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Study of anorectal physiology pre and pos neoadjuvant therapy for rectal cancer by anorectal manometry and Jorge-Wexner score

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ABSTRACT – Background – The treatment of distal rectal cancer may be accompanied by evacuation disorders of multifactorial etiology. Neoadjuvant chemoradiotherapy (NCRT) is part of the standard treatment for patients with locally advanced extraperitoneal rectal cancer. The assessment of anorectal function after long-term NCRT in patients with cancer of the extraperitoneal rectum has been poorly evaluated. **Objective –** The aim of the present study was to evaluate the effects of NCRT on anorectal function and continence in patients with extraperitoneal rectal cancer. **Methods –** Rectal adenocarcinoma patients undergoing neoadjuvant therapy were submitted to functional evaluation by anorectal manometry and the degree of fecal incontinence using the Jorge-Wexner score, before and eight weeks after NCRT. The manometric parameters evaluated were mean resting anal pressure (ARp), maximum voluntary contraction anal pressure (MaxSp) and average voluntary contraction anal pressure (ASp). All patients underwent the same NCRT protocol based on the application of fluoropyrimidine (5-FU) at a dosage of 350 mg/m^2 associated with folic acid at a dosage of 20 mg/m^2, intravenously, in the first and last week of treatment, concomitantly with conformational radiotherapy with a total dose of 50.4Gy, divided into 28 daily fractions of 1.8Gy. For statistical analysis of the quantitative variables with normal distribution, the mean, standard deviation, median and interquartile range were calculated. For comparison of two related samples (before and eight weeks after NCRT), Wilcoxon's non-parametric test was used. **Results –** Forty-eight patients with rectal cancer were included in the study, with a mean age of 62.8 (39–81) years, 36 (75%) of whom were male. The use of NCRT was associated with a decrease in the values of ARp (55.0 mmHg vs 39.1 mmHg, P<0.05) and ASp (161.9 mmHg vs 141.9 mmHg, P<0.05) without changing MaxSp values (185,5 mmHg vs 173 mmHg, P=0.05). There was no worsening of the incontinence score eight weeks after the use of NCRT (3.0 vs 3.3; P>0.05). **Conclusion –** NCRT was associated with a reduction in the values of ARp and the ASp. There was no change in MaxSp, as well as in the degree of fecal continence by the Jorge-Wexner score.

Keywords – Rectal cancer; radiotherapy; chemotherapy; fecal incontinence; evacuation; manometry.

INTRODUCTION

The treatment of local advanced lower rectal cancer has evolved in recent years, reducing the local recurrence rates of 20–45%[1] to 4%[2]. Contributing to these advances are the improvement of knowledge of the biological behavior of the tumor, the better understanding of the lymphatic dissemination pathways of the disease, the use of neoadjuvant chemoradiotherapy (NCRT) protocols, and the introduction of the total mesorectal excision technique (TME)[2-4]. However, although these strategies increase the chance of sphincter preservation, they are related to a series of functional disorders, mainly represented by low anterior rectal resection syndrome (LARS) and disturbance of the fecal continence[5]. Despite sphincter preservation, these functional disorders are associated with worsening patients' quality of life (QOL). It is estimated that 11% and 22% of patients with distal rectal cancer undergoing sphincter-saving resection, require a lifetime definitive stoma, after 10 and 20 years, respectively[6].

The mechanisms involved in the etiology of LARS are not yet fully understood. The loss of distensibility due to partial or total replacement of the rectum by a colon segment with great motor activity, low colorectal or coloanal anastomosis, neurogenic or muscle injuries resulting from surgical intervention, and NCRT may contribute to the occurrence of LARS. Although many patients show progressive symptoms improvement up to 24 months after surgery, it is estimated that 60% to 80% of patients persist with symptoms for the rest of their lives, with worsening QOL[7]. The impact of long-course NCRT on postoperative bowel function and QOL remains controversial. The results of a recent study with 220 patients after a median follow-up of 40.2 months showed that long-course NCRT, along with low anastomosis, are likely independent risk factors for postoperative bowel function and QOL[8].

