Analysis of factors associated with anterior resection syndrome in patients operated on for rectal tumors. Can the surgeon prevent its appearance?

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ABSTRACT

Introduction: *Patients with low anterior resection for rectal cancer often suffer functional disorders related to bowel movements defined as low anterior resection syndrome (LARS). Symptoms include increased frequency, urgency, clustering and fecal incontinence. Some predisposing factors for its appearance have been demonstrated.*

Objective: *To determine LARS prevalence, and factors related with its appearance and severity.*

Design: *Retrospective, cross-sectional, observational study.*

Material and methods: *Patients submitted to low anterior resection with extraperitoneal primary anastomosis for confirmed/suspected rectal adenocarcinoma not considered for endoscopic resection, operated on by members of the same surgical staff in two institutions, between June 2012 and March 2021. A questionnaire on bowel function was administered to patients between November 2020 and April 2021. LARS score (range 0-42) and related variables were also analyzed.*

Results: *Sixty-nine patients met the inclusion criteria. With a median time from surgery to questionnaire of 31 (range 3-97) months, 40.6% (28/69) patients obtained a LARS score ≥ 30 (major LARS). The risk of major LARS was significantly increased in females (OR 3.4; 95% CI 1.08-11.8), and patients that underwent neoadjuvant radiotherapy (OR 3.8; 95% CI 1.4-10) and total mesorectal excision (OR 4.1; 95% CI 1.06-15.9). No association was found with age, the use of reservoir, hand-sewn coloanal anastomosis, or temporary ostomy.*

Conclusions: *The prevalence of major LARS in our service is similar to that reported in the literature. Radiotherapy and total mesorectal excision are variables associated with a higher LARS score, but are based on oncological rather than functional results. Potentially preventive measures, such as the type of anastomosis, do not seem to be decisive.*

Keywords: *Rectal Cancer; Anterior Resection Syndrome; LARS Score*

INTRODUCTION

Rectal cancer is a common disease in our setting. The different therapeutic regimens, which include chemoradiation therapy as well as surgery, have made it possible to broaden the horizons of sphincter preservation.[1]

Ideally, patients operated on for rectal cancer will maintain intestinal continuity. Despite this, those in whom a low anterior resection (LAR) with anastomosis and ostomy reversal is performed, present functional disorders related to bowel evacuation. The manifestations most frequently reported by patients are related to the frequency, urgency and clustering of bowel movements, as well as fecal incontinence.

Generally, these symptoms are of greater intensity immediately after surgery and decrease after the first year.[2] To assess them, the LARS (Low Anterior Resection Syndrome) score, has established in recent years as a valid tool for the categorization of these patients.[3] According to this score, individuals who suffer from major LARS have a significant deterioration in quality of life, compared to those with minor LARS or no LARS. On the other hand, factors related to the appearance of symptoms have been described, especially pelvic radiotherapy, tumor height, total or partial excision of the mesorectum, the type of anastomosis, and the use of a protective ostomy.

In the available databases, we did not find national publications that analyze the occurrence of this syndrome and the risk factors that predispose to its appearance in our population.

In this sense, the objective of this research is to determine the prevalence of LARS in a sample treated by the same professional team in two different institutions and to analyze the predisposing factors for its development and severity, seeking to interpret the preventable mechanisms of its appearance.

MATERIAL AND METHODS

An observational, retrospective and cross-sectional study of patients undergoing LAR by a member of the same team was carried out in two institutions (Hospital J. M. Ramos Mejía and Sanatorio Sagrado Corazón) in the city of Buenos Aires during the period from June 2012 to March 2021.

All patients who underwent rectal resection and primary extraperitoneal anastomosis without or with a protec-

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TABLE 1: LARS SCORE

	Points
1. Do you ever have occasions when you cannot control your flatus (gas)?	
No never.	0
Yes, less than once a week.	4
Yes, at least once a week.	7
2 Do you ever have any accidental leakeage of liquid stool?	
No never.	0
Yes, less than once a week.	3
Yes, at least once a week.	3
3. How often do you open your bowels?	
More than 7 times per day (24 hours).	4
4 to 7 times per day (24 hours).	2
1 to 3 times per day (24 hours).	0
Less than once per day (24 hours).	5
4. 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
5. ¿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
0-20 no LARS; 21-29 LARS menor; 30-42 LARS mayor	

tive stoma (with subsequent reversal surgery), who expressed their consent to participate in the study, were included. The diagnosis included both adenocarcinoma of the rectum (regardless of its distance from the anal margin, with partial or total resection of the mesorectum) and suspicious lesions (adenomas with dysplasia or carcinoma in situ not resectable endoscopically or transanally).

Patients with local transanal resections, rectal amputation, resections without anastomosis, as well as those who did not have stoma reversal or needed to redo it were excluded. Those who had major colonic resections (right colectomies, total proctocolectomies, or left colectomies extended to the splenic flexure) were also excluded.

