# Analysis of Clinical and Pathological Prognostic Factors of Survival in Rectal Adenocarcinoma Treated with Preoperative Radio chemotherapy

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## ABSTRACT

**INTRODUCTION**

The treatment of rectal cancer is based on surgery. Pelvic recurrence is accompanied by significant morbidity and worsening quality of life, leading, in most cases, to death. Preoperative radiochemotherapy aims at pathological tumor regression, reducing the risk of local recurrence and the distance from the tumor. The oncological evolution as a function of clinical and pathological factors is not fully understood.

**OBJECTIVE**

To identify the prognostic variables related to the survival of patients operated on for adenocarcinoma of the rectum who underwent preoperative radiochemotherapy.

**METHODS**

We studied 70 patients from the Discipline of Surgical Gastroenterology at Escola Paulista de Medicina - UNIFESP from 2000 to 2019, with rectal cancer located up to 10 cm from the anal verge and with stages II or III, submitted to preoperative radiochemotherapy and curative surgery. (R0) and with follow-up of at least 12 months. Clinical restaging was performed 4 to 6 weeks after the end of neoadjuvant treatment to characterize the degree of clinical tumor regression. Surgery by laparotomy or videolaparoscopy was performed 6 to 12 weeks after neoadjuvant therapy. The primary endpoint parameters were: overall survival (OS), disease-free survival (DFS), metastasis-free survival (MSS), and neoplasm-specific survival (SEN). These outcomes were compared with gender, age, carcinoembryonic antigen (CEA) dosage, distance from the tumor to the anal verge, radiation dose, radiotherapy-surgery interval, clinical regression, type of surgery, pT classification, pN, TNM stage, tumor, number of nodes, circumferential resection margin and complete pathological response. Survival was assessed by Kaplan-Meier curves. Univariate and multivariate Cox analyzes were calculated to identify factors associated with survival outcomes.

## RESULTS

The mean follow-up time was 62 months. The pathological complete response rate was 18.6%. Kaplan-Meier survival curves showed that patients with CEA greater than or equal to 4 ng/mL had worse SLD (p=0.02) and MLS (p=0.009). The pT3/pT4 staging was related to the shorter time of SLD (p=0.002), SLM (p=0.005) and SEN (p=0.01). The lymph node involvement determined a statistically significant difference in OS (p=0.04), SLD (p=0.001), SLM (p=0.007) and SEN (p=0.009). Patients with stages II and III had lower SLD (p=0.04) and SLM (p=0.008). Univariate Cox regression showed a significant relationship of CEA equal to or greater than 4 ng/mL with SLD and SLM, pT3/pT4 staging with SLD, SLM and SEN, pN1/N2 with SLD, SLM and SEN and stages II and III with SLD and SLM. Multivariate regression found that CEA, pT, and pN staging are independent prognostic factors for SLD, SLM, and SEN.

## CONCLUSIONS

Carcinoembryonic antigen level prior to radiotherapy, pT staging and pN staging were independent prognostic factors for survival in patients with rectal adenocarcinoma who are treated with preoperative radiochemotherapy.

## KEYWORDS

Prognostic factors; Rectal adenocarcinoma; Preoperative radiochemotherapy; Univariate Cox regression; Carcinoembryonic antigen level

## INTRODUCTION

Colorectal cancer is a highly prevalent malignancy. The estimated numbers of new colorectal cancer cases in the United States in 2022 will be 151,030 [1]. In 44,850 of these cases, the malignancy would be located in the rectum, and the expected mortality is of 52,580 people.

In Brazil, as predicted by the INCA [2], for the year 2022, 45,630 new cases of colorectal cancer are expected. In 2020, there were 20,245 deaths.

The treatment of rectal cancer is based primarily on surgery. The local recurrence of the malignancy ranges from 20% to 30% and is an indicator of the success of the surgical treatment, since most of the times the recurrence is surgically unresectable [3].

Radiation therapy and chemotherapy are part of the treatment of rectal cancer and aim to reduce the risk of local and distant recurrence and thus increase the time of disease-free survival and reduce the mortality caused by this type of cancer [4].

