OSWALDO CRUZ
HOSPITAL ALEMÃO
INTERNATIONAL RESEARCH SITE

Chemoradiotherapy and consolidation chemotherapy with or without oxaliplatin for distal rectal cancer and Watch and Wait. (CCHOWW)

Clinical trials - NCT: 05000697

Version 3.0
23/January/2024

This document is confidential and its use, reproduction, disclosure, and publication are restricted to primary investigators and the sponsor

OSWALDO CRUZ
HOSPITAL ALEMÃO
INTERNATIONAL RESEARCH SITE

Chemoradiotherapy and consolidation chemotherapy with or without oxaliplatin for distal rectal cancer and Watch and Wait. (CCHOWW)

Clinical trials - NCT: 05000697

Version 3.0
23/January/2024

LIST OF ABBREVIATIONS

nCRT: Neoadjuvant Chemoradiotherapy

Ccr: Complete Clinical Response

WW: Watch and Wait (Strict Surveillance Program)

TME: Total Mesorectal Excision.

APR: Abdominal Perineal Amputations

ISR: Intersphincteric Resections

pCR: Complete Pathological Response

CRT: Chemoradiation

5-FU: Fluorouracil

TNT: Total Neoadjuvant Therapy

RT: Radiotherapy

IMRT: Modulated Intensity Radiotherapy

ICRU: International Commission on Radiation Units and Measurements SIB-IMRT: Modulated Intensity Technique With Integrated Reinforcement

BED: Biological Effective Dose

CTV: Clinical Target Volume

GTV: Macroscopic tumor volume

PTV: Target Planning

ITV: Internal Target Volume

RM: Magnetic Resonance Imaging

T2 - Thoracic

CIP: International Research Site

HAOC: Hospital Alemão Oswaldo Cruz

CONEP: National Research Ethics Committee

Postal code: Institutional Review Board or Ethics Committee

CRF [Regional Pharmacy Council]: Case Report Form

ICF: Informed Consent Form

LIST OF TABLES

Compliance Statement

This document is a protocol for a research project. This study will be conducted in compliance with all the stipulations of this protocol, the current IRC/CONEP rules, and the guidelines established by the Documento das Américas and the Good Clinical Practice Guide (E6/R2) of the ICH- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

SUMMARY

1. TRIAL INFORMATION

1.1 PROTOCOL SYNOPSIS

Data Category	Information
Main Sponsor	**Hospital Alemão Oswaldo Cruz**
Contact for public queries	+55 11 -3549-0729 / +55 11 -98159-4568 dvilanova@haoc.com.br
Contact for scientific queries	roperez@haoc.com.br
Public title	Chemoradiotherapy and consolidation chemotherapy with or without oxaliplatin for distal rectal cancer and Watch and Wait. (CCHOWW)
Health condition(s) or problem(s) studied	Distal Rectal Cancer
Inclusion Criteria	1. Age ≥18 years; 2. ECOG 0-2 or KPS≥70; 3. Primary rectum adenocarcinoma (biopsy-confirmed) accessible on digital rectal examination (at least the lower border) by the assistant colorectal surgeon; 4. Endoscopic documentation of the primary lesion; 5. Chest CT scan and contrast-enhanced CT or abdomen magnetic resonance without evidence of metastatic disease;

	6. High-resolution magnetic resonance imaging performed on a 1.5T or 3.0T system using a surface coil with: sagittal T2-weighted images including the anal margin and sacrum; T2-weighted oblique axial images acquired in a perpendicular plane to the long axis of rectal wall guided by the sagittal images; coronal images acquired parallel to the anal canal plane. Small FOV (field of view) (16-18cm), section thickness of 3mm, matrix size increased so that the voxel is from 1.0 to 1.5mm^3) and number of excitations increased to get a satisfactory signal; 7. Radiological criteria (centralized): a. Inferior border of tumor ≤1cm (including tumors at or below) the anorectal ring defined in sagittal or coronal views by magnetic resonance imaging; b. mrT2, mrT3 (any subclass) c. mrN0 or mrN1; d. mrEMVI: any status e. mrCRM: any status

Exclusion Criteria	1. Pregnancy 2. ECOG ≥3 or KPS<70 3. mrT4 4. mrN2 5. Not consenting to participation 6. Metastatic disease (any type; internal iliac and obturator lymph node involvement are considered local disease and not metastatic disease, so not considered exclusion criteria) 7. Prior pelvic radiotherapy 8. Underlying neuropathy 9. Receiving treatment with another anticancer drug or method 10. Presence of uncontrolled life-threatening illnesses.
Study Type	Randomized prospective clinical trial
Sample size	216 subjects (108 per group)
Purposes	To compare the results of consolidation chemotherapy with fluoropirimidine alone or fluoropirimidine + oxaliplatin in reaching a cCR after nCRT in the context of a randomized prospective clinical trial.
Clinical endpoints	Primary endpoints: • To reach a complete or nearly complete clinical response achieved at 18 weeks from the end of the last day of radiotherapy using clinical (rectal digital), endoscopic and radiological exams (mrTRG classification).

	Endoscopy and radiology will be assessed by the Central Committee of Response Assessment. Secondary endpoints: • Surgery-free survival in 3 years • TME-free survival in 3 years • Metastasis-free survival in 3 years • Regrowth-free survival in 3 years • Colostomy-free survival in 3 years
Treatment	1- Consolidation group with 1 drug: RT (54Gy) with daily capecitabine 825mg/m2 twice daily, followed by capecitabine 1000mg/m2 twice daily for 14 days in a 21-day cycle for 4 cycles (12 weeks), starting 1 to 2 weeks after the end of radiotherapy; 2- Consolidation group with 2 drugs: RT (54Gy) plus daily capecitabine 825mg/m2 twice daily, followed by mFOLFOX6, XELOX for 6 cycles (12 weeks), starting 1 to 2 weeks after the end of radiotherapy.
Length of Study	The study lasts 4 years. If the arm with 2 drugs shows response rate ≥25% after 72 patients, the study will be stopped (efficacy).

	If the 2-drug arm shows a response rate of less than 5% after 72 patients, the study will be stopped.
Ethical Aspects	The study will be conducted according to Resolutions no. 466/12 and 251/97 of the National Health Council - Ministry of Health, Declaration of Helsinki's principles and International Conference of Harmonisation (ICH) Good Clinical Practices/Good Clinical Practices: Document of Americas, as well as the local legislation.

1.2 Protocol Background

Protocol	
Version	**Final date**
1	10/Nov/2021
2.0	22/Jun/2023

1.3 Contributions

Author Name	Function
Angelita Habr-Gama	Conception, Project writing,
Rodrigo Oliva Perez	Conception, Project writing, Initial assessment of patients (central endoscopic review); Final assessment of patients (central endoscopic review - related to the primary clinical endpoint)
Guilherme Pagin São Julião	Conception, Project writing, Initial assessment of patients (central endoscopic review); Final assessment of patients (central endoscopic review - related to the primary clinical endpoint)

Bruna Borba Vailati	Conception, Project writing, Initial assessment of patients (central endoscopic review); Final assessment of patients (central endoscopic review - related to the primary clinical endpoint)
Cinthia Denise Ortega	Conception, Project writing, Initial assessment of patients (central radiological review); Final assessment of patients (central radiological review - related to the primary clinical endpoint)
Thiago Jorge	Conception, Project writing
Renata D'Alpino	Conception, Project writing
Jorge Sabbaga	Conception, Project writing
Patricia Bailão Aguilar	Conception, Project writing
Fabio Roberto Kater	Conception, Project writing

1.4 Sponsorship

Hospital Alemão Oswaldo Cruz (HAOC) will assume the responsibilities regarding RDC No. 09/2015 related to ICH E6 (R2), ethical submission and project follow-up. This trial will not be financially supported by an external institution.

