes it practically impossible to accurately identify and report LARS due to the heterogeneity of its symptoms [2, 3]. The LARS score, a validated patient-reported outcome measure, has helped the standardisation of reporting [4]. However, the LARS score may significantly underestimate the impact of evacuation dysfunction and may not accurately assess the impact of symptoms on an individual patient's quality of life. For these reasons, a recent international consensus definition of LARS has been established using input from patients, colorectal surgeons and healthcare specialists involved in the care of low anterior resection patients [5].

LARS is defined by at least one of the following symptoms resulting in at least one of the following consequences that occur after a sphincter-sparing rectal procedure (modified from 5) (**Table 1**).

3. The LARS score

The LARS score was developed to surpass discrepancies in reporting functional outcomes and was designed to be a quick clinical evaluation screening tool for patients suffering from LARS symptoms. It is a validated questionnaire for assessing a patient's bowel function after sphincter-sparing surgery and comprised mainly five questions [4]: incontinence for flatus, incontinence for liquid stool, faecal frequency (number of bowel movements per day), clustering (the need to defecate less than an hour from the last one) and urgency. The score has a scale from 0 to 42 points. Outcome is defined as no LARS (0–20), minor LARS (21–29) and major LARS (30–42). Significant differences have been found between no LARS and major LARS in nearly all functional scales of quality of life [6]. The LARS score, widely accepted by colorectal surgeons, suffers from certain disadvantages. It appears to be insensitive to evacuation dysfunction, and in some patients, it might overestimate the impact LARS symptoms have on their quality of life [7]. Furthermore, studies have shown it to have a high sensitivity but a low specificity,

Symptoms	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	• Impact on mental and emotional well-being
• Urgency	• Impact on social and daily activities
• Incontinence	• Impact on relationships and intimacy
• Soiling	• Impact on roles, commitments and responsibilities

Table 1.
Consensus definition of low anterior resection syndrome (LARS) (modified from Keane et al. [5]).

as it was found to exist in the general population free of any rectal procedures, in significant numbers [8].

Other scoring systems, like the MSKCC Bowel Function Instrument, have been developed but never gained wide acceptance [9].

4. Epidemiology

LARS is frequent. It is estimated that 50–90% of patients undergoing a low anterior resection will face at least some degree of bowel dysfunction [10]. The reported incidence of LARS varies in the literature. The pooled incidence of major LARS was reported to be 44% (ranging from 10 to 72%) in one of the biggest and most recent meta-analyses from 50 studies on the subject [11]. When the epidemiology of specific symptoms is reported, variation persists. Faecal incontinence is reported to occur in 6–87% of low anterior resection patients, 8–75% of patients having three or more defecations per day with 5–87% reporting urgency [12].

The previously accepted notion that LARS was a short-term phenomenon after low rectal surgery with a transitory character has been proven false, as patients report long-term effects up to 15 years after their operation with evacuatory disorders varying from 12 to 74% [1].

5. Aetiology

LARS pathophysiology remains a matter of debate and appears to be multifactorial. A combination of colonic dysmotility, neorectal reservoir dysfunction, anatomical and sensory alterations, anal sphincter dysfunction and pelvic floor function.

5.1 Colonic dysmotility

Patients with major LARS problems have been shown to have an increased postprandial response and higher neorectal pressures postprandially, suggesting that severe bowel dysfunction may be attributed to abnormal gastrointestinal motility [13]. These patients have been found to have increased bowel contractions as also increased neorectal tone compared with healthy patients [13]. Bryant et al. reported that patients after LAR have small, irregular waves at the site of the neorectum and the presence of these waves was associated with faecal soiling, urgency and multiple evacuations. Furthermore, meal-induced colonic motility reported significantly earlier contractions in patients with increased bowel frequency compared to those without [1].

