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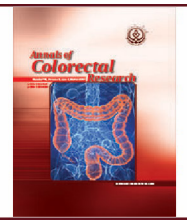

Analysis of Rectal Neoplasms Operated After Neoadjuvant Therapy in A Period of 10 Years

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Abstract

Introduction: With the advances of neoadjuvant chemoradiotherapy, the identification of complete tumor responses, and the reduction of local recurrence even with the adoption of expectant approaches aimed at sphincter preservation, several authors have published results analyzing these aspects with conflicting results. This highlights the need for further investigation. This study aims to evaluate the anatomopathological changes in surgical specimens of rectal resection due to adenocarcinoma in patients undergoing neoadjuvant therapy, including the complete response rate, in addition to estimating the sensitivity and specificity indices of the imaging methods used in the preoperative period.
Methods: This was an observational, retrospective, cross-sectional study in which 44 medical records of patients with cancer of the middle and lower rectum who underwent neoadjuvant chemoradiotherapy and subsequently underwent oncological surgical resections over 10 years were studied. Demographic data, CT scans, colonoscopies, anatomopathological reports and surgical reports were analyzed.
Results: Abdominoperineal resection of the rectum (APR) was performed in 16 cases (36.4%), and abdominal rectosigmoidectomy (AR) was performed in 28 cases (63.6%). Preoperative computerized tomography (CT) showed a sensitivity of 75% and specificity of 77.8% for the detection of lymph node metastases. The complete pathological response to neoadjuvant chemoradiotherapy was found in 11.36% of cases. The local recurrence was detected in 23.9% cases and distant metastasis in 15.2% of the patients in the follow-up period; additionally, there was a 77.7% five-year disease-free survival rate and the overall survival was 73.9%.
Conclusion: The rate of complete pathological response to neoadjuvant therapy was 11.36%. Locally advanced disease and angiolymphatic embolization were associated with a higher frequency of lymph node involvement. CT obtained high rates of sensitivity and specificity in comparison with anatomopathological results.

Keywords: Colorectal neoplasms, Neoadjuvant therapy, Rectal neoplasms, Organ preservation

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Introduction

Colorectal cancer (CRC) is considered the third most prevalent type of cancer in the world and represents the most common neoplasm of the gastrointestinal tract (1, 2).

The treatment of rectal cancer is a challenge for the surgeon as its main objectives are to increase survival and control/decrease local recurrences while simultaneously preserving sexual, bladder, and anal sphincter functions, which significantly impact the quality of life of the patient (3, 4).

It has been demonstrated in the literature that adequate local disease control and decreased pelvic recurrence are achieved with complete surgical removal of the mesorectum (5) through the use of different surgical techniques according to the anatomical characteristics and location of the lesion (4, 6-10).

At the beginning of the 21st century, some prospective randomized clinical trials demonstrated the benefits of neoadjuvant chemoradiotherapy in rectal tumors at clinical stages T3 and T4 with or without apparent lymph node disease. These trials found a decrease in the rates of local recurrence and an increase in disease-free time in those given neoadjuvant therapy compared to those who received adjuvant treatment; less toxic cumulative effects were also seen in the former group (11-13).

A multicenter, prospective, randomized clinical trial with an average follow-up of 12 years was published in 2011 and concluded that there was a significant decrease in the rate of local recurrence in the group undergoing neoadjuvant chemoradiotherapy with a short period at low dosage (5%) in comparison to the group where only the surgical procedure was performed (11%) (P<0.0001), albeit without a significant increase in overall survival (14).

All these different findings and controversial results in the literature related to the strategy for the treatment of rectal malignant neoplasms that fully respond to neoadjuvant therapy indicate the need for further studies to determine the safest and most effective strategy for patient management.

This study aimed to evaluate the anatomopathological changes in surgical specimens of rectal resections due to adenocarcinoma in patients undergoing neoadjuvant therapy. We examined the complete response rate, in addition to estimating the sensitivity and specificity indices of the imaging methods used in the preoperative period.

Methods

In this observational, cross-sectional, retrospective, descriptive and analytical study, information was collected from a secondary database and medical records stored by the Coloproctology Unit for all patients undergoing colorectal oncological surgeries (abdominal rectosigmoidectomy and abdominoperineal resection) between January 2008 and October 2018 at the University Hospital of the Federal University of Santa Catarina (UH-FUSC).

