World Journal of Surgery and Surgical Research

Research Article
Published: 21 Apr, 2023

Multimodal Prehabilitation during Neoadjuvant Chemotherapy in Patients with Colorectal Liver Metastases: Protocol for a Randomized Controlled Trial

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Received Date: *01 Apr 2023*

Accepted Date: *17 Apr 2023*

Published Date: *21 Apr 2023*

Citation:

Estalella L, Espina B, Minguez P, Renzulli M, Guasch A, Sirgo A, et al. Multimodal Prehabilitation during Neoadjuvant Chemotherapy in Patients with Colorectal Liver Metastases: Protocol for a Randomized Controlled Trial. World J Surg Surgical Res. 2023; 6: 1460.

Abstract

Background: The current management for patients with Colorectal Liver Metastases (CRLM) requires a multidisciplinary approach. Most of them undergo Chemotherapy (CT) before liver surgery. However, CT objectively decreases functional capacity. It has already been demonstrated that a structured training program carried out during the 4 weeks following CT, while the patient is waiting for liver resection, is able to return functional capacity to baseline levels. Despite this, Multimodal Prehabilitation Programs (MPP) during preoperative CT have not been evaluated or implemented. The aim of this study is to investigate whether a 16-week MPP applied during and following CT in CRLM patients will result in a significant increase in physical fitness when compared to those that undergo MPP only during the 4-weeks, between the end of CT and liver resection.

Methods: Prospective Randomized Controlled Trial (RCT). Eighty-four patients with CRLM who will undergo preoperative CT and surgery will be randomized to 16 weeks or to 4 weeks of a prehabilitation program. Interventions: in-hospital high-moderate intensive exercise training, high-protein supplementation, smoking cessation, psychological support and comorbidity and frailty assessment. The primary outcome will be functional capacity, assessed using the six-minute walk test. Secondary outcomes will include postoperative complications, length of hospital stay, readmission rates, quality of life and feasibility of the program.

Discussion: This is the first RCT implementing a MPP for CRLM patients during preoperative CT. This may allow us to determine the optimum period for prehabilitation, in order to achieve the best improvement in patient physical fitness before liver surgery.

Keywords: Prehabilitation; Physical fitness; Colorectal liver metastases; Neoadjuvant therapy; Liver resection

Abbreviations

6MWT: Six-Minute Walk Test; 30CST: 30-Second Sit to Stand Test; BIA: Bio-electrical Impedance Analysis; BMI: Body Mass Index; CCI: Comprehensive Complication Index; CPET: Cardiopulmonary Exercise Testing; CRC: Colorectal Cancer; CRLM: Colorectal Liver Metastases;

CT: Chemotherapy; HPB: Hepato-Pancreato-Biliary; HRQoL: Quality of Life; LOS: Length of Hospital Stay; MPP: Multimodal Prehabilitation Program; NAC: Neoadjuvant Chemotherapy; NACRT: Neoadjuvant Chemo-Radiotherapy; PG-SGA: Patient-Generated Subjective Global Assessment; PM&R: Physical Medicine and Rehabilitation physician; RCT: Randomized Controlled Trial; UMA: Mid-Upper Arm Muscle Area

Background

Colorectal Cancer (CRC) is the third most prevalent cancer and the second most deadly cancer worldwide [1]. Approximately 25% of CRC patients will present with synchronous metastases and 30% to 40% will develop metachronous metastases during the course of their disease [2].

Liver resection is the only curative treatment for patients with Colorectal Liver Metastases (CRLM) [3]. It is currently considered a safe and feasible procedure, although with significant morbidity and low but some mortality risk. In order to improve the outcomes, current management of these patients requires a multidisciplinary approach combining different therapeutic strategies [4]. It is worth noting that most patients with CRLM undergo neoadjuvant and/or adjuvant systemic Chemotherapy (CT). Moreover, in the event of synchronous metastases, the patient also undergoes an additional procedure due to the need for resection of the primary colorectal tumor before or after liver resection, unless synchronous resection is feasible.

Cancer is associated with cachexia, characterized by loss of muscle mass, fatigue and higher risk of postoperative complications, longer hospital stays and higher mortality rates [5,6]. Major surgery is associated with a significant decrease in functional health capacity even in the absence of complications. In fact, a significant proportion of patients (10% to 50%, depending on the measure used) need up to 6 months to recover their preoperative baseline functional status [7]. Likewise, Neoadjuvant Chemotherapy (NAC) is associated with a reduction in physical fitness [8-10] measured by Cardiopulmonary Exercise Testing (CPET). This evidence suggests that oncologic patients undergoing both treatments, CT and surgical resection, incur a significant increased risk of reduced functional capacity and subsequent adverse postoperative outcomes. Thereby, identifying a suitable prehabilitation program to optimize preoperative physical fitness should be a priority [11].

