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The feasibility of sequential short-course radiation therapy and chemotherapy in the neoadjuvant treatment of rectal adenocarcinoma: Cases series treated in a Brazilian public health service

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Abstract

Introduction: Total Neoadjuvant Therapy (TNT) is now recognized as the preferred standard for the treatment of locally advanced rectal cancer. With recent progress in surgery, radiotherapy and chemotherapy, management strategies have become more complex but also more refined, in order to adapt to each situation. Short-course radiotherapy can be an excellent alternative to reduce radiotherapy waiting lists in public institutions, with the possibility of good oncological results and good cost-effectiveness.

Objective: This study aims to evaluate the feasibility, safety and pathological response of short-course scheme of radiotherapy followed by neoadjuvant chemotherapy at the Brazilian Public Health System in patients with locally advanced middle/distal rectal cancer.

Methods: This was a descriptive, unicentric, retrospective survey of case series. Data were collected from 24 medical records. Patients were aged 18 years or older, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, had a biopsy-proven, newly diagnosed, primary, locally advanced rectal adenocarcinoma, which was classified as high risk on pelvic MRI (with at least one of the following criteria, clinical Tumor [cT] stage cT4a or cT4b, extramural vascular invasion, clinical Nodal [cN] stage cN2, involved mesorectal fascia, or enlarged lateral lymph nodes). All the patients were diagnosed between August 2020 and March 2022. The clinical characteristics were evaluated related to each patient at the time of diagnosis, the initial clinical staging, the type of chemotherapy performed and analyzed the pathological response obtained after treatment. All of them received the same protocol of short-course radiotherapy (25Gy/5fr).

Results: A total of 24 patients were evaluated, and only 1 did not undergo surgery. All the patients who underwent surgery had tumor downstaging. Of these, 9 patients (39%) had a complete pathological response, and 14 (61%) had a partial pathological response. One patient chose not to undergo the surgery by his or her own decision and in this case a complete clinical response was observed. In neoadjuvant treatment after short course radiotherapy, 22 (91.7%) patients were treated with Capox and 2 (8.3%) with Folfox. Four (16.6%) patients were unable to complete the chemotherapy regimen due to toxicity.

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Conclusion: Short-course radiation therapy represents a treatment alternative to long-course chemoradiation, with adequate adherence and with the possibility of shortening radiotherapy waiting lists for patients with locally advanced rectal cancer treated in the Brazilian Public Health System.

Introduction

Colorectal cancer represents an important disease in terms of incidence, morbidity and mortality [1]. In Brazil it represents the second most common cancer in the male and female population, behind only prostate and breast cancer respectively [2]. Surgical resection is the cornerstone of curative treatment for localized and/or locally advanced Rectal Cancer (RC). According to recent literature, two neoadjuvant treatments with radiotherapy are effective: Long-Course Chemoradiotherapy (LCCRT) (50.4 Gy in 28 fractions with concurrent fluorouracil-based chemotherapy) or short-course radiotherapy (SC-RT) (25 Gy in 5 fractions followed by chemotherapy). Some prospective randomized trials have compared these two treatment approaches and suggested no difference in short-term disease outcomes, but there's some exceptions. There were two published phase III trials that explored whether SC-RT plus chemotherapy is superior to LCCRT: The STELLAR and Polish II trials. The Polish II trial hypothesized that delaying surgery following SC-RT and adding consolidation chemotherapy would increase the radical resection rate compared with CRT alone. The preliminary results showed that acute toxicity and 3-Year Overall Survival (OS) were better with SC-RT combined with chemotherapy than LCCRT. In the STELLAR trial, patients were randomly assigned to receive either 5 Gy × 5 and 4 courses of CAPOX (SC-RT group) or 50 Gy in 25 fractions concurrently with capecitabine (LCCRT group). There was no significant difference in metastasis-free survival or locoregional recurrence, but the SC-RT group had better 3-year OS than the LCRT group (86.5% vs. 75.1%, p = 0.033) [3].

Multimodal approaches in the treatment of localized rectal adenocarcinoma have changed the natural history of the disease. In the scenario of the unified Brazilian public health system, it is extremely important to evaluate more cost-effective treatments. Short-course radiotherapy can be an excellent alternative to reduce radiotherapy waiting lists in public institutions, with the possibility of good oncological results and good cost-effectiveness.