2. INTRODUCTION

The significant response to neoadjuvant chemoradiotherapy (nCRT) has resulted in a dramatic change in the treatment of distal rectal cancer.[1] The observation that some patients have an near complete and complete tumor response to treatment has led experts to consider organ preservation strategies to avoid the need for radical surgery. [2-5] Patients who developed a complete clinical response (cCR) defined by clinical, endoscopic and radiological criteria were followed up without immediate surgery and enrolled in a strict surveillance program (Watch and Wait - WW) with oncological results comparable to those of radical surgery. [6-9] Ultimately, these patients would avoid the risk of immediate postoperative morbidity and mortality, in addition to the potential negative consequences on urinary, sexual, and anorectal function often observed after total mesorectal excision (TME).[10-12] In addition, patients treated using the WW strategy would avoid the need for a temporary/permanent stoma - a particularly relevant aspect among patients with distal tumors. [13] In this group of patients, abdominoperineal amputations (APR) with a definitive ostomy or intersphincteric resection (ISR) with poor postoperative anorectal function are the only radical surgical alternatives available. [14.15]

On the other hand, patients treated without immediate surgery after reaching a cCR remain at risk of local regrowth of the primary tumor. Recent evaluation of large international databases suggests that the 3-year risk of local regrowth is nearly 25%. [5,16] Local regrowths are often restricted to the intestinal wall and usually amenable to salvage resection with proper long term local disease control. [17-19] Furthermore, patients reaching a cCR are still at risk of developing distant metastases. Comparison between patients with cCR treated by WW and patients with pathological complete response (pCR) treated by radical surgery shows similar rates of distant metastases. [9,20] However, patients with initial cCR followed by local regrowth appear to have a higher risk of metastatic disease development.[20] These latter patients may represent a distinct group of patients, because full pathologic response was never actually reached. It is still controversial whether immediate radical surgery in this specific subgroup of patients would have prevented the development of distant metastases observed after the diagnosis of local regrowth.[21]

Ultimately, organ preservation has become an attractive alternative for patients with distal rectal cancer when the surgical alternatives are APR or ISR. Most studies until the present moment have reported cCR rates of nearly 25% in sites practicing WW and using standard CRT regimens similar to the experimental arm of the German study (2 cycles of 5FU-based chemotherapy).[9] In this scenario, several alternatives were suggested to increase the chances of reaching a complete clinical response and allow the opportunity for an organ preservation strategy.[22]

Several particularities of neoadjuvant treatment can affect tumor regression rates in rectal cancer.[23-25] Studies suggest that specific characteristics of the radiotherapy and chemotherapy regimen can influence complete response rates. Data provided by several studies using different doses of radiation in rectal cancer suggest that there is an increase in complete response rates as total doses increase.[24] Radiosensitizing chemotherapy may also affect response rates to neoadjuvant treatment. Additional incorporated chemotherapy after completion of radiotherapy (consolidation chemotherapy) also significantly increased clinical and pathological complete response rates.[22,25-27] Early retrospective studies (before the introduction of total neoadjuvant therapy concept - TNT) suggested that including additional chemotherapeutic agents (beyond 5FU / fluoropirimidines concomitantly used with RT) in nCRT regimens would significantly increase pCR rates. Oxaliplatin was the most commonly chemotherapeutic agent used with 5FU. Unfortunately, subsequent randomized controlled trials have failed to demonstrate significant increases in pCR rates when oxaliplatin is added to standard nCRT regimens. Instead, a significant increase in treatment-related toxicity was observed. [28]

A single phase 2 study was performed using additional 5FU bolus cycles with the purpose of improving cCR rates (rather than pCR). This study included 4 additional cycles of bolus infusion of 5FU (for the usual 2 cycles) to be administered during RT but also during the “washout” period. Surprisingly, cCR rates were nearly 50% of all treated patients, including tumors with initial stage T2/T3.

While the increase in cCR rates could have been attributed to the increase in the number of chemotherapy cycles dosed during and after completion of RT ("consolidation" chemotherapy, although not named as such at that moment), an additional change in regimen could also have contributed to the increase in cCR rates: the RT dose escalation that was also incorporated into this nCRT regimen (50.4Gy to 54Gy).[27,29] Therefore, it was not possible to establish a direct cause-effect relationship between rates of cCR and consolidation chemotherapy or dose escalation of RT. Regardless of the difficulty of establishing the relationship between cause and effect, this “new” nCRT regimen with consolidation chemotherapy using fluoropirimidine alone started to be used as the choice regimen (standard) in some institutions after seeing such very promising preliminary results and minimal negative impact on treatment toxicity.

Another non-randomized prospective study also suggested the potential effects of consolidation chemotherapy on treatment response. The clinical trial known as the “Timing Trial” included patients with locally advanced disease in 4 different arms (sequentially, non-randomized).[26] The main purpose of the trial was to investigate progressively longer interval periods between the completion of RT and surgery in response rate: 6, 12, 18 and 24 weeks. However, patients included in 12, 18 and 24 received consolidation chemotherapy with 2 drugs (fluoroprimidine and oxaliplatin - mFOLFOX for 2, 4 or 6 cycles, respectively). A significant increase in pCR rates was observed the higher the number of chemotherapy cycles with 2 consolidation drugs (pCR 25%, 30% and 38%, respectively) compared to lack of consolidation chemotherapy in patients who went on surgery at 6 weeks (pCR 18 %).[26] Once again, although the increase in pCR rates could have been attributed to the increase in the number of chemotherapy cycles (consolidation), the effect of longer intervals in time could also have contributed to this observation.

Finally, with the introduction of the TNT concept in which adjuvant chemotherapy is administered immediately before nCRT (induction) or after nCRT (consolidation), early experiences (using regimens with 2 or 3 drugs) have shown an increase in complete response and chances of organ preservation in these patients.[30,31]

Both studies using consolidation (RAPIDO) and induction (PRODIGE) compared to the “conventional” nCRT regimen demonstrated significantly higher rates of complete pathologic response. Even though there was no possibility of organ preservation in either study, the higher rates of pathological complete response in the experimental arms of both trials suggest the potential impact of consolidation/induction with additional chemotherapy in increasing the possibility of organ preservation.[31] (Conroy et al. Lancet Oncol 2021 in press) A prospective randomized trial (OPRA) showed preliminary results of the comparison between induction and consolidation chemotherapy (FOLFOX). Although there was no difference in disease-free survival rates in 3 years between arms, organ preservation rates were significantly better for consolidation chemotherapy compared to induction chemotherapy.

In summary, there is evidence to support that consolidation chemotherapy can contribute to increased response rates in rectal cancer after nCRT. Both 5FU and 5FU/oxaliplatin-based chemotherapy consolidation regimens have shown promising results.

