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Brazilian Journal of Oncology

ORIGINAL ARTICLES CLINICAL ONCOLOGY

Preoperatory treatment of adenocarcinoma of the rectum: historical analysis and correlation between tumor regression grade and the outcomes

Tratamento pré-operatório de adenocarcinoma de reto: análise histórica e correlação entre o grau de regressão do tumor e os resultados

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ABSTRACT

Introduction: Treatment of locally advanced rectal cancer is based on chemoradiation associated with surgery. Tumor regression grade (TRG) appears to be a prognostic factor and be influenced by the interval between neoadjuvant treatment and surgery. **Material and Methods:** A retrospective database was formed. We included patients submitted to neoadjuvant chemoradiotherapy and rectal surgery, treated at the Hospital de Clínicas, Porto Alegre. TRG was mensurated by the modified Ryan method, as the American Joint Committee on Cancer (AJCC) suggests. We analyzed outcomes, pathological tumor regression and treatment toxicity data. We also sought to analyze the optimal timing for surgery after chemoradiotherapy, comparing different intervals after chemoradiotherapy with the rate of pCR. Statistical analysis was done with Kaplan Meier, Pearson's chi-square, and the Cox regression method. **Results:** We accrued 156 patients between 2006 and 2018. The rate of DFS at 3 and 5 years were 75% and 70%, respectively. The 5-year overall survival was 88%. The rate of pCR was 12.8%. TRG 3 was associated with an increase in mortality, HR 3,148 (95%CI: 1.6-12.2, p<0.003) and a decrease in DFS, HR 3,148 (95%CI: 1.7-5.8, p<0.0001). The 5-years DFS with TRG 0,1, 2 and 3 were 95%, 87%, 73.3%, and 48%, respectively. Comparing the interval between the end of radiotherapy treatment and surgery of less than 8 weeks versus 8 and 12 weeks versus above 12 weeks, the rates of pCR were 4.3%, 18.6% and 7.1% and the rates of TRG 3 were 32.6%, 18.6%, and 57,1% (p<0.016), respectively. **Conclusion:** The outcomes found are favorable. The pathological tumor regression grade is an important prognostic factor. The interval between the neoadjuvant treatment and surgery seems to influence the tumor regression grade, with the best results of surgery observed when performed between 8 and 12 weeks.

Keywords: Rectal neoplasms; Neoadjuvant therapy; Antineoplastic agents; Radiotherapy.

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Financial support: none to declare.
Conflicts of interest: The authors declare no conflict of interest relevant to this manuscript.
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Received on: Apr 6, 2021 | **Accepted on:** Jul 23, 2021 | **Published on:** Feb 18, 2022
DOI: https://doi.org/10.5935/2526-8732.20220265

RESUMO

Introdução: O tratamento do câncer retal localmente avançado é baseado na quimiorradiação associada à cirurgia. O grau de regressão tumoral (TRG) parece ser um fator prognóstico e é influenciado pelo intervalo entre o tratamento neoadjuvante e a cirurgia. **Material e Métodos:** Um banco de dados retrospectivo foi formado. Foram incluídos pacientes submetidos à quimiorradioterapia neoadjuvante e cirurgia retal, atendidos no Hospital de Clínicas de Porto Alegre. O TRG foi mensurado pelo método de Ryan modificado, como sugere o American Joint Committee on Cancer (AJCC). Analisamos os resultados, a regressão patológica do tumor e os dados de toxicidade do tratamento. Também procuramos analisar o momento ideal para a cirurgia após a quimiorradioterapia, comparando diferentes intervalos após a quimiorradioterapia com a taxa de pCR. A análise estatística foi feita com Kaplan Meier, qui-quadrado de Pearson e o método de regressão de Cox. **Resultados:** Registramos 156 pacientes entre 2006 e 2018. A taxa de DFS em 3 e 5 anos foi de 75% e 70%, respectivamente. A sobrevida global em 5 anos foi de 88%. A taxa de pCR foi de 12,8%. TRG 3 foi associado a um aumento na mortalidade, HR 3.148 (IC95%: 1,6-12,2, p<0,003) e uma diminuição na DFS, HR 3.148 (IC95%: 1,7-5,8, p<0,0001). O DFS de 5 anos com TRG 0,1, 2 e 3 foram 95%, 87%, 73,3% e 48%, respectivamente. Comparando o intervalo entre o final do tratamento de radioterapia e cirurgia de menos de 8 semanas versus 8 e 12 semanas versus acima de 12 semanas, as taxas de pCR foram 4,3%, 18,6% e 7,1% e as taxas de TRG 3 foram 32,6%, 18,6% e 57,1% (p<0,016), respectivamente. **Conclusão:** Os resultados encontrados são favoráveis. O grau de regressão patológica do tumor é um importante fator prognóstico. O intervalo entre o tratamento neoadjuvante e a cirurgia parece influenciar o grau de regressão tumoral, sendo os melhores resultados da cirurgia observados quando realizada entre 8 e 12 semanas.