5.2 Iatrogenic nerve damage

LARS might be attributed to iatrogenic nerve damage during the initial operation affecting not only colonic motility but also urinary and sexual function. The left colon starting from the distal third of the transverse to the end of the sigmoid, receives their sympathetic, parasympathetic and sensory supply via nerves from the inferior mesenteric plexus. Evidence that denervation of the left and sigmoid colon results in increased motility with shorter transit time has been shown in the literature [14–16]. The rectum receives a sympathetic nervous supply from the lumbar splanchnic nerves and superior and inferior hypogastric plexuses. Parasympathetic supply is provided from S2–4 via the pelvic splanchnic nerves and inferior hypogastric plexuses with associated afferent sensory fibres following this parasympathetic supply. The risk of pelvic nerve injury during surgery depends on the surgical technique and the underlying pathology, with pre-operative radiotherapy contributing to the potential injury. The sympathetic component may be damaged during ligation of the inferior mesenteric artery (IMA) on the aorta or while dissecting at the pelvic brim. The possible locations of parasympathetic nerve damage are during perineal dissection if the plane extends out of the mesorectal fascia, especially during lateral pelvic wall dissection. In men, the risk of injury is higher during anterior rectal dissection of the Denonvillier fascia and at the base of the prostate [17].

5.3 Neorectal reservoir dysfunction

Removal of the rectum and in particular the rectosigmoid junction, which normally is the physiologic distal control centre for the regulation of bowel transit, can leave bowel mobility without an inhibitory mechanism. This lack of distal negative feedback signals to oppose increased proximal colonic motility further exacerbates the symptoms of LARS. LARS can also be manifested with rectal evacuatory dysfunction. Symptoms include infrequent defecation, incomplete rectal emptying and excessive straining [1]. The suspected mechanism is loss of recto-anal coordination, presenting as paradoxical anal contraction and impaired rectal contraction [1]. These patients also present a lowered rectal sensation possibly due to impairment of the parasympathetic and sympathetic nerve supply to the rectum [1]. Another suspected mechanism is the neo-reservoir decreased compliance and capacity that can lead to frequent defecation. Additionally reduced capacity can lead to higher pressures in the neorectum that can itself lead to soiling even with a small amount of faecal matter present in the low anal canal [18].

5.4 Recto-anal inhibitory reflex loss (RAIR)

LARS patients can exhibit loss of their RAIR resulting in disordered evacuation due but not limited to poor sampling and impaired discrimination of liquid versus gas rectal content. It can be manifested as faecal soiling, incontinence urgency, or incomplete evacuation [12]. Patients with an absent RAIR present worse functional outcomes when associated with a lower reservoir capacity and a shortened high-pressure zone [19].

5.5 Anal sphincter dysfunction

The anal sphincter complex can sustain injury directly due to stapling during surgery [12], neoadjuvant radiotherapy, or damage to its innervation. A decrease in mean anal resting pressures and maximum squeeze pressures that do not recover over time has been shown in studies evaluating anal sphincter function after LAR [1, 18]. These changes can be transitory as they have been shown to improve after 6 months [18].

6. Risk factors

Several risk factors have been identified that may predispose patients to develop LARS after a low anterior resection. The most recent systematic review and metaanalysis including 50 studies that used the validated LARS score determined the following [11]:

6.1 Tumour location-level of anastomosis

Worse functional outcomes have been associated with a lower anastomotic distance to the anal verge. Tumour and subsequently anastomotic height were assessed as comparing Total versus partial mesorectal resections: the results showed that the risk of major LARS was significantly increased in patients after TME compared to PME (pooled OR 2.13, 95% CI 1.49–3.04) [11]. Similar results were confirmed by other studies [20]. It is therefore fundamental to retain a longer rectal remnant after ensuring radical resection for low third rectal cancer in order to improve anorectal function.

6.2 Anastomotic leak

Anastomotic leak negatively affects anorectal function, and this effect has been found to be valid when seen as a directly measured outcome in various studies and also after sensitivity analysis (OR 1.98, 95% CI 1.34–2.93) [11]. The mechanism involved suggests a combination of scarring and adhesion formation decreasing the neorectum compliance and capacity, combined with possible nerve injury due to pelvic sepsis [12, 20, 21]. Particular consideration is advised when deciding to take down a diverting stoma in these patients.

