Original Article

LOW ANTERIOR RESECTION SYNDROME, A PREDICTABLE COMPLICATION?

O SÍNDROME DA RESSECÇÃO ANTERIOR BAIXA É UMA COMPLICAÇÃO PREVISÍVEL?

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ABSTRACT

Introduction: Rectal cancer is the fifth most frequent neoplasm in both sexes in Portugal. With the evolution of preoperative imaging tests, surgical techniques and neoadjuvant therapy, anterior rectal resection (ARR) has become the gold standard in the treatment of this condition. Nevertheless, functional outcomes arise, namely the development of Low Anterior Resection Syndrome (LARS). It is defined as LARS major when the LARS SCORE is calculated and a value greater than 30 is obtained. This study aims to determine the incidence of LARS in patients undergoing ARR for rectal cancer treatment at the *Centro Hospitalar de Setúbal* and to identify LARS predictors. **Methods:** A cohort retrospective study was conducted in rectal cancer patients electively undergoing ARR, from January 2019 to December 2020. The LARS diagnosis was made by applying the LARS score. Risk factors were assessed using the software SPSS® (Mann-Whitney U test and Chi-square test). **Results:** The studied population consisted of 60 patients, of whom 32 (53.3%) had LARS, and 6 patients (6.6%) had major LARS. Low intestinal anastomosis (ρ <0.001) and ileostomy (ρ <0.001) were identified as statistically significant LARS predictors. **Conclusions:** These results show that some clinical variables should be considered as predictive factors of LARS and need to be evaluated preoperatively when deciding which treatment to perform in each patient's rectal cancer.

Keywords: *rectal cancer, LARS, predictive factors.*

RESUMO

Introdução: O cancro do reto é a quinta neoplasia mais frequente em ambos os sexos em Portugal. Com a evolução dos exames de imagem pré-operatórios, técnicas cirúrgicas e terapêutica neoadjuvante, a resseção anterior do reto (RAR) tornou-se o procedimento de preferencia no tratamento nesta condição. No entanto, podem surgir problemas funcionais, nomeadamente o desenvolvimento da Síndrome de Resseção Anterior Baixa (LARS). Define-se como LARS importante quando o cálculo do SCORE LARS revela um valor superior a 30. Este estudo visa determinar a incidência de LARS em doentes submetidos a RAR para tratamento do cancro do reto no Centro Hospitalar de Setúbal e identificar os seus preditores. **Métodos:** Foi realizado um estudo com uma coorte retrospetiva em doentes com cancro

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do reto submetidos a RAR eletivamente, de janeiro de 2019 a dezembro de 2020. O diagnóstico de LARS foi feito com recurso ao SCORE LARS. Os fatores de risco foram avaliados utilizando o software SPSS® (teste U de Mann-Whitney e teste do Qui-quadrado). **Resultados:** A população estudada consistiu em 60 doentes, dos quais 32 (53,3%) tinham LARS, e 6 doentes (6,6%) tinham LARS importante. A anastomose intestinal baixa (ρ <0,001) e a ileostomia (ρ <0,001) foram identificadas como preditores de LARS. **Conclusões:** Estes resultados mostram que algumas variáveis clínicas devem ser consideradas como fatores preditivos de LARS e precisam ser avaliadas no pré-operatório ao decidir qual o tratamento a realizar em cada doente com cancro do reto.

Palavras chave: *cancro do reto, LARS, fatores preditivos*

INTRODUCTION

According to the 2020 data from the World Agency for Research on Cancer, rectal cancer is the 5th most frequent cancer (both sexes) in Portugal and in about 33% of the cases it affects the distal rectum.[1,2] In the therapeutical approach to rectal cancer, surgical intervention is the only treatment with curative potential, being the main surgical procedures abdominal perineal resection (APR) or anterior rectal resection (ARR).[3,4] With the evolution advance of neoadjuvant treatment and ARR with total mesorectal excision becoming the gold standard of treatment for rectal cancer, there has been an increase in the number of sphincter sparing surgeries performed with a decrease in patients with terminal colostomy.[4,5,6]

