

## Features of anorectal function after radiation therapy in patients with rectal cancer

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### ABSTRACT

**Purpose of the study.** To study the function of the sphincter in patients with rectal cancer after chemoradiotherapy using the method of high-resolution anorectal manometry.

**Patients and methods.** The study included 30 patients with cancer of the middle and lower ampullary rectum, who underwent combined treatment at the National Medical Research Center of Oncology. The patients underwent a course of neoadjuvant gamma radiation therapy using capecitabine. High-resolution anorectal manometry was performed before the start of treatment and 2 months after completion of chemoradiotherapy to study the functional parameters of the sphincter apparatus. The severity of anorectal dysfunction was assessed using the Wexner anal incontinence scale.

**Results.** According to high-resolution anorectal manometry, the average pressure of the anal canal at rest decreased by 1.4 times ( $p < 0.05$ ), and the average absolute compression pressure with voluntary contraction decreased by 1.2 times ( $p = 0.0012$ ) after neoadjuvant chemoradiotherapy. A comparative assessment of the maximum absolute compression pressure at this stage of treatment did not allow us to trace a significant difference between its value before the start of radiation therapy and 2 months after its completion ( $p > 0.05$ ). An increase in threshold sensitivity volumes was noted in 23 patients ( $p = 0.16$ ). The use of the Wexner scale didn't show a statistically significant change in the median scores according to the results of patient surveys following the completion of treatment (5.2 vs. 5.5 points,  $p > 0.05$ ).

**Conclusions.** Radiation therapy has an effect on anorectal function, which may contribute to the occurrence of low anterior resection syndrome after surgical treatment. For this reason, it is now necessary to carefully consider the risks of developing anorectal dysfunction. Equally important is the use of methods for the prevention of low anterior resection syndrome for patients who have received combined treatment for rectal cancer.

**Keywords:** low anterior resection syndrome, high-resolution anorectal manometry, neoadjuvant chemoradiotherapy

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## Особенности аноректальной функции после лучевой терапии у больных раком прямой кишки

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### РЕЗЮМЕ

**Цель исследования.** Изучение функции сфинктерного аппарата у больных раком прямой кишки после химиолучевой терапии с помощью метода аноректальной манометрии высокого разрешения.

**Пациенты и методы.** В исследовании принимали участие 30 больных раком среднеампулярного и нижнеампулярного отделов прямой кишки, проходивших комбинированное лечение в ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации. Пациентам выполнялся курс неоадьювантной дистанционной гамма-терапии с применением капецитабина. Для изучения функциональных параметров сфинктерного аппарата выполняли аноректальную манометрию высокого разрешения до начала лечения и через 2 мес. после завершения химиолучевой терапии. Степень выраженности аноректальной дисфункции оценивали с использованием шкалы анальной инконтиненции Wexner.

**Результаты.** После проведения неоадьювантной химиолучевой терапии по данным аноректальной манометрии высокого разрешения показатель среднего давления анального канала в состоянии покоя снижался в 1,4 раза ( $p < 0,05$ ), а среднее абсолютное давление сжатия при волевом сокращении уменьшалось в 1,2 раза ( $p = 0,0012$ ). Сравнительная оценка максимального абсолютного давления сжатия на данном этапе лечения не позволила проследить достоверного отличия между его значением до начала лучевой терапии и через 2 мес. после ее завершения ( $p > 0,05$ ). У 23 пациентов было отмечено увеличение пороговых объемов чувствительности ( $p = 0,16$ ). Применение шкалы Wexner не показало статистически значимого изменения медианы баллов по результатам опросов пациентов после завершения лечения (5,2 против 5,5 баллов,  $p > 0,05$ ).

**Заключение.** Лучевая терапия оказывает влияние на аноректальную функцию, что может способствовать возникновению синдрома низкой передней резекции после хирургического лечения. По этой причине в настоящее время необходимо учитывать риски развития аноректальной дисфункции. Не менее важным является использование методов профилактики синдрома низкой передней резекции для больных, получивших комбинированное лечение по поводу рака прямой кишки.