Descritores: Neoplasias retais; Terapia neoadjuvante; Agentes antineoplásicos; Radioterapia.

INTRODUCTION

Colorectal neoplasia has a high prevalence and lethality. In Brazil, the incidence estimated for each year of the 2020-2022 triennium is 20,520 cases of colon and rectal cancer in men and 20,470 in women. In the South Region, it is the third most frequent tumor, with an estimated risk of 25.11 cases per 100 thousand people.[1]

The treatment of locally advanced rectal neoplasia is based on chemoradiotherapy (CRT) associated with surgery. The neoadjuvant treatment has a benefit in reducing local disease recurrence compared with adjuvant CRT.[2,3] Pathological complete response (PCR) is a valid surrogate outcome for disease-free survival (DFS) and has important prognostic value.[4-10,14] The presence of tumor regression in the pathological analysis was classified in tumor regression grade (TRG).[11] One study estimated the 10-year DFS for patients with PCR, moderate response, and poor response to be 89.5%, 73.6%, and 63%, respectively.[16]

Although several different scoring systems for tumor regression have been advocated, the AJCC recommends the modified Ryan scheme, a four-point tumor regression score that provides good interobserver reproducibility and prognostic significance. This method was adopted by de College of Americans Pathologists.[11,12]

CRT can produce substantial tumor regression and approximately 15% will achieve PCR, reaching up to 40% in more favorable tumors. Whether the degree of response to neoadjuvant therapy should change, the subsequent treatment is subject to discussion. Although the excellent prognosis of CPR, some evidence still suggests the benefit of adjuvant chemotherapy.[13] The phase 2 ADORE study looked at FOLFOX escalation in patients who performed neoadjuvant treatment and had no response. The study showed benefit mainly if lymph nodes positive.[15]Another subject of research is the strategy of delaying the interval between the end of CRT and the surgery, in addition to the classic interval of 6 to 8 weeks. This strategy aims to increase the rate of complete pathological response and possibly other outcomes.[5]

This study aims to evaluate the long-term results of treatment of locally advanced rectal neoplasia in the *Hospital de Clínicas de Porto Alegre*. We also aim to analyze the tumor regression grade as a prognostic factor and demonstrate relationships between variables that could be useful and generate hypotheses. Finally, we want to compare the interval between the end of the neoadjuvant treatment and surgery in weeks, seeking the time of higher pathological response rate.

MATERIAL AND METHODS

A retrospective cohort of patients 18 years of age or older with locally advanced rectal adenocarcinoma treated at the clinical oncology and radiation oncology service of *Hospital de Clínicas de Porto Alegre*, between 2006 and 2018. The patients have been treated with neoadjuvant CRT and underwent tumor resection surgery. All of them must have had documentation of surgical pathology analyzed by our department of pathology. The chemotherapy protocols used in the neoadjuvant treatment included 5-flourouracil bolus, 5-flouruoacil infusion, and capecitabine.

The tumor regression grade was formally reviewed in the pathology records and graduated by the investigators according to the AJCC classification, in grades from 0 to 3, with 0 – complete pathological response, 1 – the presence of minimal residual neoplastic focus, 2 – the presence of evident tumor regression but with evidently residual tumor and 3 – the absence of tumor regression.

We analyzed medical records and data on clinical history, analysis of imaging tests and surgical pathology as well as other factors relevant to the treatment of the rectal neoplasia. The TRG was correlated with overall survival and DFS. We documented the interval between the end of the CRT (the last day of radiotherapy) and surgery in weeks, correlating with the TRG, seeking the time of higher pathological response rate.

Statistical analysis

Demographic data, tumor data, chemotherapy and radiotherapy treatments performed, CPR rate, tumor recurrence rate and treatment toxicities were presented through descriptive statistics. The sample size was by convenience, according to the patients treated in the historical cohort. Comparative analyzes were performed using the methods: Kaplan Meier, Pearson's chi-square or Fischer's exact and the Cox regression method. A *p*-value of ≤0.05 was considered statistically significant.

RESULTS

We accrued 156 patients who met the inclusion criteria, underwent CRT and surgery between 2006 and 2018. Most were men (65%), with a median age of 65 years. Most were of the inferior rectum (49%).

The clinical staging was T3 and N1 in 87% and 54.7%, respectively. The median number of lymph nodes resected was 15. The pathological staging was ypT3 and ypN0 in 46% and 77.7%, respectively. The rate of pathological complete response was 12.8%.

More than 80% of patients received dose of radiotherapy above 45Gy. Adjuvant chemotherapy was performed in 69.4% of the patients. However, in the remaining patients who weren't able to receive adjuvant treatment, 16.6% were lymph node positive. Sphincter-sparing surgery was performed in 56.6%. These data and other characteristics of the patients are shown in Table 1 and Table 2.