Several studies have supported the efficacy of exercise interventions to increase physical fitness among cancer patients and showed improvement in clinical outcomes [12]. Most describe using prehabilitation protocols at the end of neoadjuvant treatment (chemo or chemo-radiotherapy), during the four or six weeks when patients are recovering before surgery. To date, only three studies in breast cancer and one in rectal cancer patients have examined the impact of exercise prehabilitation during neoadjuvant treatment. Although these are pilot studies and limited by their small sample size, they show encouraging results [13-15].

Prehabilitation programs performed in liver surgery are scarce and commonly conducted during the four weeks before surgery, after patients have completed systemic treatment [16,17]. CT produces a broad range of toxic effects; hence, the months during which the patients receive preoperative CT may be a valuable time period to engage in improving functional capacity using a multimodal approach. To our knowledge, our study will be the first Randomized Controlled Trial (RCT) to assess the feasibility of a MPP for CRLM patients during preoperative CT.

Objectives

The primary aim of this study is to evaluate the effectiveness of a MPP in CRLM patients that will be implemented right through the period of neoadjuvant CT and during the 4-weeks of recovery before liver resection. Improvement in physical fitness will be measured by the difference in meters achieved in the Six-Minute Walk Test (6MWT), compared with patients that will follow the MPP only during the 4-weeks before surgery.

Secondary Aims Include

- To evaluate postoperative complications, Length of Hospital Stay (LOS) and re-admission rate between both groups.
- To evaluate Quality of Life (HRQoL) and psychological health between both groups.
- To evaluate nutritional and functional capacity outcomes between both groups.
- To evaluate protocol feasibility by monitoring all interventions.
- To identify target patients who would benefit most from prehabilitation before planned liver resection.

Methods

Study design

This is a single center RCT with two study groups. The study will be performed at University Hospital of Tarragona Joan XXIII. Ethical approval was granted by the Research Ethics Board of the institution (Pere Virgili Health Research Institute, Tarragona, Spain), under reference number 043/2020. The study has also been properly registered on ClinicalTrials.gov (NCT04520737).

Study population

Participants will be patients previously evaluated by the HPB multidisciplinary team and diagnosed with potentially resectable CRLM who are scheduled to undergo CT before liver resection. Eighty-four subjects will be included, 42 in each arm. We expect a dropout rate of 10% based on previous studies.

Eligibility criteria for inclusion of participants will be: Age ≥ 18 years, written informed consent obtained from subject to participate in the study.

Exclusion criteria will include the following: Age <18 years, ASA health class status IV-V, mental conditions or disabling orthopedic and neuromuscular disease that prevent physical exercise or may compromise adherence to the program, inability to perform CPET or bicycle exercise due to known contraindication, inability to obtain informed consent.

Recruitment and randomization

Potentially eligible patients will have an appointment at the HPB outpatient clinic where they will receive a detailed written explanation about the trial. If patient agrees to participate in it, a first research appointment will be organized where written informed consent will be obtained. At that time, the participant will be randomized (1:1) using seed, a Stata's random-number generated function. The subjects will be allocated into one of these two groups:

- 16W group: MPP will be implemented during 16 weeks, 12 weeks during CT and 4 weeks while waiting for surgery.

- 4W group: MPP will start at the end of preoperative CT until surgery (4 weeks in total).

Interventions

The MPP is composed of 5 elements: Exercise training, nutritional intervention, psychological intervention, smoking cessation and co-morbidity and frailty assessment. A participant flow diagram and exact interventions and evaluations are shown in Figure 1 and described in detail below.

Physical prehabilitation

Subjects will be referred to the Physical Medicine and Rehabilitation physician (PM&R) to assess patients' baseline characteristic (as obtained from the results of Clinical Frailty Scale and Charlson Comorbidity Index) and to perform a medical examination to rule out any contraindication to aerobic exercise. At that appointment, baseline functional capacity will be measured by the 6MWT.

Exercise training protocol: Exercise prescription will be done using the FITT principle (frequency, intensity, time, type).

Frequency will be determined depending on the group to which the patient is allocated and the time of the CT cycle:

16W group: The most common CT regimen, is administered in continuous infusion for 48 h every 14 days. Weeks of CT administration and weeks without treatment would be alternated. Training exercise will be structured as follows:

- Week of CT administration: individual home exercises, adapted to possible side effects of CT, will be prescribed.