**Ключевые слова:** синдром низкой передней резекции, аноректальная манометрия высокого разрешения, неоадьювантная химиолучевая терапия

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## INTRODUCTION

In 2020, 1,931,590 new cases of colorectal cancer and 935,173 deaths were detected worldwide, while in Russia these morbidity and mortality rates were 77,213 and 42,079 cases, respectively [1]. Statistical data indicate that the problem of diagnosis and treatment of rectal cancer continues to be relevant.

The standard of treatment for patients with locally advanced cancer of the middle and lower ampullary parts of the rectum is neoadjuvant chemoradiotherapy followed by surgical treatment with total mesorectumectomy. An important aspect in the treatment of rectal cancer remains an organ-preserving strategy using nerve-sparing techniques [2]. Maintaining the integrity and functional activity of the sphincter avoids the need for the formation of a lifelong colostomy and improves the quality of the patients' lives [3].

The use of radiation therapy at the first stage of combined treatment can reduce the risk of local recurrence by reducing the size of the tumor process and improve the long-term survival of patients [4, 5]. Modern modified radiation therapy not only reduces the size of the primary tumor, but also reduces the area of radiation for surrounding tissues [6]. Nevertheless, neoadjuvant chemoradiotherapy may negatively affect the work of the sphincter of the rectum [7]. Due to the increase in the number of sphincter-preserving surgical interventions and non-adjuvant radiation therapy in recent years, more and more attention has been paid to functional results [8, 9]. Systematic reviews consider radiation therapy as one of the significant risk factors for intestinal dysfunction [10].

According to a number of authors, the effect of radiation therapy is associated with the development of fibrous changes in structures and tissues exposed to radiation [6, 11]. By reducing the elasticity of the rectum by thickening its wall, radiation therapy leads to a deterioration in long-term functional results [12]. When the primary tumor is located close to the anal canal, the sphincter apparatus is often also in the field of high radiation doses, which can affect the tone of the sphincters, reducing the contractility of the locking apparatus [10].

Changes in the functioning of the sphincter apparatus may include an increase in the frequency of urges and a deterioration in the control of gas

discharge and defecation with the possible development of incontinence [13]. Similar clinical manifestations may occur with varying frequency in patients with rectal cancer after low anterior resection [14]. Therefore, it is relevant to study anorectal function at different stages of treatment in order to develop individual methods for preventing the development and correction of these symptoms.

The anorectal dysfunction symptom assessment system includes various questionnaires, the most widely used of which are the low anterior resection syndrome and Wexner scales. In the analysis of the randomized clinical trial of FOWARC, neoadjuvant radiation therapy was associated with a worse low anterior resection syndrome score and quality of life [15]. However, the question of the effect of neoadjuvant therapy on functional outcomes in patients after combined treatment of rectal cancer currently remains controversial.

An objective assessment of the function of the sphincter apparatus of the rectum can be obtained by performing high-resolution anorectal manometry. This method of investigation represents the pressure distribution in the anal canal, both at rest and when performing physiological tests. The advantage of high-resolution anorectal manometry is the use of a higher physiological resolution created by the increased density of sensitive sensors and their location around the circumference [16]. High-resolution anorectal manometry displays changes in anorectal activity at rest and with various functional tests in the form of a colored contour graph [17].

**The purpose of the study:** to study the indicators of the functional state of the sphincter apparatus in patients with rectal cancer after chemoradiotherapy using the method of high-resolution anorectal manometry.

## PATIENTS AND METHODS

The analysis of changes in the anorectal function of the sphincter was performed in patients undergoing observation and treatment in the period from 2022 to 2023 at the National Medical Research Center for Oncology, Ministry of Health of the Russian Federation. The study included 30 patients with a confirmed diagnosis of cancer of the middle and lower ampullary rectum. At the time of treatment, the average age of patients was 63.2 years

(patients ranged in age from 40 to 76 years). At the same time, 60 % of men (18 patients) and 40 % of women (12 patients) were men. According to the results of histological analysis, adenocarcinoma with a predominance of a moderately differentiated tumor form was observed in patients (56.7 %). In 16 patients (53.3 %), the primary tumor site was located at a distance of < 5 cm from the anorectal junction. The median distance from the lower edge of the tumor to the anodermal junction was 6.5 cm (3–10 cm).