6.3 Diverting stoma

Despite the fact that stomas are not only effective in reducing the severity of anastomotic leak consequences but also protective against it [22], they have been found to negatively affect functional outcomes leading to various degrees of LARS (OR 1.89, 95% CI 1.58–2.27) [11]. A very recent paper studying patients after TME and comparing functional outcomes using the LARS score found that patients with a stoma (ileostomy or colostomy) had increased postoperative functional disturbances. These disturbances were shown to be proportional to the attending time for closure, especially for patients with ileostomy. When ileostomy closure was performed after 90 days, there was a statistically significant difference ($p = 0.05$ between 90 and 180 days and $p = 0.01$ after 180 days). The LARS score after ileostomy was significantly worse compared to patients without a stoma ($p = 0.04$), and while the trend was similar, no significance was found in the LARS score after colostomy compared with patients without a stoma ($p = 0.2$) [23]. Previous papers also confirmed better outcomes after early closure and hypothesised that the length of the excluded bowel seems to be relevant to the functional outcome, considering that patients with ileostomy may experience worse and more persistent functional dysfunction compared to those after colostomy [24]. The precise reason of stoma-related bowel dysfunction is not clear, but it is possible to be attributed to diversion colitis, enteric nervous system alterations, or changes in epithelial function of the terminal ileum, causing bile acid malabsorption, small bowel bacterial overgrowth, or bacterial recolonization of the colon after stoma reversal [23].

6.4 Pelvic radiotherapy

Irradiation-induced pelvic fibrosis combined with subsequent direct nerve and vascular injury from radiation seems to be the culprit for the functional disturbances leading to LARS [25–28]. Whether long course or short course, studies have shown that pelvic radiotherapy is consistently associated with LARS independent of the timing of administration (adjuvant vs. neoadjuvant) [11, 25–28].

6.5 Type of surgical approach and type of anastomosis

Given the high incidence of LARS after rectal resections, the different types of surgical approaches and different types of anastomoses have been studied in order to examine possible advantages. LARS after TaTME compared with LapTME showed no statistical significance as far as LARS incidence is concerned [11]. The same applies for pouch reconstruction versus straight anastomosis [11], although there are some studies that found decreased bowel frequency, reduced fragmentation and less urgency during the first year in patients with colonic J pouch compared with straight anastomosis [29, 30]. This advantage, however, seems to disappear after the first year. Side-to-side anastomosis does not seem to provide significant advantages either [31].

7. Treatment

LARS treatment, similar to its aetiology, is multimodal and can be treated with lifestyle changes, medications, trans-anal irrigation, pelvic floor rehabilitation, neurostimulation, or surgery [32]. LARS management is often empirical and symptom-based with limited evidence as most studies are observational and noncontrolled [33]. Patients with persistent functional disturbances after stoma closure or 4–6 weeks after the cardinal operation are evaluated using the LARS score and treated according to the character, variety, severity and duration of their symptoms. The colorectal surgeon should ensure that there is no underlying cause for the patient's symptoms (e.g., radiation-related mucosal lesions, anastomotic stricture and local recurrence). Conservative measures will help most of the patients with LARS up to some point, but patients presenting with major LARS (LARS score ≥ 30) typically require multimodal therapy with advanced treatments. The treatment options are reviewed hereafter.

7.1 Conservative measures

7.1.1 Diet modifications

High-fibre low-fat diet, avoidance of alcoholic beverages, cold beverages and spicy or stimulating food. However, insoluble fibre may worsen symptoms as diarrhoea, defecation frequency and bloating [34]. Based on expert opinion, bulking agents are well tolerated and may be beneficial in decreasing clustering and improving stool consistency [33].

7.1.2 Probiotics

Popular treatment used for IBS-D and IBD acts as gut microbiota modulator. A randomised control trial comparing a probiotic agent (lactobacillus plantarum) to placebo in patients with LARS did not find any significant difference in the LARS scores. The authors attributed the result in the short treatment period and the use of a single strain of beneficial bacteria instead of a multispecies one [35].