- "CT rest" week: three in-hospital supervised training sessions per week.

4W group: three in-hospital supervised sessions per week.

Intensity: intervals of moderate and high intensity aerobic exercise calculated by heart-rate (70-80 and >80% of your maximum heart rate respectively) and controlled by Borg Score [18].

Time or training duration: between 45 min to 60 min each session

Type or training program includes:

- Respiratory re-education program to prevent pneumonia: Pursed lip breathing technique. Diaphragmatic Breathing (Belly Breathing): Make the patient aware of the mobility of the diaphragm. Directed ventilation. Decrease respiratory work: Relax accessory muscles, decrease respiratory rate.

- Resistance exercise focused on upper limb consists of 3 series of 10 repetitions interspersed with rests, first one limb and then the other.

- Aerobic training performed with 5 min of warm-up, 4 intervals of moderate or high intensity (2 min to 3 min) and 4 intervals of moderate intensity (4 min).

- Relaxation and stretching exercises.

The in-hospital supervised training exercise will be carried out on a cycle ergometer. Participants will also be given instructions about how to conduct aerobic exercises at home. They will be instructed to aim for 60 min of walking or cycling a day, with a minimum of at least 30 min a day. In the event of a low exercise capacity, it will be advised to walk/cycle 2 to 3 times a day for periods of 10 min to 20 min.

Nutritional assessment and intervention

Each participant will be evaluated by a nutritionist from the research team, who will conduct a nutritional assessment using the following measures: Patient-Generated Subjective Global Assessment (PG-SGA) [19], Body Mass Index (BMI), hand grip strength, mid-Upper arm Muscle Area (UMA) and body composition using the Bio-electrical Impedance Analysis (BIA).

Based on these results, individual nutritional advice and dietary guidelines will be provided to each subject and daily oral protein supplementation will be prescribed. In addition, participants will receive a supplement of 18.8 g of protein (normal caloric and high protein nutritional supplement) to take within one hour following the three weekly supervised exercise sessions.

Psychological intervention

Participants will have an initial appointment with a psycho-oncologist, who will perform an interview and assessment focused on the three anxiety-response systems (physiological, behavioral and cognitive), depressive symptoms, sleep disorders, worries about cancer and coping strategies. They will be assessed using the SF-36 [20] questionnaire and the Hospital Anxiety and Depression Scale (HADS) [21].

The intervention model will be based on cognitive-behavioral techniques to reduce anxiety-depression symptoms, and to reinforce coping strategies adapted to each case.

Smoking cessation

The intervention program will start with a motivational conversation with all subjects who smoke. Written and online information will be also provided. If the participant is encouraged to stop smoking, he or she will start a program consisting of behavioral counseling and pharmacotherapy intervention. The program will be carried out by a trained smoking cessation counselor and will include individual sessions.

Comorbidity and frailty assessment

The primary preoperative risk factor for poor post-operative outcome in older people is not age, but co-morbidity [22,23]. Subjects with co-morbidities (uncontrolled hypertension, ischemic heart disease, arrhythmia, poorly controlled diabetes, Chronic Obstructive Pulmonary Disease (COPD), significant memory problems, history of confusion, dementia) or with a positive screening for frailty using the Geriatric 8 (G8) [24] and the Vulnerable Elders-13 Survey (VES-13) [25] scores, will be scheduled for a geriatrician outpatient clinic. The aim will be to identify and modify preoperative risk factors and optimize their subsequent postoperative management.

Study outcomes and measures

Primary outcome: The initial primary outcome will be changes in physical fitness, fitness, which will be assessed using the 6MWT. This will be performed following standardized protocols [26] and interpreted by a PM&R.

The 6MWT has been validated as a measure of postsurgical recovery [27]. It is an objective, non-invasive, low-cost and widely applied clinical tool that integrates all the components of functional

