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Predictive Factors for the Occurrence of Low Anterior Resection Syndrome after Surgical Intervention

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Abbreviations:
CRT: chemoradiotherapy;
CT: computed tomography;
cT4: clinical T4 stage;
DCA: delayed coloanal anastomosis;
LAR: low anterior resection;
LARS: low anterior resection syndrome;
MRI: magnetic resonance imaging;
SPSS: Statistical Package for the Social Sciences;

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Rezumat

Factori de predicție în apariția sindromului de rezecție anterioară joasă după intervenția chirurgicală

Introducere: Intervențiile chirurgicale pentru cancerul rectal se soldează adesea cu disfuncție intestinală ce determină o serie întreagă de simptome digestive cu intensitate şi persistență diferită. Astfel, pacienții supuşi unei rezecții rectale anterioare joase cu conservarea sfincterului anal, acuză frecvent incontinență pentru materii fecale, urgență fecală, evacuare incompletă sau dificilă şi obstrucție. Toate aceste simptome sunt cunoscute drept sindrom de rezecție anterioară joasă (LARS). Studiul analizează factorii care duc la apariția LARS la pacienții care au beneficiat de rezecție rectală anterioară joasă cu anastomoză colorectală sau ultrajoasă cu anastomoză coloanală.
Material şi Metode: Articolul are la bază un studiu retrospectiv care a inclus pacienți cu cancer rectal internați şi tratați în două centre de chirurgie cu experiență în chirurgia colorectală în perioada ianuarie 2018 - decembrie 2023.
Rezultate: Din totalul de 86 pacienți (55 bărbați, 31 femei), cu vârsta medie 64 ani, tratați prin rezecție rectală anterioară joasă cu anastomoză colorectală sau rezecție ultrajoasă cu anastomoză coloanală (simplă/întârziată), 40 pacienți (27 bărbați, 13 femei) au dezvoltat LARS postoperator (vârsta medie 65 ani). Cele mai frecvente cazuri de LARS au fost înregistrate în cadrul rezecției ultrajoase cu anastomoză coloanală întârziată 18/40 (45%), urmat de rezecția rectală joasă 12/40 (30%) şi rezecția ultrajoasă cu anastomoză coloanală simplă 10/40 (25%).
Concluzii: Sindromul de rezecție anterioară joasă are la bază mai mulți factori printre care tipul intervenției chirurgicale, tipul anastomozei, distanța tumorii față de orificiul anal, stadiul tumoral avansat.

Cuvinte cheie: sindromul de rezecție anterioară joasă, rezecție rectală anterioară joasă, rezecție ultrajoasă, anastomoză

TME: total mesorectal excision;
ULAR: ultralow anterior resection;
ypN: pathological N stage after neoadjuvant therapy;
ypT: pathological T stage after neo-adjuvant therapy;
ypTNM: pathological staging (TNM) after neoadjuvant therapy.

Abstract

Introduction: Surgical procedures for rectal cancer frequently result in intestinal dysfunction, leading to a wide range of digestive symptoms with variable intensity and duration. Thus, patients undergoing low anterior resection with anal sphincter preservation often report fecal incontinence, fecal urgency, incomplete or difficult evacuation, and obstruction. All these symptoms are known as low anterior resection syndrome (LARS). This study analyzes the factors leading to the occurrence of LARS in patients who underwent low anterior resection with colorectal anastomosis or ultralow anterior resection with coloanal anastomosis.

Materials and Methods: This study is based on a retrospective analysis of patients with rectal cancer, hospitalized and treated in two surgical centers experienced in colorectal surgery, between January 2018 and December 2023.

Results: Out of a total of 86 patients (55 men, 31 women) with a mean age 64 years, who underwent low anterior resection with colorectal anastomosis or ultralow anterior resection with coloanal anastomosis (immediate or delayed), 40 patients (27 men, 13 women) developed postoperative LARS (mean age 65 years). The most frequent cases of LARS were recorded after ultralow anterior resection with delayed coloanal anastomosis (18/40), followed by low anterior resection (12/40), and ultralow anterior resection with immediate coloanal anastomosis (10/40).