Although the single-drug consolidation regimen had already been incorporated into the services routine for more than a decade, consolidation chemotherapy including oxaliplatin has been reaching significant space in different sites in Brazil and in the world, and its regular use in neoadjuvant therapy is already widely adopted. However, no studies have addressed the benefit of oxaliplatin during consolidation to improve response rates compared to consolidation with 5FU alone. Although prior studies including oxaliplatin were negative and associated with increased toxicity, all of these trials used oxaliplatin concurrently with RT and we do not have the real dimension of benefit that oxaliplatin can add in the context of consolidation chemotherapy. Both strategies (consolidation with 5FU alone or 5FU/oxaliplatin) are already widely used, however, no study has directly compared these two types of treatment. The addition of oxaliplatin may be associated with higher response rates, but it may also simply add higher rates of morbidity/toxicity without a significant increase in response.

3. RATIONALE

Patients with rectal cancer near the anus often require delicate and time-consuming surgery to treat the disease. This surgery can result in some important consequences such as difficulties in urinating, difficulties to have sexual intercourse (in men with difficulty in penis erection) and use of a feces collection bag in the belly (colostomy/ileostomy). Despite this, in patients treated with radiotherapy and chemotherapy before this surgery, near to one in three patients have complete tumor elimination.

In some specialized centers for the cancer treatment, such patients have been followed up with periodic exams, without the immediate need for surgery. In these cases, surgery would only be performed if exams show that the tumor has grown or appeared again. Several researches studied different combinations and doses of radiotherapy and chemotherapy to try increasing the chances of the tumor disappearance and, therefore, to avoid surgery in a larger number of patients.

In general, the treatment is performed with radiotherapy and chemotherapy together (for approximately 6 weeks) and then a second part with chemotherapy alone. However, it is unknown if combining chemotherapy with 2 drugs leads to a greater chance of tumor disappearance than chemotherapy with one drug. Many hospitals have used both treatment methods (with one or two drugs in this phase of treatment). But if the combination of two drugs increases the chances of tumor disappearance was not studied yet.

4. OBJECTIVES

To compare the results of consolidation chemotherapy with fluoropyrimidine alone or fluoropirimidine + oxaliplatin in reaching a complete or near-complete clinical response after neoadjuvant chemoradiotherapy (nCRT).

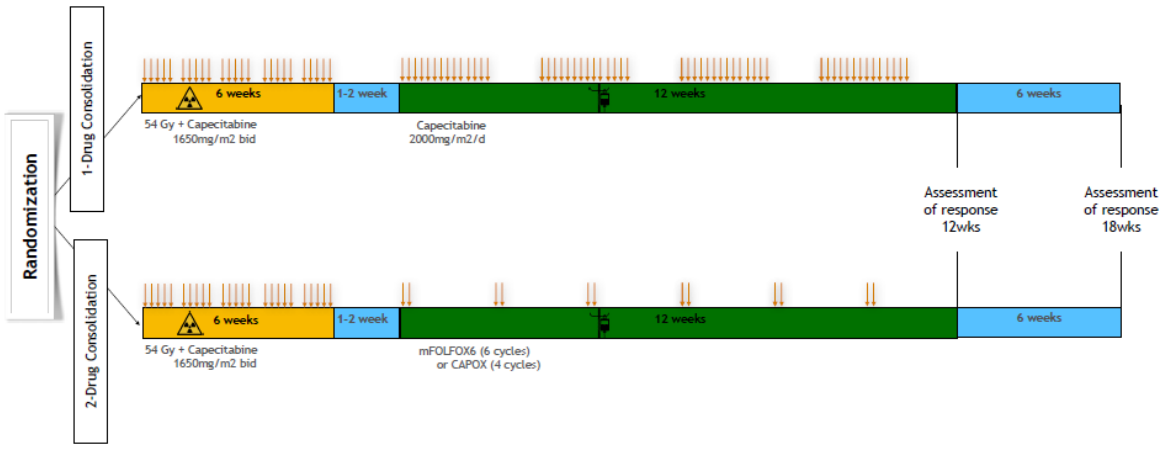
5. STUDY DESIGN

5.1 Treatment

1) Consolidation group with 1 drug: RT (54Gy) with daily capecitabine 825mg/m2 twice daily, followed by capecitabine 1000mg/m2 twice daily for 14 days in a 21-day cycle for 4 cycles (12 weeks), starting 1 to 2 weeks after the end of radiotherapy; (Alternative consolidation regimens will include infusion or bolus FU);

2) Consolidation group with 2 drugs: RT (54Gy) plus daily capecitabine 825mg/m2 twice daily, followed by mFOLFOX6, XELOX for 6 cycles (12 weeks), starting 1 to 2 weeks after the end of radiotherapy.

Figure 1. Study design



5.2 Radiotherapy

Preoperative radiotherapy will be administered on a linear accelerator in the prone or supine position, preferably with a full bladder. The use of an abdominal board is allowed.

Three or four isocentric fields as well as the IMRT technique are allowed as long as all bundles are treated daily. Dose distribution and calculation should be performed on CT or RM and specified according to ICRU 50 guidelines.

Dose specification: All patients will receive 25 daily fractions of 1.8 Gy up to a total dose of 45 Gy in the pelvic field, including the tumor bed with a margin and the regional lymph nodes. A field reduction after 45 Gy is recommended up to 54 Gy. The last 5 fractions will then be delivered to the tumor bed with a margin.

Alternatively, radiotherapy can be administered using the intensity modulated technique with integrated reinforcement (SIB-IMRT). The prescribed dose for regional lymph nodes and areas at risk for microscopic disease will be 45Gy in 25 fractions (1.8 Gy per fraction); while the 'raw' tumor (i.e., primary tumor and enlarged/metabolically active lymph nodes) is primed with a higher dose of 52.5Gy in 25 fractions (2.1 Gy per fraction). The entire SIB-IMRT course will be administered once a day, 5 fractions per week for 5 weeks.

Table 1: Administration of Radiotherapy

change native 1	30 x 1.8Gy	Total Dose 54Gy	BED=63.72Gy10	BED=62.10Gy12
change native 2	25 x 2.1Gy	Total Dose 52.5Gy	BED=63.53Gy10	BED=61.69Gy12

5.2.1 Target volume:

pelvic CTV

- Primary tumor
- mesorectum: Distally, only lymph nodes or tumor deposits up to 4cm are included. For tumors in the lower rectum, this means that the entire mesorectum area up to the pelvic floor is included.
- Pre-sacral ganglia and ganglia throughout the superior rectal artery: As local recurrences are very uncommon above S1 - S2, lymph nodes above this level should not be included unless there are signs of pathological presacral lymph nodes. In this case, the cranial limit of the CTV must be at least 1 cm above the most cranial pathological lymph node.

- Lateral pelvic lymph nodes: until they reach the level of the obturator canal, internal iliac artery to the bifurcation of external iliac artery. The CTV cranial border is, in most cases, just below the bifurcation of internal and external iliac arteries. In most patients, it occurs at the level of S1 - S2.
- Ischiorectal fossa and anal canal: Included in pelvic CTV only if the tumor grows into the levators or down into the anal canal.
- Lymph nodes along the external iliac artery: Included if tumor grows in anterior organs such as prostate, urinary bladder, cervix, vagina or uterus to such an extent that external lymph nodes are at risk of metastases.

5.2.2 Boost GTV:

GTV is the visible primary tumor and visible pathological lymph nodes.

The GTV boost plus a 2 cm margin within the same anatomical compartment where the tumor is, for the 45-Gy dose, also around the radiologically compromised lymph nodes.

5.2.3 Target Planning

Target Planning (PTV) should normally be defined and includes CTV and internal target volume (ITV) and a required margin for the configuration. Such margins depend on several factors related to the equipment of each radiotherapy center.