The median follow-up was 50.5 months. The overall survival (OS) rate at 5 years was 88% (Figure 1 – Supplemental). The 5-year disease-free survival rate (DFS) was 70.7%, similar to the 3-year (DFS) rate, which was 72.9% (Figure 1). The 5-year metastasis-free survival (MFS) rate was 75.2%, similar to the 3-year MFS rate, 77.6% (Figure 2 – Supplemental).

Analysis of tumor regression grade

The comparison between patients who had no tumor regression after CRT (TRG 3) versus those who had a response (TRG 0, 1 and 2) showed increased risk of progression with RR 3.14 (95%CI: 1.7-5.8) $p<0.0001$ (Figure 3) and increased risk of death with RR of 4.52 (95%CI: 1.66-12.2, p<0.003) (Figure 3 – Supplemental).

Table 1 - Demografic and clinical-pathologic data

Total of patients	156
Male (%)	101 (64)
Median age (years)	65 (37-85)
Low rectum (0-5 cm) (%)	78 (49)
Middle rectum (6-10) (%)	74 (47)
High rectum (11-15) (%)	4 (2)
MRI at staging (%)	6 (3,8)
Well differentiated (%)	9 (5,7)
Moderate differentiated (%)	141 (89)
Poor differentiated (%)	6 (3,8)
cT2 (%)	6 (3,8)
cT3 (%)	138 (8,7)
cT4 (%)	12(7,6)
cN0 (%)	40 (25,4)
cN positive (%)	116 (74,6)
Treatment between 2006-2010 (%)	40 (25,4)
Treatment between 2011-2014 (%)	60 (38,2)
Treatment between 2015-2018 (%)	57 (36,3
Neo 5FU bolus (%)	118 (75,1)
Neo Capecitabine (%)	30 (19,1)
Neo 5FU infusional (%)	9 (5)
Perfomed adjuvant chemotherapy	109 (69,4)
Radiotherapy dose of 50 Gy (%)	101 (64)
Radiotherapy dose of 45 Gy (%)	26 (16,5)
Completed planned RDT	117 (74,5)
Disease progression (%)	42 (26,7)
Systemic progression (%)	32 (20)
Local progression (%)	10 (6,4)
Grade ¾ adverse efects (%)	34 (21,6)

Table 2. Surgical and histopathological

Total of patients	156
ypT0	23 (14,6)
ypT1	11 (7)
ypT2	38 (24,2)
ypT3	73 (46,5)
ypT4	12 (7,6)
ypN0	122 (77,7)
ypN1	22 (14
ypN2	13 (8,3)
TRG 0 (%)	20 (12,8)
TRG 1 (%)	32 (20,3)
TRG 2 (%)	63 (40)
TRG 3 (%)	41 (26)
Resected lymph nodes (median)	15 (0-64)
Positive margin	12 (7)
Median time to surgery (days)	63(25-629)
Median time to surgery (weeks)	9 (3,5- 89)
Sphincter- sparing surgery (%)	89 (56,6)
Surgery - sphincter sparing of low rectum (%)	27 (34,1)

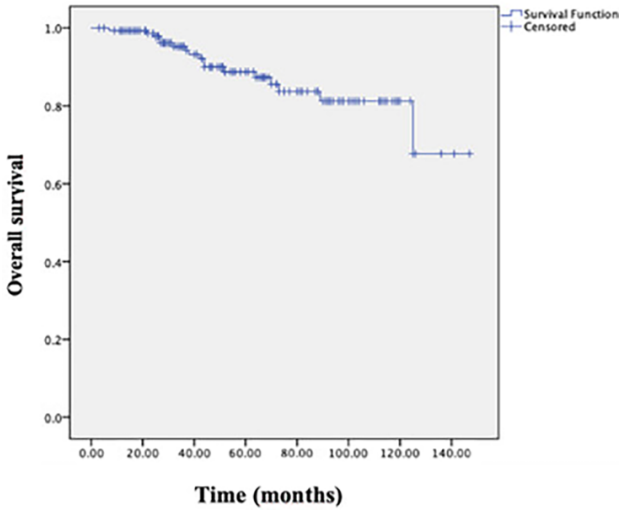

Figure 1. Kaplan Meier curve of disease free survival

Analyzing the outcomes according to the tumor regression grade, the observed 5-year DFS rate in the TRG 0, 1, 2, and 3 were: 94.7%, 84.9%, 67.3%, and 44%, respectively; $p<0.0001$ (Figure 2). The overall survival rate at 5-year was: 100%, 88.3%, 91.9% and 74.2%, respectively; $p<0.009$ (Figure 4 – Supplemental).