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Anorectal function is greatly disturbed after rectal surgery with or without radiotherapy (RT)[9,10]. To clarify the underlying mechanisms, studies were designed to evaluate the effect of RT and surgery on anorectal function and clinical outcome of patients with a local advanced lower rectal carcinoma. Most of them showed that anorectal function after rectal surgery with or without RT is greatly hampered because of a decreased rectal compliance especially in those submitted to RT[9,11-14]. These findings might have implications for alleviating LARS and improving QOL by informing selection of neoadjuvant treatment. For this reason, it is imperative that the colorectal surgeon has access to the largest number of tools that allow the identification of patients with rectal cancer who are at a higher risk of developing LARS. To date, only a few studies have prospectively evaluated the effect of rectal surgery and NCRT on both anal and rectal function, including rectal sensation as well as rectal motility[15-17]. Particularly, prospective studies evaluating anorectal function before surgery are lacking; thus, the aim of this study, is to evaluate the preoperative short-term effects of NCRT on anorectal function.

METHODS

Ethics

This prospective controlled study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Campinas (CAAE no 61605916.1.0000.5404), Registry number: 2.245.538. All participants read and signed a written informed consent form for study participation.

This study was carried out in the Gastrocentro Multidisciplinary Rectal Cancer Outpatient Unit (Colon and Rectal Surgery Unity, Faculty of Medical Sciences of the State University of Campinas) from August 2018 to July 2019. Anorectal manometric data and clinical evaluation regarding fecal incontinence were collected before and eight weeks after NCRT in patients with extraperitoneal adenocarcinoma of the rectum, confirmed by histopathological analysis. The tumor level was defined by magnetic resonance imaging (MRI) before NCRT. Local stage was determined by MRI according to the American Joint Committee on Cancer Staging System (AJCC 7th edition). Indications for NCRT were all T3, T4, N+ or T2N0 below the anorectal ring. The protocol for neoadjuvant radiotherapy with conventional fractionation was as follows: 1.8 Gy per day (five fractions per week) and total dose, 50.4 Gy/28 fractions (45 Gy/25 fractions initially to the whole pelvis, followed by 5.4 Gy/3 fractions as a boost to the gross tumor), and two cycles of concurrent chemotherapy with RT (5-fluoropyrimidine [5-FU], 350–400 mg/m^2 [IV] 1 h before RT and leucovorin, 20 mg/m^2 [IV] immediately before each dose of 5-FU, on days 1 to 5 and days 29 to 33). Patients with adenocarcinoma of the rectum, and candidates for neoadjuvant therapy were included in this study; and patients who had undergone RT and previous pelvic surgery for other diseases, patients who had lesions that invaded the anal canal, were under 18 years of age, and who had degenerative neuromuscular diseases were excluded.

Anorectal manometry was always performed before NCRT and eight weeks after the end of NCRT with the water-perfusion technique using an 8-channel micro tip axial catheter connected to a perfusion pump (MULTIPLEX-AR; Alacer Biomédica, São Paulo, Brazil). The channels were arranged in a spiral shape and 5 mm apart, with a latex balloon at their end.

Manometric data including resting pressure (RP) and maximum squeezing pressure (MSP) were evaluated. For the evaluation of RP, the average pressure of the anal canal, measured in the four central channels for 60 seconds and called average value of the resting pressure (ARp), was considered. For the evaluation of the voluntary contraction pressure, the average of the maximum squeeze pressure measured in the four central channels was calculated, and was called the average value of squeeze pressure (ASp). For evaluation of the maximum squeeze pressure, the highest value of the pressure of contraction was considered, denominated as maximum squeeze pressure (MaxSp). All manometry procedures were performed by an experienced single practitioner who had been performing anal physiologic tests for over five years. The grade of incontinence of the patients before and eight weeks after NCRT was stratified according to the Jorge-Wexner classification (CHART 1)[18]. The questionnaire to assess the degree of continence was always applied by the same researcher.

CHART 1. Jorge-Wexner – Continence Grading Scale.