Published in January 2021, the RAPIDO trial, a randomized, open-label, phase 3 trial, shows that short-course radiotherapy followed by 18 weeks of chemotherapy before surgery decreases the probability of disease-related treatment failure compared with chemoradiotherapy with or without adjuvant chemotherapy and high rate of pathological complete response in the experimental group. Since then, it has become one of the treatment options, bringing a promising treatment in locally advanced rectal cancer [4].

This study aims to evaluate the feasibility, safety and pathological response rate of the short-course scheme of radiotherapy followed by neoadjuvant chemotherapy at the Brazilian Unified Health System in patients with locally advanced middle/distal rectal adenocarcinoma.

Material and methods

Patient population

Patients were aged 18 years or older, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, had a biopsy-proven, newly diagnosed, primary, locally advanced rectal adenocarcinoma, which was classified as high risk on pelvic MRI (with at least one of the following criteria, clinical Tumor [cT] stage cT4a or cT4b, extramural vascular invasion, clinical Nodal [cN] stage cN2, involved mesorectal fascia, or enlarged lateral lymph nodes). All the patients were diagnosed between August 2020 and March 2022. Patients with secondary malignancy, insufficient data on electronic medical record, metastatic disease were excluded from the study.

Methods

This was a descriptive, unicentric, retrospective survey of case series. The data were collected from electronic medical records by one investigator. TASY system was used, and the medical records were screened through searching. The clinical characteristics were evaluated related to each patient at the time of diagnosis, the initial clinical staging, the type of chemotherapy performed and the pathological response obtained after treatment was analyzed. All of them received the same protocol of short-course radiotherapy (25Gy/5fr).

Results

A total of 24 patients were analyzed. The characteristics of the study population are detailed in the Table 1.

A total of 24 patients were evaluated and 62% of them were men. The median age at diagnosis was 59 years. All of them had good clinical performance and about 70% had no history of smoking. Histological grade 2 was present in 70% of diagnoses and tumor location was in the middle (45.83%) or distal (54.17%) rectum. The predominant clinical staging was IIIB representing 58.33% of patients.

In neoadjuvant treatment after short course radiotherapy, 22 (91.7%) patients were treated with Capox and 2 (8.3%) with Folfox (Table 2). One patient chose not to undergo the surgery by his or her own decision and in this case a complete clinical response was observed. All the patients who underwent surgery had tumor downstaging. Of these, 9 patients (39%) had a complete pathological response, and 14 (61%) had a partial pathological response (Table 3).

The mean time interval between diagnosis and the onset of radiotherapy was 97.58 days. The shortest time interval was 32 days and the longest time interval was 159 days. The mean time interval between the end of neoadjuvant chemotherapy and the surgery was 59.21 days. The shortest time interval was 30 days and the longest time interval was 132 days (Table 4).

There were no serious side effects related to radiotherapy and no treatment-related deaths. The most common were radiodermitis and low-grade retitis. Four (16.6%) patients were unable to complete the chemotherapy regimen due to grade 3 diarrhea-related toxicities. Adverse effects data were consistent with the literature and the treatment regimen was confirmed safe.

Table 1: Descriptive analysis.

Population	Total: 24 (%)
Sex	
Male	15 (62.5 %)
Female	9 (37.5 %)
Age (median)	59.5 years (47.5 – 65)
ECOG	
0	14 (58.33 %)
1	10 (41.67 %)
Smoking	
Active	5 (20.83 %)
Former smoker	2 (8.33 %)
Never smoked	17 (70.83 %)
Tumor grade	
Grade 1	4 (16.67 %)
Grade 2	17 (70.83 %)
Grade 3	3 (12.50 %)
Tumor localization	
Middle rectum	11 (45.83 %)
Distal rectum	13 (54.17 %)
cT Stage	
cT3	9 (37.50 %)
cT4a	2 (8.33 %)
cT4b	13 (54.17 %)
cN Stage	
cN0	4 (16.67 %)
cN1	12 (50.00 %)
cN2	8 (33.33 %)
Mesorectal fascia diseased	
Yes	16 (66.67 %)
No	8 (33.33 %)
Clinical stage	
IIC	4 (16.67 %)
IIIB	14 (58.33 %)
IIIC	6 (25.00 %)

Table 2: Chemotherapy regimens.