Conclusions: Low anterior resection syndrome is influenced by multiple factors, including the type of surgical intervention, anastomosis technique, tumor distance from the anal verge, and advanced local tumor stages.

Keywords: LARS, low anterior resection, ultralow anterior resection, anastomosis

Introduction

According to GLOBOCAN 2020 estimates, colo rectal cancer is among the most commonly diagnosed cancers worldwide and remains a leading cause of cancer-related mortality (1).

Radical surgical resection remains the mainstay of treatment for rectal cancer. Sphincter-preserving surgery (performed either via conventional or minimally invasive techniques) is routinely recommended for mid and upper rectal cancer (2).

This approach involves aggressive intervention, especially due to significant changes to the sphincter apparatus, either morphological or neural, which can lead to the development of low anterior resection syndrome (LARS).

This pathological entity involves persistent gastrointestinal dysfunction, characterized by symptoms such as fecal incontinence, fecal urgency, incomplete or difficult evacuation, and obstruction (3). Between 41% and 69% of patients develop major LARS in the first 12 months post-surgery or after closure of a protective ileostomy (4,5). In approximately half of patients, symptoms persist for 7 to 16 years (6).

The main risk factors cited in the literature for LARS include female sex, temporary ileostomy/colostomy, total mesorectal excision (TME), neo-adjuvant or adjuvant chemoradiotherapy, low tumor location, anastomoses close to the anal verge, and anastomotic fistula (7,8).

Although LARS has a profound impact on quality of life and remains a topic of significant interest, many controversies persist due to often contradictory reports (9). In principle, most patients receive conservative management (antidiarrheal agents, diet, small-volume enemas) (10); however, these are ineffective in one out of five patients (11).

The main limitations of current clinical studies concerning LARS are small sample sizes, lack of consistent inclusion and exclusion criteria, and heterogeneous evaluation methods. Consequently, high-quality meta-analyses are difficult to perform. Standardized treatment for LARS remains difficult to establish in the absence of large, multicentric clinical studies.

Most current research and management strategies target specific subgroups of patients with LARS, mainly considering the impact of urgent incontinence on quality of life (12).

The objective of this article is to analyze and identify the risk factors involved in the development of low anterior resection syndrome (LARS), as well as protective factors, in patients with locally advanced rectal cancer (T3-T4, N+ locoregional lymph node involvement). The information obtained, processed statistically and interpreted alongside a review of the literature, aims to facilitate better management of patients with low rectal cancer.

Materials and Methods

This study consists of a retrospective analysis conducted over a five-year period (2018 – 2023) and includes 124 patients with locally advanced rectal cancer who were hospitalized and treated in two surgical centers with expertise in colorectal surgery.

This study included patients who met the following inclusion criteria: age over 18 years, locally advanced rectal cancer (T3-T4, N+ locoregional lymph node involvement), low anterior resection. The patients included in the study were followed for a minimum of 12 months and received complete treatment as determined by a multidisciplinary oncological board.

Patients were excluded if they had early-stage rectal cancer (stage I, IIA), watch-and-wait approach, other types of surgical intervention (Hartmann's procedure, abdominoperineal resection), patients with secondary (metastatic) disease, patients for whom postoperative follow-up was not appropriately conducted.

After applying the inclusion and exclusion criteria, 86 patients were included in the final analysis.

Diagnosis was established by colonoscopy with biopsy, and oncologic evaluation included thoracoabdominal-pelvic CT for all patients. Local tumor status and the diagnosis of locally advanced rectal cancer also involved additional pelvic MRI with contrast.

All 86 patients in the study received neoadjuvant radiotherapy combined with radiosensitizing chemotherapy.

Patients at risk of bowel obstruction underwent diverting laparoscopic colostomy before neoadjuvant treatment. Radiotherapy technique consisted of either long-course irradiation (5 sessions per week for 5 weeks, total dose 50.4 Gy) or short-course irradiation (5 sessions per week for 5 days, total dose 25 Gy). None of the 86 patients experienced specific radiotherapy-related complications.