5.3 Chemotherapy

5.3.1 Concomitant chemotherapy:

Capecitabine: 825mg/m2 twice daily on radiotherapy days

5.3.2 Consolidation chemotherapy:

Consolidation capecitabine: 1000mg/m2 bid, for 14 days, in 3-week cycles, for 4 cycles.

Consolidation options with oxaliplatin:

➢ mFOLFOX6: Oxaliplatin 85mg/m2 plus Leucovorin 400mg/m2 in 2-hour infusion. 5FU 400mg/m2 bolus infusion, followed by 5FU 2400mg/m2 as a 46-hour infusion Q2W for 6 cycles

➢ CAPOX: Oxaliplatin 130mg/m2 in 2-hour infusion. Capecitabine 1000mg/m2 bid for 14 days, starting on the night of oxaliplatin infusion. Repeating Q3W for 4 cycles.

6. Clinical Response Assessment

Response assessment will be performed at 12 weeks (and 18 weeks from the last date of radiotherapy if cCR or near complete response is detected at 12 weeks). All patients will perform endoscopic reassessment, digital rectal examination and high-resolution MRI. Endoscopic biopsies will be at the discretion of the research site/institution responsible for the patient, not as a part of the trial.

Patients with complete or near complete clinical response at 12 weeks (assessed by the trial's Central Committee) will be suggested to perform a new reassessment after 18 weeks of the last dose/day of RT. The decision regarding the definitive treatment of the patient 18 weeks after the end of treatment will be entirely responsibility of each patient's institution, regardless the result and evaluated by the trial's Central Committee.

6.1 Definition of Complete Clinical Response:

- **Endoscopic**: whitish scar, telangiectasias, no masses or ulcerations[6]
- **Clinical:** no irregularities or hardened areas[6]
- **Radiological:** mrTRG1: fibrosis with low signal seen on images

T2-weighted replacing the primary tumor; no diffusion restriction on diffusion-weighted images; no lymph nodes with border irregularity or mixed signal intensity; without extramural vascular invasion[32-35]

6.2 Definition of Near Complete Response

- **Endoscopic:** residual tumor ≤2cm (or ≥70% reduction in original tumor volume/size) [4,36,37]
- **Clinical:** Superficial ulceration or small (questionable) irregularity of mucosa, rectal wall

- **Radiologic:** mrTRG2 with predominantly low-signal fibrosis with foci of tumor signal in intermediate intensity seen on T2-weighted images with or without diffusion restriction; mrTRG1: fibrosis with low signal intensity seen on T2-weighted images replacing primary tumor with diffusion restriction; no lymph nodes with border irregularity or mixed signal intensity; without extramural vascular invasion [36]

The decision to undergo a surgery or not after 12 or 18 weeks is entirely at the discretion of each assisting surgeon/institution and subject. Such a decision does not interfere in any way with the primary clinical endpoint of the trial regarding the response assessment.

Only those patients with an near complete/complete response at the time of response assessment at 12 weeks will be recommended for a second response assessment at 18 weeks after the end of treatment. Patients with incomplete response (poor response) at 12 weeks will be recommended for surgery at that moment.

The definition of complete radiological response, described below (centralized), as well as the clinical and endoscopic findings will be discussed by the central evaluation committee. The meetings for findings validation will be by means of regular virtual meetings of the central committee along with the surgeon and radiologist assistant of each patient.

6.3 Suggested protocol for Clinical Response Assessment

- **Suggested magnetic resonance imaging assessment:**

➢ **1.5T** - FRFSE; TR/TE: 3300/120 (ms); cut thickness/interval: 3.0/0; matrix: 256 x 256; NSA 8)

➢ **3.0T** - FRFSE; TR/TE: 8000/150 (ms); cut thickness/interval: 3.0/0; matrix: 288 x 288; NSA 5) Diffusion (DWI) -inclusion of a high b-value of at least 800.

- **Suggested Endoscopic Assessment:**

Endoscopic assessment with flexible endoscope (preferably gastroscope for retroflexion); direct endoscopic view and retroflexion of the primary tumor/scar. Endoscopic biopsies will be at the discretion of the participating site and will not be part of the trial.

6.4 Suggested Complete or Nearly Complete Clinical Response Follow-up Protocol (“Watch & Wait”)

As it is a controversial strategy in the medical literature, the decision to under a surgery or not in patients with complete or near complete clinical response at 12 and 18 weeks after the end of radiotherapy will be entirely optional and the decision of each participating institution and the subject. The use or not of the follow-up scheme without surgery (Watch & Wait) will not interfere with the primary clinical endpoint and will not be recommended by the trial. For this reason, the exact protocol for clinical, endoscopic and radiological follow-up of patients included in this therapeutic strategy will not be suggested by the trial and will be the sole responsibility of the participating institution. Therefore, the trial will not be responsible for the costs, organization or follow-up of forms outside the standard of care of each institution.

6.5 Central Response Assessment Committee

The definition of complete radiological response, described previously (centralized), as well as the clinical and endoscopic findings will be discussed by the central evaluation committee. Meetings of findings validation will regularly occur (every 2 weeks) by virtual meetings of the central committee. As indicated in the list of authors of the paperwork and their respective contributions, the central committee for response assessment will include 1 radiologist and 3 surgeons.

7. METHODOLOGY

7.1 Type of study

Randomized prospective clinical trial with two parallel groups.

7.2 Screening Participating and Co-Participating Sites

The International Research Site (CIP) - HAOC team will identify and invite the sites to take part in the trial. Sites will be identified according to experience, recommendation and capacity to conduct the trial (population, site structure, availability of site staff and handling cases of distal rectal cancer). The site will be approved for the trial, if it includes:

- Structure to assist potential patients for this trial;
- Experience in conducting clinical trials;
- Potential to screen subjects;
- Team with availability to conduct the trial activities;

All selected participating institutions have their own infrastructure, sufficient and adequate to offer the same conditions and include subjects in the trial. No intervention, method or examination is foreseen that is not already an integral part of the routine treatment and evaluation of patients diagnosed with rectal cancer.

All institutions are aware that all procedures, treatments and clinical follow-up of the subjects included in the trial will be defined and will be the responsibility of each institution, and not of the clinical trial or the coordinating site. And aware that there will be no funding and/or sponsorship for any of the treatment/follow-up arms/parts already routinely employed in the treatment of patients with rectal cancer.

The sites will receive the regulatory package after inclusion in the *Plataforma Brasil* and approval of the study by CONEP to start submission to the local ethics committee.

The team responsible for performing the trial in each selected site shall include at least: 1 Clinical Oncologist, 1 Radiologist, 1 Endoscopist, 1 Trial Coordinator, 1 Biomedical and 1 Regulatory Affairs Analyst.

7.3 Patients

Patients with distal rectal cancer will be screened for the trial after initial clinical, endoscopic and radiological assessment. Initial staging will define eligible patients to take part in the trial. These patients must agree with the randomization and sign the informed consent form before inclusion in the research protocol.

Enrolled patients will be randomized to the one-drug group or the two-drug group.

