Review Article

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Low Anterior Resection Syndrome: Pathophysiology, Risk Factors, and Current Management

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Low anterior resection syndrome (LARS) is a condition of anorectal dysfunction that occurs frequently following anal sphincter-preserving surgery for rectal cancer and can reduce the quality of life. In this review, we summarize the main symptoms and pathophysiology of this syndrome and discuss the treatment approaches. Early evaluation and initiation of appropriate treatment postoperatively are crucial. The most frequently used tool to evaluate the severity of LARS is the LARS score, and an anorectal manometer is used for objective evaluation. LARS is believed to be caused by multiple factors, and some of its causes include direct structural damage to the anal sphincter, damage to the innervation, loss of rectoanal inhibitory reflex, and decreased rectal volume and compliance. Diet modifications, medications, pelvic floor muscle training and biofeedback are the primary treatments, and rectal irrigation can be added as a secondary treatment. If LARS symptoms persist even after 1 to 2 years and significantly reduce the quality of life, antegrade irrigation, sacral nerve stimulation or definitive stoma may be considered. High-quality evidence-based studies on LARS treatment are lacking, and randomized controlled trials aimed at developing severity-based treatment algorithms are needed.

Introduction

The annual incidence of colorectal cancer (CRC) in Korea is 44.5 cases per 100,000 persons, which is one of the highest in the world [1]. According to a recent review article, the incidence of early onset cancer per 100,000 people aged 20–49 years was 12.9, which was the highest of 42 countries that were investigated [2]. In addition to stage 0-I CRC, locally advanced stage II-III CRC is also resected en bloc together with surrounding organs or structures; therefore, surgical treatment is the most important treatment for CRC [3]. Multidisciplinary approaches to the treatment of rectal cancer and improved surgical techniques, including laparoscopic [4] and robotic total mesorectal excision [5], have improved the rate of local recurrence and postoperative complications [6] following rectal resection. Owing to the development of surgical techniques and multimodal treatment in rectal cancer, sphincter preservation surgery is preferred over abdominoperineal resection which requires a permanent colostomy [7]. Up to 80% of patients with rectal cancer have undergone sphincter preservation surgery [8] and up to 90% of them have impaired anorectal function, which is called low anterior resection (LAR) syndrome (LARS) [9]. This review describes the definition, epidemiology, risk factors, and evaluation tools of LARS and

introduces treatments with an emphasis on rehabilitation to improve LARS.

Definitions of Low Anterior Resection Syndrome (LARS)

LARS is defined as "a combination of symptoms, such as increased frequency and urgency of bowel movements, fecal incontinence, sense of incomplete emptying, and fragmentation after rectal resection, which reduces the quality of life [10]." Patients with LARS can be divided into two overlapping groups: those with urgency and fecal incontinence primarily, and those with evacuatory dysfunction. Recently, an international consensus Delphi process was conducted for patients who received LAR to refine the definition of LARS. This study has defined eight symptoms and eight consequences considered the highest priority in LARS, and are summarized in Table 1. To meet the definition of LARS, a patient receiving LAR should experience at least one of these symptoms that result in at least one of these consequence [11].

Epidemiology and Evaluation Tools of Low Anterior Resection Syndrome (LARS)

Since LARS is a syndrome that includes various symptoms, varying prevalence rates have been reported depending on the evaluation tools used. Prevalence surveys using the LARS questionnaire [12] have been conducted in recent years. The reported prevalence of major LARS, the most severe anorectal dysfunction, ranges from 17.8% to 56.0% [13–15]. According to the most recent meta-analysis, the prevalence of major LARS was reported to be 44% [15] and 41% [14], and the combined rate of minor and major LARS was reported to be 65% [14].