Post-radiotherapy assessment was performed approximately 6 weeks later by colonoscopy and pelvic MRI. All patients subsequently underwent surgical resection.

Surgical procedures were performed either via open or laparoscopic approaches (robotic surgery was not performed), approximately 6–8 weeks after radiotherapy and consisted of low anterior resection or ultra-low anterior resection, with either colorectal anastomosis, classical or delayed coloanal anastomosis.

At 6 months postoperatively, the LARS score was determined using a five-question questionnaire (*Table 1*) evaluating symptoms such as incontinence for liquid feces and gas, fecal

Table 1. LARS Questionnaire

No.	Question	Possible answers	Score
Q1	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
Q2	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
Q3	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
Q4	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
Q5	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

urgency, stool frequency, and clustering (13).

The cumulative LARS score varies between 0-42. Severity is graded as follows:

- No LARS (score 0 – 20);
- Minor LARS (score 21 – 29);
- Major LARS (30 – 42).

There are several methods to assess functional outcomes after sphincter-preserving rectal surgery, such as the Memorial Sloan Kettering Cancer Center Bowel Function Instrument (14) or anorectal manometry (15). Our study utilized the LARS score, introduced in 2012 and now widely used, especially for its optimal correlation with patients' quality of life. The LARS score is a questionnaire of five items developed by Danish researcher Emmertsen (16). The incidence of LARS in our study was 46.5% (n=40). Patients were divided into three categories: 27 patients (31.4%) developed major LARS (score 30-42), 13 patients (15.1%) had minor LARS (score 21-29), and the remaining 46 patients (53.5%) exhibited specific LARS symptoms but had a score under 20 points.

Statistical Analysis

After entering the study protocol data into the database, statistical analysis was performed using SPSS version 23.0 and Microsoft Excel.

Descriptive statistics included calculation of mean, standard deviation, median, and quartiles for quantitative variables, and frequencies and percentages for qualitative variables. For comparison of quantitative data, depending on data normality Mann-Whitney U test (for two groups without normal distribution), or Kruskal-Wallis test (for more than two groups without normal distribution) were used. Levene's test was used to assess homogeneity of variances for quantitative data.

For categorical data (reported as frequencies and percentages), the Likelihood Ratio test was applied. In cases where more than two groups were compared and a significant overall result was found; post hoc multiple comparison tests were used to identify statistically significant subgroup differences.

Results

Following the inclusion criteria, 86 patients were included in the study and underwent sphincter-preserving surgery. Of these, 55 were men (64%) and 31 were women (36%), with a median age of 64 years (57.5-73.0). Fifty-four patients were operated by laparoscopic approach, while 32 underwent open surgery. Anastomotic fistulas were reported in 11 patients and managed conservatively. The clinicopathological characteristics of the patients included in the study are detailed in *Table 2*.

All patients received neoadjuvant chemoradiotherapy. After surgery, histopathological examination revealed a complete pathological response in 28 patients and an almost complete response in 7 patients; the remaining 51 patients either showed obvious tumor regression with residual tumor or failed to respond to radiotherapy.

Sex distribution was as follows: 27/40 (67.5%) men, and 13/40 (32.5%) women developed LARS (p=0.523).

The median age in the LARS group was 65 years, compared to 64 years in the no-LARS group. Statistical analysis showed no significant age difference between the groups (p=0.362).

Tumors located ≤6 cm from the anal verge (lower rectum) often require resections that may affect the pelvic musculature and increase the risk of postoperative bowel dysfunction.

Although endoscopic tumor location in the lower rectum was not statistically significant (p=0.164), the tumor distance from the anal verge measured preoperatively by MRI was significantly correlated with the development of LARS. The mean tumor distance in the LARS group was 55 mm versus 80 mm in the group without LARS (p=0.001).

Statistical analysis revealed a significant association between advanced local tumor stage (cT4) and the occurrence of low anterior resection syndrome (p = 0.029), indicating that patients with cT4 are at higher risk for LARS compared to those with lower T stages.