The main goals of these patients' surgical treatment are complete excision of the tumor (with tumor-free surgical margin) and respective lymphatic drainage (following the principle of total mesorectal excision); maintenance of intestinal transit continuity and sphincter preservation with low morbidity and mortality rates.[3,7,5] There was always concern about immediate postoperative complications and oncologic outcomes. With the increase in survival, the functional outcomes and long-term quality of life have begun to deserve more interest by surgeons.[2,4,8]

Low Anterior Resection Syndrome (LARS) is defined as the wide spectrum of symptoms after RAR that can compromise the quality of life, including faecal urgency, evacuatory dysfunction, increased flatulence and/or frequency of stools, and stool with a liquid consistency, among others.[2,7,9,8,10]

About 60-90% of patients undergoing ARR develop LARS, and although most resolve after 6-24 months, long-term studies begin to show symptoms after 10-15 years in some patients.[5,11] we designed a prospective study to evaluate the effect of RT and surgery on anorectal function and clinical outcome of patients with a rectal carcinoma.\nMETHODS: Thirty-four patients with a rectal carcinoma participated in this study. They filled out a symptom questionnaire and underwent anal manometry, anal and rectal mucosal electrosensitivity testing, and a rectal barostat, before surgery, 4 and 12 months postoperatively. Thirteen patients were lost to follow-up, 14 underwent surgery alone (total mesorectal excision [TME]

LARS pathophysiology is still poorly understood but it is believed that anatomical and physiological factors affecting defecation may be compromised by performing surgery[12,13] low anterior resection syndrome (LARS The risk factors for developing LARS most frequently described in the literature are: undergoing neoadjuvant or adjuvant radiotherapy, adjuvant chemotherapy, low anastomosis, total mesorectal excision, shunt ostomy, obstructive symptoms and anastomosis complications.[8,12,14,15] also known as low anterior resection syndrome (LARS

The diagnosis of LARS is predominantly clinical and the diagnostic suspicion occurs in the presence

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of at least two symptoms and is confirmed by the persistence of the condition 1 month after surgery (with exclusion of other possible diagnoses for the condition). The LARS Score should be used for severity classification as well as a tool in the therapeutic decision.[2,7]

The treatment of LARS depends on the score: for minor LARS, surgeons opt for pharmacological treatment directed to the symptoms (Loperamide for diarrhoea; serotonin receptor inhibitors in case of postprandial incontinence/urgency; among others); for major LARS, transanal irrigation and pelvic rehabilitation are normally performed.

This study was developed to determine the incidence of LARS in patients undergoing RAR for rectal cancer treatment at Centro Hospitalar de Setúbal, attempting to identify predictors of LARS.

METHODS

Q.1 : 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
Q.2: 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
Q.3: How often do you open our 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
Q.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
Q.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

Figure 1: **LARS Score**

This was a cross-sectional, retrospective, cohort study with patients electively submitted to anterior resection of the rectum for rectal cancer treatment (as described in the operative protocol), from January 2019 to December 2020 in the general surgery service of Centro Hospitalar de Setúbal. Patients' data was collected from the clinical files (telephone contact if incomplete record) referring to the above-mentioned period. The surgical description report was considered to define the performed surgery and the distance of the anastomosis to the anal margin. For the evaluation of TNM staging (including the extent of the tumor (T), extent of spread to the lymph nodes (N), and presence of metastasis (M)), the anatomopathological examination of the surgical specimen was used. The distance between the lower end of the distal tumor growth margin and the dentate line ranged from 2 cm to 7 cm, with a median distance of 4 cm.

The diagnosis of LARS was made based on the LARS score[2], consisting of 5 questions with scores, and a result was obtained. (Figure 1) The LARS score in this study was calculated using clinical records and complemented by telephone interview (after verification of informed consent given or signed by the patients) 3 months postoperatively.

Study Population

All patients with rectal cancer who underwent ARR, regardless of age or gender, and with tumor from 5 to 15 cm from the anal margin were included

Score 0-20	• Absence of LARS
Score 21-29	• LARS minor
Score 30-42	• LARS major

Figure 2: **LARS Score classification**

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in the study. All patients underwent laboratory evaluation colonoscopy, abdominopelvic NMR (Nuclear Magnetic Resonance), and other tests when necessary. Exclusion criteria for this study were unresectable tumors, undergoing APR, or patients with a terminal colostomy or shunt ileostomy on the date of data collection.

