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## Prediction of anorectal dysfunction in the combined treatment of rectal cancer

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**ABSTRACT** AIM: to assess the risk of severe low anterior resection syndrome (LARS) in patients with rectal cancer after combined treatment.

**PATIENTS AND METHODS:** from July 2022 to November 2023, 50 patients with rectal cancer underwent radiation with a total focal dose of 50–54 Gy with radiomodification with capecitabine and low anterior rectal resection with preventive ileostomy. The ileostomy was closed after 4 months. Prior to and after radiation, the anorectal function was assessed using high-resolution anorectal manometry (HRAM) and the LARS scale.

**RESULTS:** the most significant predicting factors for severe LARS were maximal contraction pressure and first sensation volume. Three months after ileostomy closure, the patients were divided into groups depending on the HRAM parameters. Group 1: nine patients with severe LARS (34 points on the LARS scale), with a decrease in maximal contraction pressure by  $\geq 30\%$  and an increased first sensation volume by  $\geq 60\%$ , according to HRAM. Group 2: four patients out of 36 had severe LARS (31 points on the LARS scale), with a decrease in maximal contraction pressure by 5–29% and an increased first sensation volume by 10–59%, according to HRAM. Group 3: in 5 patients with a decreased maximal contraction pressure by  $\leq 4\%$  and an increased volume of the first sensation by  $\leq 9\%$ , LARS did not develop.

**CONCLUSION:** a decrease in the maximal contraction pressure by 30% or more and an increase in the volume of the first sensation by 60% or more after radiation therapy can increase the risk of severe LARS. This group of patients requires prevention and correction of anorectal dysfunction.

**KEYWORDS:** rectal cancer, low anterior resection syndrome, high-resolution anorectal manometry

**CONFLICT OF INTEREST:** The authors declare that there is no conflict of interest.

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## INTRODUCTION

Colorectal cancer is the third most commonly diagnosed form of cancer, and it accounts for about 10% of all new cancer cases in the world every year [1]. In 2022, the incidence of rectal cancer in Russia is 21.43 cases per 100 thousand people [2]. The combined treatment of rectal cancer has now reduced the risk of recurrence and increased the five-year survival by 20% [3,4]. An organ-preserving strategy, including neoadjuvant chemoradiotherapy and low anterior resection with total mesorectumectomy, ensures the integrity and

functional activity of the rectal sphincter and avoids the need for the lifelong stoma [3].

However, patients receiving combined treatment for local advanced rectal cancer are at risk of anorectal dysfunction in 42% of cases [5]. Systematic reviews consider radiation therapy and low anterior rectal resection with total mesorectumectomy as significant risk factors for impaired defecation [6]. The change in anorectal function is diverse and can manifest itself as rapid stools more than 5 times a day, the appearance of imperative urges, changes in the evacuation function of the rectal sphincter, as well as a deterioration in

the recognition of gases and intestinal contents with the possible development of incontinence [7]. These clinical manifestations, combined in the concept of low anterior resection syndrome (LARS), can occur with varying incidence in patients with rectal cancer, and are associated with a deterioration in the quality of life in 19–52% of patients after combined treatment [8]. Therefore, more and more attention currently being paid to the functional consequences of combined treatment of rectal cancer [9,10]. The severity of symptoms of anorectal dysfunction is reflected in the LARS questionnaire, which separately takes into account the frequency of defecation, imperative urges, cases of incontinence of gases and liquid stools [10,11,19].

An objective assessment of the functioning of the rectal sphincter allows for high-resolution anorectal manometry (HRAM) [12]. Recently, the examination of anorectal function at the stages of treatment is relevant in order to develop individual methods for preventing and correcting LARS.

## THE AIM OF THE STUDY

To assess risk of severe LARS in patients with rectal cancer after combined treatment using high-resolution anorectal manometry (HRAM).

## PATIENTS AND METHODS

The cohort single-center study included 50 patients with local advanced cancer of the middle and low rectum who were treated between July 2022 and November 2023 (Table 1).

The patients underwent remote gamma therapy with a total focal dose of 50–54 Gy to the primary focus and 44 Gy on the path of regional metastasis with radiomodification with capecitabine (1650 mg/m<sup>2</sup> per day orally in two doses on the days of radiotherapy sessions).