Preoperative radiation therapy enables the reduction of tumor volume and therefore safer curative surgical resection, decreasing the chances of leaving inadequate circumferential margins. In the absence of surgical manipulation, the blood supply and oxygenation level of the tumor tissue are preserved, making it up to three times more sensitive than tissue with fibrosis. Sterilization of tumor cells from perirectal tissues and malignant cell aggregates in the lymphatic ducts and tissue spaces reduce tumor spread and prevent local recurrence. In the postoperative period of rectal abdominoperineal resection (APR), there is some risk of actinic complications in the small intestine. Obtaining a distal margin to the tumor may enable sphincter preservation surgery instead of resection of the rectum [5-9].

The disadvantages are related to the loss of reliability of the pathology staging due to the changes promoted by radiation and the occasional use of radiation therapy in patients with initial rectal tumors who would not need this type of treatment [10].

Because of the better anatomical knowledge of the dissemination pathways of the rectal cancer, represented by the mesorectum, associated with the good results achieved with radiation therapy associated with preoperative chemotherapy, there was an improvement in curative resection rates for rectal cancer, as well as a significant decrease in the rates of local recurrence, indicating better local control of the malignancy [11-14].

Despite this better local control of the malignancy, many authors have tried to find prognostic markers of response to the radiochemotherapy (RCT) treatment. These predictive factors could predict patients at higher risk of local recurrence and those with better results in terms of survival. The studied markers are based on the patient's clinical characteristics, distance of the tumor from the anal verge, clinical staging, radiation therapy or chemotherapy protocol, degree of tumor regression achieved with the treatment, pathology staging and molecular blood, histopathological and genetic markers. With these markers, one could predict the possibility of a tumor's complete pathological response to radiation therapy, the chance of local tumor recurrence and of disease progression, thus helping both patients and physicians. The knowledge of these markers after neoadjuvant treatment helps the attending physician be better able to predict the patient's prognosis and could make the follow up with greater care.

## OBJECTIVE

Identification of prognostic factors related to the survival of patients with rectal adenocarcinoma undergoing preoperative radiation therapy and chemotherapy and surgical treatment.

## METHOD

The selected cases were patients with rectal cancer treated by the Discipline of Surgical Gastroenterology of the Escola Paulista de Medicina of the Federal University of São Paulo (Unifesp) from 2012 to 2018.

The research was approved by the Research Ethics Committee of Escola Paulista de Medicina – Unifesp after the submission of the project to the National Commission for Research Ethics (CONEP) of the Ministry of Health (National Health Council – Resolution CNS 196/96), according to opinion n. 66.318.

### Research Methodology

The study was conducted with 70 rectal cancer patients who underwent neoadjuvant treatment followed by surgery from November 2012 to February 2018 and followed up for at least 12 months.

Rectal cancer with biopsy of the adenocarcinoma located up to 10 cm from the anal verge with stage II or III in the classification of the American Joint Committee on Cancer [15], with treatment that included preoperative radiation therapy and chemotherapy, followed by curative surgery (R0) with follow-up of at least 12 months. Patients who were unable to complete neoadjuvant treatment for clinical reasons and those in whom palliative surgery was performed (R1 or R2) were excluded, as well as those with synchronous colorectal cancer, cancer in other locations, previous radiation therapy and chemotherapy treatment or those with distant metastases.

The initial clinical staging included clinical examination, laboratory tests, carcinoembryonic antigen (CEA), proctological examination, colonoscopy, CT of the chest, abdomen and pelvis. The radiation therapy used three (posteroanterior and latero-lateral) or four (posteroanterior, anteroposterior and latero-lateral) irradiation fields according to the dose distribution in the target volume and in normal tissues, with a dose of 45 Gy and boost of 5.4 Gy, completing a total dose of 50.4 Gy. The treatment was administered daily, 5 times a week, for 5 weeks, with a fraction of 1.8 Gy per day, with weekly assessment. The chemotherapy regimen provided for the bolus delivery of 5-fluorouracil (5-FU) at a dosage of 325 mg/m2/day and

folinic acid at a dosage of 20 mg/m2/day at the first and last week of radiation therapy. With the exception of patients with complete pathological response, all patients received postoperative chemotherapy treatment. The drugs and dosages used were the same, starting 4 to 6 weeks after surgery and administered once a week for 6 months. During chemotherapy treatment, patients were assessed every two weeks with clinical examination and laboratory analysis.