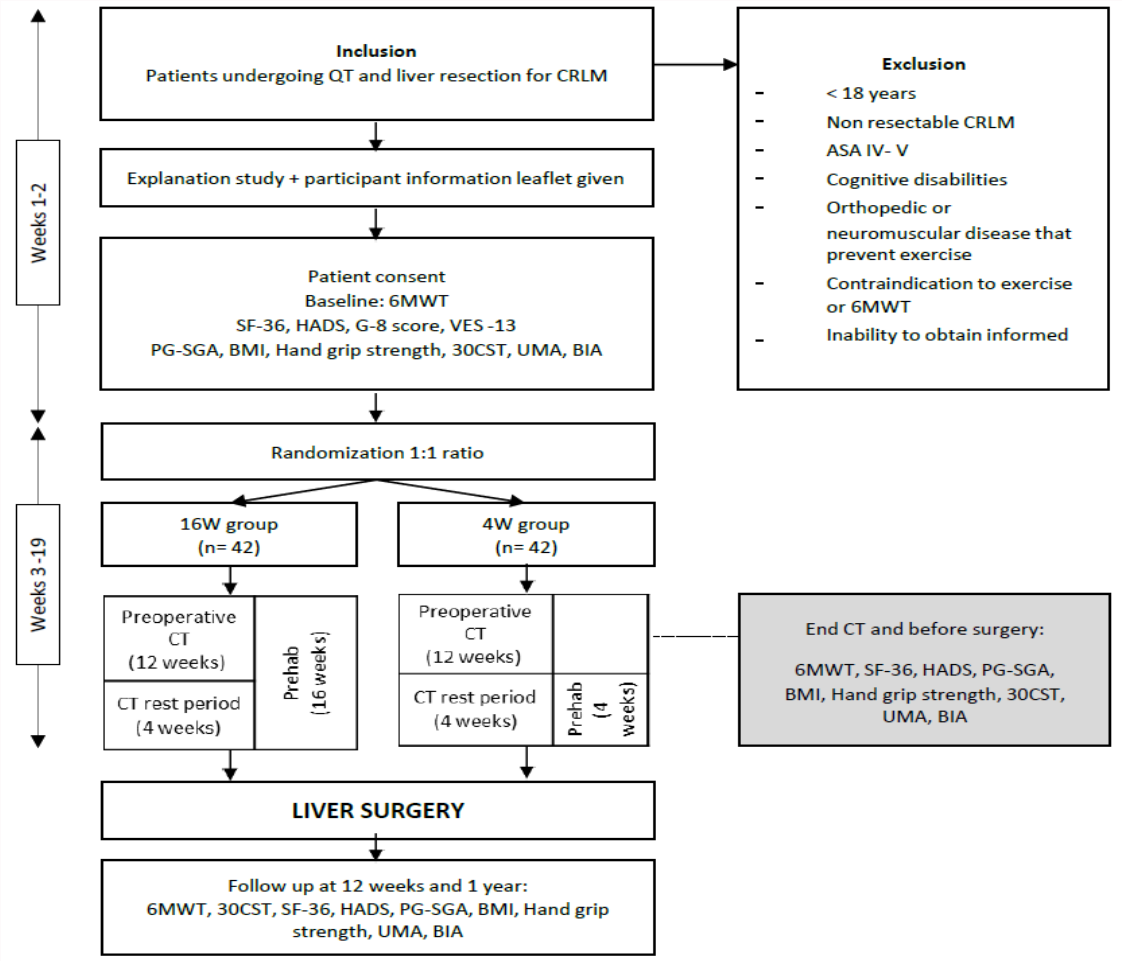

Figure 1: Flow diagram and interventions for study participants.
BIA: Bio-electrical Impedance Analysis; BMI: Body-Mass Index; CT: Chemotherapy; G8: Geriatric Screening Tool; HADS: Hospital Anxiety and Depression Scale; PG-SGA: Patient-Generated Subjective Global Assessment; Prehab: Multimodal Prehabilitation Program; 6MWT: Six-Minute Walk Test; SF-36: Mental Health Score; 30CST: 30-Second Sit to Stand Test; VES-13: Vulnerable Elders Survey Score; UMA: Mid-Upper Arm Muscle Area

walking ability such as balance, speed and endurance. It also integrally evaluates the response of the respiratory, cardiovascular, metabolic, musculoskeletal and sensorineural systems during exercise [28]. It is carried out in a corridor of 30 meters in length (at least 20 meters), with a flat surface, preferably indoors to avoid interruption from other persons. Registration of the heart rate, oxygen saturation, blood pressure, and Borg Scale [18] of perceived exertion is performed before and after the test. To carry it out, the subject is asked to walk the maximum possible distance, as fast as possible within their usual pace (without running), for 6 min. The distance traveled is expressed in meters. Age- and gender-specific predicted distances can be calculated using the following formula: Predicted distance walked in 6 Min (m) = 868 - (age x 2.9) - (female x 74.7), where age is in years, and the value "1" is assigned for females [29].

Participants of both groups will undergo 6MWT at baseline (before the start of CT), end of CT, the week before surgery and at 12 weeks and 1 year postoperative.