Tools for evaluating LARS include the LARS score [12], Wexner score [16], Kirwan classification [17], Fecal incontinence severity index [18] and anal examination scoring system (PASS) [19]. Of them, the LARS score is a simple and valid scoring system, and it is a questionnaire that reflects

Table 1. International consensus definition of LARS. LARS is defined as having at least one of eight symptoms and at least one of eight consequences after anterior resection

Symptoms	Consequences
Variable, unpredictable bowel function	Toilet dependence
Altered stool consistency	Preoccupation with bowel function
Increased stool frequency - Compared with preoperative state	Dissatisfaction with bowels
Repeated painful stools - Pain on urge, pain on and/or after passing a bowel movement	Strategies and compromises
Emptying difficulties - Inability to completely empty the bowel after defecation, returning to the toilet multiple times	Mental and emotional wellbeing
Urgency - Need to rush to the toilet to defecate, inability to delay passing a bowel movement	Social and daily activities
Incontinence - Unintended passage of a large volume of fecal material	Relationships and intimacy
Soiling - Involuntary passage of a small amount of material onto clothing or a sanitary item	Roles, commitments and responsibilities

LARS, low anterior resection syndrome.

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incontinence, frequent bowel movements, bowel emptying difficulties, and urges that occur following LAR. It has been translated into Korean [20], validated, and used in several studies.
For objective evaluation, most studies have assessed the anorectal function using manometry. The parameters assessed using anorectal manometry include resting pressure, squeeze pressure, rectoanal inhibitory reflex (RAIR), rectal sensitivity (first sensation volume, urge to defecate volume, and discomfort volume), and compliance [21].

Pathophysiology of Low Anterior Resection Syndrome (LARS)

Although the exact pathophysiology of LARS is not fully understood, it is believed that the symptoms result from multiple causes and mechanisms [10].

1. Structural damage to the internal anal sphincter

The internal anal sphincter (IAS) is an involuntary muscle that plays an important role in maintaining resting continence. The internal sphincter is contracted by the parasympathetic nerves of S2-4. The internal sphincter is often resected during intersphincteric resection. It has been reported that direct structural damage occurs during this procedure with a resultant lowering of the resting pressure of the IAS. It is also known that the lower the pressure, the more major LARS that occurs. Additionally, the direct damage depends on the device used for anastomosis, such as a stapler, which results in the lowering of the mean resting pressure of the IAS. Structural damage to the IAS is evaluated using endosonography [22].

2. Damage to the nerve supply

IAS function can also be impaired by damage to the autonomic nervous system. The risk of damage to the sympathetic/parasympathetic nerves entering the rectal wall is high during total mesorectal excision [23]. It is known that anal canal sensitivity is reduced secondary to a loss of the sensory branch of the pudendal nerve, which is responsible for sensations of the rectum, along with other nerves of the autonomic nervous system, which result in significant effects on postoperative incontinence [24].

3. Loss of the rectoanal inhibitory reflex (RAIR)

RAIR refers to temporary IAS relaxation due to rectal distention. This reflex makes it possible to distinguish between liquids, solids, and gases. Although the role of RAIR in incontinence is not well known, previous studies have revealed many cases of RAIR loss following LAR [25]. Previous studies have demonstrated that the frequency of soiling is higher in patients in whom RAIR does not recover and that RAIR loss is a predictor of bowel dysfunction 1 year after LAR [26].

4. Decreased rectal volume and compliance

Rectal volume and compliance of the rectum serve as reservoirs for feces and gases between evacuations. Surgical treatment reduces the maximal rectal volume by removing varying lengths of the rectum [27], and radiotherapy reduces rectal compliance [28]. Reduced volume and compliance correlate with urgency, frequency, and urge incontinence [29]. Additionally, the volume required to initiate the urge to defecate is lowered in patients with LAR and further reduced in patients with a short remnant rectum [30] and those who undergone irradiation [28]. For this reason, surgeons have developed techniques to increase the neorectal volume by constructing a remnant rectum. Side-to-end anastomosis, colonic J-pouch, and

transverse coloplasty are known to significantly reduce bowel frequency for up to 24 months postoperatively.