	Total: 24
Folfox	21 (91.7 %)
Capox	3 (8.3 %)

Table 3: Response assessment in patients who underwent surgery.

Patients	Total: 23
Downstaging	23 (100 %)
Partial response	14 (61.00 %)
Complete response	9 (39.00%)

Table 4: Treatment time intervals.

Diagnosis and start of treatment	97.58 (32-159) days
End of neoadjuvant treatment and surgery	59.21 (30-132) days

Discussion

The treatment of rectal cancer represents a major challenge in clinical practice, especially in the context of the Brazilian Public Health System, where we have a delay in starting treatment. Currently, TNT is considered as a standard procedure in the treatment of locally advanced rectal cancer. This treatment is related to an important tumor downstaging, which leads to less aggressive surgeries and increases the possibilities of organ preservation strategies, without compromising the oncological treatment [5].

Surgery still plays a key role in the treatment of rectal cancer. However, there are prospects that for certain subgroups, such as patients with microsatellite instability, immunotherapy may open new horizons for non-surgical treatments [6]. However, considering the characteristics of the Brazilian Public Health System, in the event of approval of these new treatment strategies, this is something challenging for our population. Therefore, the different neoadjuvant therapy strategies will remain in the medium and long term as standard treatment. Thus, the discussion of cost effectiveness is necessary in this context.

There are TNT options consisting of long course or short course radiotherapy strategies. We still don't have a head-to-head study that compares the best strategy in terms of oncological outcomes, but the short course strategy can be considered more cost-effective in this context, despite existing a limitation of our study that is the absence of pharmacoeconomic evaluation [7].

Short-course radiotherapy followed by TNT has emerged as a potential treatment paradigm in the management of locally advanced rectal cancer. Despite the emerging evidence for SCRT-TNT, data comparing the cost-effectiveness of SCRT-TNT with conventional LCCRT are scarce. It demonstrates the cost-saving economic advantage of SCRT-TNT compared with LCCRT with or without adjuvant chemotherapy using data from a single prospective phase 3 randomized clinical trial. The results corroborate the analyses from a previously published economic study by Raldow et al., [3] which demonstrated that LCCRT was not cost-effective compared with SCRT when combined with conventional adjuvant chemotherapy. Notably, the consolidation chemotherapy regimen in the SCRT group of the Polish II trial only used 3 cycles of FOLFOX4 (FOLFOX regimen including both

a bolus and infusion of fluorouracil), whereas the RAPIDO trial used CAPOX for 6 cycles or FOLFOX4 for 9 cycles [7].

Compared with conventional treatment strategies using adjuvant chemotherapy, TNT is hypothesized to be advantageous owing to the decreased rate of toxic effects and increased tolerability, higher rates of clinical complete response and pathological complete response, increased tumor regression that could enhance complete (R0) resection rates, and early introduction of systemic treatment to address micrometastasis that may translate to disease-free survival benefits. Together, optimization of adaptive treatment strategies through TNT allows for patient selection for potential organ preservation via nonoperative management, which is another emerging paradigm for the management of rectal cancer [7].

The results found in the descriptive analysis of our study were compatible with those of the phase 3 RAPIDO trial, which makes us consider this strategy as a great treatment option in public health system. Of the 912 eligible patients in the RAPIDO trial, 462 of them were treated with short course radiotherapy and had a complete pathological response rate of 28% [4].

The long waiting times among diagnosis, staging and initiation of treatment are a reality of the Brazilian Public Health System and can have a negative impact on the oncological results obtained. In this sense, short course radiotherapy treatment strategies can reduce the waiting period for the start of treatment, as they allow more patients to be treated in a short period of time. Although we are dealing with high-grade radiodermatitis and low-grade retitis, these side effects are manageable, making this treatment feasible for patients in our center.

In conclusion, neoadjuvant treatment with short course radiotherapy is a feasible strategy, with good oncological results and should always be discussed as an option for patients with locally advanced rectal cancer who will be treated in public health.

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