Clinical restaging was done 4 to 6 weeks after the end of the neoadjuvant treatment. The new clinical staging was done to discover the degree of tumor regression.

In order to assess the clinical response to the neoadjuvant treatment, a regression scale was created based on the change in lesion size, distance from the anal verge and mobility, which was stratified in 5 grades, as described below:

Grade 0: no change

Grade 1: regression up to 25%

Grade 2: regression from 25% to 50%

Grade 3: regression from 50% to 75%

Grade 4: regression greater than 75%

Surgeries were performed at intervals that ranged from 6 to 12 weeks, using laparotomy or laparoscopy. All of them observed the mesorectum dissection rules described by Heald et al. [16]. Three types of operative procedures were performed: local resection (LR), lower anterior resection (LAR) with colorectal anastomosis or rectal abdominoperineal resection (APR). The option of local resection of the rectal lesion was made when the patient did not accept a definitive colostomy or when the surgeon, upon finding a small lesion in the rectum with negative previous biopsy, performed a complete excisional biopsy of the lesion. The operative procedure of this excision always followed the technical principles of local resection of rectal cancer, with removal of the lesion in its full

thickness from the rectum wall, repair of the specimen in a cork piece and identification of the edges for better evaluation by the pathologist.

In the pathological examination of the tumor, the diameter and distance from the distal edge of the specimen were measured, and all lymph nodes were examined histologically. The pTNM staging of the tumor was done according to the depth of penetration into the rectal wall (pT) and the number of compromised lymph nodes (pN). Complete pathological response was considered when no malignancy was found in the specimen (pT0) or in the lymph nodes (pN0). The circumferential resection margin was considered positive when it showed less than 1 mm of the tumor. The grade of pathological tumor regression was based on the scheme proposed by Dworak [17]:

Grade 0: no sign of regression

Grade 1: dominant tumor mass associated with fibrosis and/or vasculopathy

Grade 2: dominant presence of fibrosis with few tumor cells isolated or in groups

Grade 3: rare tumor cells within fibrotic tissue with or without the concomitant presence of mucin

Grade 4: absence of tumor cells, with fibrosis only – total regression.

The outpatient postoperative evolution was assessed every 3 months during the first two years, with physical and proctological examination, CEA, chest CT – abdomen every 6 months and colonoscopy every year. From the third year onward, appointments every six months, and from the fifth year onward, annual CT and colonoscopy.

Local recurrence was defined as the recurrence of the manifestation of the disease inside the pelvis, confirmed by reoperation and surgical resection or biopsy or by finding a lesion in the imaging exams (CT or MRI) that had an increase in size after some time. Distant recurrence or

metastasis were defined as any recurrence outside the pelvic cavity.

The primary endpoint parameters were:

- Overall Survival (OS) – defined as the interval between the start date of radiation therapy until death from any cause or last appointment.
- Disease-free survival (DFS) – defined as the interval between the start date of radiation therapy and the date of detection of any recurrence, either local or distant, or last appointment.

- Metastasis-free survival (MFS) – defined as the interval between the start date of radiation therapy and the date of detection of any distant recurrence or last appointment.
- Cancer-specific survival (CSS) – defined as the interval between the start date of radiation therapy and death from rectal cancer or last appointment.

As secondary endpoint parameters, we studied the relationship of OS, DFS, MFS and CSS with several secondary parameters, which were subdivided for the search for survival-related prognostic factors (Table 1).