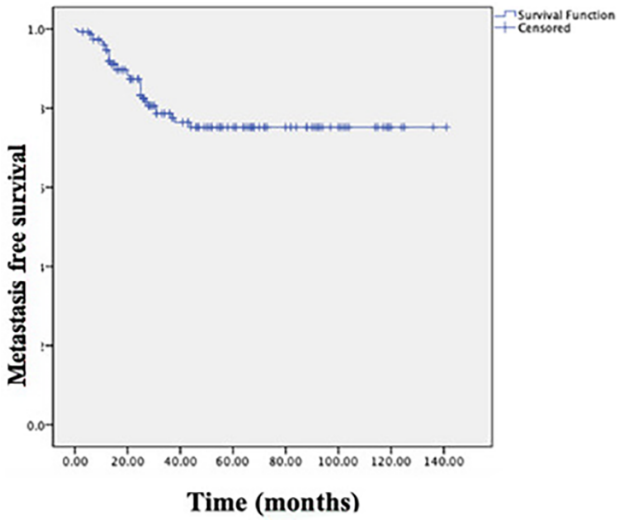

Figure 2. Comparison of disease-free survival according to TRG

Analyzing patients with paired pathological staging and different tumor regression grade

We performed a subgroup analysis with 50 patients with pathological stage T3N0. In this group 15 had TRG grade 3 and 35 had TRG grade 1 or 2. We observed a better prognosis for patient with TRG 1 + 2 versus TRG 3. The 5-year SLP rate was 77.5% versus 55.7% (Figure 4). This trend is also seen in ypT3 and ypN1 patients (Figure 9).

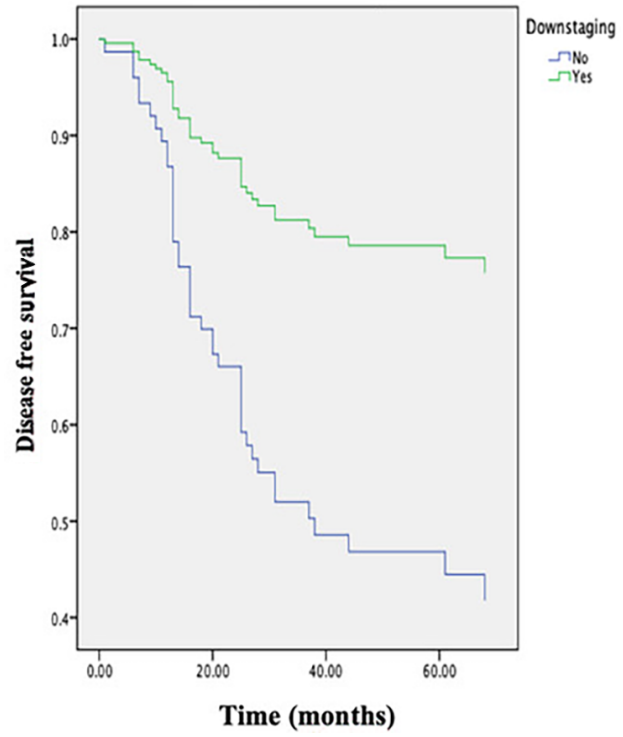

Figure 3. Comparison of disease-free survival according to the presence or absence of tumor regression

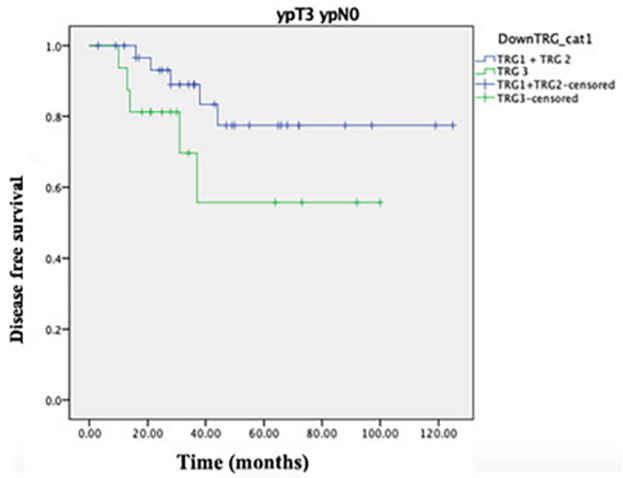

Figure 4. Comparison of disease-free survival in patients with ypT3ypN0 with or without tumor regression.

Analysis of pathological staging

The DFS analysis according to the different subgroups of tumor pathological staging (T) and lymph node (N) showed a significant difference between the groups.

The groups ypT3 and ypT4 showed an increased risk of progression compared with the group with ypT0, with RR of 8.9 (95%CI: 1.2-66.3, $p<0.03$) and 22.7 (95%CI: 2.8-182, $p<0.003$), respectively. (Figure 5 – Supplemental). The OS analysis showed worsening of survival for the ypT4 group (Figure 6 – Supplemental).

The comparison was between different pathological lymph node staging, N1 and N2. Comparing the DFS in patients N1 versus N0, we observed RR 2.32 (95%CI: 1.0-5.2, p<0.041) in detriment of N1 patients and between N2 vs N0, RR 8.3 (95%CI: 3.9-17.8, p<0.001) in detriment of N2 (Figure 7 – Supplemental). The analysis of OS shows worse survival in N2 patients, with RR of 1.9; however, without reaching a statistical difference (Figure 8 – Supplemental).