5. Altered colonic motility

LAR involves ligation of the inferior mesenteric artery and sympathetic denervation of the left colon. Studies conducted in rats to investigate the changes in colonic motility following denervation confirmed that colonic migrating contractions increased in the distal colon early after denervation, which is the basis for multiple evacuations after LAR [31,32]. A previous study evaluated the colonic motility following meals in patients with and without an increase in stool frequency following LAR and in healthy controls [33]. The results demonstrated that colonic contractions proximal to the anastomosis site were increased in patients who underwent LAR than those in healthy controls; additionally, colonic contractions occurred earlier in patients with increased stool frequency who underwent LAR than those in patients with normal stool frequency who underwent LAR. In a study that evaluated the colonic transit time using single-photon emission CT/CT scintigraphy, patients with major LARS had significantly faster colonic transit time than those without LARS [34]. In cases of a longer denervated neorectum due to proximal inferior mesenteric artery dissection, propagated contractions disappeared more often and spastic minor contractions were higher in the neorectum [35], which correlated with the urgency of defecation and multiple evacuations [36].

Risk Factors of Low Anterior Resection Syndrome (LARS)

In recently published papers and systematic reviews, low tumor height and thus low anastomotic height, and radiotherapy were the highest risk factors for LARS [14,15,37]. Furthermore, some studies have identified anastomotic leak [38] and diverting stoma as additional risk factors for LARS. The formation of a neorectal pouch was more common with no functional advantage. Additionally, radiotherapy (OR, 2.89, 95% CI, 2.06–4.05), low tumor height (OR, 2.13, 95% CI, 1.49–3.04), anastomotic leak (OR, 1.98, 95% CI, 1.34–2.93), and diverting stoma (OR, 1.89, 95% CI, 1.58–2.27) were associated with an increased risk of major LARS [15].

Management of Low Anterior Resection Syndrome (LARS)

A multimodal approach, rather than a single treatment, could represent the best management option for patients with LARS. Diet modifications, medications, pelvic floor muscle training (PFMT) and biofeedback are the primary treatments, and rectal irrigation can be added as a secondary treatment. If LARS symptoms persist even after 1 to 2 years and significantly reduce the quality of life, antegrade irrigation, sacral nerve stimulation (SNS) or definitive stoma may be considered. The treatment algorithm proposed by the author is shown in Fig. 1.

1. Self-care strategies including diet and practice management

Self-care strategies and dietary modifications are the easiest and earliest interventions for patients with LARS. Although the evidence is rare, these strategies include the advantage of being simple and that they can be controlled by the patient. It was reported that 96% of patients with rectal cancer who underwent LAR changed their diet postoperatively [39]. It is important to avoid foods that stimulate the bowels and loosen stools, such as alcohol, caffeine, and spicy foods. Although studies on LARS are lacking, it is known that a high intake of soluble