| | | Nº | % | | Nº | % |
|---|---|---|---|---|---|---|
| **Gender** | men | 37 | 52,9 | women | 33 | 47,1 |
| **Age group** | < 56,5 | 35 | 50,0 | ≥ 56,5 anos | 35 | 50,0 |
| **CEA ( ng/mL )** | < 4 | 31 | 53,4 | ≥ 4 | 27 | 46,6 |
| **Tumor distance from anal verge ( cm )** | < 5 | 54 | 77,1 | ≥ 5 | 16 | 22,9 |
| **Radiation dose** | 45 Gy | 37 | 52,9 | 50,4 Gy | 33 | 47,1 |
| **Grade of tumor clinical regression** | Grade 0/ 1 | 27 | 38,6 | Grade 2/ 3/ 4 | 43 | 61,4 |
| **Interval RT – surgery ( weeks )** | ≤ 8 | 20 | 28,6 | > 8 | 50 | 71,4 |
| **Type of surgery** | APR* | 46 | 65,8 | ARR/ LRRC* | 24 | 34,2 |
| **Tumor size ( cm )** | < 3 | 34 | 48,6 | ≥ 3 | 36 | 51,4 |
| **TMN staging ( pT )** | pT0/pT1/pT2 | 40 | 57,2 | pT3/pT4 | 30 | 42,8 |
| **TMN staging ( pN )** | pN0 | 57 | 81,4 | pN1/pN2 | 13 | 18,6 |
| **Number of lymph nodes** | < 8 | 23 | 39,7 | ≥ 8 | 35 | 60,3 |
| **TMN staging** | 0/1 | 35 | 50,0 | 2/3 | 35 | 50,0 |
| **Grade of Dworak's pathological tumor response** | Grade 0/1/2 | 45 | 64,3 | Grade 3/4 | 25 | 35,7 |
| **Circumferential resection margin** | Positive | 8 | 11,4 | Negative | 62 | 88,6 |
| **Complete pathological response** | Yes | 13 | 18,6 | No | 57 | 81,4 |

**Table 1:** Secondary outcome parameters related to survival. **Note**: APR - abdominoperineal resection of the rectum; ARR - anterior resection of rectum; LRRC - Local resection of rectal cancer; CEA - carcinoembryonic antigen

*Statistical Analysis*

Continuous asymmetric and normal distribution variables were described with median (interquartile range) and mean ± standard deviation, respectively. Categorical variables were described with absolute and relative frequencies. Survival curves were calculated using the Kaplan-Meier product-limit method and compared with the Log-rank test when the assumption of proportional hazards was satisfied. Otherwise, the Wilcoxon test was applied.

Survival probabilities were estimated with a 95% confidence interval. Cox univariate analyses were calculated and Cox multivariate analyses were performed in order to identify factors associated with survival

outcomes. All the probabilities of significance (p values) presented are bilateral. Values below 0.05 were considered statistically significant. Statistical analysis of the data was performed using SAS 9.3 (Statistical Analysis System, Cary, NC) and R software version 2.15.1.

## RESULTS

The analysis of patient survival has shown that the average follow-up time was 62 months and ranged from 12 months to 134 months. In this period, 16 (22.8%) deaths occurred, ten of which (14.2%) from cancer and six (8.6%) from other causes. The overall recurrence rate was 20%(14 patients). Local recurrence accounted for 4.3%, whereas

distant recurrence accounted for 15.7%, in lungs (6), liver (2), bones (2) and adrenal (1) .

The 5-year survival analysis has shown that (OS) was 75.6% (95% CI 62.2% - 84.9%, (DFS) was 76.4% (95% CI) 63.1% - 85.5%), (MFS) was 77.4% (95% CI 63.8% - 86.4%) and (CSS) was 84.4% (95 CI % 72.0% to 91.6%)

There was no difference in the OS, DFS, MFS and CSS curves regarding gender, age group, tumor distance from the anal verge, radiation dose used, grade of tumor clinical regression, interval between the end of radiation therapy and surgery, type of surgery, tumor size, number of lymph nodes in the specimen, TNM staging, grade of Dworak's pathological tumor response, circumferential resection margin and complete or incomplete pathological response.

Regarding the DFS and MFS curves, when the CEA was greater than 4 ng/mL, the evolution was worse in comparison with patients with CEA < 4ng/mL, with a statistically significant difference.

pT1/pT2 staging in the DFS, MFS and CSS curves has shown better results than pT3/pT4.

All survival curves revealed that the evolution of patients with malignant lymph node involvement was worse, with a statistically significant difference.

The DFS and MFS curves have shown a statistically significant difference between stages 0 and I in relation to stages II and III.