Multivariate analysis correlating pathological staging, tumor regression and progression-free survival (Table 3)

A multivariate analysis was made comparing different variables and correlating to DFS. This analysis showed that the variables correlated to a worst DFS with a statistical significance difference were: ypN2 and the absence of tumor regression (TRG 3) (Table 3).

Table 3. Multivariate analysis correlating pathological staging and TRG 3 to disease-free survival.

	RR	IC 95.0%		P
ypT				.244
ypT(1)	3.203	0.289	35547	.343
ypT(2)	3.059	0.356	25.628	.303
ypT(3)	4843	0.621	37.771	.132
ypT(4)	8.430	0.982	72.839	.052
ypN				.001
ypN (1)	1.845	0.807	4.221	.147
ypN (2)	4.861	2.180	10.840	.000
absence of tumor regression	1.956	1.017	3.764	.044

Analysis of the interval between neoadjuvant treatment and surgery

The median time from the end of the CRT to surgery was 9 weeks. Analyzing this interval, the highest rates of pCR were accomplished in weeks 8, 9, 11, and 12 (Figure 10 – Supplemental).

We compared different intervals between the CRT to surgery: less than 8 weeks, between 8-12 weeks and above 12 weeks (Figure 5). The rate of CPR was 4.3%, 18.6% and 7.1%, respectively. The difference between 4.3 and 18.6% was statistically significant. Analyzing the TRG 3 in the same periods, the rates were 32.6%, 18.6%, 57.1%, respectively (Figure 12 – Supplemental). The difference between 18.6% and 57.1% had a statistically significant difference (Figures 11 and 12 – Supplemental). Analyzing only the period after 12 weeks, the median time for surgery for this group was 15 weeks and only one patient was operated with more than 6 months of interval.

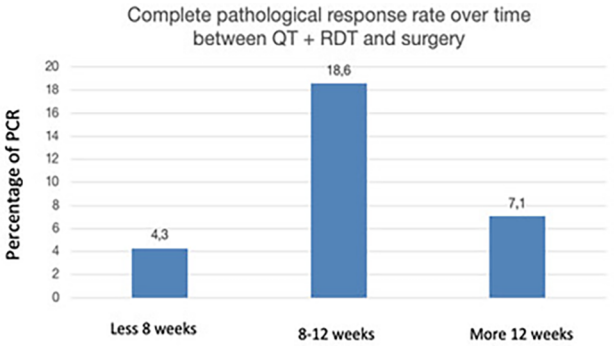

Figure 5. Comparison of the complete tumor response rate between different intervals between chemoradiotherapy and surgery.

DISCUSSION

Our retrospective cohort during a period of 12 years showed an overall survival of 88% in 5 years. The recurrence rate was 26.7%, similar to that found in the main studies with this modality of treatment.[2,3] The rate of local recurrence was identical to that found in the study published by Sauer et al. (2004)[2] of 6%. The rate of pathologic complete response was 12.8%. The pathological (yP) stage in N, mostly N2 and the TRG 3 showed a significant difference in a worse prognosis for these patients in the multivariable analysis.

The TRG is an important prognostic factor. We were able to show a statistically significant difference in DFS according to the TRG. The difference in survival is large when comparing patients with response versus no response. It is also important to note that in our multivariate analysis, the factors related to a worse DFS with statistical significance were: TRG 3 and ypN2.

These findings are in consonance with the literature. In a study analyzing TRG as a prognostic factor, patients with CPR had an incidence rate of distant metastasis of 10.5%, while in those with poor regression it was 63%. The presence of lymph node metastasis and TRG were the only independent prognostic factors for the incidence of distant metastases and DFS.[16] It is interesting that in our analysis, even comparing the same pathologic stage of patients, the presence of pathologic response against no response conferred a trend to better outcomes.

We compared the rate of pathologic response according to the interval between CRT and surgery. Surgery performed before 8 weeks and between 8-12 weeks, the PCR were 4.3 and 18.6%, and TRG 3 were 32.6% and 18.6%, respectively. This difference has statistical significance. This finding reinforces some data in the literature. A meta-analysis published in 2016 analyzed the strategy of delaying surgery beyond the classical 6 to 8. The probability of obtaining PCR, when waiting more than 6-8 weeks, was increased by 42%.[5] A review of the Brazilian systematic published in 2019 sought to analyze the ideal time between neoadjuvant therapy and surgery. The analysis concludes that waiting longer than 8 weeks seems preferable, increasing the degree of tumor regression.[17]

A previous study was published looking for which factors have a greater influence on the CPR found that the use of 2 drugs, the use of infusional fluorouracil and a dose of radiotherapy higher than 45Gy[4] were important. In our study, 74.5% of the patients were able to complete the desired full dose of radiotherapy. This aspect is important to explain the good results achieved in DFS and OS.