7.4 Inclusion Criteria

01. Age ≥18 years;
02. ECOG 0-2 or KPS≥70;
03. Primary rectum adenocarcinoma (biopsy-confirmed) accessible on digital rectal examination (at least the lower border) by the assistant colorectal surgeon;
04. Endoscopic documentation of the primary lesion;
05. Chest CT scan and contrast-enhanced CT or abdomen magnetic resonance without evidence of metastatic disease;
06. High-resolution magnetic resonance imaging performed on a 1.5T or 3.0T system using a surface coil with: sagittal T2-weighted images including the anal margin and sacrum; T2-weighted oblique axial images acquired in a perpendicular plane to the long axis of rectal wall guided by the sagittal images; coronal images acquired parallel to the anal canal plane. Small FOV (field of view) (16-18cm), section thickness of 3mm, matrix size increased so that the voxel is from 1.0 to 1.5mm^3) and number of excitations increased to get a satisfactory signal;
07. Radiological criteria (centralized):
a. Inferior border of tumor ≤1cm (including tumors at level or below) of the anorectal ring defined in the sagittal or coronal section by magnetic resonance imaging;
b. mrT2, mrT3 (any subclass)
c. mrN0 or mrN1;
d. mrEMVI: any status
e. mrCRM: any status

7.5 Exclusion Criteria

01. Pregnancy
02. ECOG ≥3 or KPS<70
03. mrT4
04. mrN2
05. Not consenting to participation
06. Metastatic disease (any type; internal iliac and obturator lymph node involvement are considered local disease and not metastatic disease, so not considered exclusion criteria)

07. Prior pelvic radiotherapy
08. Underlying neuropathy
09. Receiving treatment with another anticancer drug or method
10. Presence of uncontrolled life-threatening illnesses.

7.6 Randomization

Subjects will be randomized and designated in the ratio 1: 1 in both groups (consolidation with 1 or 2 drugs) according to the randomization method by permutation of blocks of size 4.

7.7 Data Collection

The study data collection form is the electronic case report form (electronic CRF) via internet. The data will be entered into the system by the site staff. Training and support for system use will be made available to investigators by the coordinating site. The data collection and management system is validated and has safety and reliability for the study. System functionalities include: patient registration, randomization with data entry, data cleaning and export for statistical analysis.

We will use data collected directly from the patient and/or family member for 24-hour allocation confidentiality. Several procedures will ensure data quality, including:

1) All researchers will participate in a training session prior to the study start to ensure consistency of study procedures, including data collection;

2) Investigators will be able to call the study Coordinating Site to resolve questions or issues that may arise;

3) Data cleaning for identifying inconsistencies will be conducted periodically (approximately every fifteen days). Sites will be notified about the inconsistencies to provide correction;

4) Statistical techniques for identifying fraud will be performed throughout the study;

5) The Coordinating/Sponsor Site will monthly review detailed reports on data screening, inclusion, follow-up, consistencies and completeness. It will immediately take action to resolve potential issues.

7.8 Statistical Analysis

The primary endpoint (WW decision due to cCR / nearly complete) was seen in 55% and 85% at 12 weeks among patients with early cT3 and cT2 rectal cancer, respectively. In this study, there was a distribution of 66% cT3 and 33% cT2. Therefore, response rates are highly dependent on the exact T-stage distribution. Considering the inclusion of more advanced disease (late mrT3 or even mrT4 rectal cancer), we would expect 40% cCR/near-CR in one-drug arm. In this scenario, if the results in the 2-drug group are ≥60% cCR / near-CR, the study will be considered POSITIVE. Incorporation of oxaliplatin into a CRT consolidation regimen that results in ≥20% increase in cCR / near complete exceeds the potential drawbacks of treatment-related toxicity.

We assumed that the primary endpoint would occur in 40% of subjects in the one-drug group and 60% in the two-drug group, which corresponds to an absolute difference of 20% between proportions. It is estimated that a sample of 194 (97 per group) provides statistical power of 80% to detect this difference between proportions at the 5% significance level using chi-squared test and assuming two-sided hypothesis and considering 1:1 allocation ratio. The estimated rate of loss to follow-up (“drop-out” rate) is 10% in each group. Thus, the sample size calculation determines 216 subjects, with 108 subjects per group. Sample size calculation was performed using SAS 9.4 (PROC POWER procedure).

7.9 Flowchart

Table 2: Subject's flowchart detailing pre- and post-randomization activities, as well as follow-up and assessment periods.

Procedures	V1	Treatment	Range [1]	Treatment	V2 12 WEEKS[2]	V3 18 WEEKS[3]
Clinical assessment	X					
Inclusion / Exclusion Criteria	X					
Signature of the Informed Consent Form	X					
Registration of previous and concurrent drugs	X	X	X	X	X	X
Randomization	X					
Administration of therapies: Consolidation groups with 1 or 2 drugs	X	X		X		
Response Assessment: Magnetic Resonance imaging, Rectal Touch and Endoscopic Evaluation.	X				X	X
Discontinuation Criteria	X	X	X	X	X	X
Assessment of adverse events	X	X	X	X	X	X
Clinical Endpoints[4,5]					X	X

1- 1- to 2-weeks interval.

2- Response Assessment after 12 weeks. Patients with incomplete response (poor response) at 12 weeks will be recommended for surgery at that moment. Only those patients with a near complete/complete response at the time of the response assessment at 12 weeks should be submitted to response assessment at 18 weeks after the end of treatment.

3- Response Assessment after 18 weeks.

4- To reach a complete or nearly complete clinical response achieved at 12 and 18 weeks from the end of the last day of radiotherapy using clinical (rectal digital), endoscopic and radiological (mrTRG classification) criteria, the last two parameters being evaluated by a central committee. (positive clinical endpoint)

5- Patients with an incomplete response (at 12 or 18 weeks) will be considered a negative clinical endpoint.

8. Ethical Aspects

The study will be conducted according to the principles of the Declaration of Helsinki and International Conference of Harmonisation's Good Clinical Practices guidelines/Good Clinical Practices: Document of the Americas. The study protocol and other relevant documents will be submitted to the Independent Ethics Committee for collegiate evaluation and approval. All subjects or, when applicable, their legal representatives, should sign and initialize the ICF together with a member of the team responsible for explaining the document. Subjects shall be informed that the study participation is entirely voluntary and that the consent to participate in the study may be withdrawn at any time without affecting the subject's treatment or the relationship with the physician.

The study database will be created without information on the study subjects' identity; therefore, all analyses will be conducted anonymously and with ensured privacy of the subjects enrolled in the research. The information collected will be solely used for the study purpose and the results found will be published in scientific journals of this field. Every individual invited to participate in the research will be informed in written about the research purpose and procedures involved, and they can only be enrolled in the study after agreeing to participate. No study evaluation or procedure should be made prior to the obtainment of the subjects' informed consent. The Principal Investigator is responsible for ensuring that the ICF obtainment procedure is conducted according to the specifications of Good Clinical Practices.

9. POTENTIAL RISKS AND BENEFITS

9.1 Chemotherapy toxicity and dose adjustment:

Dose reduction is planned in case of severe hematological and/or non-hematological toxicity. Dose adjustments should be made according to the system showing the greatest degree of toxicity. Toxicities will be assessed using the NCI CTC, version 5.0. Treatment will be delayed until: neutrophils ≥1.5 x 109 / L and platelets ≥75 x 109 / L.