Statistical analysis showed no significant association between ypTNM, ypT, ypN staging and LARS occurrence.

Regarding comorbidities, although some studies suggest that obesity and diabetes may be associated with LARS, our result did not identify a statistically significant association; rates of these comorbidities were similar in both groups with LARS and without LARS (p = 0.843 - obesity, p = 0.575 - diabetes).

The most frequent symptoms among patients without LARS were flatulence incontinence (28.3%) and increased stool frequency (23.9%), with some patients reporting up to ten bowel movements per day. While both groups presented LARS-specific symptoms, symptom frequency was

Table 2. Characteristics of patients included in the study

No. of patients	LARS=No (N=46)	LARS=Yes (N=40)	p-value
Age in years	64.0 [57.5, 73.0]	65.0 [53.25, 69.75]	0.362*
Sex			
Women	18 (39.1%)	13 (32.5%)	0.523**
Men	28 (60.9%)	27 (67.5%)	
Tumor location			0.164***
Lower rectum	26 (56.5%)	30 (75%)	
Middle rectum	14 (30.4%)	8 (20%)	
Upper rectum	6 (13%)	2 (5%)	
Distance to anal verge	80.0 [60.0, 90.0]	55.0 [50.0, 80.0]	0.001*
cT4	0 (0%)	5 (12.5%)	0.029***
Obesity = Yes	10 (21.7%)	8 (20.0%)	0.843**
Diabetes = Yes	14 (30.4%)	10 (25.0%)	0.575**
ypTNM stage			0.683***
0	14 (30.4%)	15 (37.5%)	
I	9 (19.6%)	10 (25%)	
II	9 (19.6%)	5 (12.5%)	
III	14 (30.4%)	10 (25%)	
ypT			0.163***
0	14 (30.4%)	15 (37.5%)	
1	1 (2.2%)	0 (0%)	
2	11 (24%)	16 (40%)	
3	17 (36.9%)	9 (22.5%)	
4	3 (6.5%)	0 (0%)	
ypN			0.527***
0	32 (69.6%)	30 (75%)	
1	11 (23.9%)	6 (15%)	
2	3 (6.5%)	4 (10%)	

cT: clinical tumor stage; ypTNM: pathological staging after neoadjuvant therapy.

*Mann–Whitney U test; **Pearson χ^2 test; *** Likelihood Ratio test.

significantly higher in the LARS cohort: stool incontinence 47.5% (p<0.001), gas incontinence 97.5% (p<0.001), increased stool frequency 95% (p<0.001), clustering stools within an hour 62.5% (p<0.001), and fecal urgency 90% (p<0.001). Detailed symptom prevalence according to LARS status is presented in *Table 3*.

Surgical Factors

One of the factors with prognostic potential in the onset of LARS is surgical intervention. The characteristics of the surgical intervention were compared between the two groups: LARS (n=40), and No LARS (n=46). Details regarding the surgical approach and postoperative complications are presented in *Table 4*.

The surgical approach was significantly associated with LARS occurrence. LARS developed in 32 patients (59.3%) after laparoscopic surgery compared with 8 patients (25%) after open surgery (p=0.002).

Regarding surgical treatment, in the group that developed LARS, most patients underwent low

Table 3. Symptom prevalence among patients

Symptom	LARS=No (N=46)	LARS=Yes (N=40)	p-value
Stool incontinence	3 (6.5%)	19 (47.5%)	<0.0001*
Flatulence incontinence	13 (28.3%)	39 (97.5%)	<0.0001*
Increased stool frequency	11 (23.9%)	38 (95.0%)	<0.0001*
Clustering stools	2 (4.3%)	25 (62.5%)	<0.0001*
Fecal urgency	3 (6.5%)	36 (90.0%)	<0.0001*

*Pearson χ^2 test.