Patients underwent conformal remote radiotherapy with a single focal dose of 2 Gy 5 times a week to a total focal dose of 50–54 Gy per primary tumor focus and 44 Gy on the path of regional metastasis. Radiation therapy was accompanied by modification with capecitabine at a dosage of 1,650 mg/m<sup>2</sup> per day orally in two doses on the days of the sessions.

To study the functional parameters of the rectal sphincter, high-resolution anorectal manometry was performed using water perfusion technology with an 8-channel catheter of the WMP Solar GI device (MMS, Holland). The study was conducted before the start of treatment and 2 months after the end of chemoradiotherapy. Anorectal manometry was performed according to a standard procedure in the position of a patient with bent knee and hip joints. The level of average anal pressure in the anal canal at rest and the levels of average and maximum compression pressure were assessed. 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.

The severity of dysfunction of the sphincter apparatus of the rectum was assessed according to clinical gradation using the Wexner anal incontinence scale. The results of the scale are presented in the form of points from 0 to 20, while intestinal incontinence is established when 12 points or more are scored.

According to the Shapiro-Wilk criterion, the parameters considered in the study had a distribution different from normal. Statistical data processing was carried out using the Statistica 13.0 package. Quantitative data in our study were represented by the median (Me) and quartile values Q1 and Q3 in the Me (Q1 – Q3) format. The nonparametric Mann-Whitney criterion was used to compare the variables of two samples (before and after chemoradiotherapy).

## STUDY RESULTS

Since the onset of rectal cancer in patients, the clinical manifestations of tumor lesions have ranged from episodes of intestinal discomfort and irregular stools to involuntary defecation. Of the total study group, 16 cases (53.3 %) had loose stools more often than 5 times a day, 12 patients (40 %) had false urges to defecate, 7 patients (23.3 %) had manifestations of anal incontinence in the form of cases of uncontrolled gas discharge and 4 of them (13.3 %) had incontinence intestinal contents.

Functional changes in the internal anal sphincter reflect the parameters of resting anal pressure. When comparing the obtained indicators, the level of average anal pressure at rest in patients has decreased by 1.4 times after completion of the course of chemoradiotherapy ( $p < 0.05$ ) (Fig. 1).

A similar trend was observed when estimating the average absolute compression pressure with voluntary contraction. 2 months after the completion of radiation therapy, its index in patients decreased by 1.2 times ( $p = 0.0012$ ). A comparative assessment of the maximum absolute compression pressure at this stage of treatment did not allow us to trace a significant difference between its value before the onset of radiation therapy and 2 months after its completion ( $p > 0.05$ ). The values of the obtained parameters of high-resolution anorectal manometry are presented in Table 1.

Attention was drawn to a decrease in the endurance of volitional contraction and an increase in muscle fatigue during functional tests. Upon completion of chemoradiotherapy, there was a decrease in the median duration of sphincter contraction from an average of 22 seconds from the initial state to 18 seconds. Also, an increase in threshold sensitivity volumes was noted in 23 patients, but no statistical difference was found when comparing these indicators ( $p = 0.16$ ).

The study of anorectal function on the Wexner scale did not show a statistically significant change in the median scores according to the results of patient surveys after completion of the neoadjuvant stage of treatment (5.2 points and 5.5 points before treatment and after radiation therapy, respectively,  $p > 0.05$ ). Before the start of treatment, a minimum score of 2 points on the Wexner scale was observed in 11 patients (36.7 %), while in 7 of them (23.3 %) after

radiation therapy, the minimum threshold increased to 4 points. At the same time, the number of patients with a maximum score of 13 points on the Wexner scale did not change after radiation therapy (13.3 %).

