



Original Article

Assessment of the non-surgical treatment of patients with rectal cancer who underwent neoadjuvant treatment with chemotherapy and radiotherapy at the oncology department



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ARTICLE INFO

Article history:

Received 29 September 2018

Accepted 30 October 2018

Available online 19 December 2018

Keywords:

Quality of life

Rectal surgery

Wait-and-see policy

Rectal cancer

ABSTRACT

Objective: To describe the partial results of a study in patients with rectal cancer who underwent neoadjuvant treatment with chemotherapy and radiotherapy regarding the rate of complete clinical response, disease-free survival, anorectal function, and quality of life.

Material and methods: This was a prospective study from June 2015 to June 2018, in patients with low- or mid-rectum adenocarcinoma and clinical stage II or III, treated with radiotherapy and chemotherapy (IMRT 54 Gy for six weeks) concomitant with 5-fluorouracil (5-FU) 380 mg/m² and folinic acid (LV) 20 mg/m² for five days in the first and fifth weeks and two cycles after radiotherapy (5-FU 400 mg/m² and LV 20 mg/m²) every 28 days. After the treatment, clinical examination, rectosigmoidoscopy, pelvic magnetic resonance imaging, chest and upper abdomen computed tomography, and CEA testing were performed. Resection surgery was performed in those with incomplete clinical response (iCR). Those with complete clinical response (cCR) are under observation (wait-and-see policy). Manometry and scintigraphic function and quality of life scales were collected before treatment and at 30 and 90 days after the end of treatment.

Results: As of June 2018, 11 patients were recruited. One was excluded from the analysis for presenting severe toxicity, suggestive of dihydropyrimidine dehydrogenase (DPD) deficiency, after the first chemotherapy cycle. All others completed the treatment. Two patients presented toxicity grade 3/4 related to chemotherapy and had their doses reduced. Seven

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<https://doi.org/10.1016/j.jcol.2018.10.015>

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patients (70%) presented iRC; three underwent rectosigmoidectomy, and the anatomopathological evaluation indicated complete pathological response in two cases (28.5%). Three (30%) presented cCR and did not present evidence of disease after a mean follow-up of 19 months. Patients presented improvement of anorectal function and quality of life.

Conclusions: Advances in the neoadjuvant treatment of rectal tumors contributed to better rates of complete pathological responses. New paradigms promote an increase in the complete clinical response rates, which would allow organ preservation and consequent reduction of surgical morbidity.

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Avaliação do tratamento não cirúrgico de pacientes com câncer de reto submetido ao tratamento neoadjuvante com quimioterapia e radioterapia no serviço de oncologia

R E S U M O

Palavras-chave:

Qualidade de vida
cirurgia retal
vigilância Watch and wait
câncer retal

Objetivo: Descrever os resultados parciais de estudo em pacientes com câncer de reto submetidos a tratamento neoadjuvante com quimioterapia e radioterapia quanto à taxa resposta clínica completa, sobrevida livre de doença, função anorretal e qualidade de vida. **Material e métodos:** Estudo prospectivo desde junho 2015 até junho de 2018, em paciente com adenocarcinoma de reto baixo ou médio e estadio clínico II ou III tratados com RT/QT (IMRT 54 Gy em 6 semanas) concomitante a 5-Fuorouracil (5-FU) 380 mg/m² e ácido folínico (LV) 20 mg/m² por 5 dias nas primeira e quinta semanas e dois ciclos após RT (5-FU 400 mg/m² e LV 20 mg/m²) a cada 28 dias. Após o tratamento, realizou-se exame clínico, retossigmoidoscopia, RNM de pelve, TC de tórax e abdômen superior e dosagem de CEA. Naqueles com Resposta Clínica Incompleta (iRC) procedeu-se à cirurgia de ressecção. Aqueles com Resposta Completa (cRC) estão em observação (*wait and see policy*). Manometria e escalas de função esfinteriana e qualidade de vida foram obtidas antes e após 30 e 90 dias do término do tratamento.