Table 4. Features of surgical intervention and postoperative complications

Variable	LARS=No	LARS=Yes	P value
Hospital length of stay (days)	10.0 [8.0, 17.25]	10.0 [9.0, 11.0]	0.726*
Surgical procedure			
Ultralow anterior resection with delayed coloanal anastomosis (DCA)	0 (0%)	18 (100%)	<0.0001**
Low anterior resection (LAR)	46 (79.3%)	12 (20.7%)	
Ultralow anterior resection (ULAR)	0 (0%)	10 (100%)	
Surgical approach			
Open	24 (75%)	8 (25%)	0.002***
Laparoscopic	22 (40.7%)	32 (59.3%)	
Anastomosis type			
Hand-Sewn Anastomosis	6 (18.2%)	27 (81.8%)	<0.0001**
Stapled Anastomosis	40 (75.5%)	13 (24.5%)	
Reoperation	4 (30.8%)	9 (69.2%)	0.075***
Anastomotic fistula	9 (81.8%)	2 (18.2%)	0.044**

DCA-delayed coloanal; LAR-low anterior resection; ULAR-ultralow anterior resection.

*Mann–Whitney U test; ** Likelihood Ratio test; *** Pearson χ^2 test.

anterior resection (LAR), of which 12/40 (30%) developed LARS, followed by delayed coloanal (DCA), which all patients, 18/40 developed LARS (45%), and ultralow anterior resection (ULAR) 10/40 (25%) patients, all developing LARS (p<0.0001).

The type of anastomosis (hand-sewn/stapled techniques) was also a factor that influenced the occurrence of LARS. Following statistical analysis, hand-sewn anastomosis was found to be a predictive factor in the occurrence of LARS compared to stapled techniques (p<0.0001).

In our cohort, fistula was significantly more frequent in the group without LARS compared to the LARS group (19.6% vs 5%, p=0.044), contrary to the data in the literature.

Hospitalization duration was similar in both patient groups: 10 days (p=0.726).

Discussion

The current standard treatment for advanced rectal cancer is a multimodal approach, consisting of neoadjuvant chemoradiotherapy (CRT) followed by rectal resection with total mesorectal excision (TME), and adjuvant chemotherapy in selected patients (17).

Radical surgical resection remains the mainstay of treatment for rectal cancer. Sphincter-preserving surgery (performed either via conventional or minimally invasive techniques) is routinely recommended for mid and upper rectal cancer (cT2-4, N0-2, M0) (2). The development of circular staplers has expanded indications for sphincter-preserving procedures, including low rectal lesions. Currently, up to 80% of rectal cancer patients are eligible for sphincter-preserving procedures (18,19). However, radical resection for rectal cancer is generally associated with severe postoperative complications and a significant decline in quality of life, with substantial physical, emotional, and financial consequences (20). The morbidity is high, with frequent bowel, sexual, and urinary dysfunctions (21).

Moreover, though effective, radical surgery for lower rectal cancer is aggressive and requires access to surgical centers with extensive colorectal experience, consuming significant material and personnel resources. Even so, the alternative of abdominoperineal resection, which results in permanent colostomy, makes sphincter-preserving techniques the first surgical choice, at least from the patient's perspective. It is notable that sphincter-preserving approaches have comparable recurrence and survival rates to abdominoperineal resection for similar tumor stages (22,23). Beyond oncological outcomes, sphincter-conserving surgery carries a quality-of-life advantage, sparing patients permanent colostomy. On these grounds, rectal cancer surgery with sphincter preservation has become the preferred treatment for low rectal cancer (24,25).

Nevertheless, it remains an aggressive intervention, especially due to significant changes to the sphincter apparatus, either morphological or neural, which can lead to the development of low anterior resection syndrome (LARS).

The high incidence of LARS has led to numerous studies focusing on estimation, management, and prevention of this syndrome (26,27). The topic

remains of great interest because the intensity of the syndrome, apart from the oncological outcome achieved after treatment, can have a significant impact, incapacitating the patient and resulting in real failure of sphincter-preserving surgery from the perspective of quality of life.

Various factors have been directly linked to LARS incidence.