In 8–10 weeks after completion of chemoradiotherapy, low anterior rectal resection with total mesorectumectomy and preventive ileostomy was performed. In 4 months or more after this, the

**Table 1.** Patient characteristics

| Indicators                                                       | Patients with local advanced cancer of the middle and low rectum<br>N = 50 |
|------------------------------------------------------------------|----------------------------------------------------------------------------|
| Age, (years), <i>Me (Q1; Q3)</i>                                 | 62 (58; 70.5)                                                              |
| Gender, <i>n (%)</i>                                             |                                                                            |
| Male                                                             | 28 (56)                                                                    |
| Female                                                           | 22 (44)                                                                    |
| Histology, <i>n (%)</i>                                          |                                                                            |
| G1 adenocarcinoma                                                | 20 (40)                                                                    |
| G2 adenocarcinoma                                                | 28 (56)                                                                    |
| G3 adenocarcinoma                                                | 2 (4)                                                                      |
| Distance to the lower edge of the tumor (cm), <i>Me (Q1; Q3)</i> | 6.5 (3;10)                                                                 |

ileostomy was closed. In 3 months after the closure of the ileostomy, the rate of LARS in patients was studied using the LARS questionnaire, and symptoms were assessed in points. According to the LARS scale, severe LARS (30–42 points), weak LARS (21–29 points) or no LARS (0–20 points) were distinguished.

At the stages of the study (before the start of the treatment and in 2 months after completion of chemoradiotherapy), high-resolution anorectal manometry (HRAM) was performed using an 8-channel catheter of the WMP Solar GI device (MMS, Netherlands) to study the functional parameters of the rectal sphincter. The assessment of the level of average pressure in the anal canal at rest was carried out, and when performing functional tests — the levels of average compression pressure and maximum compression pressure with volitional contraction, average and maximum increments of anal compression pressure. To study the sensitivity and reservoir function of the rectum, the first rectal sensation, the volume at the first urge to defecate and the maximum tolerable volume when filling the balloon with air were recorded. When performing HRAM, the greatest changes were observed in the indicators of maximum compression pressure and volume of the first sensation. Normally, the level of maximum compression pressure varies between 78–352 mmHg and the volume of the first sensation is 10–40 ml. Depending on the degree of change in

**Table 2.** *Distribution of patients into groups*

| Group  | The percentage of reduction of the maximum compression pressure from the initial level | The percentage of increase in the volume of the first sensation from the initial level | The degree of severity of manometric indicators |
|--------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------|
| First  | ≥ 30%                                                                                  | ≥ 60%                                                                                  | Severe                                          |
| Second | 5-29%                                                                                  | 10-59%                                                                                 | Moderate                                        |
| Third  | ≤ 4%                                                                                   | ≤ 9%                                                                                   | Minor                                           |

HRAM indicators, patients were divided into three groups (Table 2).

The first group included patients with severe changes in manometric parameters (a decrease in maximum compression pressure by 30% or more from the initial level and an increase in the volume of the first sensation by 60% or more from the initial level). In the second group, patients with moderate HRAM changes were observed (a decrease in the maximum compression pressure in the range of 5–29% and an increase in the volume of the first sensation by 10–59%). Minor changes in the HRAM were observed in patients of the third group (a decrease in the maximum compression pressure by 4% or less and an increase in the volume of the first sensation by 9% or less).

### **Statistical Analysis**

Statistical data processing was carried out using the Statistica 10 package (StatSoft Inc., USA) and RStudio (R v. 4.3.2 (R Core Team, Vienna, Austria)) using the base library. In accordance with the Shapiro-Wilk test, all quantitative variables studied in this work had a distribution different from normal, and therefore were represented by the median (Me) and quartiles Q1 and Q3 in the format Me (Q1; Q3). When comparing the groups, Fischer's two-way exact test was used. The differences were considered statistically significant at  $p < 0.05$ .

## **RESULTS**

Clinical manifestations of anorectal dysfunction ranged from episodes of intestinal discomfort and irregular stools to involuntary defecation. Of the total study group, in 32/50 (64%) cases, liquid stools occurred more often 4 times a day,

