Study Protocol Clinical Trial

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Use of ginger to control nausea and vomiting caused by chemotherapy in patients with cervical cancer undergoing treatment

An experiment

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Abstract

Introduction: Uterine cervix tumors have an invasive nature, with the capacity to proliferate to surrounding organs such as the vagina, bladder, and rectum, as well as the capacity for dissemination and involvement of structures distant from its place of origin. According to the International Federation of Gynecology and Obstetrics, patients with stages IB I, IB I microscopic (small dimension <4 cm) are indicated for radiotherapy or adjuvant chemoradiotherapy with cisplatin (40 mg/m^2). However, cisplatin has side effects such as hematological implications (anemia, neutropenia, and thrombocytopenia), gastrointestinal disorders (nausea, vomiting, diarrhea, constipation), and fatigue. *Zingiber officinale* contains bioactive compounds that act on pregnancy and postoperative nausea, chemotherapy-induced nausea and vomiting, and also in the management of fatigue, myalgia, and insomnia. This study aimed to evaluate the effects of ginger on chemotherapy-induced nausea and vomiting in patients with cervical cancer undergoing treatment with cisplatin and radiotherapy.

Methods and analyses: A randomized intervention clinical and controlled trial with a triple-blind design is described, comparing the effects of institutional antiemetic therapy alone, as well as in combination with 2 different ginger concentrations.

Ethics and dissemination: Due to the nature of the study, we obtained approval from the Division Ethics Committee of Liga Contra o Câncer. All participants signed an informed consent form prior to randomization. The results of this study will be published in peer-reviewed journals. The data collected will also be available in a public repository of data.

Trial registration number: This study is registered in the Brazilian Registry of Clinical Trials under number RBR-47yx6p9. This study was approved by the Division Ethics Committee of Liga Contra o Câncer under CAAE 40602320.0.0000.5293.

Abbreviations: CINV = chemotherapy-induced nausea and vomiting, CTCAE = common terminology criteria for adverse events, HPV = human papillomavirus.

Keywords: ginger, antineoplastic agents, vomiting, nausea

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These funding sources have no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

All investigators will maintain full autonomy and involvement in the design, conduct, and reporting of the trial and will have full access to the final data.

The original documents and files will be kept at the trial sites for 15 years. The lead investigator is responsible for data and file storage.

All participants will be asked to sign an informed consent form to participate in the trial. This form explicitly contains all stages of the research.

The trial was approved by the local Division Ethics Committee (date of approval: April 17, 2018; reference number: 81973618.2.0000.5292) and registered in the Brazilian Clinical Trials Registry (REBEC: RBR-47yx6p9).

The authors have no conflicts of interest to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first randomized controlled trial comparing ginger doses with placebo doses for controlling chemotherapy-induced nausea and vomiting (CINV).
- Inclusion criteria allow for homogeneity of subjects and less risk of bias.
- Blinding of assessors and standardization of protocols enhance this trial's internal validity.
- The primary outcome includes controlling nausea and vomiting or common terminology criteria for adverse events (CTCAE) (gastrointestinal disorders - nausea/vomiting).

1. Introduction

Cancer is a leading cause of morbidity and mortality worldwide, with 19.2 million new cases reported annually.[1] In 2020, an estimated 9.9 million deaths occurred due to cancer, and the estimated prevalence over the past 5 years involved 50.1 million people. Among the malignant neoplasms, cervical cancer predominantly affects females. It is the fourth most frequent cancer worldwide with a prevalence of 1.5 million cases, and an incidence of 605,000 new cases worldwide.[1] The cervix tumor has an invasive feature with the capacity to proliferate to surrounding organs such as the vagina, bladder, and rectum, as well as dissemination and involvement of structures distant from its place of origin.[1,2] This neoplasm is mainly caused by human papillomavirus (HPV) infection, early sexual activity with multiple partners, smoking, and prolonged use of oral contraceptives.[3]

The treatment of cervical cancer has 3 aspects: surgery, chemotherapy, and radiotherapy, which can be performed alone or in combination. According to the International Federation of Gynecology and Obstetrics staging system, patients with stages IB I, IB I microscopic (small dimension <4 cm), are indicated for radiotherapy (RDT) or adjuvant chemoradiotherapy with cisplatin (40 mg/m^2). Administration of weekly cisplatin with radiotherapy shows superior results compared to isolated radiotherapy, and promotes less toxicity than in conjunction with other drugs.[4] However, cisplatin has side effects, such as hematological abnormalities (anemia, neutropenia, and thrombocytopenia), gastrointestinal disorders (nausea, vomiting, diarrhea, constipation), and fatigue.[1,5,6]