Type of incontinence	Frequency				
	Never	Rarely	Sometimes	Usually	Always
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Wears pad	0	1	2	3	4
Lifestyle alteration	0	1	2	3	4

z0: perfect; 20: complete incontinence; never: 0 (never); rarely: <1/month; sometimes: <1week, ≥1 month; usually: <1/day ≥1/week; always: ≥1/day.

The continence score is determined by adding points from the above table, which considers the type and frequency of incontinence and the extent to which it alters the patient's life.

For statistical analysis of the quantitative variables with normal distribution, the mean, standard deviation (SD), median and interquartile range were calculated. For comparison of two related samples (before and eight weeks after NCRT), Wilcoxon's non-parametric test was used. The data were analyzed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corporation, Armonk, NY, USA). The statistical significance considered was 5% (P<0.05).

RESULTS

Fifty-one patients who underwent anorectal manometry and clinical evaluation using the Jorge-Wexner score before and after neoadjuvant therapy were eligible for the study. Three patients were excluded from the final analysis, one for previous diagnosis of myasthenia gravis not informed previously and two for not signing the consent form.

Of the 48 patients included, 36 were male (75%) with average age of 62.86 years (39–81 years). The average body mass index (BMI) was 27.84±5.58 kg/m^2. (TABLE 1). Four (8%) patients had diabetes mellitus (DM), 23 (47.9%) had systemic arterial hypertension. Four men also had coronary disease (11.1%), one previous history of stroke (2.8%) and three (8.3%) with other comorbidities (TABLE 1). Among women there were no other comorbidities, and regarding the obstetric history, only one patient was nulliparous. Regarding TNM staging by MRI, most patients were classified as T3, and four had no information (TABLE 2).

TABLE 1. Demographic variables.

Gender	N
Men	36 (75%
Woman	12 (25%)
Age (years)	62.8 (39–81)
BMI (kg/m^2)	27.84±5.58
Comorbidities	
Systemic arterial hypertension	23 (47.9%)
Diabetes mellitus	4 (8.0%)
Coronary diseases	4 (11.0%)
Stroke	1 (2.8%)
Others	3 (8.3%)

TABLE 2. TNM staging by magnetic resonance imaging.

	N0	N+	Total
T2	3	4	7
T3	9	27	36
T4	0	5	5

Manometric values and continence score before and after neoadjuvant chemoradiotherapy are shown in Tables 3 to 8.

Manometric values and continence score before and after NCRT are shown on TABLES 3 to 8.

DISCUSSION

The adoption of neoadjuvant chemoradiotherapy for the treatment of locally advanced extraperitoneal cancer of the rectum, in addition to the benefits regarding better oncological control of the disease, increased the possibility of sphincter preservation[19,20]. However, despite the better oncological outcomes and greater possibility of sphincter preservation, the use of NCRT followed by anterior resection of the rectum with TME was associated with higher rates of bowel dysfunction, mainly represented by fecal incontinence[13,21]. Similar to what happens with patients with prostate, cervical, and bladder cancer treated by RT, patients with locally advanced rectal cancer when submitted to NCRT have a higher incidence of functional disorder, mainly represented by fecal incontinence, urgency, and increase of the evacuation frequency[22,23]. It has been shown that severe dysfunctions are significantly associated with the use of long-course NCRT protocols used in tumors of the lower third of the rectum, especially when associated with colorectal or coloanal anastomoses[24]. In a systematic review of nine studies, Krol et al.[25] evaluated the anorectal function after RT in patients with prostate cancer; in six studies there was a significant decrease in anal pressure at rest, and five studies observed a reduction in voluntary contraction pressure. These results were similar to those found in the present study, even with differences between application techniques and RT dose and the time of anal function assessment after treatment.

The unique effects of neoadjuvant therapy on anorectal function are poorly evaluated. Some recent studies have evaluated the anorectal function of patients treated exclusively by NCRT, and demonstrate that these patients suffer less functional alterations than patients undergoing NCRT and surgery[26]. Thus, in the present study, we sought to evaluate the exclusive action of NCRT

TABLE 3. Manometric values before neoadjuvant chemoradiotherapy.