- 5FU dose modification:

Recovery from mucositis, diarrhea. If 5-FU treatment is delayed, the associated oxaliplatin dose should also be delayed. If 5-FU is permanently discontinued, oxaliplatin should also be discontinued. If toxicity requires a dosing delay of more than four weeks, the patient will be permanently withdrawn from study treatment due to toxicity. Dose modifications for hematological or GI toxicity will be based on the worst toxicity observed during the previous cycle. Upon recovery, standard dose adjustments for 5-FU toxicity should be applied. The 5-FU dose should be reduced by 20% in subsequent cycles for the following toxicities: febrile neutropenia, grade 4 thrombocytopenia, or failure of hematologic recovery to neutrophils ≥1500/□L and platelets ≥75000/□L within 2 weeks the scheduled start of the next treatment cycle; Grade 3-4 mucositis, diarrhea, or nausea or vomiting despite optimal antiemetic prophylaxis. In the mFOLFOX6 protocol, the 5FU bolus should be discontinued prior to the aforementioned reduction of continuous 5FU infusion. A second 5-FU dose reduction of 20% of the original dose may be made if the above toxicities occur again. After reducing the doses, they should not be increased again and should be continued for the rest of the treatment.

- Capecitabine:

Patients with a creatinine clearance of 30-50 mL (minutes should start CAPE treatment with 75% of the total dose). Dose modifications for hematological, skin, or gastrointestinal toxicity will be based on the worst toxicity observed during the previous cycle. Upon recovery, standard dose adjustments for capecitabine toxicity should be applied. The capecitabine dose should be reduced by 25% in subsequent cycles for the following toxicities: febrile neutropenia, grade 4 thrombocytopenia, or failure of hematologic recovery to neutrophils ≥1500/ □L and platelets ≥75000/ □L within 2 weeks the scheduled start of the next treatment cycle; Grade 3-4 mucositis, hand-foot syndrome, diarrhea, or nausea or vomiting despite optimal antiemetic prophylaxis.

- Oxaliplatin;

If a 5FU dose reduction is performed, the oxaliplatin dose should also be reduced by 25%. The neurotoxicity of oxaliplatin should be assessed prior to each dose of oxaliplatin. If neurotoxicity is grade 3, the dose of oxaliplatin should be reduced by 25%. If toxicity is grade 4, oxaliplatin should be permanently discontinued. For Grade 2 or less oxaliplatin infusion reactions to occur, oxaliplatin can be infused for up to 6 hours and the patient must receive pre-drugs such as H1 antagonists, H2 antagonists and corticosteroids. If it happens again or is grade 3 or higher, administration of oxaliplatin should be discontinued. Where available, desensitization protocols can be applied, 5FU can be continued even if oxaliplatin is discontinued.

9.2 Radiotherapy toxicity and discontinuation rules

Toxicity will be evaluated and registered according to acute radiation morbidity score criteria of the CTCAE v4.0.

Table 3: Interruption rules for radiotherapy during chemoradiation.

Adverse Event	Definition	Action
Diarrhea	Grade 4	It should be stopped until the symptoms associated with the treatment are reduced.
Other Gastrointestinal Toxicities	Grade 4	It shall be stopped and restarted according to the patient's conditions.

10. SUBJECT DISCONTINUATION

If the subject experiment any of the reasons below, the investigator must discontinue the study drug, the subject must be followed up until the end of the study and all procedures described in this Protocol must be performed:

a) Any medical condition that, at the sponsor or the investigator discretion, prevents the subject from continuing on treatment, describing the reason, with the respective proof;
b) Subjects experiencing a serious adverse event that compromise the compliance and safety of the subject;

The investigator should follow up patients until the adverse event resolves or stabilizes and is considered clinically irrelevant at the physician's discretion. In cases where the subject presents any reason for discontinuing the clinical trial protocol, the sponsor must be informed by the investigator.

In the event of any eventuality related to participation, the subject can be admitted to the hospital, with the full commitment of the medical team that will provide assistance to any intercurrences and/or adverse events.

The criteria for subject discontinuation from clinical trial are:

a) Consent withdrawal: subjects who revoke consent for any reason. The study drug used by that subject will be discontinued and follow-up will also be stopped;

b) Loss of protocol follow-up: In this case, the participating site must enter information regarding telephone contact attempts in the source document and case report form;

c) Any medical condition that, at the sponsor or the investigator's discretion, prevents the subject from comply with the protocol, describing the reason, with the respective proof. The study drug will be discontinued and follow-up will also be stopped.

11. ADVERSE EVENTS

11.1 Classification of adverse events.

An adverse event is defined as any medical adverse occurrence in a patient or subject to whom a pharmaceutical product was given and which does not necessarily have a causal relationship to the treatment (RDC no. 09, dated 20/Feb/2015).

The following are considered an adverse event:

- Suspicion of adverse drug reaction (SADR);
- Adverse event due to drug quality deviation;
- Adverse event from unapproved use of drugs;
- Drug-drug interactions;
- Total or partial therapeutic ineffectiveness;
- Intoxications related to drugs;
- Abusive use of drugs;
- Potential and real medication errors;
- Pregnancy;

- If the following occurs, it will be considered an adverse event:
- Any change to laboratory parameters, clinical evaluation, and complementary exams.

The following will not be considered an adverse event:

Elective procedures planned before the study onset, even when performed during the study period, except any complications occurring during the procedure.

All adverse events observed or spontaneously reported after the signature of the Informed Consent Form, regardless of the potential causal relationship with the study drug, shall be reported in the “Adverse Event Report Form”, in the case report form, as well as the subject’s medical report (source document). Events involving drug adverse reactions, diseases occurring during the study should also be notified.

Classifications and Evaluations made by the investigator regarding the adverse event

The investigator should evaluate each one of the adverse events according to the following parameters and definitions:

Classification of Predictability of adverse event(s)

To classify the predictability of adverse events reported during the clinical trial, we will use the investigator’s brochure as the drug safety reference document.

- Unexpected: event not described as an adverse reaction in the experimental drug brochure or in the package leaflet;
- Expected: event described as an adverse reaction in package leaflet.

Classification of the Intensity of adverse event(s)

- Mild: a problem is present in less than 25% of the time, with an intensity that a person can tolerate and rarely occurs in the last 30 days;

- Moderate: it means that a problem is present in less than 50% of the time, with an intensity that interferes in the daily life of a person and occasionally occurs in the last 30 days;

- Severe: it means that a problem is present in more than 50% of the time, with an intensity that partially changes the daily life of a person and frequently occurs in the last 30 days;

- Complete impairment: it means that a problem is present in more than 95% of the time, with an intensity that completely changes the daily life of a person and occurs every day in the last 30 days;

- Unspecified: it means that there is no sufficient information to specify the intensity;

- Not applicable: it means that it is not appropriate to use a rating (e.g., menstrual functions).

Information on the need to treat adverse events

Investigators shall report whether a clinical, pharmacological, or surgical treatment was required, as well as the need of any other clinical conduct to solve the adverse events experienced.

Classification of the seriousness of adverse event(s)

All adverse events shall be assessed for seriousness and any event resulting in any adverse experience with drugs, biological products or devices, occurring at any dose level and resulting in any of the following outcomes will be considered as serious:

- Death;
- Threat to life;
- Persistent or significant incapability/disability;
- Requires hospital admission or prolongs the admission;
- Congenital anomalies or birth defects;
- Any suspicion of infectious agent transmission by means of a
- drug product or;
- Clinically significant event.
- All situations that do not result in above-mentioned clinical endpoints

are considered as non-serious events.