It is relevant to discuss that 16.8% of patients with positive pathologic lymph nodes could not be exposed to adjuvant chemotherapy. The strategy of adding more chemotherapy in the preoperative is established in gastric cancer, bladder cancer and others tumors. Nowadays, the total neoadjuvant treatment, which consists of adding cycles of chemotherapy in addition to preoperative CRT is becoming the new standard of care in selected patients.[20] Two studies in this context, phase 3 were recently published: the RAPIDO and PRODIGE 23. The RAPIDO used a short course radiotherapy followed by CAPOX or FOLFOX-4 and surgery. The PRODIGE 23 protocol experimental protocol included FOLFIRINOX, chemoradiotherapy, surgery and adjuvant chemotherapy. Both studies achieved their primary outcomes. Both were able to increase the rate of CPR and reduced the rate of disease recurrence.[18,19]The major strength of our study is to show the outcomes of a curable disease in a historical cohort at the *Hospital de Clínicas de Porto Alegre*, a public hospital. The treatment of rectal neoplasia is complex and involves a multidisciplinary team. Our data are according to the literature and show high overall survival. The main limitations of our study are that it is a retrospective cohort and our comparisons are of non-randomized groups.

CONCLUSION

The outcomes found are favorable, mainly because they are long-standing data from a public institution. The pathological tumor regression grade (TRG) is an important prognostic factor. The interval between the neoadjuvant treatment and surgery seems to influence the tumor regression grade, with the best results of surgery occurring between 8 and 12 weeks.

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SUPPLEMENTARY FIGURES

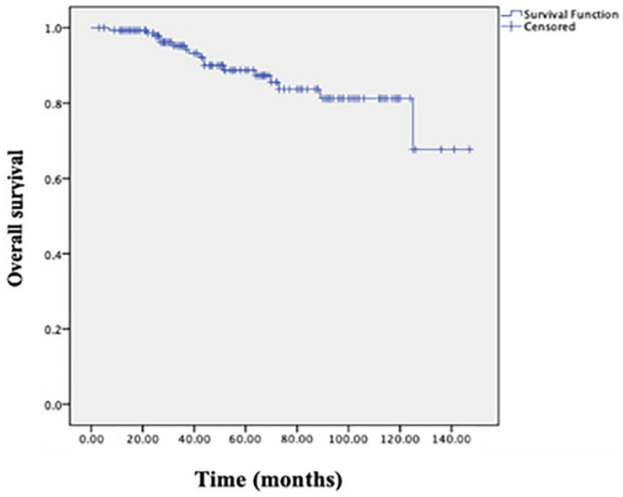

Figure 1. Supplemental - Kaplan meier curve of overall survival

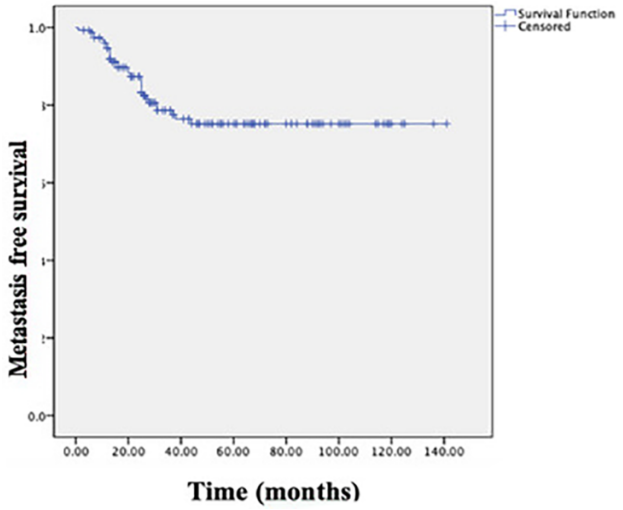

Figure 2. Supplemental - Kaplan meier curve of metastasis-free-survival.

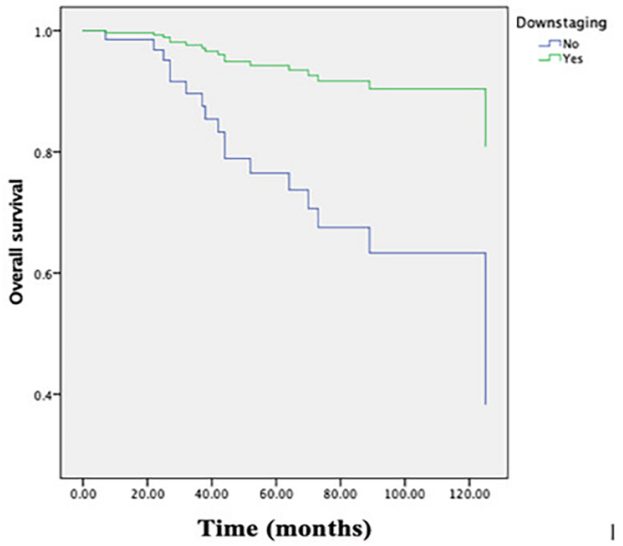

Figure 3. Supplemental. Comparison of overall surival according to the presence or absence of tumor regression