Resultados: Até junho de 2018, recrutaram-se 11 pacientes. Um foi excluído da análise, pois apresentou toxicidade severa sugestiva de deficiência de DPD após o primeiro ciclo de QT. Todos os demais concluíram o tratamento. Toxicidades graus 3/4 relacionadas à QT ocorreram dois pacientes, reduzindo-se sua dose. Sete (70%) apresentaram iRC, submetendo três à retossigmoidectomia cuja avaliação anatomopatológica evidenciou Resposta Completa (pRC) em dois casos (28,5%). Três (30%) apresentaram cRC e estão sem evidência de doença com seguimento médio de 19 meses. Houve melhora da função anorretal e da qualidade de vida.

Conclusões: Avanços no tratamento neoadjuvante dos tumores de reto contribuíram para melhores taxas de pRC. Novos paradigmas promovem crescentes índices de cRC, o que possibilitaria a preservação do órgão e consequente redução da morbidade cirúrgica.

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Introduction

The standard treatment for rectal neoplasia is multidisciplinary. Neoadjuvant chemotherapy and radiotherapy are considered the gold standard for the preoperative treatment in patients from clinical stage II onwards. In clinical studies addressing locally advanced rectal cancer, neoadjuvant treatment presented advantages over adjuvant treatment, such as lower toxicity, greater tolerability, lower rate of local recurrence, better PFS, reduction of pathological staging, and greater probability of sphincter-sparing surgery.^{1,2} In

turn, no benefit was observed regarding to overall survival.² Approximately 10% to 30% of neoadjuvant concomitant radiotherapy (RT) and chemotherapy (CHT) cancer patients present complete pathological response (cPR).³ Thus, patients with complete clinical response to RT/CHT could be spared from the morbimortality of the surgery, such as definitive colostomy and genitourinary and sexual dysfunction. With the objective of evaluating patients with rectal cancer submitted to neoadjuvant treatment with RT/CHT regarding the rate of response to treatment, disease-free survival, anorectal function, and quality of life, a research was conducted in the

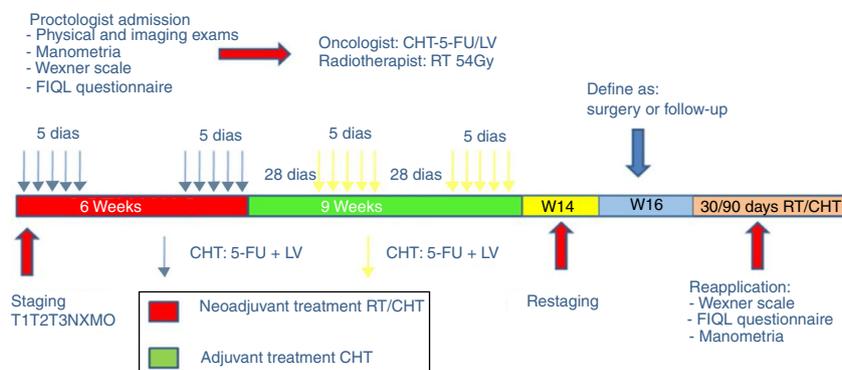


Fig. 1 – Radiotherapy and chemotherapy scheme.

oncology sector of Hospital Santa Isabel – Santa Casa da Bahia. The present article describes the partial results of the study.