Initially, 71 patients were selected, and 11 patients were excluded (figure 3).

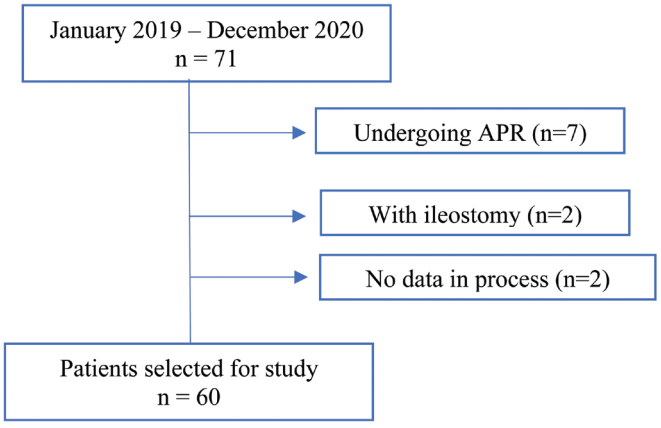

FIGURE 3: **Diagram of patients included in the study**

Statistical Analysis

Data were analyzed using the statistical software IBM SPSS (Statistical Package for the Social Sciences) Statistics 23. For the descriptive characterization of the sample, the mean, median, mode, standard deviation, coefficient of variation, Skewness, Kurtosis, minimum, maximum, first quartile and third quartile values were evaluated in the continuous variables. Whenever necessary, a diagram of extremes and quartiles was evaluated to analyze the existence, or not, of outliers. In the quantitative analysis of the variables, by group, the counts and respective percentages were analyzed.

For group comparison, the hypothesis tests appropriate for each situation under analysis were used, the Mann-Whitney U test, to analyze the existence of statistically significant differences between LARS/age, the Chi-square test, to analyze the independence/dependence of variables LARS/Tumor site, LARS/Presence of preoperative obstructive symptoms, LARS/Chemotherapy, LARS/Radiotherapy, LARS/Low Anastomosis, LARS/Protective Ileostomy, LARS/Anastomosis complications. The odds ratio value was also calculated, to identify which of the variables under analysis had a more intense influence about the LARS variable. A 95% confidence level (5% significance level) was considered throughout the study.

RESULTS

The sample includes 60 patients, consisting of 40 men (66.7%). The average age was 65.2 years, in a range between 39 and 86, with 50% of the sample's central values being between 59 and 75 years, with a moderate dispersion (table 1).

TABLE 1: **Sample characteristics**

	Risk factors	Nr. of patients (%)
Anamnesis	Males	40 (66,7)
	Age > 65	
	Smoking	
	BMI>30 kg/m^2	
	Cardiac disease	
	Diabetes	
	Neurologic alterations	
	DPOC	
	Prior Surgeries	
Preoperative data	Hemoglobin < 12 g/dL	
	Tumour localization	
	Upper	24 (40)
	Midle	24 (40)
	Lower	12 (20)
	Obstructive symptoms	20 (33,3)
Surgical Technique	Derivative stoma	29 (48,3)
	Low anastomosis	18 (30)

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Of the 60 patients evaluated, 32 (53.3%) had LARS, with only 6.6% of patients having major LARS (table 2).

Table 2: **LARS Score (nr of patients/%)**

Classification	nr of patients/%
No LARS	28 / 46,7%
Minor	28 / 46,7%
Major	4 / 6,6%

Table 3: **Sample characterization by LARS concerning age**

	LARS presence		LARS Absence	
Age	Samples's average age		Samples's average age	
	65,39		64,96	
	Minimum	Maximum	Minimum	Maximum
	39	83	44	86

All patients had at least one symptom. The most frequent gastrointestinal complaints were: urgency (51.6%), diarrhea (46.7%), gas incontinence (31.7%), stool incontinence (28.3%) and sensation of incomplete emptying (28.3%).