In our study, 13 patients (15.1%) had a score between 21-29, 27 patients (31.4%) had a score between 30-42, and the remaining patients in the study, 46 (53.5%) showed LARS-related symptoms but with a score lower than 20, the proportion of LARS in our study being similar to previous literature (4,28,29).

Tumor Distance from the Anal Verge

Our results confirm the association between anal verge distance and LARS occurrence (p=0.001). The lower the tumor is located, the closer the anastomosis will be performed to the pectineal line, which leads to the occurrence of LARS. The literature even distinguishes between two subtypes of the syndrome: incontinence-dominant and frequency-dominant (30). There may be different risk factors for the two entities. Incontinence-dominant LARS is related to preoperative radiotherapy and postoperative complications, while frequency-dominant LARS is linked to low tumor location and is more frequently associated with poor quality of life (31). Our study cannot specify such details due to a lack of information in this regard.

Local Tumor Extension (cT4)

Advanced local tumor stage (cT4) was significantly associated with LARS. This can be explained by the invasion of adjacent structures and the need for more extensive resections impacting sphincter integrity and pelvic innervation. The results of our study are consistent with the study conducted by Pieniowski et al., which showed that in the case of advanced tumors (cT3-T4), the majority of patients experienced major LARS (32).

ypTNM/ypT/ypN Status

Statistical analysis did not show an association between these variables and LARS, contrary to other studies, where advanced N stage correlated with neural invasion and anorectal dysfunction and implicitly leading to the onset of LARS (33,34). According to Muttillo Em et al., the more advanced the pT, the higher the risk of LARS (26). In another study conducted in China, statistical analysis showed that both pT and N can be factors in the onset of LARS (35). However, the evidence is not extensive, as there are a limited number of studies confirming these theories.

In other studies, focused on developing predictive models for LARS, T staging and pathological staging were not selected for inclusion in the final models, suggesting either a lack of statistical significance in multivariate analyses or a reduced predictive value compared with other clinic-therapeutic factors (36-39).

Surgical Technique

The type of surgery is a determining factor in the occurrence of LARS. Ultralow anterior resection with coloanal anastomosis (standard or delayed) more often leads to the appearance of symptoms specific to this entity, such as fecal or gas incontinence, multiple stools, and fecal urgency. Coloanal anastomosis is clearly closely related to the low location of the tumor, whose correlation with the incidence of LARS has already been established as statistically significant. The occurrence of the syndrome after ultralow anterior resection can be explained by the fact that anterior resection leads to the loss of the reservoir function of the rectum, which will be replaced by a much smaller colonic segment, and the evacuation function is affected by the absence of longitudinal fibers in the rectum, leading to significant impairment of rectal compliance (40) and increased frequency of false defecation.

Rectal compliance, which is physiologically greater than that of the colon, can cause stool to remain in the rectum up to a certain capacity without increasing pressure (41). It has been reported that the neorectum, which is created with the participation of the distal colon after removal of the rectum, exhibits hyperactive motility, and this change in rectal motility physiology ultimately leads to increased stool frequency and urgency (42, 43). Interception of extrinsic autonomic innervation can affect colonic motility by increasing smooth muscle contractions or causing defecation disorders due to improper evacuation (44,45). However, even without control of extrinsic innervation, the intrinsic nerve plexus can create colonic peristalsis. Because the colon propels intraluminal contents from the proximal to the distal section as soon as they enter the lumen, it has been thought

that colonic patterns of contraction and relaxation cannot take the place of the storage function of the rectum (46,47).

Neoadjuvant Radiotherapy

With advances in radiotherapy and chemotherapy, the treatment of colorectal cancer has evolved significantly, leading to increased resectability rates, improved success in sphincter preservation, as well as higher survival and clinical cure rates (48).

Neoadjuvant radiotherapy is a risk factor for the development of LARS, as suggested in the literature (49). Post-irradiation bowel dysfunction has been attributed to locoregional inflammation/ fibrosis (50), or secondary neuropathy (9). We could not evaluate radiotherapy as a risk factor because all patients received neoadjuvant CRT.