### Research on Prognostic Variables that Influenced Patient Survival

To identify variables related to survival outcomes, Cox's univariate and multivariate analysis was used. In the variables related to overall survival by univariate regression, there was no statistically significant correlation, and therefore multivariate regression was not performed. The variables related to OS, DFS, MFS and CSS with a statistically significant association in the univariate analysis are shown in Table 2. In multivariate regression, CEA prior to radiation therapy, pT staging and pN staging are independent prognostic factors for the patients' DFS, MFS and CSS. (Table 3).

| | p | RR | 95% CI | |
|---|---|---|---|---|
| **Overall Survival** | | | | |
| There was no statistical difference between the variables | | | | |
| **Disease-free survival** | | | | |
| CEA < 4 ng/mL x CEA ≥ 4 ng/mL | 0,021 | 3,635 | 1,214 | 10,88 |
| pT0/pT1/pT2 x pT3/pT4 | 0,0069 | 5,819 | 1,62 | 20,896 |
| pN0 x pN1/pN2 | 0,0036 | 4,755 | 1,664 | 13,585 |
| Staging TNM 0/1 x TNM 2/3 | 0,0134 | 6,62 | 1,481 | 29,595 |
| **Metastasis-free survival** | | | | |
| CEA < 4 ng/mL x CEA ≥ 4 ng/mL | 0,017 | 4,21 | 1,294 | 13,703 |
| pT0/pT1/pT2 x pT3/pT4 | 0,0127 | 5,165 | 1,419 | 18,793 |
| pN0 x pN1/pN2 | 0,0135 | 3,958 | 1,329 | 11,794 |
| Staging TNM 0/1 x TNM 2/3 | 0,0204 | 5,952 | 1,319 | 26,863 |
| **Cancer-specific survival** | | | | |
| pT0/pT1/pT2 x pT3/pT4 | 0,0343 | 5,345 | 1,132 | 25,245 |
| pN0 x pN1/pN2 | 0,018 | 4,471 | 1,293 | 15,462 |

**Table 2:** Analysis of variables related to survival by univariate Cox regression. Note: CEA - carcinoembryonic antigen; APR - abdominoperineal resection of the rectum; ARR - anterior resection of rectum; LRRC - Local resection of rectal cancer; RR - Relative risk; CI - Confidence interval.

| | p | RR | 95% CI | |
|---|---|---|---|---|
| **Disease-free survival** | | | | |
| CEA < 4 ng/mL x CEA ≥ 4 ng/mL | 0,0235 | 3,645 | 1,19 | 11,161 |
| pT0/pT1/pT2 x pT3/pT4 | 0,0162 | 4,827 | 1,338 | 17,411 |
| pN0 x pN1/pN2 | 0,0028 | 5,174 | 1,759 | 15,224 |
| **Metastasis-free survival** | | | | |
| CEA < 4 ng/mL x CEA ≥ 4 ng/mL | 0,0169 | 4,302 | 1,3 | 14,234 |
| pT0/pT1/pT2 x pT3/pT4 | 0,0317 | 4,129 | 1,132 | 15,051 |
| pN0 x pN1/pN2 | 0,0118 | 4,141 | 1,371 | 12,511 |
| **Cancer-specific survival** | | | | |
| pT0/pT1/pT2 x pT3/pT4 | 0,0134 | 5,086 | 1,402 | 18,449 |
| pN0 x pN1/pN2 | 0,0105 | 3,994 | 1,384 | 11,526 |

**Table 3:** Analysis of variables related to SLD, SLM and SEN by Cox multivariable regression. Note: CEA - carcinoembryonic antigen; RR - Relative risk; CI - Confidence interval

## DISCUSSION

In the treatment of rectal cancer, surgery with excision of the mesorectum is the most important therapeutic modality, but the use of radiation therapy associated or not with chemotherapy in the preoperative period has been well studied in the literature.

The Swedish Rectal Cancer Trial [18] and Kapiteijn et al. [11] compared preoperative radiation therapy followed by surgery with surgery alone. In the first study, there was a reduction in local recurrence (27% - 11%) and an increase in survival (overall 48% - 58%). The second author found no improvement in overall survival, but less local recurrence in the irradiated group.

In order to compare the preoperative RCT with that performed in the postoperative period, Sauer et al. [13] studied 823 patients in two groups with preoperative and postoperative RCT. There was no difference in overall or disease-free survival in 5 years. The rate of local recurrence was lower in the group that received preoperative radiation therapy.

Habr-Gama et al. [19], in a sample of 183 patients who received preoperative RCT and a Watch and Wait strategy, found a complete tumor response rate of 49.0%. The 5-year cancer-specific overall survival and disease-free survival for all patients (including all recurrences) were 91% and 68%, respectively.