LAR was considered to be partial or total excision of the rectum and mesorectal fatty tissue. Complete resection of the mesorectal tissue was considered total mesorectal excision (TME), interpreted after reviewing the preoperative studies, the surgical protocol and the photograph of the excised specimen. Cases in which excision of the entire mesorectal volume was not confirmed were categorized as partial mesorectal excision (PME). Cases in which there was no dissection below the peritoneal reflection were discarded.

Data were obtained from a prospective database, as well as from the search of files and medical records.

Overt clinical leaks (outflow of pus or feces through the drain, pelvic abscesses, rectovaginal fistulas, or peritonitis), or strictures that required dilation were considered anastomotic complications.

A protective ileostomy was routinely performed for all TME and some PME, according to the surgeon's decision. In some cases (advanced age, comorbidities) a transverse colostomy was chosen.

Side-to-end (S-E) anastomoses, coloplasties, and colonic pouches were considered neo-reservoirs.

LARS score

The patients were sequentially surveyed between November 2020 and April 2021, in person or by telephone survey. For the classification, the LARS score translated and validated into Spanish was used.7 This score consists of 5 multiple-choice questions related to the bowel habits (Table 1). It was classified as no LARS when the total score obtained was between 0 and 20 points, minor LARS when it was between 21 and 29, and major LARS between 30 and 42.

Statistical analysis

For comparison of patient characteristics, categorical variables were compared using the Chi-square test, or Fisher's test when events were less than 5. For continuous variables, the t-test and for data with non-normal distribution the Wilcoxon's test was used. Logistic regression was performed to estimate the odds ratio for major LARS adjusted for the impact of sex, use of radiotherapy, resection technique (TME vs. PME), anastomotic leak, and use of neo-reservoir. A significant statistical value was considered at $p<0.05$. For the final model, all variables with a value <0.1 in the Wald test were incorporated. All analyzes were performed using Stata 14.1 (StataCorp 4905® Lakeway Dr, College Station, TX 77845 USA).

RESULTS

During the study period, 268 patients with a diagnosis of rectal tumor (adenocarcinoma or suspicious lesion) un-

TABLE 2: CHARACTERISTICS OF THE PATIENTS

Characteristics	Patients (n=69)
Sex, n (%)	
Men	46 (66.6)
Women	23 (33.3)
Age, median (range)	58 (18-89)
BMI, median (range)	27.3 (17.8-39.6)
ASA, n (%)	
1-2	41 (59)
3-4	28 (41)
Time since ostomy reversal, months, median (range)	31 (3-97)
Tumor stage, n (%)	
0	14 (20.3)*
I	16 (23.2)
II	12 (17.4)
III	23 (33.3)
IV	4 (5.8)
Tumor height, median (range)	8.6 (2.2-15)
Radiotherapy, n (%)	31 (48)
Type of anastomosis, n (%)	
End to End	59 (85.5)
Reservoir	10 (14,5)
Side-to-end	8
	2
Coloplasty Mesorectal excision, n (%)	
TME (total)	43 (63.2)
PME (partial)	25 (36.8)

** Complete pathological response or adenoma with dysplasia.*

derwent surgery. Of these, 69 met the inclusion criteria and agreed to participate in the study (Fig. 1).

The median follow-up time after ostomy reversal was 31 (range 3-97) months. The demographic, tumor and therapeutic data of the included individuals can be seen in Table 2.

To analyze the representativeness of the sample, the main variables were compared between the included and excluded patients. There were no differences between both groups (Table 3).

LARS score

The prevalence of major LARS in the surveyed patients was 40.6% (28/69) (Table 4). In our sample, the female sex was related to the presence of major LARS (OR 3.4; 95% CI 1.08-11.8). Among the other risk factors, those patients who received radiation therapy were more likely to develop major LARS (OR 3.8; 95% CI 1.4-10). Those who had a TME are also at an increased risk of developing the most severe degree of LARS, compared with those who received partial resections (OR 4.1; 95% CI 1.06-15.9). Tumor height was excluded due to collinearity with the PME/TME variable. In the bivariate analysis, the complications of the anastomoses, as well as the fact that one year had elapsed since the last surgery, had a statistical difference, which was lost when adjusting for the other variables (OR 6.3; CI 95% 0.7-58 and OR 0.2, CI 95% 0.06-1.2, respectively). The risk of developing a major LARS was not associated with age, the creation of a reservoir (coloplasty or side-to-end anastomosis, since no colonic pouch was created in the series), a hand-sewn coloanal anastomosis, or a temporary ostomy (Table 5).