Chemotherapy-Induced Nausea and Vomiting (CINV) are considered severe side effects that most commonly occur during cancer treatment, including treatment with cisplatin.[7–9] The management of these side effects becomes difficult to control owing to the multiple central and peripheral neural stimuli caused by the drugs.[4,10,11]

Repetitive episodes of nausea and/or emesis may result in decreased food intake causing loss of nutrients and water, metabolic disorders due to gastric losses, anorexia, fatigue, and increased risk of acute renal failure. In addition, psychosocial aspects such mental deterioration and acceptance of body self-image can compromise treatment adherence and cause abandonment.[7,12]

As *Zingiber officinale* contains bioactive compounds, such as gingerols, shogaols, zingiberene, zingerone and paradol (gingerol and shogaol) it is affective against pregnancy and postoperative nausea such as CINV, as well as in the management of fatigue, myalgia, and insomnia.[13–17] However, these active components directly influence the antral motility, optimizing gastric emptying and intestinal peristalsis. They also affect the central nervous system, thus modulating serotoninergic pathways of 5-HT^3 receptors, as well as the drugs mentioned above.[16] Experimental studies confirm the safety of the root and its effectiveness in the treatment and prevention of secondary symptoms of chemotherapy.[18,19]

Therefore, this study aims to evaluate the effects of ginger on CINV in patients with cervical cancer undergoing treatment with cisplatin and radiotherapy.

1.1. Objectives

To evaluate the effects of ginger on CINV in patients with cervical cancer treated with cisplatin and radiotherapy.

2. Methods and analysis

Our protocol adheres to the Standard Protocol Items for Randomized Trials (SPIRIT) and Consolidated Standards of Reporting Trials (CONSORT) statements.[20]

2.1. Trial design

This is a protocol of a randomized clinical and controlled intervention trial with a triple-blind design, which compares the effects of institutional antiemetic therapy alone as well as with the use of 2 different ginger concentrations.

2.2. Population

The treatments will be carried out in a reference center for cancer care in Brazil. Recruitment of participants is ongoing at a referral center for cancer treatment. After reading and signing the informed consent form, patients who meet the eligibility criteria will be included in the research.

2.3. Eligibility criteria and recruitment

The study will include patients over 18 years of age, who were diagnosed with cancer of the uterine cervix on histological confirmation. Furthermore, they were indicated for treatment with cisplatin 40 mg/m^2 associated with radiotherapy and had capsule swallowing capacity. Figure 1 shows the study flow.

2.4. Interventions

The control group will swallow capsules containing 500 mg of placebo (77.80% pharmaceutical starch + 10.10% pharmaceutical talc + 10.10% microcrystalline cellulose + 1% magnesium stearate + magnesium dioxide 1% colloidal silicon, contained in white/blue gelatin capsules of size No. 00). Placebo capsules will be swallowed with approximately 250 ml of water every 12 hours, totaling to 1 g per day.

Experimental group 1 will be composed of patients who will receive capsules containing 250 mg of the ginger extract contained in white/blue gelatin capsules No. 00. The capsules