	Men (mm/Hg)	Women (mm/Hg)	*P*
Arp			
Median (min-max)	51.1 (20.2–94.5)	63.5 (20.6–88.3)	>0.05
Asp			
Median (min-max)	172.6 (63.7–314.8)	140.4 (57.8–194.4)	<0.05
MaxSP			
Median (min-max)	199.9 (68.6–261.3)	159.0 (65.1–234.8)	<0.05

Values are present as median (interquartile range). Arp: resting anal pressure; Asp: average value of squeeze pressure; MaxSp: maximum squeeze pressure.

TABLE 4. Grade of continence in men and women and in all patients before the treatment with neoadjuvant chemoradiotherapy.

	Men (n=35*)	Women (n=12)	*P* (total=47)
Median (min–max)	1.0 (0–12)	2.5 (0–14)	>0.05

Values are present as median (interquartile range). *1 was not evaluated.

TABLE 5. Manometric values after neoadjuvant chemoradiotherapy.

	Men (mm/Hg)	Women (mm/Hg)	*P*
Arp			
Median (min-max)	39.8 (14.4–70.2)	42.4 (18.6–64.2)	>0.05
Asp			
Median (min-max)	139.0 (47.4–273.0)	131.9 (40.2–184.0)	>0.05
MaxSP			
Median (min-max)	168.5 (62.2–299.0)	152.4 (49.6–229.8)	>0.05

Values are present as median (interquartile range). Arp: resting anal pressure; Asp: average value of squeeze pressure; MaxSp: maximum squeeze pressure.

TABLE 6. Grade of continence in men and women and in all patients after the treatment with neoadjuvant chemoradiotherapy.

	Men (n=33*)	Women (n=12)	Total (n=45)
Median (min–max)	1.0 (0–18)	0 (0–8)	>0.05

Values are present as median (interquartile range). *3 patients were not evaluated.

TABLE 7. The results of the values of Arp, Asp and MaxSP comparing the results before and eight weeks after neoadjuvant chemoradiotherapy.

	Before NCRT	After NCRT	Mean difference	*P*
Arp				
Mean ± SD	55±19.4	39.1±12.8	-15.98	
Median	54.8	40.0		<0.05
Min-max	20.2–94.5	16.4–70.2		
Asp				
Mean ± SD	161.9	141.9±49	-20.01	
Median	161.85	135.3		<0.05
Min-max	57.8–314.8	40.2–273		
MaxSP				
Mean ± SD	185.5	173±54.7	-12.41	
Median	187.8	164		>0.05
Min-max	40.2–299	49.6–299		

SD: standard deviation; min: minimum value; max: maximum value. Arp: resting anal pressure; Asp: average value of squeeze pressure; MaxSp: maximum squeeze pressure.

TABLE 8. Incontinence score (before and after neoadjuvant chemoradiotherapy).

	Before NCRT n=47	After NCRT n=45	Difference	*P*
Mean ± SD	3.3±4.0	3.0±4.6	-0.3	>0.05
Median	2.0	1		
Min-max	0–14	0–18		

SD: standard deviation; min: minimum value; max: maximum value; NCRT: neoadjuvant chemoradiotherapy.

through manometric and clinical data before and after its use in the preoperative period. For the analysis of manometric values, the values published by Papaconstantinou in 2005 were considered as a normality reference[27].

The assessment of resting pressure in four central channels, considering the mean value, represents the most important functional aspect of the internal anal sphincter (IAS), which is the resting pressure of the anal canal. A decrease in resting pressure values was observed after neoadjuvant therapy. Anatomical characteristics of the IAS may explain greater functional susceptibility in relation to the external anal sphincter (EAS), such as less muscle fibers and innervation formed by a thin network of nerve fibers from the pelvic plexus. The correlation of these findings did not correspond to the Jorge-Wexner functional score, even though this was not the object of analysis. It can be assumed that manometric changes are subclinical in a preoperative phase, and that at this time it can be useful to identify patients at higher risk of developing functional problems. Postoperatively, these changes can be accentuated in the form of incontinence, in which surgical trauma can cause neurogenic damage by mobilizing the rectum, sphincter trauma due to distal resections, use of staples, and replacement of the rectum by a segment of colic loop with greater motor activity. The findings of the present study are in agreement with other studies[9,25,28-30] regarding the greater impairment of resting pressure values with the use of neoadjuvant therapy, even considering methodological differences.