## DISCUSSION

Chemoradiotherapy at the first stage of treatment in patients with cancer of the middle and lower ampullary rectum increases the possibility of performing organ-preserving treatment and improves oncological treatment results by reducing the frequency of local tumor recurrence by less than 6 % [13]. However, along with this advantage, the use of radiation therapy followed by anterior rectal resection and total mesorectectomy is associated with higher rates of intestinal dysfunction [18]. The development of anorectal dysfunction of varying severity after combined treatment of rectal cancer was associated with a deterioration in the quality of life in 19–52 % of patients [19].

There are many works in the modern literature describing a more significant effect of combined treatment on the sphincter apparatus of the rectum compared with surgical intervention [13, 20]. Surgical trauma can cause neurogenic damage to the locking apparatus due to mobilization, especially with low rectal resections [21]. Intraoperative trauma in the form of anal dilation can affect both the external and internal anal sphincters with a transient zone and the so-called "hemorrhoidal cushion" [22]. However, there are much fewer studies providing data

on the direct effect of neoadjuvant radiation therapy on the sphincter apparatus [9, 10]. In this study, the effect of radiation therapy on the function of the sphincter apparatus of the rectum was evaluated in accordance with manometric parameters and clinical manifestations.

Anorectal function is a complex physiological mechanism, an important role in the implementation of which belongs to the sphincter apparatus of the rectum. The activity of the smooth muscles of

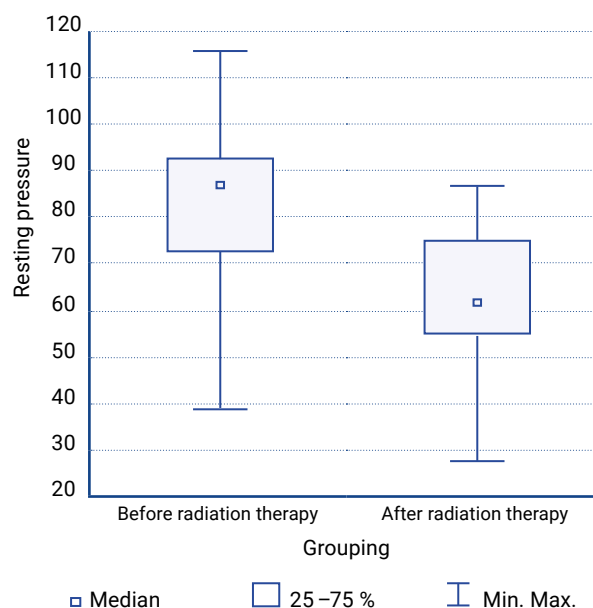


Fig. 1. Comparative assessment of the resting pressure index in the anal canal

Table 1. Parameters of anorectal manometry of the subjects studied during radiation therapy

Parameter	Before the start of treatment Me (Q1; Q3)	After radiation therapy Me (Q1; Q3)	<i>p</i>
Average anal pressure at rest (mmHg)	87 (73; 92)	61 (55; 74)	<i>p</i> < 0.05
Average absolute compression pressure (mmHg)	154 (128; 173)	124 (102; 139)	<i>p</i> = 0.0012
Maximum anal compression pressure (mmHg)	196 (161; 221)	176 (149; 139)	<i>p</i> > 0.05
Endurance Test time (sec)	22 (17; 25)	18 (11; 23)	<i>p</i> > 0.05
Threshold sensitivity volume (ml)	35 (28; 49)	46 (41; 54)	<i>p</i> = 0.16
Threshold sensitivity volume (ml)	35 (28; 49)	46 (41; 54)	<i>p</i> = 0.16



the internal anal sphincter maintains pressure in the anal canal at rest. While the striated musculature of the external anal sphincter and pelvic floor is involved in the implementation of arbitrary contraction, especially over a long period [23]. The coordinated functioning of the anal sphincters and the ampoule of the rectum provides the possibility of adequate implementation of the locking function [24].