Causality assessment of the adverse event(s) with the Investigational product (IP)

For a standardized causality assessment, investigators shall use the WHO-UMC (The WHO Uppsala Monitoring Center) system:

- **Certain / Defined:**

➢ Event or change (abnormal) in laboratory test with plausible temporal relationship to the administration of the intervention;
➢ It cannot be explained by disease or other intervention, drug product;
➢ Plausible response to interruption or withdrawal (pharmacologically, pathologically);
➢ Pharmacologically or phenomenologically defined event (i.e., an objective and specific disorder or a pharmacologically recognized phenomenon);
➢ Satisfactory rechallenge, if necessary;

- **Probable**

➢ Event or change (abnormal) in laboratory test with reasonable temporal relationship to the administration of the intervention;

- Unlikely to be attributed to a disease or other intervention, drug product;
- Clinically reasonable response to interruption or withdrawal;
- Rechallenge not required.

- **Possible**

- Event or change (abnormal) in laboratory test with reasonable temporal relationship to the administration of the intervention;
- It can also be explained by disease, other interventions or drug products;
- Information on the treatment withdrawal or interruption may be absent or unclear.

- **Unlikely**

- The relationship with an event or change (abnormal) in laboratory test which at the time of intervention administration seems to be unlikely (but not impossible);
- Disease or other treatment support feasible explanations.

- **Conditional / Unclassified**

- Event or change (abnormal) in laboratory test;
- More data is required for an appropriate assessment, or;
- Additional data under investigation.

- **Inaccessible / Unclassifiable**

- The report narrative suggests an adverse reaction;
- It cannot be classified as the information is not sufficient or conflicting;
- The data cannot be complemented or verified.

Information on the action taken for the Investigational Product

- None;
- Reduction;
- Held;
- Temporary withdrawal;
- Increase of dose level.

Information on the subject's evolution

The investigator should report the status evolution (clinical outcome), considering the following evolution:

- Recovered;
- Not recovered;
- Recovered with after-effects;
- Worsened;
- Death

In cases of death, the registration of the cause of death data, availability of the death certificate or medical autopsy report, if possible, is essential.

11.2 Follow-up of adverse event reports.

For all adverse event reports, regardless of their seriousness, in case additional information, follow-up is required or if any inconsistency is noted for the registry and/or assessment of the adverse event(s), this is under the investigator's responsibility.

Only adverse events considered to be serious occurring in the country must be reported to the IEC/Conep System. Report of a NON-serious adverse event is optional, and this is the prerogative of the researcher or sponsor.

12 PROCEDURES AND SPECIAL INSTRUCTIONS

12.1 Changes to Protocol

Any changes to the study protocol that may be done and influence its conduction or the safety of subjects shall be made as an amendment.

All amendments will be obligatorily submitted for approval by the Independent Ethics Committee/Independent Review Board of the participating institutions before being implemented, except administrative amendments.

12.2 Discontinuation of Subjects and Study Interruption

The study interruption may occur by investigator-sponsor or study Independent Ethics Committee/Independent Review Board's initiative, provided that there is a safety-related reason for the subjects at any time during the study conduction or other strong reason for such decision.

In case a subject who has not met the inclusion criteria was inadvertently enrolled, this subject shall be discontinued from the study, and the investigator-sponsor or its representative should be informed. Another reason that may lead to the subject's discontinuation is the consent withdrawal at any time. The date and reason for discontinuation should be noted on the case report form.

13. CONFIDENTIALITY

By signing the protocol, the investigator-sponsor agrees to keep all information collected for the study in strict secrecy, and to request the same from his/her teams and local Independent Ethics Committee/Independent Review Board. All data discovered or evidenced by the research results is confidential information which belongs to the investigator-sponsor. All information is confidential up to the publication of results.

No study subject shall be identified by their names or personal characteristics, and their data should be treated in aggregate and confidential manner, and its designation shall be made by a unique identification number. Personal information will be omitted throughout data analysis.

14. CLINICAL ENDPOINTS

14.1 Primary endpoint

To reach a complete or nearly complete clinical response achieved at 12 and 18 weeks from the end of the last day of radiotherapy using clinical (rectal digital), endoscopic and radiological (mrTRG classification) criteria, the last two criteria being evaluated by a central committee.

They will be considered as a negative event (negative clinical endpoint) if at the assessment of week 12 or 18 the response assessment (defined by the central review committee) is incomplete clinical response.

They will be considered as a positive event (positive clinical endpoint) if at assessment of week 12 and 18 the decision (defined by the central review committee) is that there was a complete clinical response or near complete clinical response.

The decision to perform WW or surgery will be at the discretion of the designated team from the participating center and the subject himself not being part of or interfering with the primary clinical endpoint previously defined by the central committee.

14.2 Secondary endpoints:

- Surgery-free survival in 3 years
- TME-free survival in 3 years
- Metastasis-free survival in 3 years
- Regrowth-free survival in 3 years
- Colostomy-free survival in 3 years

15. SCHEDULE

Identification of the Step	Start	End
Research Ethics Committee's Approval	26/Nov/2021	22/Feb/2022
Study Start	01/Feb/2022	01/Feb/2026
Enrollment of Participants	01/Feb/2022	01/Feb/2026
Data analysis, Manuscript preparation	31/Aug/2026	31/Dec/2026

16. INTERIM ANALYSIS

The Interim analysis have been established a priori by an independent committee of experts in order to provide safety and efficacy monitoring of the study.

Safety monitoring – Considering the limited sample size of the target accrual (≤220 patients), an interim analysis of safety will be performed after accrual of 50% of the sample size to estimate grade 3-5 toxicity across both arms of the study. The stopping rule for safety will be a 1-sided p-value < 0.01 (Haybittle–Peto boundary) for grade 3-5 treatment-related toxicity between study arms at the 50% accrual interim reviews.

Efficacy monitoring - Similar to safety monitoring, the independent committee will consider the outcomes for interim efficacy analysis after recruiting 50% of the desired sample for the study's primary outcome - decision to perform Watch and Wait due to a complete clinical response 18 weeks after the end of radiotherapy. The study interruption rule for efficacy will be the observation of a unilateral p-value <0.001 (Haybittle-Peto limit) for the decision to perform Watch and Wait for complete clinical response (complete clinical response rate at 18 weeks) among the study arms in the interim analysis of 50% of the sample.

17. BUDGET

Costs estimation usually charged at the Institution during diagnostic planning, treatment and patients' follow-up.

The exams used to evaluate the response to treatment (endoscopy, digital examination of the rectum and magnetic resonance imaging) are already well-established methods, widely used routinely for therapeutic decisions for patients with this diagnosis. No intervention, method or examination is foreseen that is not already an integral part of the routine treatment and evaluation of patients diagnosed with rectal cancer.

The procedures listed here include procedures that are routinely used for patients with rectal cancer as indicated by international guidelines available in the literature.

Table 4. Estimated budget for Research costs.