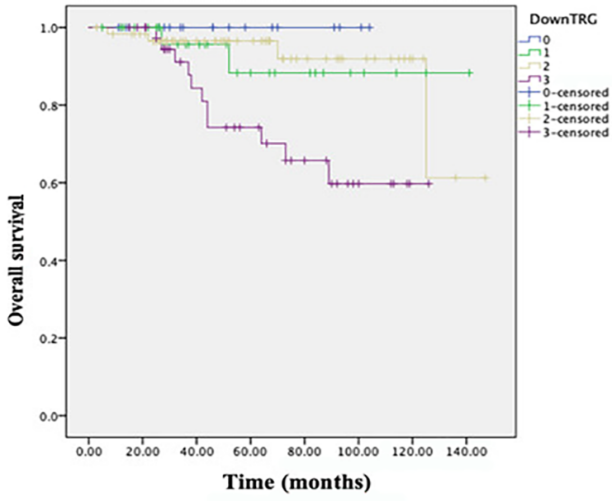

Figure 4. Supplemental - Comparison of overall survival according to TRG

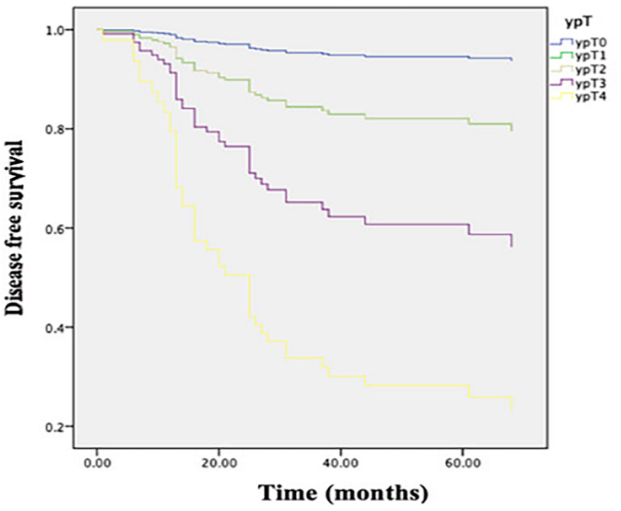

Figure 5. Supplemental - comparison of disease-free survival according to ypT

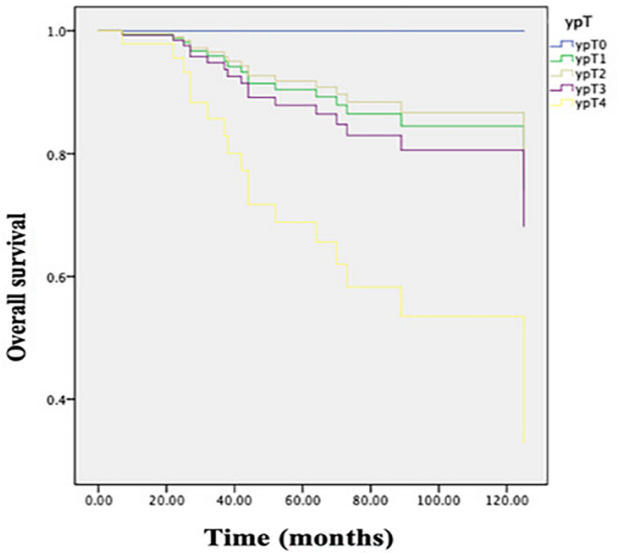

Figure 6. Supplemental - Comparison of overall survival according to ypT

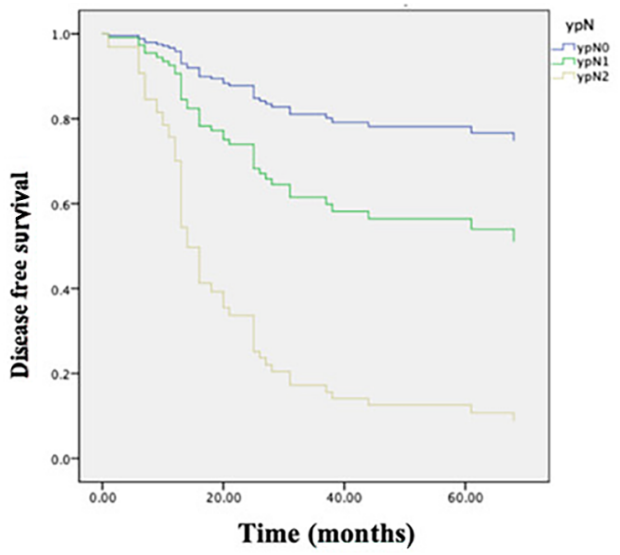

Figure 7. Supplemental - Comparison of disease-free survival according to ypN

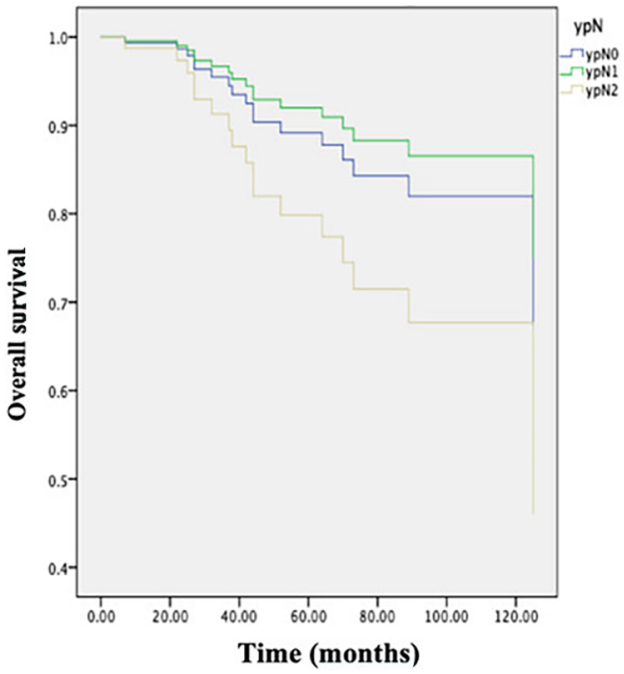

Figure 8. Supplemental - Comparison of overall survival according to ypN

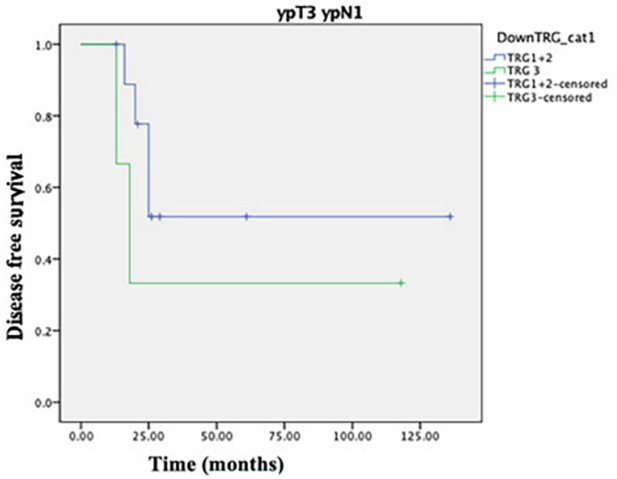