The results of the analysis demonstrate a decrease in resting pressure after a neoadjuvant course of radiation therapy, which is confirmed by information from other studies found in modern literature [25, 26]. At the same time, the above data did not reveal a significant change in the work of the external anal sphincter compared with the work of the internal sphincter. Also, several publications showed no changes in the work of the external anal sphincter after radiation therapy [26–28]. However, in our study, a decrease in the average values of anal compression pressure was observed, which can be considered as a possible prerequisite for a decrease in the strength and endurance of arbitrary contraction.

Randomized studies demonstrate a decrease in resting pressure in the postoperative period after neoadjuvant radiation therapy due to deterioration of the internal sphincter [29, 30]. Irradiation is associated with damage to the sacral plexus and with fibrous changes in the muscle fibers of the sphincters [31]. The greater susceptibility to radiation exposure of the internal sphincter compared with the external one may be due to such features as a smaller number of muscle fibers and innervation by a thin network of nerve fibers of the pelvic plexus [28].

Changes in the locking apparatus of the rectum were also noted during morphological examination. Histological analysis revealed damage to the myenteric plexus of the internal anal sphincter, and there was also a tendency to increased collagen deposition in this structure [32].

The pathogenetic aspects of the effect of radiation therapy on the blocking function are studied in many studies. In the work of Rahbari N. N. et al., (2013) it was found that radiation therapy can not only cause difficulties in performing total mesorectomies, but also reduce the ability of irradiated tissues to repair, thereby leading to an increase in a number of complications in patients after low anterior rectal resection [33]. The literature has also described

the relationship between radiation therapy and the development of colorectal cancer failure (Kit O. I. et al., 2018) [34].

On the other hand, the pathogenetic factor of the negative effect of radiation therapy on the function of anal sphincters is vascular fibrosis, pelvic and musculoskeletal plexus [11, 32, 35]. Some researchers describe a malfunction of the function of the internal anal sphincter, which is not even included in the radiation field, which can also affect the capacity and pliability of the rectum [36]. The above facts contribute to the development of anorectal dysfunction and the occurrence of anal incontinence in some of the treated patients.

Irradiation of the rectum causes weakening of the anal sphincter, as well as impaired processing of anorectal sensory stimuli [36]. According to a study conducted by van der Sande M. E. et al. (2019), the relationship between the dose of radiation therapy and the severity of anorectal dysfunction in patients with rectal cancer was monitored [37].

Clinical manifestations of the negative effects of radiation therapy on the function of the rectal occlusion apparatus may be characterized by a specific pattern. Most authors report a higher frequency of loose stools and urge to defecate after radiation therapy, signs of anal incontinence in the form of incontinence of gases and intestinal contents and laundry contamination are less common [13, 26, 28]. However, according to the data obtained in our study, there was no significant difference in the clinical picture before and after radiation therapy. The most frequent complaints, as well as before the start of treatment, were frequent loose stools and false urge to defecate. Only a small number of patients had cases of uncontrolled gas discharge and incontinence of intestinal contents.

De Nardi and co-authors studied 39 patients with rectal cancer before and after radiation therapy. The results of anorectal manometry showed a significant decrease only in resting pressure after the treatment. When assessing incontinence on the Wexner scale before neoadjuvant therapy, 5 patients already had mild incontinence with an average score of 3, and after neoadjuvant therapy, 11 reported incontinences with an average score of 3.8 [38].

When assessing the quality of the function of the sphincter apparatus according to the Wexner scale, no significant difference in the median scores was

noted in our work according to the results of the patient survey. This fact suggests that radiation therapy does not always cause deterioration of clinical symptoms on the part of the evacuation function.

Thus, in our study, changes in the manometric parameters of the internal and external anal sphincters, a decrease in the endurance of contractions of the rectal locking apparatus were not accompanied by significant clinical manifestations. However, the changes we have identified may become a prerequisite for the development of anal incontinence after completion of treatment.

## CONCLUSION

Radiation therapy may affect the function of the rectal occlusion apparatus, especially the internal anal sphincter. These changes may contribute to the formation of low anterior resection syndrome after surgery. For this reason, it is now necessary to consider the risks of developing anorectal dysfunction. Equally important is the use of methods for the prevention of low anterior resection syndrome for patients who have received combined treatment for rectal cancer.

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