A research protocol was prepared with demographic data of the patients, physical exams determining the distance from the tumor to the anal margin (low rectum: <5 cm, middle rectum: 5.1 to 10 cm, and upper rectum: 10.1 to 15 cm), reports of colonoscopies, laboratory exams, radiological exams, anatomopathological reports, hospitalization data, and outpatient follow-ups.

This study included all patients who underwent elective oncological procedures for rectal adenocarcinoma resection with curative intent operated by the team of colon and rectal surgeons and who underwent neoadjuvant chemoradiotherapy. Patients who underwent noncancer surgery, patients with neoplasms not classified as adenocarcinomas, patients with benign diseases, patients who did not receive neoadjuvant therapy, and those who underwent urgent or emergency surgery were excluded (Figure 1).

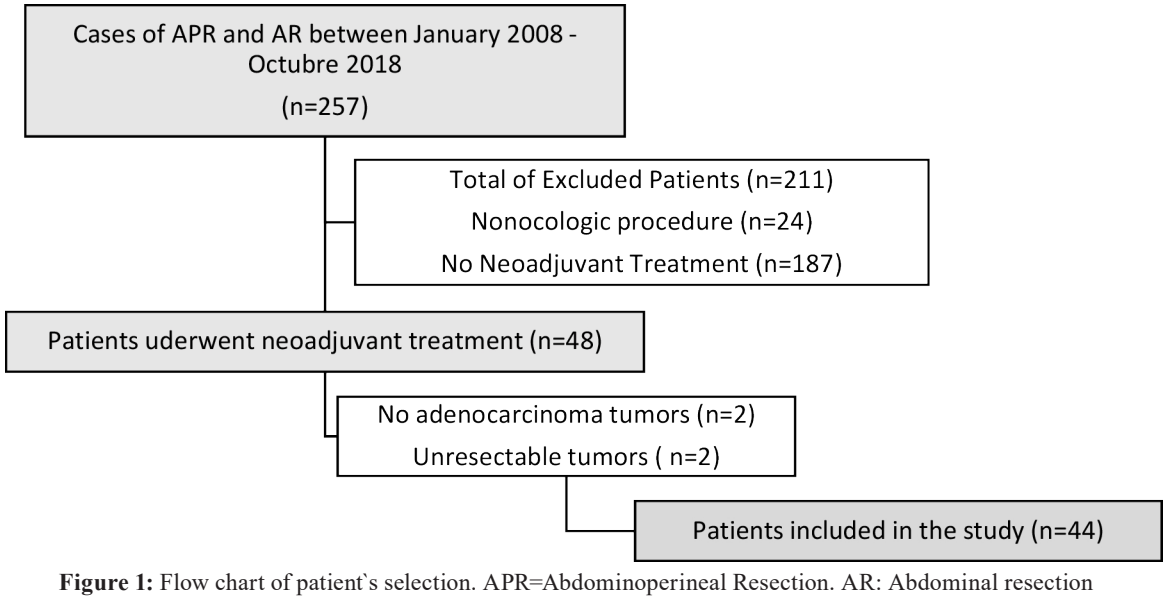

Figure 1: Flow chart of patient`s selection. APR=Abdominoperineal Resection. AR: Abdominal resection

All patients included in the analysis were submitted to a standardized protocol of 6 cycles of chemotherapy with 5-fluoracil (5-FU) and radiotherapy with an accumulated dose of 50.4 Gy fractionated across 28 sessions. The time between the end of radiotherapy and the surgical procedure was 8 to 12 weeks.

All anatomopathological (AP) evaluations of the surgical specimens were performed by the Pathological Anatomy Laboratory of UH-FUSC, describing the classification of TNM, the tumor regression grade (TRG), and the quality of surgical resection of the mesorectum. Ryan`s scale was adopted to assess the TRG, where grade 0 means complete response (without viable cells), grade 1 indicates moderate response with some viable cells or groups, grade 2 means minimal response where there is residual tumor and fibrosis, and grade 3 signifies a weak response and residual tumor with little cell destruction (15).

The database was created using SPSS 20.0 software. Statistical analysis was performed using the EpiInfo V7.2.2.16 program, with the construction of frequency distributions; the presence of an association between the independent variables and the dependent variable was assessed using the Chi-squared test (X^2) for qualitative variables. The normality of quantitative variables was checked using the Kruskal-Wallis test. The P-value considered for statistical significance was 0.05.

The study was approved by the local ethics committee of FUSC (Code: 03604818.4.0000.0121).