Material and methods

This was a prospective study from June 2015 to June 2018, in patients with low- or mid-rectum adenocarcinoma and clinical stage II or III, treated with RT/CHT (IMRT 54Gy for six weeks) concomitant with 5-fluorouracil (5-FU) 380 mg/m² and folinic acid (LV) 20 mg/m² for five days in the first and fifth weeks and two adjuvant cycles after RT, using 5-FU 400 mg/m² and LV 20 mg/m² every 28 days (Fig. 1). After the treatment, clinical examination, rectosigmoidoscopy, pelvic magnetic resonance imaging (MRI), chest and upper abdomen computed tomography (CT), and CEA testing were performed. Resection surgery was performed in those with incomplete clinical response (iCR), while those who presented cPR are followed-up monthly, with rectal examination and other exams. Those with complete clinical response (cCR) are under observation (wait-and-see policy). Manometry and scintigraphic function and quality of life scales are collected before treatment and at 30 and 90 days after the end of treatment. Anorectal function will be assessed through the Wexner fecal incontinence questionnaire and manometry measurements; the quality of life, through the Fecal Incontinence and Quality of Life Questionnaire (FIQL).

Results

Until June 2018, 11 patients were recruited; one was excluded from the analysis for presenting severe toxicity, suggestive of dihydropyrimidine dehydrogenase (DPD) deficiency, after the first CHT cycle.

Most patients were male (60%) and the mean age was 45.9 years, ranging from 28 to 59 years. The lesions were located in the mid- and lower rectum, at a mean height of 2.7 cm from the anal border, ranging from 0.5 to 6 cm from the anal border. Most patients (six) had clinical staging IIIB on admission; one patient was classified as stage III and two as stage II.

All ten remaining patients completed the treatment. Two patients presented toxicity grade 3/4 related to chemotherapy and had their doses reduced during treatment. Regarding RT, two patients also presented Grade III toxicity (Table 1).

Table 1 – Toxicity related to chemotherapy (CHT) and radiotherapy (RT).

Toxicity	G1	G2	G3	G4
CHT	5	3	1	1
RT	4	4	2	–

Seven patients (70%) presented iCR and underwent surgical treatment according to the indication of the lesion; cPR was achieved in two cases (28.5%; Fig. 2). Three patients (30%) presented cCR and are being followed-up through clinical examination, CEA dosage, and periodic imaging tests (chest, abdomen, and pelvis CT, positron emission tomography [PET], and retosigmoidoscopy), with no evidence of disease to date. Patients presented improvement of anorectal function and quality of life after the end of treatment.

Of the three patients with cCR, all had CEA normalization and did not present changes to the rectal examination; flexible rectosigmoidoscopy (Fig. 3) and pelvic MRI presented alterations compatible with cCR. Two of these patients underwent a PET scan to complement the investigation, and no areas of increase in FDG uptake were identified. The mean follow-up of these patients is of 19 months, ranging from 14 to 27 months.

All patients presented improvement in the quality of life score and in the Wexner scale, without significant alterations in manometric pressure when compared to those observed prior to treatment.

Discussion

In localized rectum cancer, clinical stage I–III, in which surgical resection is considered curative, the survival rate is approximately 60% at 5 years and 50% at 10 years.⁴ However, even surgical treatment can present high morbimortality. The mortality rate in total mesorectal excision (TME) is of approximately 4%, with a directly proportional increase in age, reaching 11.8% in octogenarian patients.⁵ Other possible complications of rectal cancer resection are urinary and rectal dysfunction, which in some series were observed in 25% of patients treated with radical surgery.^{6,7}

Randomized studies and a meta-analysis by Luigi Zorcolo et al. demonstrated a cPR rate ranged from 10% to 20% and

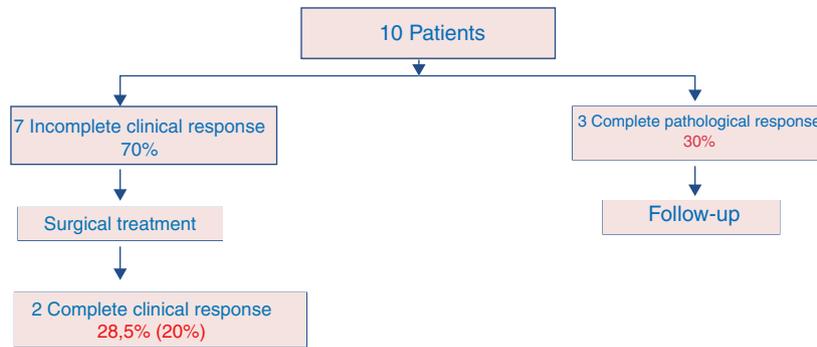


Fig. 2 – Results.