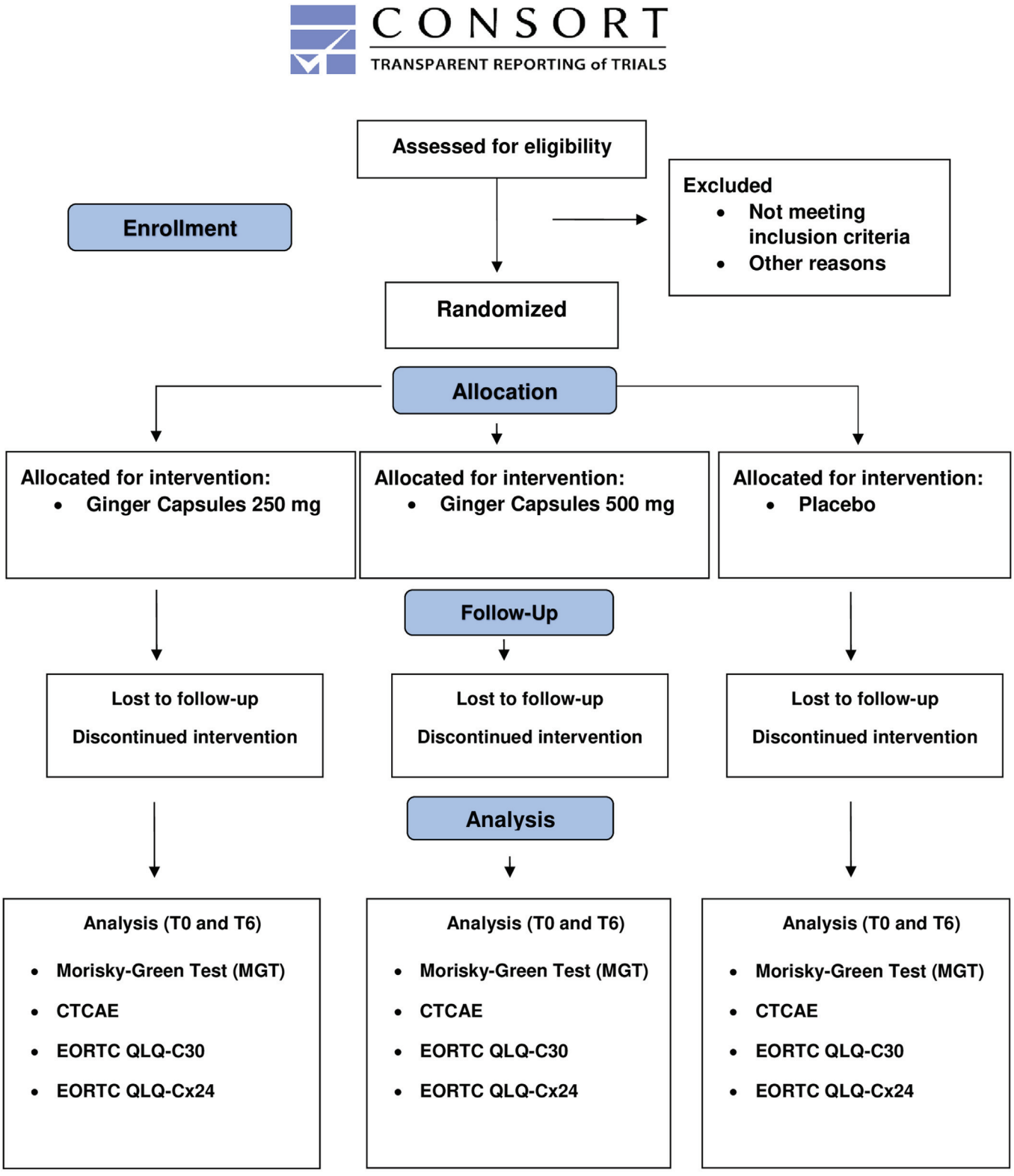

Figure 1. CONSORT 2010 flow diagram.

will be swallowed with approximately 250 ml of water every 12 hours, totaling to 500 mg per day. The ginger used will be dehydrated and crushed into a powder form without any chemical additives.

Finally, experimental group 2 will receive capsules containing 500 mg of the ginger extract contained in white/blue gelatin capsules No. 00 and will be swallowed with an average of 250 ml of water every 12 hours totaling to 1 g per day. The ginger will be

Table 1

Outcome measurements.

Outcome measurement	Explanation	Time points for assessment
CTCAE	Common terminology criteria for adverse events	T1, T2, T3, T4, T5, and T6
EORTC QLQ C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30	T1, T2, T3, T4, T5, and T6
EORTC QLQ Cx24	EORTC quality of life cervical cancer module	T1, T2, T3, T4, T5, and T6
MGT	Morisky-Green Test to evaluate medication adherence	T1, T2, T3, T4, T5, and T6

dehydrated and crushed into a powder form without any chemical additives.

2.5. Questionnaire

In the first query, the participants will answer a standardized questionnaire with information on demographic characteristics, including age, marital status, profession, schooling, socioeconomic classification, and risk factors (alcoholism, smoking, HPV, use of oral contraceptives, and whether Pap test was regularly performed).

2.6. Outcomes

2.6.1. Primary outcome. Seven relevant time points will be considered for evaluating the results based on the chemotherapy protocol of cisplatin with radiotherapy: baseline (P0), 7 days after the first dose of medication (P1), on every consecutive 7th day during a break in treatment (P2, P3, P4, P5, and P6), and 15 days after the last dose (P7).

The primary outcome includes controlling nausea and vomiting as evaluated using the Common Terminology Criteria for Adverse Events or CTCAE (gastrointestinal disorders-nausea/vomiting).[21] The CTCAE for nausea (a disorder characterized by a queasy sensation and/or the urge to vomit) will be classified as Grade 1 (loss of appetite without alteration in eating habits), Grade 2 (oral intake decreased without significant weight loss, dehydration, or malnutrition), or Grade 3 (inadequate oral caloric or fluid intake; tube feeding, parenteral nutrition, or hospitalization indicated). Vomiting (a disorder characterized by the reflexive act of ejecting the stomach contents through the mouth) will be classified as Grade 1 (intervention not indicated), Grade 2 (outpatient IV hydration: medical intervention indicated), Grade 3 (tube feeding, parenteral nutrition, or hospitalization indicated), Grade 4 (life-threatening consequences), or Grade 5 (death) (Table 1).