7.1.3 Loperamide

Although not specifically examined in LARS, its wide use is supported by its efficacy in treating two pathologies with similar symptoms, IBS-D and bowel dysfunction after restorative proctocolectomy. It has been evaluated in randomised trials were it was shown to be more effective when compared to placebo in decreasing frequency and improving stool consistency in patients with IBS-D [36].

7.1.4 Serotonin receptor antagonists

Serotonin (5-hydroxytryptamine (5-HT)) is a central and enteric nervous system neurotransmitter. It is an important mediator in the gut that influences gut motility and secretion, inhibiting colon mobility and causing constipation [37–39]. There is high-level evidence from randomised control trials studying Ramosetron (unavailable in European countries) vs. "conservative treatment" and recently Ondansetron versus placebo in LARS patients, suggesting that 5-HT inhibitors can lead to improvement of symptoms, decrease in LARS score and improvement in quality of life [40–42].

7.2 Advanced treatments

7.2.1 Pelvic floor rehabilitation (PFR)

PFR includes a variety of treatments consisting of biofeedback, pelvic floor muscle training, electrostimulation and volumetric/rectal balloon training. It seems to improve bowel function and quality of life, but its long-term efficacy remains under question. An RCT where pelvic floor muscle training was performed regularly, starting at 1 month after sphincter-sparing resection or ostomy closure, reported statistically significant improvement compared to the control group at 4 and 6 months, but this effect disappeared at 12 months [43]. The heterogeneity of the different protocols used in pelvic floor rehabilitation, the recommended duration of the various treatments and methods, still do not permit solid conclusions.

7.2.2 Transanal irrigation (TAI)

TAI represents one of the most efficacious treatments for LARS. It has been suggested that regular TAI (once/day or 3–4 times/week) has a mechanical effect of a high volume of water irrigating the colon and stimulating its motility [44]. Two randomised trials, one comparing TAI with posterior tibial nerve stimulation and another comparing medical treatment to TAI both reported significantly lower LARS scores and improvement in the quality of life [45, 46]. TAI was also associated with the best outcomes among all treatments reviewed in a recent systemic review and meta-analysis [32]. Perforation is a rare complication that can be avoided if a rectal and endoscopic evaluation prior to the start of the treatment excludes anatomical anomalies [33]. In case of stenosis, a soft Foley catheter can be used.

7.2.3 Neuromodulation

Sacral nerve modulation (SNM) and lately posterior tibial nerve stimulation (PTNS) are the two main methods used for patients who present with major LARS after a year of multimodular therapies. SNM decreases anterograde colonic motility while increases retrograde colonic motor activities and in the same time impairs postprandial changes in rectal motility, mechanisms important for the improvement of symptoms in LARS patients [47, 48]. SNM is an invasive procedure, which requires the placement of electrodes in the sacral foramen and the installation of an electric impulse-generating device in the subcutaneous tissue. A few studies showed promising results from the SNM application on LARS patients. They reported improvement in symptomatology and quality of life [49–52]. However, studies are small, often retrospective and with high heterogeneity. A systematic review of SNM in LARS patients showed an improvement of symptoms in the vast majority of patients with permanent implantation, with an additional improvement in quality of life and the ability to defer defecation. However, its small size (43 patients from 7 studies) does not permit definitive conclusions, and further studies are required [21]. PTNS also has been shown to reduce LARS score and faecal incontinence scores in two randomised control trials that compared it with sham simulation and medical treatment, respectively [53, 54]. Despite these promising results, a meta-analysis of these two trials failed to show any significant differences in follow-up scores or faecal incontinence scores [32].

7.2.4 Surgery

Patients with severe LARS refractory to any of the aforementioned treatment modalities will eventually benefit from a terminal stoma.

8. Conclusion

LARS is very frequent in patients undergoing surgery for rectal cancer and can lead to significant decrease in quality of life. Recent research has led to a better understanding of the underlying causative mechanisms of this syndrome, and several treatment modalities have been developed. Further research is still needed to provide better evidence for the prevention and treatment of LARS.

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