There is some controversy in the literature, Parnasa et al. (27) report no correlation with neoadjuvant therapy. However, a recent meta-analysis clearly establishes that neoadjuvant radiotherapy increases the incidence of LARS (51).

Recent evidence indicates that severe LARS occurs more frequently after neoadjuvant chemoradiotherapy compared to neoadjuvant chemotherapy alone (48,52). In addition, some studies have reported a higher incidence of postoperative complications in patients treated with chemoradiotherapy, compared with those who received chemotherapy only (53,54).

Furthermore, a recent study highlighted the occurrence of symptoms similar to severe LARS even in patients who underwent radiotherapy without surgery, suggesting that irradiation may have a direct toxic impact on anorectal function, sometimes comparable to or even greater than that induced by sphincter-preserving resection (52). These functional changes may be explained by damage to the anal sphincter complex, pelvic autonomic innervation, and intestinal microecology, all of which contribute to decreased bowel function following multimodal oncological treatments (55).

Comorbidities (Diabetes, Obesity)

Diabetes and obesity are mentioned in the literature as potential risk factors in patients who develop LARS (29,49). Although the mechanism linking diabetes and this postoperative syndrome has been described in the literature, studies and results are inconsistent (49). The subject is of interest because approximately 10% of newly diagnosed colorectal cancer patients have type II diabetes (56). Furthermore, it has been documented that type II diabetes worsens the oncological prognosis in these patients (57,58). In addition, non-specific abdominal pain and digestive transit disorders are described in patients with type II diabetes, including patients who do not have colorectal cancer (59). These symptoms are thought to be caused mainly by diabetic neuropathy, but also by digestive myopathy, fluctuating blood sugar levels, or the side effects of antidiabetic medication (60,61). Despite the common symptoms in people with type 2 diabetes and colorectal cancer survivors, few studies have investigated whether intestinal dysfunction and abdominal pain after colorectal cancer resection occur more frequently in those with type 2 diabetes (62). Our study did not find a statistical correlation between these comorbidities and the occurrence of LARS, maintaining the current controversy, which is at odds with other studies that claim the opposite (62).

Surgical Approach

The surgical approach (open/ laparoscopic) has been shown as a potential predictor of LARS. The results of our study are not entirely consistent with reports in the literature that have paid particular attention to this aspect.

It is considered that there are no significant differences in the incidence of major LARS for the laparoscopic and transanal approaches. In addition, there is insufficient data in the literature for the intrasphinteric technique (63). A 2021 meta-analysis that evaluated 32 studies, including 5565 patients (64), showed a higher incidence of LARS in laparoscopic resection (33.3%) and open approach (46.5%) compared to the robotic approach (21.7%).

However, the largest number of patients underwent an open procedure (90%). Only one of the studies strictly compared the open approach with the laparoscopic approach, concluding that there was no statistical difference in the occurrence of LARS (65).

Anastomosis Type

The method of performing the anastomosis was also a factor that influenced the occurrence of LARS, with much higher incidence for hand-sewn anastomosis than for those performed using stapled anastomosis. This is probably due to more intense local inflammation for hand-sewn anastomosis, which, due to the limited operating field,

require vigorous exposure maneuvers with additional trauma to neighboring structures. This aspect is more of a speculation, justified theoretically, as it is difficult to quantify using concrete parameters.

Shen et al. assessed continence function using the Wexner score in patients with anastomoses performed less than 4 cm from anal verge, comparing hand-sewn versus stapled techniques. At the 3-year postoperative follow-up, the authors reported significantly higher Wexner scores in the hand-sewn anastomosis group compared with the stapled group. This discrepancy was mainly explained by a higher frequency of incontinence episodes for flatus and solid stool in patients with hand-sewn anastomoses (66).

Similar findings have been reported in other studies, suggesting less favorable anal function after hand-sewn anastomosis compared with stapled anastomosis. Matsunga et al. analyzed anorectal function in patients with tumors located 4-6 cm from the anal verge, comparing the two anastomotic techniques, with evaluations performed at 3, 6, 12, 24 months postoperatively. The authors reported higher Wexner scores in the hand-sewn group at all follow-up time points, suggesting a greater impairment of continence in this group (63).