In the evaluation of the EAS, two aspects are important in the action of the striated and voluntary muscles for normal continence - the maximum capacity of voluntary contraction that allows to delay the evacuation, relevant in patients with fragmented evacuation, observed in LARS; as well as the maintenance of values of voluntary contraction for longer periods, from 30 to 40 seconds. Carrying capacity was not evaluated in this study, only the maximum pressure values. Several studies[9,29,30] did not show changes in voluntary contraction pressure values. Similarly, it can be inferred from the findings of the present study that the EAS function was less compromised compared to the IAS. However, functional impairment was observed in the mean pressure values in the four channels and this finding can be interpreted as a worsening in the quality of voluntary contraction.

It can be inferred that the impairment of anorectal function after neoadjuvant therapy is secondary to irradiation, which can damage the sacral plexus, the pudendal nerve, in addition to the direct action on the sphincter muscle fibers that could be associated with the occurrence of fibrosis. These findings were described in 1986 by Varma et al.[30] who analyzed ten patients with complaints of bowel dysfunction and who had been submitted to RT for prostate cancer. These were evaluated by anorectal manometry and histological examination and compared with healthy individuals. The results demonstrate an impairment of resting pressure in the RT group ($P<0.001$) and the histological analysis found damage to the myenteric plexus due to greater radiosensitivity of the smooth muscle. The study by Lorenzi et al. in patients undergoing NCRT for rectal cancer, confirmed the susceptibility of the intrinsic innervation and the IAS through histological evaluation[31]. In fact, as in the present study, there was greater functional impairment of the IAS, as it is responsible for up to 80% of the resting pressure. A decrease in resting pressure values in the postoperative period with neoadjuvant radiotherapy was also evidenced by other studies[9,28,29,32].

In a randomized study in patients with rectal cancer, Pollack et al.[32] demonstrated that the use of RT was associated with a higher occurrence of fecal incontinence, fecal leaking type "soiling", higher evacuation frequency, and lower pressure values. Regarding QOL, there was no significant difference in the scores evaluated between the groups. Although the present study did not make a comparison before and after neoadjuvant therapy, it demonstrates that RT impairs the function evidenced by anorectal manometry and a greater occurrence of evacuatory symptoms.

De Nardi et al.[9] evaluated 39 patients with rectal cancer who underwent anorectal manometry and Jorge-Wexner before and after RT, and the results showed a significant reduction only in the resting pressure after neoadjuvant therapy. In the evaluation of incontinence by Jorge-Wexner before neoadjuvant therapy, five patients already had a degree of mild incontinence with a mean score of 3, and after neoadjuvant therapy 11 reported incontinence and a mean score of 3.8. This work is the only work described in the literature with the same methodological design as the current study, and its results are similar to ours regarding resting pressure, maximum contraction pressure, and Jorge-Wexner score.

Study participants with adenocarcinoma of the rectum presented a mild degree of fecal incontinence according to the Jorge-Wexner score, with no variations in the values of resting pressure and voluntary contraction in relation to the normal manometric parameters considered[27].

The findings show functional impairment of the anal sphincter after neoadjuvant therapy and, in agreement with similar studies, greater involvement of the IAS. Although these alterations do not present clinical manifestations in the postoperative period, the

findings may interfere with process related to the indication of neoadjuvant therapy and surgery. Some studies advocate the use of neoadjuvant therapy in tumors with early stages (T1 or T2) because these lesions would respond more favorably and with a greater chance of total histological regression, in up to 50% of cases[33-35]. But the benefits of this therapy in early cases do not improve the results in terms of survival or local recurrence when compared to exclusive surgery, and may add morbidity to these patients[34].