40/50 (80%) patients had soiling, impaired differentiation of gases and stools was revealed by 40/50 (80%) patients, 38/50 (76%) patients had manifestations of anal incontinence as episodes of uncontrolled gas discharge and fecal incontinence 12/38 (24%) patients. Generally, LARS developed in 35/50 (70%) cases: 13/50 (26%) patients had severe LARS, 22/50 (44%) patients had minor LARS, 15/50 (30%) patients had no LARS. Incidence of anorectal dysfunction showed that in the first group, among all 9 patients who, according to the HRAM data, had a decrease in maximum compression pressure by 30% or more from the baseline level and an increase in the volume of the first sensation by 60% or more from the baseline level, a severe LARS developed (34 (32;35) points according to the LARS scale). In the second group, where there was a decrease in the index of maximum compression pressure in the range of 5–29% and an increase in the volume of the first sensation by 10–59%, 11% of patients showed severe LARS (32 (31.25;33.5) points on the LARS scale), 61% — slight LARS (23 (22;26) points on the LARS scale), 28% of patients did not develop LARS. In the third group, among all 5 patients in whom, according to the HRAM data, a decrease in the index of maximum compression pressure by 4% or less and an increase in the volume of the first sensation by 9% or more were detected, LARS did not develop (Table 3).

The indicators of the maximum compression pressure and volume of the first sensation and their changes after radiation therapy are shown in Figures 1–3.

Statistically significant differences in the incidence of LARS were detected between groups: the first and second ( $p < 0.0001$ ), the first and third

**Table 3.** The severity of LARS in patients of different groups after ileostomy closure

| Indicator                             | First Group<br>N = 9 | Second Group<br>N = 36 | Third Group<br>N = 5 | p-value            |
|---------------------------------------|----------------------|------------------------|----------------------|--------------------|
| The degree of severity of LARS, n (%) |                      |                        |                      | < 0.0001           |
| Severe                                | 9 (100)              | 4 (11)                 | 0                    | $p_{1-2} < 0.0001$ |
| Minor                                 | 0                    | 22 (61)                | 0                    | $p_{1-3} = 0.0008$ |
| Absent                                | 0                    | 10 (28)                | 5 (100)              | $p_{2-3} = 0.011$  |

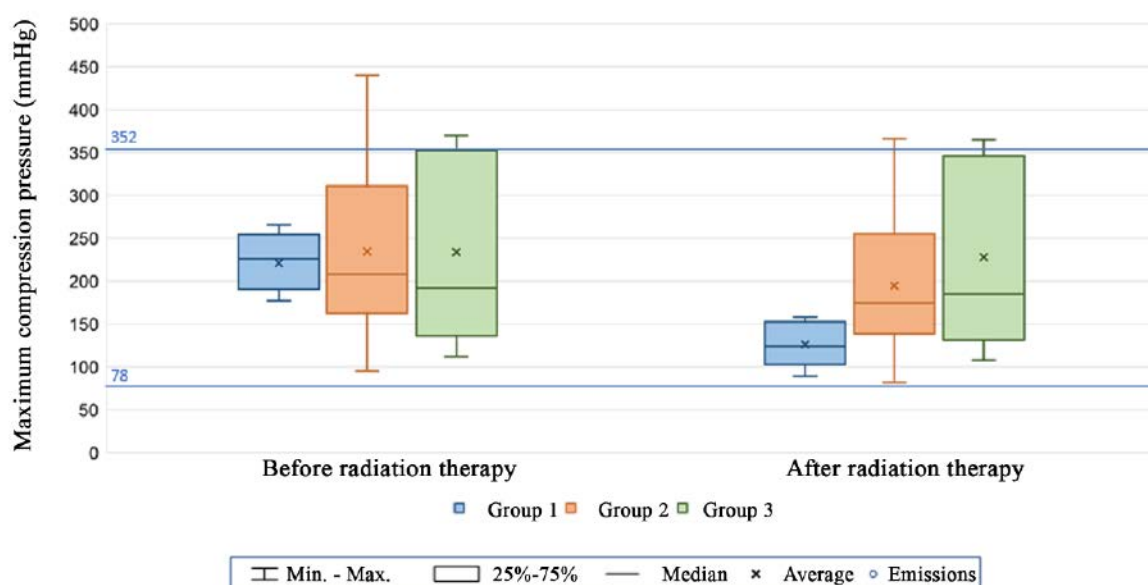
Note: Group comparisons were performed using a two-way Fisher's exact test; in pairwise comparisons, significance levels were adjusted using the Benjamin-Hochberg method

( $p < 0.0001$ ), the second and third ( $p = 0.01$ ). To risk of severe LARS, correlated with decrease of maximum compression pressure by 30% or more from the initial level and increase the volume of the first sensation by 60% or more after neo-adjuvant chemoradiotherapy and low anterior resection.