Results

A total of 257 medical records of patients who underwent abdominal rectosigmoidectomy (AR) or abdominoperineal resection (APR) at the Coloproctology Unit were analyzed in the determined period, with 44 patients being eligible for inclusion in the study. Among the excluded patients, 187 did not undergo neoadjuvant therapy, 24 underwent non-oncological procedures, two did not have adenocarcinoma, and two were found to have unresectable tumors during the operation (Figure 1).

The age ranged from 16 to 86 years, and the average was 58.7 years, with 27.3% being in the age group below 50 years. The most frequent clinical finding was hematochezia in 75% of cases, followed by abdominal pain in 42.3%, changes in bowel habits in 36.4%, and weight loss in 34.1% (Table 1).

Regarding the primary tumor location, 26 (59.1%) were in the lower rectum, while 18 (40.9%) were in the middle rectum. In two cases of lesions located in the lower rectum, there was macroscopic regression of the tumor after neoadjuvant therapy, which started to be considered in the middle rectum. Sixteen (36.4%) APR and 28 (63.6%) AR were performed in the patients included in the study (Table 1).

The predominant pre-neoadjuvant therapy histological type was moderately differentiated adenocarcinoma (Grade 2) in 68.2% of cases. The postoperative histopathological evaluation showed that in 79.5% of cases, there was complete excision of the mesorectum. The distal and radial margins were considered free in 93.2% of the samples, and the frequency of a distal margin greater than or equal to 2 cm was 47.7% (Table 2).

Table 1: Characteristics of patients related with neoadjuvant chemoradiation therapy for rectal cancer

Characteristics	n (%)
Gender	
Male	25 (56.8)
Female	19 (43.2)
Median age (years)	Mean±SD
Male	57±17.9
Female	61±13.1
Overall	58.72±16
Symptoms	
Abdominal pain	19 (43.2)
Weight loss	15 (34.1)
Anemia	2 (4.5)
Mucus	4 (9.1)
Tenesmus	7 (15.9)
Hematochezia	33 (75)
Bowel habits change	16 (36.4)
Tumor site	
Lower rectum	26 (59.1)
Middle rectum	18 (40.9)
Surgical procedure	
APR[1]	16 (36.4)
AR[2]	28 (63.6)

[1]Abdominoperineal resection; [2]Abdominal resection

The mean number of lymph nodes resected and isolated was 14, and there was no significant difference when comparing the mean lymph nodes of tumors located in the lower rectum with those of the middle rectum (P=0.844). In 15 (34.1%) cases, lymph node metastasis was detected on histopathological examination. There was also no significant difference in the mean number of resected lymph nodes when comparing the two surgical techniques (P=0.575). Regarding the degree and invasion, most tumors were classified as pT3 (54.5%), followed by pT2 (25%). Perineural infiltration was detected in 22.7% and angiolymphatic embolization in 25%, and in 13.6% of the cases, there were tumor deposits in the pericolic adipose tissue. There was no correlation between the number of lymph nodes resected and lymph node involvement (P=1) (Table 3).

A complete pathological response to neoadjuvant therapy was evidenced in 11.6% of the studied specimens and there was a partial response in 54.4%, being classified as Grade 1 or 2, respectively (15). When comparing the degree of response and the location of the pre-neoadjuvant tumor, there was a better response to chemoradiotherapy in tumors of the lower rectum compared to those of the middle rectum (P=0.0346) (Table 4).

Among the patients included in the study, only 22

Table 2: Histopathological features of the specimens resected

Histopathological findings	Cases n (%)	CI 95%
Perineural invasion		
Yes	10 (22.73)	11.47%-37.84%
No	34 (77.27)	62.16%-88.53%
Angyolinphatic embolization		
Yes	11 (25.00)	13.19%-40.34%
No	33 (75.00)	59.66%-86.81%
Nodal metastasis		
Yes	15 (34.09)	20.49%-49.92%
No	29 (65.91)	50.08%-79.51%
Tumoral deposits		
Yes	6 (13.64)	5.17%-27.35%
No	38 (86.36)	72,65%-94,38%
T3/T4 tumors		
Yes	15 (34.09)	20.49%-49.92%
No	29 (6.91)	50.08%-79.51%
Mesorrectum		
Complete	35 (79.55)	64.70%-90.20%
Partially complete	4 (9.09)	2.53%-21.67%
No complete	5 (11.36)	3.79%-24.56%
Microscopic extension		
pT0	5 (11.36)	3.79%-24.56%
pT2	11 (25.00)	13.19%-40.34%
pT3	25 (54.55)	38.85%-69.61%
pT4	4 (9.09)	2.53%-21.67%
Distal margin		
<2cm	21 (47.73)	32.46%-63.31 %
>ou=2cm	23(52.27)	36.69%-67.54%
Mean distance (cm)	1.2	1.7 SD
Ryan`s TRG		
Grade 0	5 (11.36)	3.79% -24.56 %
Grade 1	8 (18.18)	8.19%-32.71%
Grade 2	16 (36.36)	22.41%-22.41%
Grade 3	15 (3.09)	20.49%-52.23%