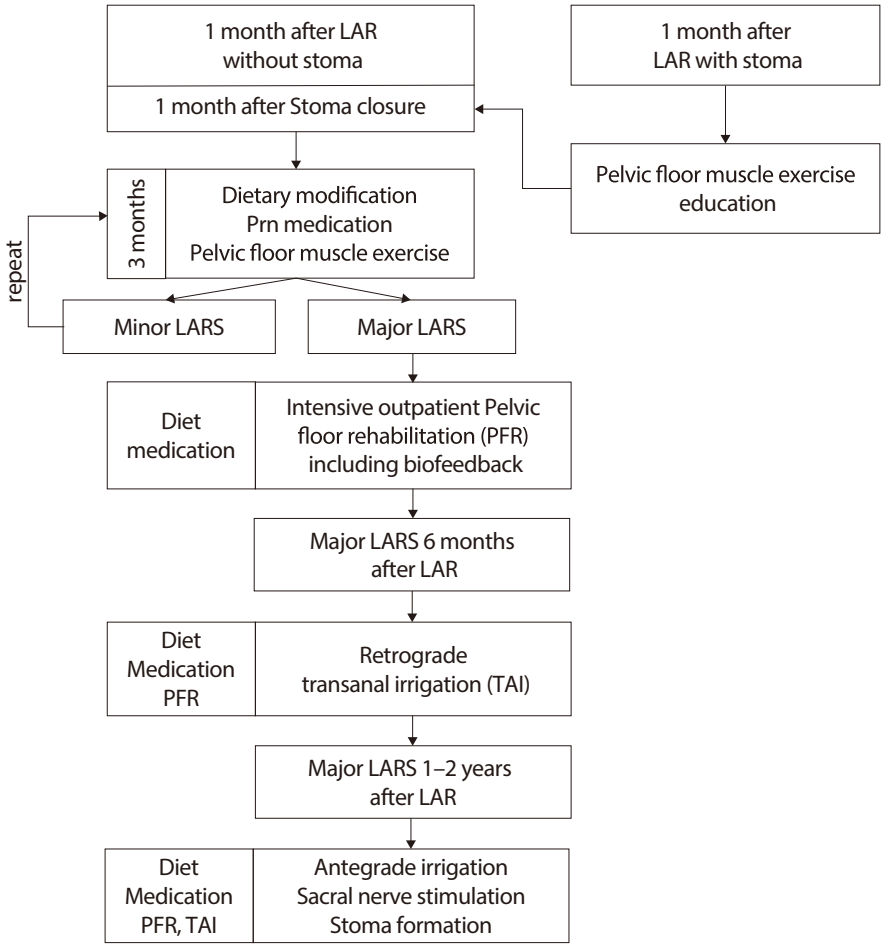

Fig. 1. Proposed treatment algorithm for low anterior resection syndrome. LARS, low anterior resection syndrome; PFR, pelvic floor rehabilitation.

dietary fibers (oats, peas, beans, apples, citrus fruits, carrots, barley, and psyllium) in the general population is associated with a decreased riskof fecal incontinence [40]; therefore, post-LAR, patients are recommended to consume these foods.

Probiotics have also been evaluated based on the hypothesis that LARS is caused by changes in the colonic mucosal physiology and the bacterial environment; however, no significant difference was found in comparison with placebo.

2. Medications

Medications are the first-line treatment for LARS, which can be attempted when symptoms cannot be controlled with self-care strategies, diet, or exercise. Loperamide, a mu-opioid receptor agonist, is the most commonly prescribed drug along with sitz baths or topical ointments and is the most effective therapy for increased bowel frequency and incontinence [41]. Loperamide is believed to decrease colonic motility and increase the tone of the IAS. Additionally, 5-HT3 antagonists (mosetron or alosetron) are known to treat intestinal hypermobility. Recently, a randomized controlled trial that included 100 patients with LARS who were treated with ramosetron in Korea reported that it significantly reduced the proportion of major LARS and improved the quality of life in comparison with the control group [42].

3. Pelvic floor rehabilitation

Pelvic floor rehabilitation consists of PFMT, biofeedback, rectal balloon retraining, and electrical stimulation aimed at improving pelvic floor muscle strength and coordination and rectal sensations. PFMT includes external anal sphincter strength training and isometric contraction exercises that strengthen the pelvic floor muscles. It can be administered along with biofeedback or electrical stimulation but can also be used as monotherapy. PFMT is thought to improve LARS by enhancing structural support, timing, and strength of autonomatic contractions [43]. The important thing to note during exercise is not to hold breath, not to contract the gluteal or abdominal muscles, and to have the same contraction and relaxation time. The anorectal angle, the angle between the anal canal and the rectum that is maintained by the puborectalis, is important for maintaining continence. Repetitive voluntary contractions during PFMT and external anal sphincter are believed to help improve incontinence by reducing the anorectal angle during the resting state.

Biofeedback training is a therapy that uses electronic equipment to inform the user of internal physiological events in the form of visual or auditory signals. Biofeedback consists of rectal sensitivity, strength, and coordination training [44]. Sensory training involves the use of a rectal balloon that gradually inflates until the patient reports the first sense of filling. Repeated reinflation is performed to teach the patient to feel inflation at progressively lower volumes. This allows the patient to detect the need to pass stools at a lower threshold of filling. Strength training is a process in which the patient contracts and relaxes the anal sphincter to reach a target signal based on hearing or watching feedback. It is also possible to receive feedback by attaching reference electrodes to the abdominal or gluteal muscles such that no force is applied to the muscles other than that from the pelvic floor muscles. Coordination training is a process in which the patient contracts the abdominal muscles and relaxes the pelvic floor muscles while evacuating the balloon from the rectum [45].