The synergistic effect of preoperative radiation therapy when combined with chemotherapy was demonstrated by three studies. Boulis-Wasiff et al. [20], when comparing two groups with 247 patients, with isolated RT and preoperative RCT, found better overall survival in the group that received CT (59% vs. 46%). Gerard et al. [21] studied 742 patients and found no difference in overall or disease-free survival. However, patients with RT alone had a higher rate of local recurrence, a lower rate of complete pathological response of the tumor and acute toxicity to the neoadjuvant treatment. Erlandsson et al. [22] demonstrated that the use of RT and CT allows waiting for surgery of 4 to 8 weeks and is oncologically safe.

Valenti et al. [23] did not find differences regarding postoperative complications and mortality in patients who received preoperative RCT and those who received surgery only.

Latkauskas et al. [24] and Abraha et al. [25] carried out a systematic literature review and meta-analysis of preoperative CRT compared to exclusive RT or surgery and concluded that preoperative CRT in stage II and III rectal cancer produces a higher rate of complete pathological tumor response and reduces the rate of local recurrence.

The data in Table 4 show the mean follow-up time, the recurrence rate and the survival rates of different studies in the literature.

|  | Nº | MFU | RR | OS | DFS | MFS | CSS |
|---|---|---|---|---|---|---|---|
| Valentini et al. [26] | 165 | 67 | NR | 74,0 | 63,0 | NR | NR |
| Pucciarelli et al. [27] | 106 | 42 | 9,7 | 83,6 | 83,6 | NR | NR |
| Hughes et al. [28] | 211 | 25 | 18,0* | NR | NR | NR | NR |
| Lindebjerg et al. [29] | 135 | 26 | 8,9 | NR | NR | NR | 82,0 |
| Kim NK et al. [30] | 178 | 52 | 14,6 | NR | NR | NR | 72,3 |
| Ha et al.2010 [31] | 615 | 58 | NR | 82,3 | 76,8 | NR | NR |
| Kim TH et al. [32] | 420 | 50,5 | 22,9 | 88,7 | 75,4 | 77 | NR |
| Kong et al.2012 [33] | 135 | 50 | 22,1* | 82,7 | NR | 67,9 | NR |
| Yeo et al.2012 [7] | 364 | 68 | 21,9 | 87,2 | 78,8 | 81,6 | NR |
| Habr-Gama et al.2014 [19] | 183 | 60 | 31,0 | NR | 68,0 | NR | 91 |
| Martens et al. [34] | 100 | 41,1 | 15,0 | 96,6 | 80,6 | 84,6 | NR |
| Fokas et al. [10] | 1179 | 50 | 3,2* | 88,4 | 73,6 | NR | NR |
| Smith et al. [35] | 249 | 43 | 20,0 | 73,0 | 75,0 | NR | 90,0 |
| Hupkens et al. [36] | 292 | 58 | 14,3 | 97,1 | NR | 94,3 | NR |
| Jimenez-Rodriguez et al. [37] | 88 | 42 | 18,2 | NR | NR | NR | NR |

**Table 4:** Mean follow-up time, recurrence rate and survival rate of studies in the literature. Note: Nº - Number; MFU - Mean follow-up time in months; RR - Recurrence rate (%); * - Local recurrence; OS - overall survival (%); DFS - disease-free survival (%); MFS - metastasis-free survival (%); CSS - cancer-free survival (%); NR - Não referred.

In this research, the mean follow-up was 62 months. The follow-up time can be considered high compared to the literature. This reflects an adequate long-term outpatient follow-up, which reinforces the findings in terms of overall survival related to recurrence, metastases and cancer-specific in the studied group.

The rate of tumor recurrence pointed out by the authors ranged from 8.9% to 31,0%. The recurrence in 14 (20%) patients in this study fell within the range presented by the different authors.

Regarding the survival rates in this study, the OS in 5 years was 75.6%, the DFS was 76.4%, the MFS was 77.4% and the CSS was 84.4%. When comparing them with the rates presented by the different studies, it was found that they were comparable.