Figure 9. Supplemental - Comparison of disease-free survival in patients with ypT3ypN1 with or without tumor regression

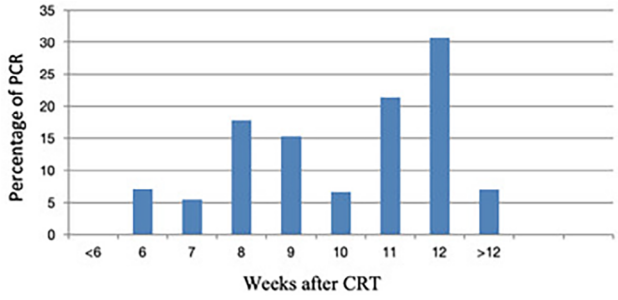

Figure 10. Supplemental - Rate of pathological complete response according to the interval in weeks between chemo-radiotherapy and surgery

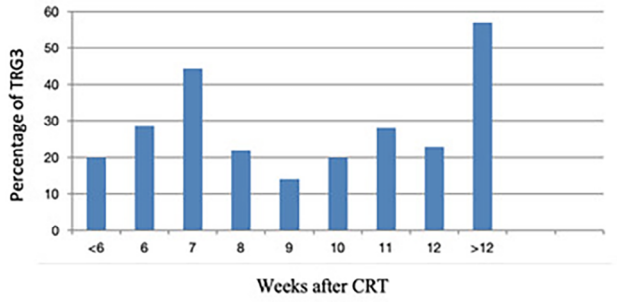

Figure 11. Supplemental - Rate of TRG 3 according to the interval in weeks between chemo-radiotherapy and surgery

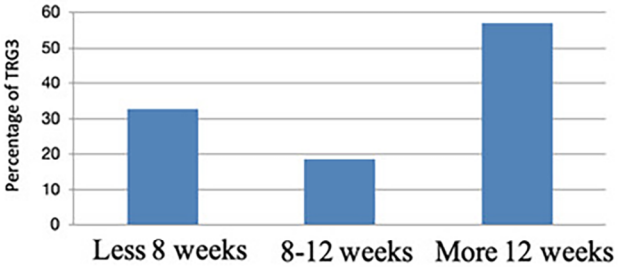

Figure 12. Supplemental - Comparison of the TRG 3 rate between different intervals between chemo - radiotherapy and surgery