In addition, Chong et al. compared functional outcomes after hand-sewn versus stapled anastomosis in tumors located less than 5cm from anal verge, evaluating patients at 6 and 36 months. The study showed a higher proportion of anal dysfunction in the hand-sewn anastomosis group at both follow-up intervals (67).

Anastomotic Fistula

Anastomotic fistula is considered to have an impact on postoperative bowel function and is considered an independent factor for the development of LARS (68-70). The mechanism is related to the healing process through fibrosis, which leads to decreased rectal capacity and compliance, affecting motility and inducing symptoms such as urgency and fragmentation of stools (4,70,71). In contrast, the result of our study did not support these conclusions. This may be due to the small sample site, shorter follow-up duration, or the protection offered by the derivative ileostomy.

Age and Sex

Although studies show that age and sex may be risk factors for the development of LARS (29,56), in our study these factors had no impact on the incidence of LARS.

In the study conducted by Tanaka et al. (7), which included 506 patients with rectal cancer who underwent sphincter-preserving surgery, the results showed that female sex was associated with higher risk of developing LARS compared with male sex.

A possible explanation may be related to the anatomical and functional characteristics of the female pelvis: the anal sphincter may be thinner than in males, and in elderly women, obstetric history (especially vaginal delivery) may contribute to weakening of the pelvic floor musculature, which can favor the development of postoperative anorectal dysfunction (7).

In addition, the presence of female reproductive organs may reduce the space available for pelvic dissection, sometimes making surgical maneuvers more difficult (7). Given these anatomical constraints, a technically challenging or suboptimal surgical procedure may increase the risk of injury to the pelvic autonomic innervation and/or the sphincter complex, thereby affecting continence function and contributing to LARS-related symptoms (54).

Hospitalization Duration

Hospitalization duration was similar in both groups of patients. This finding can be explained, on the one hand, by the onset of the syndrome after discharge and, on the other hand, by the high tolerance threshold for these symptoms, at least in the initial phase. It should not be forgotten that this tolerance threshold is "set" at a high level by the patient, who is certainly aware that the alternative is most often permanent colostomy. However, regardless of the intensity of the symptoms, the often-tenacious nature of LARS can reset this threshold over time. These are strictly subjective aspects, which depend on the particularities of each individual patient.

The limitations of the study are that it is retrospective, and a prospective study may be more effective in understanding the risk factors for the onset of LARS. The small number of patients and the fact that it was conducted in two distinct

surgical centers, each with a certain lack of homogeneity in terms of surgical experience, is also a limitation of the study.

Conclusions

The lower the tumor is located, the closer the anastomosis will be performed to the pectineal line, which leads to the occurrence of LARS.

Advanced local tumor stage (cT4) was significantly associated with LARS.

Statistical analysis showed no significant association between ypTNM, ypT, ypN staging and LARS occurrence.

The type of surgery is a determining factor in the occurrence of LARS. Ultralow anterior resection with coloanal anastomosis (standard or delayed) more often leads to the appearance of symptoms specific to this entity, such as fecal or gas incontinence, multiple stools, and fecal urgency. Our study did not find a statistical correlation between comorbidities and the occurrence of LARS. Laparoscopic surgery reports a higher incidence of LARS in contrast with the existing literature. Hand-sewn anastomosis predisposes to an increased incidence of LARS compared to stapled anastomosis. Anastomotic fistula was significantly more frequent in the no-LARS group compared with the LARS group. Age and sex were not statistically correlated with the incidence of LARS. The onset of LARS did not impact the length of hospital stay.

Patient's perception of LARS development is essential, given the major effect of symptoms on quality of life. There are many controversies and the results are inconsistent due to the lack of standardization of studies and the often-small number of patients included in the reported groups. In this regard, randomized, well-structured studies with large cohorts are needed to reduce the multiple variables created in the evaluation of patients with LARS.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethical Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee (No 12287/23 May 2023).

All patients provided an informed consent for data collection and research participation.

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