The manometric changes found in the present study were not accompanied by clinical changes. It should be noted that tumor lesion regression, particularly in more distal lesions, may be accompanied by clinical improvement and fewer symptoms such as tenesmus and fecal escape episodes. However, the manifestations of LARS in distal colorectal anastomoses are well known, the most frequent being the occurrence of fecal incontinence, which can occur in up to 97% of cases[36,37].

Aspects related to characteristics such as age, female gender, vaginal births, history of orifical surgeries, diabetes, and obesity are frequent in patients with rectal cancer, and when associated with surgical trauma, increase the occurrence of fecal incontinence. The treatment of rectal cancer allows the prospect of longer survival and thus, QOL acquires a relevant importance. The present study provides information that makes it possible to identify that the action of neoadjuvant therapy in bowel disorders should be considered.

CONCLUSION

NCRT was associated with a reduction in resting pressure values and in the mean value of voluntary contraction pressure. There was no change in the values of maximum pressure of voluntary contraction, as well as in the degree of fecal continence according to the Jorge-Wexner score.

Authors' contribution

Fratta CL and Pinheiro LV performed the manometries, the questionnaires and analyzed the data. Pinheiro LV, Fratta CL and Martinez CAR selected candidates for the neoadjuvant therapy. Fratta CL, Magro DO and Coy CSR performed the statistical analysis and interpretation of data. All authors participated in the elaboration of the paper. All authors participated in the elaboration of the research.

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RESUMO – Contexto – O tratamento do câncer retal distal pode ser acompanhado por distúrbios evacuatórios de etiologia multifatorial. A quimiorradioterapia neoadjuvante faz parte do tratamento padrão para pacientes com câncer retal extraperitoneal localmente avançado. A avaliação da função anorretal após neoadjuvância de longa duração em pacientes com câncer de reto extraperitoneal tem sido pouco estudada. **Objetivo –** O objetivo do presente estudo foi avaliar os efeitos da neoadjuvância na função anorretal e na incontinência em pacientes com câncer retal extraperitoneal. **Métodos –** Pacientes com adenocarcinoma de reto candidatos à terapia neoadjuvante foram submetidos a avaliação funcional por manometria anorretal e avaliação do grau de incontinência fecal pelo escore de Jorge-Wexner, pré e oito semanas após a neoadjuvância. Os parâmetros manométricos avaliados foram pressão anal média de repouso, pressão anal de contração voluntária máxima e pressão anal média de contração voluntária. Todos os pacientes foram submetidos ao mesmo protocolo de neoadjuvância baseado na aplicação de fluoropirimidina (5-FU) na dosagem de 350 mg/m^2 associada ao ácido fólico na dosagem de 20 mg/m^2, por via intravenosa, na primeira e última semana de tratamento, concomitantemente à radioterapia conformacional com dose total de 50,4Gy, dividida em 28 frações diárias de 1,8Gy. Para análise estatística das variáveis quantitativas com distribuição normal, foram calculados a média, desvio padrão, mediana e intervalo interquartil. Para comparação de duas amostras relacionadas (antes e oito semanas após a neoadjuvância, foi utilizado o teste não paramétrico de Wilcoxon. **Resultados –** Quarenta e oito pacientes com câncer retal foram incluídos no estudo, com média de idade de 62,8 (39–81) anos, sendo 36 (75%) do sexo masculino. O uso de neoadjuvância foi associado à diminuição dos valores de média de pressão de repouso (55,0 mmHg vs 39,1 mmHg, P<0,05) e média de pressão de contração voluntária (161,9 mmHg vs 141,9 mmHg, P<0,05) sem alterar os valores de pressão de contração voluntária máxima ((185,5 mmHg vs 173 mmHg, P=0.05)). Não houve piora do escore de incontinência oito semanas após o uso da quimiorradioterapia neoadjuvante (3,0 vs 3,3; P>0,05). **Conclusão –** A neoadjuvância associou-se à redução dos valores de média de pressão de repouso e média dos valores contração voluntária. Não houve alteração nos valores de contração voluntária máxima, bem como no grau de continência fecal pelo escore de Jorge-Wexner.

Palavras-chave – Cancer retal; radioterapia; quimioterapia; incontinência fecal; evacuação; manometria.

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