2.6.2. Secondary outcome. Secondary outcomes will be quality of life module of the European Organization for Research and Treatment of Cancer and Cervical Cancer- Specific Quality of Life Questionnaire, and medication adherence as evaluated using the Morisky-Green Test.[22–25]

The European Organization for Research and Treatment of Cancer is an internationally validated and widely used cancer-specific health related quality of life (HRQoL) instrument. It contains 5 scales of functioning (physical, social, role, cognitive, and emotional functioning), 8 symptom scales (fatigue, nausea/vomiting, pain, dyspnea, sleep disturbances, appetite loss, constipation, and diarrhea), and evaluations of financial impact and overall quality of life. Raw scores are linearly converted to a scaled score in a range between 0 and 100.[22] For the functioning scales and global QOL, higher scores indicate better functioning; for the symptom scales, higher scores indicate higher symptom burden. Furthermore, the cervical cancer-specific EORTC QLQ-CX24 consists of 5 multi-item scales on clinically distinct dimensions (sexual functioning, body image, gastrointestinal, urologic, and vaginal symptoms) and several single-item measures.[23]

To evaluate medication adherence, we will use the version of the Morisky-Green Test which includes the following questions: Do you sometimes have difficulty remembering to take your medication? Do you sometimes not pay attention to taking your medication? When you feel better, do you sometimes stop taking your medication? Sometimes, if you feel worse after taking medication, do you stop taking it?[24]

The evaluation of the results is described in Table 2. All possible adverse effects will be recorded and qualified during the treatment period using questionnaires developed for this protocol. Any adverse events will be reported and discussed in the Results section of the manuscript. Any breach of confidentiality, study protocol, or adverse events attributable to this study will be reported to the research ethics committees.

2.7. Screening

After a nursing consultation, the elected patient will fill a registration form containing patient identification data and clinical and demographic information. Next, a pharmacist will dispense a bottle of capsules corresponding to the participant's previously determined group allocation.

2.8. Follow-up

Follow-up data including a general condition assessment will be recorded during the follow-up period corresponding to the multiple time points. The details are presented in Table 2.

Each patient will remain in the study for 7 weeks or until the end of chemotherapy treatment if the chemotherapy period is scheduled to end before the 7-week intervention. Recruitment and data collection will take place at the following times:

Period 1: Recruitment (Day 0) at the time of chemotherapy initiation.
Period 2: Intervention (Weeks 16), data will be recorded every 7 days or at the time of each new weekly chemotherapy dose.
Period 3: Time after intervention (at least 7 but within 15 days after completion of treatment), follow-up for long-term results. The last meeting between the researcher and patient can take place via phone call or in-person, as it will be at least 1 week after the last infusion of the antineoplastic therapy.
At the weekly chemotherapy session, the principal researcher will check the number of remaining capsules to assess the adherence to study protocol. In all, will be 7 in-person

Table 2

Schedule of enrollment, interventions, assessments and data collection.

Study period	Enrollment/baseline	Intervention						Follow-up
Time point	T0	T1	T2	T3	T4	T5	T6	15 d
Enrollment	X							
Eligibility screen	X							
Informed consent	X							
Randomization	X							
Interventions								
Ginger capsules 250 mg		X	X	X	X	X	X	
Ginger capsules 250 mg		X	X	X	X	X	X	
Placebo		X	X	X	X	X	X	
Assessments								
General condition								X

possibilities for data collection. If no return is established, telephone contact will be attempted in the last week.

2.9. Sample size

The sample size calculation will be established using G Power Software version 3.1.9.2 (https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower), considering a Cohen effect size of 0.40, a test power of 0.80, and a significance level of 5% (P value $<.05$).[26] The sample is estimated to be of 39 patients with a potential addition of 20%, totaling 48 participants, which will be equally allocated (1:1:1) into 3 groups of 16 patients each (the ginger capsules 250 mg group, ginger capsules 500 gm group, and placebo group).

2.10. Randomization and allocation concealment

On providing informed consent, eligible participants will be randomized by the Software Research Randomizer program using block design (1:1:1; experimental group 1, experimental group 2, or control group). Patients will be randomized into 3 intervention groups.