TABLE 3: COMPARISON BETWEEN EXCLUDED AND INCLUDED PATIENTS

	Included patients (n=69)	Excluded patients (n= 101)	p
Sex n (%)	W 23 (33.3)	W 42 (42)	
	M 46 (66.6)	M 59 (58)	0.29
BMI median (range)	27.3 (17.8-39.6)	27.1 (19.1-52.1)	
Tumor height median (range)	8.6 (2.2-15)	8.3 (3-15)	0.515
TME n (%)	43 (63.2)	63 (62)	0.742
Radiotherapy n (%)	31 (48)	73 (72)	0.475
Anastomosis with reservoir n (%)	10 (15)	17 (17)	0.128
Ostomy n (%)	61 (88)	96 (95)	0.286

TABLE 4: PREVALENCE OF LARS IN THE SERIES

No LARS	Minor LARS	Major LARS
22 (31,9 %)	19 (27,5 %)	28 (40,6 %)

DISCUSSION

Rectal cancer surgery has broadened its horizons in recent decades. The new treatment regimens brought patients closer to an increase in the rates of sphincter preservation, and even organ preservation.

However, regardless of oncologic outcomes, patients undergoing radical surgery with low anastomoses develop troublesome, often disabling, bowel movement symptoms. Urgency, incontinence and, above all, clustering, alter the quality of life of these patients, although these symptoms improve over time, especially after the first year.[3]

To objectify the disorder, different surveys have been validated in recent years, highlighting the score developed by the Memorial Sloan Kettering Cancer Center (MSKCC score)8 and the LARS score. The latter, published by Emmersten and Laurberg,[9] evaluates the different domains of bowel movement (continence, frequency and urgency) through 5 questions, giving a higher score to patients who develop these symptoms more frequently. Validated in multiple populations and languages,[10] due to its ease and applicability and its correlation with quality of life surveys, it has gained more and more adhesions.

The prevalence of 40% of major LARS in our casuistry series is similar to that of different publications. Reports from Denmark and other European countries showed a rate of 41 to 52%.[4,11] To treat it, the different schemes have not gained consensus in practice, due to lack of effectiveness or inaccessibility due to costs. Transanal irrigation, biofeedback and sacral neuromodulation are the those with the most evidence of results.[12-18]

Due to the difficulty in treating the severe symptoms in these individuals, it seems promising to determine conditions that can prevent their appearance.

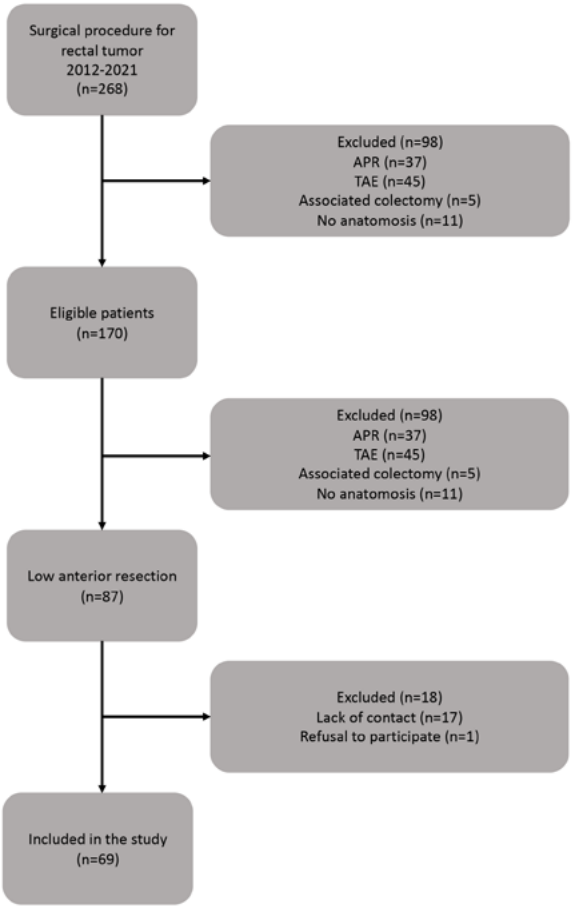

Figure 1: Patient flowchart. Chemotherapy: includes patients undergoing adjuvant consolidation or palliative treatment. Without closure: anastomotic complications, patient decision, comorbidity and others.