Chemoradiotherapy and consolidation chemotherapy with or without oxaliplatin for distal rectal cancer and Watch and Wait. (CCHOWW)	Quantity	HAOC cost (BRL)	Randomization V0	Week 6 V1	Week 12 V2	Week18 V3
Magnetic resonance imaging of pelvis	3		1		1	1
Flexible sigmoidoscopy with biopsy	3	BRL 2,416.00	0	0	1	1
Capecitabine 1000 mg	84	BRL 91.32	0	42	42	0
Capecitabine 850 MG	42	BRL 72.46	42	0	0	0
Chemotherapy per hour QT	126	BRL 469.40	42	42	42	0
Oxaliplatin	0	Included in QT	0	0	0	0
Leucovorin	0	Included in QT	0	0	0	0
radiotherapy per hour	127	BRL 482.00	1	42	42	42

Total HAOC	BRL 30,092.33	BRL 43,794.24	BRL 43,794.24	BRL 22,660.00

Total HAOC value (per patient)	BRL 140,340.81

18. BIBLIOGRAPHY

1. Kosinski L, Habr-Gama A, Ludwig K, Perez R. Shifting concepts in rectal cancer management: a review of contemporary primary rectal cancer treatment strategies. *CA Cancer J Clin* 2012; **62**(3): 173-202.
2. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg* 2004; **240**(4): 711-7; discussion 7-8.
3. Garcia-Aguilar J, Renfro LA, Chow OS, et al. Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. *Lancet Oncol* 2015; **16**(15): 1537-46.
4. Rullier E, Rouanet P, Tuech JJ, et al. Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. *Lancet* 2017; **390**(10093): 469-79.
5. van der Valk MJM, Hilling DE, Bastiaannet E, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet* 2018; **391**(10139): 2537-45.
6. Habr-Gama A, Perez RO, Wynn G, Marks J, Kessler H, Gama-Rodrigues J. Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: characterization of clinical and endoscopic findings for standardization. *Dis Colon Rectum* 2010; **53**(12): 1692-8.
7. Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2017.
8. Chadi SA, Malcomson L, Ensor J, et al. Factors affecting local regrowth after watch and wait for patients with a clinical complete response following chemoradiotherapy in rectal cancer (InterCoRe consortium): an individual participant data meta-analysis. *Lancet Gastroenterol Hepatol* 2018; **3**(12): 825-36.

9. Dattani M, Heald RJ, Goussous G, et al. Oncological and Survival Outcomes in Watch and Wait Patients With a Clinical Complete Response After Neoadjuvant Chemoradiotherapy for Rectal Cancer: A Systematic Review and Pooled Analysis. *Ann Surg* 2018; **268**(6): 955-67.

10. Lange MM, Maas CP, Marijnen CA, et al. Urinary dysfunction after rectal cancer treatment is mainly caused by surgery. *Br J Surg* 2008; **95**(8): 1020-8.

11. Sorensson M, Asplund D, Matthiessen P, et al. Self-reported sexual dysfunction in patients with rectal cancer. *Colorectal Dis* 2020; **22**(5): 500-12.

12. Diers J, Wagner J, Baum P, et al. Nationwide in-hospital mortality rate following rectal resection for rectal cancer according to annual hospital volume in Germany. *BJS Open* 2020; **4**(2): 310-9.

13. Celerier B, Denost Q, Van Geluwe B, Pontallier A, Rullier E. The risk of definitive stoma formation at 10 years after low and ultralow anterior resection for rectal cancer. *Colorectal Dis* 2016; **18**(1): 59-66.

14. Denost Q, Laurent C, Capdepont M, Zerbib F, Rullier E. Risk factors for fecal incontinence after intersphincteric resection for rectal cancer. *Dis Colon Rectum* 2011; **54**(8): 963-8.

15. Rullier E, Denost Q, Vendrely V, Rullier A, Laurent C. Low rectal cancer: classification and standardization of surgery. *Dis Colon Rectum* 2013; **56**(5): 560-7.

16. Fernandez LM, Sao Juliao GP, Figueiredo NL, et al. Conditional recurrence-free survival of clinical complete responders managed by watch and wait after neoadjuvant chemoradiotherapy for rectal cancer in the International Watch & Wait Database: a retrospective, international, multicentre registry study. *Lancet Oncol* 2021; **22**(1): 43-50.

17. Nasir I, Fernandez L, Vieira P, et al. Salvage surgery for local regrowths in Watch & Wait - Are we harming our patients by deferring the surgery? *Eur J Surg Oncol* 2019; **45**(9): 1559-66.

18. Kong JC, Guerra GR, Warrier SK, Ramsay RG, Heriot AG. Outcome and Salvage Surgery Following "Watch and Wait" for Rectal Cancer after Neoadjuvant Therapy: A Systematic Review. *Dis Colon Rectum* 2017; **60**(3): 335-45.

19. Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. *Int J Radiat Oncol Biol Phys* 2014; **88**(4): 822-8.

20. Smith JJ, Strombom P, Chow OS, et al. Assessment of a Watch-and-Wait Strategy for Rectal Cancer in Patients With a Complete Response After Neoadjuvant Therapy. *JAMA Oncol* 2019: e185896.

21. Habr-Gama A, Perez RO, Proscurshim I, et al. Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: does delayed surgery have an impact on outcome? *Int J Radiat Oncol Biol Phys* 2008; **71**(4): 1181-8.

22. Habr-Gama A, Perez RO, Sabbaga J, Nadalin W, Sao Juliao GP, Gama-Rodrigues J. Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. *Dis Colon Rectum* 2009; **52**(12): 1927-34.

23. Sanghera P, Wong DW, McConkey CC, Geh JI, Hartley A. Chemoradiotherapy for rectal cancer: an updated analysis of factors affecting pathological response. *Clin Oncol (R Coll Radiol)* 2008; **20**(2): 176-83.

24. Appelt AL, Ploen J, Vogelius IR, Bentzen SM, Jakobsen A. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. *Int J Radiat Oncol Biol Phys* 2013; **85**(1): 74-80.

25. Petrelli F, Trevisan F, Cabiddu M, et al. Total Neoadjuvant Therapy in Rectal Cancer: A Systematic Review and Meta-analysis of Treatment Outcomes. *Ann Surg* 2020; **271**(3): 440-8.

26. Garcia-Aguilar J, Chow OS, Smith DD, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. *Lancet Oncol* 2015; **16**(8): 957-66.

27. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? *Dis Colon Rectum* 2013; **56**(10): 1109-17.

28. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol* 2010; **28**(10): 1638-44.

29. Habr-Gama A, Perez RO, Sabbaga J, Nadalin W, São Julião GP, Gama-Rodrigues J. Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. *Dis Colon Rectum* 2009; **52**(12): 1927-34.

30. Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer. *JAMA Oncol* 2018.

31. Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2021; **22**(1): 29-42.

32. Patel UB, Brown G, Rutten H, et al. Comparison of magnetic resonance imaging and histopathological response to chemoradiotherapy in locally advanced rectal cancer. *Ann Surg Oncol* 2012; **19**(9): 2842-52.

33. Lambregts DM, Vandecaveye V, Barbaro B, et al. Diffusion-weighted MRI for selection of complete responders after chemoradiation for locally advanced rectal cancer: a multicenter study. *Ann Surg Oncol* 2011; **18**(8): 2224-31.

34. Lambregts DM, Rao SX, Sassen S, et al. MRI and Diffusion-weighted MRI Volumetry for Identification of Complete Tumor Responders After Preoperative Chemoradiotherapy in Patients With Rectal Cancer: A Bi-institutional Validation Study. *Ann Surg* 2015; **262**(6): 1034-9.

35. Lambregts DM, Maas M, Bakers FC, et al. Long-term follow-up features on rectal MRI during a wait-and-see approach after a clinical complete response in patients with rectal cancer treated with chemoradiotherapy. *Dis Colon Rectum* 2011; **54**(12): 1521-8.

36. Hupkens BJP, Maas M, Martens MH, et al. Organ Preservation in Rectal Cancer After Chemoradiation: Should We Extend the Observation Period in Patients with a Clinical Near-Complete Response? *Ann Surg Oncol* 2018; **25**(1): 197-203.

37. Habr-Gama A, São Julião GP, Fernandez LM, et al. Achieving a Complete Clinical Response After Neoadjuvant Chemoradiation That Does Not Require Surgical Resection: It May Take Longer Than You Think! *Dis Colon Rectum* 2019.