4. Transanal irrigation

Transanal retrograde irrigation is a method of mechanical colon flushing using a pump or an irrigation bag. A cone-shaped end attached to the distal tip is inserted into the anal canal, and 500–1000 cc of water with a temperature similar to the body temperature is injected. It is usually administered daily, and the amount and frequency of water injected may vary between patients. The patient is instructed to evacuate the rectum until urgency is felt. If it is difficult to maintain a cone-shaped end, irrigation can be performed by inserting a balloon catheter into the rectum. Rectal irrigation does not result in true continence; rather, it produces pseudocontinence between washouts. However, it is known to be safe and improve patients' quality of life by preventing nocturnal soiling, improving fecal incontinence, and regularizing of defecation. Since patients irrigate large volumes by themselves, education regarding the correct method is essential. The treatment algorithm used in one study suggested that rectal irrigation could be performed 30 days after LAR [46], but the algorithm in another paper suggested that it should be performed after 6 months [37]. A recent study evaluated prophylactic rectal irrigation early after stoma closure in high-risk patients with LARS and reported that early rectal irrigation was safe and improved LARS [47].

5. Antegrade irrigation

Antegrade irrigation refers to daily irrigation using an external catheter after performing percutaneous endoscopic colostomy (PEC). The largest case series report of antegrade

irrigation in rectal cancer was a study involving 25 patients, of which 4 (16%) had catheters removed, meaning that the procedure was ineffect in 16%. LARS score significantly decreased from 33 to 4 after PEC procedure and antegrade irrigation, and rate of major LARS decreased significantly from 73% to 9%. However, PEC shoulder be chosen carefully as there are some complications such as local pain, sweating, granulation at the PEC entry, leakage, and wound infection [48].

6. Sacral stimulation and tibial nerve stimulation

Given the evidence that SNS affects not only the anus and rectum but also the upper gastrointestinal tract and colon, the effects of SNS on anorectal function appear to originate at the pelvic afferent or central level. Recently, a systematic review article on studies that used SNS to improve LARS was published [49]. Before permanent SNS implantation, a temporary electrode was inserted through the S3 foramen to confirm the effectiveness of SNS, and percutaneous nerve evaluation (PNE) was performed. Permanent SNS was implanted when PNE confirmed improvement in fecal incontinence. A total of 94 patients underwent PNE and 79.8% of them underwent permanent SNS implantation. Although each study was different, stimulation was used with a pulse width of 210 μs and a frequency of 14 pulses/s; the amplitude was controlled by determining the degree to which the patient felt perineal and anal sphincter contractions. Although the studies included in the systematic review were not randomized controlled trials and the sample size was small, it is a meaningful result that the degree of fecal incontinence and LARS score improved significantly with implantation, especially because the patients who received SNS had chronic LARS. The use of SNS can be a treatment option in patients with refractory LARS.

Tibial nerve stimulation (TNS) is a novel, cost-effective and less invasive form of indirect neuromodulation of sacral nerve function. The tibial nerve is a mixture of sensory and motor nerves originating from the L4 to S3 spinal nerve roots, overlapping with the from S2 to S4 spinal nerve roots, from which nerves to the pelvic floor muscle and sphincter originate. TNS is thought to improve the resing and stress pressure of the sphincter and enhance rectal sensitivity by triggering multiple nerve pathways at the medulla and brain levels. TNS can modulate higher perception of afferent information and is thought to modulate colonic motility by triggering local somato-visceral reflexes [50]. A small electrode is inserted close to the posterior tibial nerve at ankle level and stimulated for 30 minutes, once a week, for a total of 16 to 20 times. Stimulation was used with a pulse width of 200 μs and a frequency of 20 pulses/s; the amplitude was ranged from 0.5 to 9.0 mA. Two of the three randomized controlled trials had no significant effect, and in one study, only the TNS group had a positive result that improvement of LARS and fecal incontinence scores were maintained up to 12 months [50].

Conclusion

With an increasing number of patients receiving neoadjuvant concurrent chemoradiotherapy and sphincter-preserving surgery for rectal cancer, the number of patients with a reduced quality of life due to LARS is increasing. After appropriate evaluations, it is important to provide treatment according to the postoperative duration and severity of LARS. Further studies are required to improve the level of evidence.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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