SD: Standard deviation, CI: Confidential interval, TRG: Tumor Regression Grade

Table 3: Comparison between positive lymph nodes by mean of resected lymph nodes

Patients (n)	Number of resected lymph nodes (mean)	Number of positive lymph nodes (mean±SD)*
7	0-4	0.14±0.38
13	5-9	1.77±2.68
7	10-14	0.71±1.50
6	15 -19	1.66±1.51
7	20 -24	0.28±0.76
2	25-29	0.50±0.50
2	>ou=30	1.00±1.41

*No significant difference between groups (P=1)

contained the reports of the computerized tomography (CT) scans for pre- and post-neoadjuvant staging. In these, lymphadenomegaly findings were described in seven cases after neoadjuvant treatment, and in this group, only three presented lymph node involvement in the histopathological evaluation. This is while in the 15 cases in which no lymphadenomegaly was detected via CT, one had lymph node involvement; this difference was statistically significant (P=0.0209). Local invasion was detected on CT in 8 cases after neoadjuvant treatment, with 2 of them also presenting lymph node involvement on histopathology (P=0.0116) (Table 5).

Local recurrence was detected in 23.9% of patients and distant metastasis in 15.2% of patients in the follow-up period. Additionally, there was a 77.7% five-year disease-free survival rate and the overall survival was 73.9%. There was no mortality in the first 30 postoperative days.

Discussion

The literature has conflicting data related to the monitoring and treatment of patients with rectal

Table 4: Comparison between histhopatological findings and positive lymph nodes

Histopathogical features	Positve lymph node		P
Microscopic extension	Yes	No	
pT0	0	5	0.003
pT2	0	11	
pT3	12	12	
pT4	1	3	
Angyolinphatic embolization			
Yes	8	3	0.0018
No	7	26	
Mesorectum excision			
Complete	12	23	0.8934
Partially Complete	1	3	
No complete	3	2	

Table 5: Comparison between CT findings and histopathological analysis

CT Findings	Histopathological analysis		P
	Lymph Node Metastasis		
Lymphoadenomegaly	**No**	**Yes**	
No	11	1	0.0209
Yes	4	3	
	Local Invasion*		
Local Invasion*	**No**	**Yes**	
No	13	1	0.0116
Yes	6	2	

*Pelvic organs, bones, plexus and muscles.

tumors who achieve a complete clinical response to chemoradiotherapy. In some studies, patients undergoing neoadjuvant chemoradiotherapy showed complete pathological response with total tumor regression, with this finding being dose-dependent and contingent upon the location of the pre-neoadjuvant tumor (16, 17). In this study, there was a better response to chemoradiotherapy in tumors of the lower rectum compared to those of the middle rectum (P=0.0346). The rate of complete response after neoadjuvant chemoradiotherapy varies between 10 to 26% (18-20), causing some authors to recommend intensive clinical monitoring of these patients instead of indicating surgical resection of the rectum as a strategy of initial choice, referring to this as the 'watch and wait' approach (18, 21). According to the literature, there are no statistically significant differences in the rates of local recurrence and distant metastasis (19, 20). Recently, a retrospective study revealed that the complete pathological response can occur only 16 weeks after the end of neoadjuvant therapy, in contrast to the 8-10 weeks usually established for surgical treatment, indicating that further research is necessary to elucidate this tumor's biological behavior after chemoradiotherapy (22).

Notably, a 2010 systematic review with 27 articles showed that disease-free survival is considerably longer when complete responders undergo surgery (P<0.0001), contrasting with the conservative follow-up strategy (23).

The comparison between the genders was similar to the data in the literature, where a higher proportion of male individuals was noted without a significant difference. With regard to age, while in 2010 Brenner et al. found approximately 10% of individuals under 60 years of age, this figure was at 27.3% in our study. One possibility for this is greater access to screening and diagnostic tests, as well as greater clarification of the population that leads to an early search from the beginning of symptoms, or even greater and earlier exposure to risk factors for CRC.