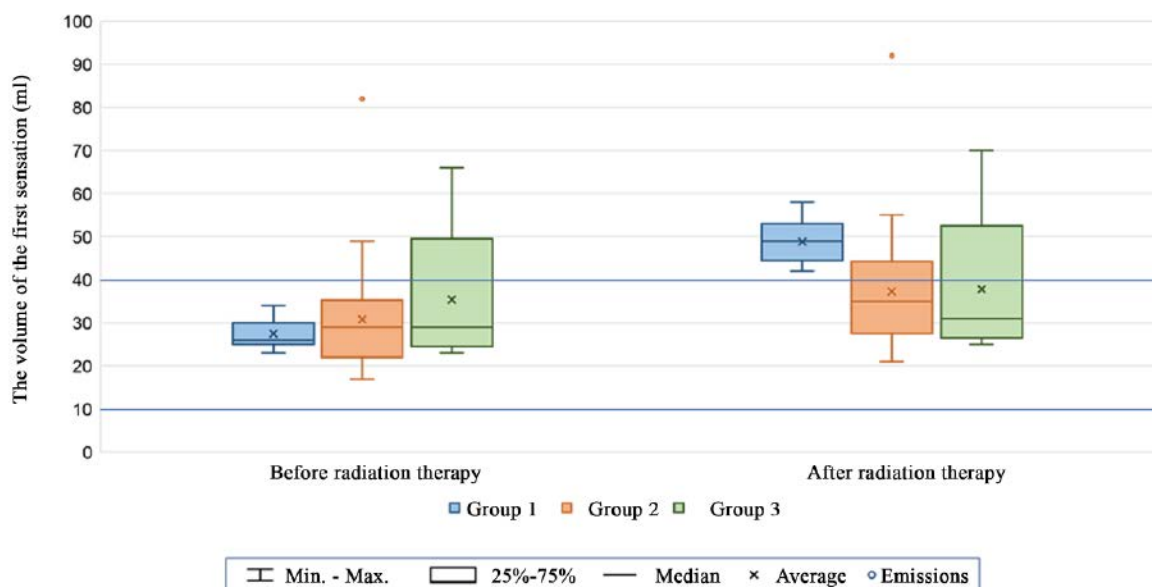
## DISCUSSION

When analyzing the results, its limitations were taken into account. The study involved only patients with cancer of the middle and low rectum, who had undergone combined treatment, which included a prolonged course of radiation. In addition, patients with impaired anorectal function before treatment or who had previously undergone

pelvic surgery were not included in the study. The results are also limited by a small number of cases, and therefore the study will be continued in the future. Anorectal function is a complex physiological mechanism that is maintained by a balance between the level of pressure in the rectum and the coordinated work of the anal sphincters [9,13,14]. The use of combined treatment improves oncological results. However, at the same time it has a negative effect on the functional activity of the anal sphincter. Patients after combined treatment of rectal cancer in the long term may be burdened with persistent symptoms of LARS. It is reliably known that the quality of life of patients correlates with the severity of LARS [15]. Manifestations of anorectal dysfunction may decrease during the first year after completion of

**Figure 1.** Box and whisker plots for the maximum compression pressure indicator in the groups before and after radiation therapy

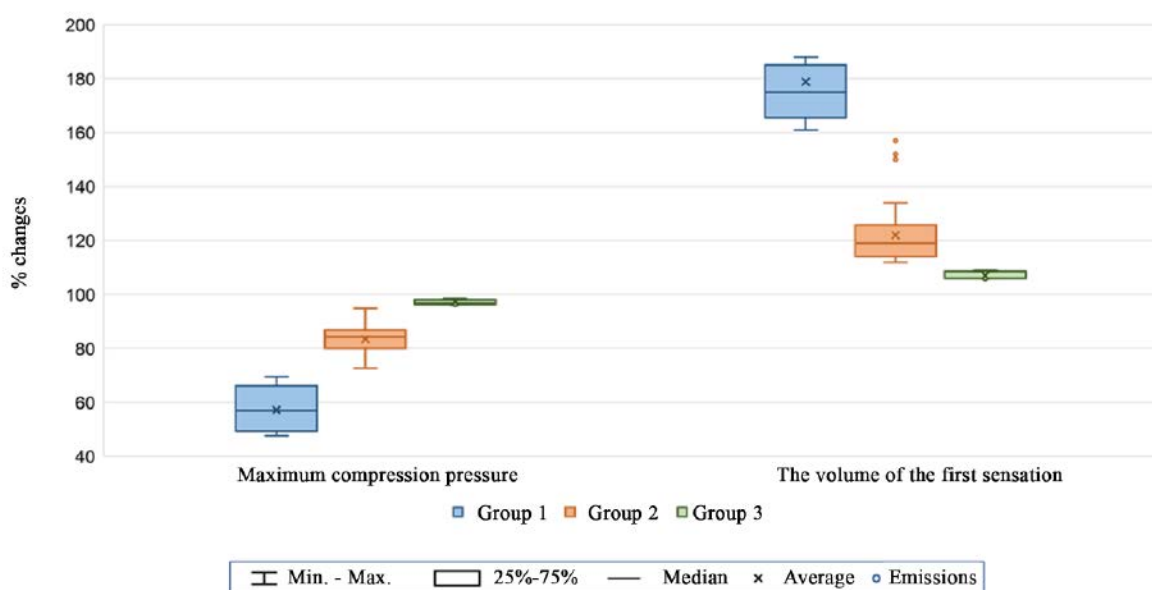
Note: the blue horizontal lines indicate the limits of the reference interval