A single prospective randomized preliminary study from 2017 using biofeedback prior to ostomy closure to prevent functional symptoms found no benefit compared to individuals who did not undergo treatment. Four years have passed and the definitive results have not yet been

TABLE 5: RISK FACTORS FOR MAJOR LARS

Risk factor	Major LARS *	p Raw	p Adjusted
Sex			
M	1.00 (ref)	0.048	0.048
F	3.4 (1.08-11.8)		
Resection technique			
TME	1.00 (ref)	0.018	0.04
PME	4.1 (1.06-15-9)		
Radiotherapy			
No	1.00 (ref)	0.037	0.008
Yes	3.8 (1.4-10)		
Anastomotic complications			
No	1.00 (ref)	0.021	0.201
Yes	2.4 (0.6-9.7)		
Reservoir			
No	1.00 (ref)	0.888	
Yes	1.1 (0.2-4.3)		
Ostomy			
No	1.00 (ref)	0.105	
Yes	5.9 (0.6-51.2)		
Coloanal anastomosis			
No	1.00 (ref)	0.102	
Yes	6.3 (0.7-58)		
Time from surgery			
< 1 year	1.00 (ref)	0.035	0.088
> 1 year	0.2 (0.06-1.2)		

** Los datos se expresan como OR (IC 95 %).*

published.[14]

On the other hand, within the factors that have a relevant weight in the generation of major LARS, the association of pelvic radiotherapy and the extension of rectal resection are recognized.[5] Radiotherapy acts by interfering with the innervation of the rectoanal unit, which depends mainly on the hypogastric nerve plexus, leading to an alteration of the signals necessary for a satisfactory bowel evacuation process, as well as to the alteration of the compliance of the remaining rectal stump.[19] Even through a meticulous surgical technique that preserves the indemnity of the autonomic nerves, complete resection of the rectum (TME vs. PME), closely related to the height of the tumor, leads to the cancellation of the reservoir function. All this, added to the colonic excitability produced by the surgical denervation, would contribute to clustering, the most important symptom according to the patients' reports. Our results showed that both radiotherapy and TME are the two factors that most contribute to the appearance of the most severe degree of this syndrome, even adjusted for the rest of the variables.

When making decisions by the multidisciplinary team, reducing the rate of local recurrence is the ultimate goal in the choice of radiation therapy in cases of locally advanced rectal cancer. In the same way, the colorectal surgeon will decide the TME trying to ensure the resection margins and the quality of the surgical specimen. In short, it will not be the functional results that will weigh decisively in decision-making.

Among the preventable factors accessible when treating these patients is the type of anastomosis. Since the 2008 Cochrane review,[20] the recommendation in favor of colonic reservoirs, ideally a J-pouch, or a side-to-end anastomosis, if the latter cannot be performed, has led the options. However, recent prospective and randomized studies showed no differences in terms of anastomotic complications or functional results (using the FISI and the MSKCC score), when comparing the colonic J-

pouch with end-to-side and end-to-end anastomosis.[21-23] A colonic pouch is not always feasible, especially in low anastomoses in which the length of the colon and its adequate perfusion are determining factors. Although we did not perform a colonic J-pouch in any case, the comparison between end-to-end and side-to-end anastomosis with a reservoir or coloplasty had no differences in the appearance of major LARS. The evidence available from the mentioned studies allows us to estimate that the construction of a direct end-to-end anastomosis is safe and does not worsen complication rates or functional results.

Although its importance declines one year after closure,[24] the use of a protective ostomy and the time elapsed until its closure were correlated with the appearance of major LARS, according to a recent meta-analysis.[6] Although it would be unlikely that a surgeon would make a decision to perform a temporary ileostomy or colostomy based on eventual functional outcomes, our model failed to find this association. The same happened with hand sewn coloanal anastomoses.

Anastomotic leak have also been postulated as a contributing factor to major LARS. The study by Hain et al.[25] found that symptomatic leaks were independently related to the appearance of a major LARS. In the same way as our results, the rest of the publications did not manage to demonstrate this difference.

Most research exclude from the analysis patients with less than a year from restoration of bowel continuity, because they have a higher proportion of major LARS. In our series, with great variability in the time elapsed (median 31 months, range 3-97), the difference lost power in the multivariate analysis, although it is likely that a higher n could have reached it (type II error).

Interestingly, the female gender had a significant weight in our model. This result is similar to that of Breghendal et al.[4] In most other studies, there is no difference between both sexes.[2] A report on the prevalence of LARS in the general population did show a predominance of females.[26] New research will be required to confirm this finding in our population.

Limitations

This work has important limitations. First of all, it is a retrospective study with a small sample number, which may explain some differences not found when processing the statistical analysis. Although the comparison of the characteristics between the included and excluded patients showed that our sample is representative, the loss of susceptible cases for the analysis was also important. Another limitation was not having an associated quality of life analysis.

CONCLUSIONS

The results of our study show a prevalence of major LARS of 40.6%, in accordance with that reported by international publications.

Among the predisposing factors, the relationship with radiotherapy and total excision of the mesorectum stand out, variables of weight in determining the syndrome. Of the few measures that can be modified by the surgeon, excluding decisions based on oncological criteria, the selection of the type of anastomosis does not seem to be decisive.

Therefore, according to the evidence available in this study, once the resection of the rectum has been decided, there do not seem to be any strategies that can prevent the appearance of major LARS.

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