To ensure blind allocation, an off-site randomization schedule will be followed. This schedule will be prepared by a researcher at the Institute of Education, Research and Innovation (Liga Contra o Câncer), who will have no contact with any participants throughout the trial and will not be involved in the recruitment, screening, assessment, enrollment, or treatment process. To enroll a participant, the primary researcher will email the consenting participant's name to the researcher at the LIGA. These details will be entered into the allocation spreadsheet, and the corresponding treatment allocation and participant identification number will be emailed to the researcher.

2.11. Blinding

Research participants, group researchers, and individuals who assess the outcomes will not have access to the details of group assignments. This ensures that bias for or against the tested treatment is unlikely to occur.

2.12. Data management

Initially, an experienced team member (RLMS) will be trained to collect data according to the study protocol. The qualification of the researcher is essential to ensure the quality of clinical trials. Data collection will be carried out through the REDCap website. Data management included baseline characteristics (demography, lifestyle, comorbidities, history of HPV treatment, history of long-term use of oral contraceptives, tumor characteristics, International Federation of Gynaecology and Obstetrics staging, and inclusion and exclusion criteria), potential confounds, and outcomes as per the QOL questionnaire. Participants who withdraw from our study will be followed up with, and data will be analyzed according to the intention-to-treat principle. All randomized participants will be followed up with for 2 months after randomization.

2.13. Data extraction and statistical analysis

For the analysis of quantitative data, repeated measures ANOVA based on the linear mixed effects model will be used. A binary variable will also be created to indicate the occurrence of nausea in the 24 hours after the infusion in at least 1 of the 6 weeks. In this case, a logistic regression model will be used and the odds ratio of occurrence of nausea will be calculated for the 3 groups. Data presented in the text and tables will be reported as means and SDs, mean, absolute values and percentages (%). Statistical significance will be set at $P <.05$. The software that will be used is the R Project for Statistical Computing for Windows, VR version 4.0.2.

2.14. Patient and public involvement

All the patient information will be anonymously analyzed and processed. The results of our trial will be disseminated to the participating patients through a letter after publication.

3. Discussion

This protocol entails a randomized trial that will determine the effects of antiemetic therapy associated or isolated with ginger on CINV is described. The strengths of this research include a triple-blind study method, which avoids ethical deviations and placebo-controlled randomization, and the ability to evaluate several simultaneous clinical outcomes. The limitations include the lack of adherence to the use of the proposed drugs, and lack of follow-up after the treatment. Subsequently, reduction of neutrophils beyond the minimum limit (neutropenia), although

not a factor disconnection from the search, will delay the progress of the search and changes to the chemotherapy protocol may be required to ensure project completion.

Few studies with the same methodological design show positive results associated with the use of ginger. A randomized clinical study revealed that ginger supplementation at doses 0.5 g and 1.0 g significantly relieves the severity of acute nausea (within 24 hours).[27] In addition, it delays CINV when associated with ondansetron and dexamethasone in a chemotherapy regimen with high emetogenic power.[17]

However, an experimental study that compared the effectiveness of ginger and chamomile in the management of cancer treatment induced gastrointestinal effects revealed that both herbal medicines reduce the frequency of vomiting with no significant difference between the 2 groups; however, ginger offered a notable reduction in the frequency of nausea.[28,29] Furthermore, a clinical trial revealed that ginger can not only control nausea and vomiting, but can also enhance the quality of life of chemotherapy patients by reducing fatigue by up to 80%.[30,31]

4. Ethics and dissemination

All procedures performed in this study involving human subjects will be conducted following the ethical standards of the 1964 Declaration of Helsinki and its subsequent amendments, the Madrid Declaration of the World Psychiatric Association, and the requirements established for manuscripts submitted to biomedical journals or ethical standards of good practice clinics. This trial was approved by the Human Research Ethics Committee of the North Riograndense Against Cancer, under the number CAAE 40602320.0.0000.5293 (approval date: February 3, 2021) and was registered in the Brazilian Registry of Clinical Trials under the number RBR-47yx6p9. Before registration of the trial participants, data confidentiality will be guaranteed through data anonymization.

Author contributions

RLMS, TTMS, RLP, and DVD were involved in drafting the study protocol. TTMS and RLP were involved in the statistical planning and drafting of the study protocol. KSM and RAND were involved in drafting and revising the study protocol. RAND and KSM developed the idea for this trial and were involved in drafting and revising the study protocol. RLMS and TTMS conceived and designed the concept for this trial, was involved in drafting and revising the study protocol, and was the trial's principal investigator. All authors will be involved in data acquisition and approval of the final version of the manuscript.

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Writing – review & editing: Daniele Dantas, Kleyton Medeiros, Renata Pessoa, Rodrigo Neves Dantas.

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