CEA is used to diagnose recurrence in the postoperative period. When measured before surgery, it can be used as a prognostic indicator. Comparing CEA results before and after neoadjuvant therapy, Perez et al. [38] concluded that, when this marker is below 5 ng/mL after radiation therapy, patients have an increase in the rate of complete clinical and pathological response, in addition to improvement in OS and DFS. This study compared patients with CEA lower than 4 ng/mL and those with a level equal to or higher than that, in a period prior to the RCT. There was a statistically significant difference with the DFS and MFS curves in relation to the two groups, as well as in the univariate analysis. Multivariate regression proved that CEA is an independent prognostic factor for DFS and MFS.

With the possibility of regression of the invasion of the rectal wall by the tumor and the sterilization of the compromised lymph nodes (downstaging), experiences of local resection of rectal tumor treated with preoperative chemotherapy and radiation therapy began to be published. Criticism of this operative conduct concerns the lack of accessibility to lymph nodes that may be involved. Creavin et al. [39] compared 50 individuals with local resection with 362 from whom the mesorectum was excised. The authors found no differences in in overall survival or disease-free survival rate between the two groups. In this study, 12 local resection surgeries were performed for rectal tumors. The survival of these patients was compared to that of patients who underwent surgeries with mesorectum excision, such as lower anterior resection. The authors found no differences in OS, DFS, MFS and CSS between these two types of operative treatment.

The pT staging was an independent factor in multivariate regression for OS and DFS what was observed Dulk et al. [40]. In the multivariate analysis done by Hwang et al. [41], the degree of pT staging was an independent prognostic factor for DFS. In this research, the pT0, pT1, pT2 staging group presented DFS, MFS and CSS curves with a statistically significant difference in relation to pT3 and pT4. Likewise, pT staging proved to be an indicative prognostic variable in univariate analysis and an independent prognostic factor in multivariate regression for DFS, MFS and CSS.

Lymph nodes involvement by the cancer is the most important prognostic factor for long-term outcome. Lee et al. [42] described pN as a variable related to OS and DFS in the univariate analysis and OS in the multivariate. Huebner et al. [43] found that lymph node involvement was associated with DFS and CSS in multivariate regression. Cho et al. [44] demonstrate the 5-year recurrence-free survival (RFS) and overall survival (OS) in patients with lymph nodes metastasis were not favorable compared with those of N0 disease. In the results obtained with the patients in this study, the importance of the pN variable as a prognostic factor was clear, since it proved statistically significant in the curves of OS, DFS, MFS and CSS, as well as in the univariate and multivariate regression for DFS, MFS and CSS.

Staging was considered a variable related to DFS, both in the univariate analysis and in the multivariate regression and it is an independent prognostic factor for recurrence, according to a study by Kim TH et al. [34]. Hayes et al [45] didn't found a relationship between downstaging of the locally advanced rectal cancer after neoadjuvant chemoradiotherapy with reduced recurrence. In this study, the comparison of the two groups ( Grade I and II x III and IV ) revealed that there was a statistically significant difference regarding DFS and MFS. This result was confirmed in univariate regression, expressing that the more advanced stage has a worse prognosis for survival in terms of recurrence in general and distant recurrence in particular.

The tumor response to radiation therapy appeared as an independent prognostic factor for DFS and OS, because patients with complete pathological response had a significantly greater DFS and OS than non-responders. [46,47]. However, this research did not identify the influence of the tumor pathological regression variable on the survival outcomes of this series.

Sterilization of the original tumor of the rectum occurs at rates ranging from 8.8% to 22.0%. In this series, the complete pathological response of the tumor was 18.6%. Although there is a significant relationship between this result and DFS and OS, as demonstrated by Lee et al. [48] and Sell et al. [49], this study could not confirm the beneficial effect of the complete pathological response on the evolution of patients.

## CONCLUSIONS

Preoperative radiation therapy and chemotherapy are safe treatments and were determinants of adequate recurrence rates and survival rates consistent with those in the literature. The level of carcinoembryonic antigen above 4 ng/mL before the beginning of radiation therapy was related to worse outcomes; and pT3 and pT4 stages have shown shorter survival than pT0, pT1 and pT2. pN1 and pN2 staging determines shorter survival than that of patients with pN0. The level of carcinoembryonic antigen prior to radiation therapy, pT staging and pN staging are independent prognostic factors for the survival of patients with rectal adenocarcinoma who are treated with preoperative radiation therapy.

## CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

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