**Figure 2.** Box and whisker plots for the volume indicator of the first sensation in the groups before and after radiation therapy  
*Note: the blue horizontal lines indicate the limits of the reference interval*

treatment. However, in almost 60% of patients, symptoms persist for more than two years [16]. According to modern literature, radiation therapy and surgery are independent risk factors for the

development of functional disorders and can lead to changes in the work of the internal sphincter, a decrease in the sensitivity of anal canal receptors, a violation of the recto-anal inhibitory reflex,



**Figure 3.** Percentage change in baseline values of maximum compression pressure and volume of the first sensation after radiation therapy

as well as a decrease in the capacity of the rectal stump [13,14]. These consequences limit the anorectal area for a proper continence [17].

In a study by Benli S. et al. (2021), the clinical manifestations of LARS on the LARS scale were analyzed in 276 patients after combined treatment of rectal cancer. A low colorectal anastomosis is indicated as a predictor of LARS (OR = 42.40 (95% CI: 11.14–161.36),  $p < 0.0001$ ). The authors also describe the effect of radiation therapy on anorectal dysfunction (OR = 2.51 (95% CI: 1.38–4.57),  $p = 0.003$ ) [18]. In the study of Nafedzov I.O. (2021), a meta-analysis showed the relationship of the severe LARS with preoperative chemoradiotherapy OR = 5.00 (95% CI: 2.73–9.13),  $p < 0.00001$ , location of the anastomosis below 5 cm from the anal verge (OR = 2.61 (95% CI 1.47–4.62),  $p = 0.001$ ), the preventive ileostomy (OR = 3.32 (95% CI: 1.99–5.55),  $p < 0.00001$ ), the anastomotic leakage (OR = 2.93 (95% CI: 2.30–3.73),  $p < 0.00001$ ), adjuvant chemotherapy (OR = 1.98 (95% CI: 1.23–3.19),  $p = 0.005$ ) [9]. At the level of colorectal anastomosis below 5 cm from the anal canal, the incidence of LARS increased 2.6 times (OR = 2.61 (95% CI: 1.47–4.62),  $p = 0.001$ ).

Luo B. et al. (2021) noted significant lower parameters of anorectal function in 146 patients after low anterior rectal resection compared with a group of healthy individuals [10]. The greatest differences were manifested both in the value of such functional indicators as anal resting pressure, maximum compression pressure, and the threshold volume of the first sensation ( $p < 0.001$ ). The limitations of this work are a small number of healthy patients who did not need surgery. Due to the multifactorial nature of the anorectal dysfunction, more careful monitoring of patients at the stages of treatment is necessary, which could open up new directions in the prevention of LARS. In this study, we found possible criteria for predicting severe LARS according to HRAM indicators. This method makes it possible to predict the severe LARS after radiation therapy and low anterior resection with preventive ileostomy in patients with rectal cancer based on individual

objective indicators of the anorectal function and its changes during radiation therapy. The level of maximum compression pressure and the volume index of the first sensation can serve as informative objective parameters for predictive assessment of the severity of anorectal dysfunction.

## CONCLUSION

A decrease in the maximum compression pressure by 30% or more and an increase in the volume of the first sensation by 60% or more after radiation therapy increase the risk of severe LARS. This group of patients needs prevention and correction of anorectal dysfunction.

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