Table 4: **Comparison of the characteristics of patients with LARS and without LARS (nr of patients/%)**

		LARS presence		LARS absence	
Gender		Male	Female	Male	Female
		22 /36,7%	11 / 18,3%	18 /30%	9 /15%
Tumor Site	Upper	12/20%		12/20%	
	Middle	15/25%		9/15%	
	Lower	6/10%		6/10%	
Obstructive preoperative symptoms		13/21.7%		7/11,3%	
Neo-adjuvant therapies		18 /30%		12/20%	
Lower anastomosis		17 /28.3%		1/ 1,7%	
Protective ileostomy		26 / 43,3%		3 / 5%	
Anastomosis' complications		7 /11,7%		2 / 3,3%	

In the statistical evaluation of the data, the Mann-Whitney test showed that there were no statistically significant differences in the age of patients with and without LARS.

The statistical evaluation showed that the location of the anastomosis has a significant impact on the development of LARS (Chi-square test: $\rho < 0.001$), and that low anastomosis was more associated with the development of LARS. The low anastomosis was defined as those performed less than 5 cm from the anal margin. The data also show, with statistical significance, that the performance of protective ileostomy in rectal surgery is related to a higher prevalence of LARS (Chi-square test: $\rho < 0.001$).

The variables for which no statistical significance was found for the development of LARS are the presence of preoperative obstructive symptoms (Chi-square test $\rho = 0.271$); tumor location (Chi-square test $\rho = 0.635$); performance of neoadjuvant QRT (Chi-square test $\rho = 0.436$); the existence of anastomosis complications (Chi-square test, with Monte Carlo approximation: $\rho = 0.166$), yet all of which are associated with a higher incidence of LARS.

DISCUSSION

Currently, the approach to rectal cancer makes it increasingly possible to perform a greater number of sphincter-sparing interventions, reducing the number of patients with intestinal stoma. Thus, there is a concomitant increase in the prevalence of LARS. The incidence of LARS in this series was 53.3%, in agreement with the values reported in the literature.[7,5,11] we designed a prospective study to evaluate the effect of RT and surgery on anorectal function and clinical outcome of patients with a rectal carcinoma.\nMETHODS: Thirty-four patients with a rectal carcinoma participated in this study. They filled out a symptom questionnaire and underwent anal manometry, anal and rectal mucosal electrosensitivity testing, and a rectal barostat, before

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surgery, 4 and 12 months postoperatively. Thirteen patients were lost to follow-up, 14 underwent surgery alone (total mesorectal excision [TME]

Regarding age, we found a mean age of patients who developed LARS of 65 years, compatible with the data from Scheer et al. [16], among other authors. No difference was found in the mean age of patients with and without LARS.

The fact that most of the patients with LARS are male does not allow us to draw any conclusions, since this is a sample population with more male patients.

The aetiology of the development of LARS is multifactorial. Several factors are described in the literature as being associated with a higher risk of developing LARS. In this study, the construction of a protective ileostomy and the presence of a low anastomosis were identified as risk factors for the development of LARS, which is in line with literature data. The odds ratio shows that a patient with a low anastomosis is about 28 times more likely to have LARS.

Regarding the relationship between performing a protective ileostomy in ARR surgery for the treatment of rectal cancer and its association with the development of LARS, this study concluded that a protective ileostomy is associated with the development of LARS, with an odds ratio of 30, and is, therefore, the variable most strongly associated with the development of LARS. The data in the literature are conflicting, but most studies report protective ileostomy as a predictor of the development of LARS.[12]

Although not statistically significant, neoadjuvant RT was associated with an increased incidence of LARS, as also found in the literature.

Since this was a small sample of patients, the data found, despite being following the state of the art on the subject, cannot be extrapolated to the general population. This study also has the limitations of being a retrospective study with data collection through clinical records.

CONCLUSION

In the evaluation of patients for treatment of rectal cancer, functional outcomes impact on the quality of life of patients has to be taken into consideration.[10] Several studies show that most patients would rather die than have an intestinal stoma and that the long-term presence of LARS is associated with a poorer quality of life. It is important to determine preoperatively which are the risk factors for developing LARS postoperatively so that the patient can be informed and the best therapeutic approach can be chosen together. On the other hand, understanding and identifying risk factors can lead to preoperative prevention of LARS in risk groups. In our study, the small number of patients (60 patients, only 18 with low anastomosis) limits the generalization of the results.

Conflict of interest statement

None of the authors have any potential conflicts of interest to declare.

Ethics declaration

This research was conducted in accordance with the Declaration of Helsink.

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