Fig. 3 – Endoscopic aspect of a patient with complete clinical response.

thus greater local and distance control, as well as better PFS and OS.⁸ Considering this data, the real need for surgery in this group was questioned; Dr. Angelita Habr-Gama, from Brazil, was the first to conduct a study in order to elucidate this question and to experimentally adopt the wait-and-see policy (no surgical resection and vigilant follow-up).

Habr-Gama et al. assessed 265 patients with distal rectal cancer (0–7 cm from the anal border) considered resectable. These patients underwent CHT and neoadjuvant RT from 1991 to 2002. Approximately 26.8% of them presented cCR, and were closely followed-up, 8.3% had almost complete clinical response (small residual lesion) and underwent lesion resection, and the others underwent conventional surgical treatment.³ The wait-and-see policy group was followed-up for 57 months and the resection group, for 48 months. In the resection group, there were nine definitive colostomies and seven temporary ileostomies. Three systemic recurrences were observed in each group, as well as two endorectal recurrences in the observation group and two deaths in the resection group. Overall five-year survival rate was 88% vs. 83% ($p=0.01$) in the resection group and in the observation group, respectively. However, no significant difference in disease-free survival was observed in both groups (100% and 92%, respectively; $p=0.09$).³

In another study, published in 2009, Harb-Gama et al. showed the results of an extended RT/CHT scheme, in which a sustained cCR rate of 65.5% was observed. In the present study, a slightly lower rate (40%) was observed.⁹ However, 20% of the patients presented cPR, which indicates that there is

still some difficulty in actually characterizing cCR with the currently available exams, showing a similarity with the results obtained with a different CHT regimen.

The present series has a mean follow-up time of 19 months, ranging from 14 to 27 months, with no relapse to date. This is a preliminary analysis, as the study is still in progress.

From 2004 to 2010, Mass et al. conducted the second study to evaluate the wait-and-see policy. Patients with T3, T4, and lymph node positive rectal cancer were treated with the standard neoadjuvant RT/CHT regimen. After seven weeks, they were reassessed clinically and through colonoscopy and MRI. Twenty-one patients presented cRC and were followed-up every 3–6 months with similar exams; in the control group, 20 patients presented cPR after TME. In the wait-and-see group, only one local recurrence was observed after 22 months. However, no significant differences were observed in the cumulative PFS rates at two years (89% vs. 93%; $p=0.77$), and overall survival (100% vs. 91%) in the cRC and pRC groups, respectively.¹⁰

In a review of thirty studies (nine series, 650 patients) on the non-surgical treatment of rectal cancer patients after RT/CHT, despite the low rates of locoregional recurrence reported in the series by Habr-Gama et al. and Mass et al., other retrospective studies presented recurrence rates of 23–83%.¹¹ These differences in outcome may be explained by heterogeneity in staging, inclusion criteria, study design, and intensity of follow-up after cCR.¹²

Thus, when considering the different treatment options for a patient, both the oncological results and the morbimortality of the treatment should be considered. The wait-and-see policy should be valued not only for elderly patients with comorbidities, but also for young patients who comply with active surveillance. The goal is to spare them from and reduce the incidence of intestinal, genitourinary, and sexual dysfunction, which are relevant to their quality of life.

Conclusion

Advances in RT and CHT protocols led to better complete response rates, as shown in the present study, in which a 40% cCR was observed in the preliminary analysis. It is still difficult to characterize cCR with the available tests; 20% of the patients who underwent surgery presented cPR. The present study is still in progress, aiming to evaluate in the future the

overall survival and disease-free survival, quality of life, and incontinence scores.

Conflicts of interest

The authors declare no conflicts of interest.

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