In the evaluation of surgical margins, some consensus recommend 2 cm as a safe distal surgical margin in surgeries for rectal cancer (3); however, more recent articles argue that this value may be lower in patients who receive neoadjuvant treatment (24). In our study, when comparing the frequencies of distal margins <2 cm with the type of surgery performed, we observed a significantly higher proportion in AR (P=0.004). Still, in relation to surgery, complete or almost complete excision of the mesorectum was achieved in more than 79.5% of the surgical specimens, which is consistent with data from the specialized literature in the treatment of rectal cancer, demonstrating a correct approach to oncological resection in our unit.

Several studies have already shown that magnetic resonance imaging (MRI) is the gold standard for CRC staging. In this research, CT demonstrated good results, reaching a sensitivity of 75% and specificity of 59.8%. In a review by Paardt et al., the sensitivity and specificity of MRI for assessing lymph node involvement were 76.5% and 59.8%, respectively. Comparatively, in the criteria adopted here, at CT,

these values were 75% and 77.8%, respectively. In contrast, the literature indicates that for the determination of lymph nodes, the specificity of CT can reach up to 45% (25). Although CT showed statistical significance for the diagnosis of positive lymph nodes (P=0.02) and local invasion (P=0.01), an important bias was the non-standardization of CT scans in the radiologic unit; the evolution of devices over the years, the variation of radiologists who issue the CT reports, the time taken for analysis, and the diversity of patients' origins may affect such findings.

A systematic review in 2019 showed that the perineural invasion rate in the studies analyzed ranged from 5 to 34%, which includes the 22.7% found here. An anatomopathological analysis of 476 rectal cancer patients who did not undergo neoadjuvant therapy showed a lymphatic invasion frequency of 52.7% (32), differing significantly from the 25% found in the present study, which demonstrates a positive effect of neoadjuvant therapy on the prognostic improvement of patients submitted to it. Angiolymphatic embolization maintained a direct relationship with the chance of finding lymph node metastasis on histopathological examination (P=0.0018), in agreement with other studies that made the same correlation (26).

The time interval between the end of neoadjuvant radiotherapy and surgery at the Coloproctology Unit is 8 to 12 weeks. Mancini et al., who included 174 patients who were submitted to the same neoadjuvant scheme used in our study, reported the following frequencies of microscopic tumor extension: pT0: 13.2%; pT1: 13.8%, pT2: 28.7%; pT3: 38.5%; and pT4: 5.8% (26); however, the procedures were performed between six to eight weeks after the end of chemoradiotherapy. Their results are different from those found in this study, i.e., pT0: 11.4%, pT2: 25.0%, pT3: 54.5%, and pT4: 9.1%, probably because there was no case of pT1 and the frequency of invasive tumors (pT3 and pT4) was considerably higher, although the waiting time for surgery after the end of chemoradiotherapy was also longer (8 to 12 weeks) (26). This contrasts with the findings of Harb-Gama et al., who suggested in their studies that rectal neoplasms need a longer waiting time to obtain a complete pathological response (22). The microscopic extent of the tumor also maintained a close relationship with the likelihood of lymph node metastasis (P=0.0034), as already demonstrated by other authors (27).

This study has limitations inherent to the retrospective analysis, such as the difficulties in accessing the imaging and colonoscopy exams of patients who underwent the exams outside the public health system network (even with the integrated telemedicine system), which reduced the number of patients eligible for comparison. It also has a limitation in relation to preoperative staging assessment because MRI or transrectal ultrasound, which have greater sensitivity and specificity for rectal lesions and lymph node evaluation, were not performed due to the high cost and unavailability at our hospital.

However, as the Coloproctology and Pathological Anatomy Units of UH-FUSC present well-established routines of surgical procedures and techniques, in addition to records in reports, surgical descriptions, and medical developments, it is believed that these negative effects have been minimized.

Conclusion

The rate of complete pathological response to neoadjuvant therapy was 11.36% in this study. Adenocarcinomas of the lower rectum had a greater degree of response to neoadjuvant treatment. Locally advanced disease and angiolymphatic embolization were associated with a higher frequency of lymph node involvement. Computed tomography obtained high rates of sensitivity and specificity for comparison with anatomopathological results. Adenocarcinomas of the lower rectum had a greater degree of response to neoadjuvant chemoradiotherapy than those of the middle rectum.

Conflicts of interests: None declared.

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