Secondary outcomes:

Postoperative morbidity: Complications will be graded by severity using the Clavien-Dindo classification [30] and the Comprehensive Complication Index (CCI) [31]. LOS and readmissions rates will be recorded.

Health-related quality of life: Impact on HRQoL will be measured using the SF-36 mental health score. This survey measures eight scales of health: physical function, role physical, role emotional, social functioning, bodily pain, general health, vitality, and mental health. All scales contribute in different proportions to the scoring of two summary scores - the Physical Component Summary (PCS) and Mental Component Summary (MCS).

Emotional health: The HADS scale is a valid instrument to identify patients who need further psychiatric evaluation. This tool contains seven items, each scored from 0 to 3 points for anxiety and depression. It provides summary measures on a scale of 0 to 21, with scores exceeding 8 suggesting the presence of a mood disorder [21].

Nutritional status: The PG-SGA is a validated questionnaire used to assess the nutritional and functional status of cancer patients. The scoring system allows patients at risk for malnutrition to be identified and triaged for nutritional intervention. A score ≥ 9 indicates a critical need for nutritional intervention.

BIA will be used to evaluate changes in body composition. Changes in UMA and BMI will be analyzed. UMA corresponds to the circumference of the left upper arm, measured at the mid-point

between the tip of the shoulder and the tip of the elbow.

Functional capacity: It will be measured using a hydraulic hand dynamometer (Handgrip strength). Three measures from each hand will be taken, with patient seated and arm bent at a 90-degree angle. The average of the three measures for each hand will be recorded.

The 30-sec sit to stand test (30CST) measures lower body strength by recording the maximum number of times an individual can go from a seated position to a standing position, without using their arms, in a 30-sec period.

Feasibility of the program: This will be assessed by monitoring patient attendance and adherence to in-hospital exercise training sessions. Attendance will be calculated by dividing the number of assisted training sessions by the total planned sessions. Adherence will be calculated by dividing the number of successfully completed sessions (at the intensity and duration prescribed) by the number of sessions attended. Adverse effects during in-hospital training sessions will be registered at that time. In order to enhance adherence to the prehabilitation program, participants will be contacted weekly by phone call. During these, they will be encouraged to continue the program and will be interviewed by a standardized questionnaire related to the exercise performed at home (intensity, frequency and time), possible adverse effects (associated with CT or exercise) and amount of protein ingested.

Statistical analysis

The size of the sample has been calculated on the basis of the primary aim: Changes in functional capacity measured by the difference of meters in the 6MWT between the two groups.

Two previous studies detected in the prehabilitation group an average of 23.7 m (SD 54.8) above baseline, compared with 21.8 m (SD 80.7) lower than baseline in the rehabilitation group [32,33]. We assumed a minimum difference in 6MWT of 45.4 m (IC 95% from 13.9 to 77.0) with 80% power, alpha of 0.05 and allowed for 10% of subjects to drop-out. With this data, the sample size required for this study will be 84 patients. Consequently, recruitment should be completed within approximately three years.

Continuous data will be reported as mean (range), mean (SD) or median and Inter-Quartile Range (IQR), depending on distribution. The continuous normal variables will be analyzed using t-test, and the Mann-Whitney U test will be used for continuous data with a non-normal distribution. Categorical data will be reported as frequency (%) and will be analyzed with the X^2 test or Fisher's exact test, as appropriate. A $p<0.05$ will be considered statistically significant.

Discussion

Over the last 20 years, the utility of liver surgery has increased dramatically due to development of aggressive CT protocols, improvements in preoperative assessment and advanced surgical techniques. However, although the boundaries of liver resection have extended, morbidity and mortality after liver resection remain high, often associated with factors related to the clinical status of the patient prior to surgery as well as to intraoperative factors [34].

Enhanced Recovery after Surgery (ERAS) programs have shown to be safe and effective in patients undergoing liver resection. These patients have less major complications, shortened postoperative stay and there have been demonstrated reduced costs [35,36]. In this regard, MPP include items of ERAS and are based on a more integrative patient approach during the preoperative period.

To date, most prehabilitation programs have the limitation of focusing only on one modal intervention. The decrease in physical fitness following CT may be multifactorial, caused by the toxicity of drugs and other factors including anemia or malnutrition. Furthermore, our patient population is becoming older, therefore the sarcopenia and frailty closely linked to this group of patients must be borne in mind. A strict assessment of pre-operative general condition and comorbidities are some of the keys to reduction of postoperative morbidity and mortality. All this evidence further supports the need for a multidisciplinary approach to improve all these factors before cancer surgery. Functional capacity cannot be improved with an exercise training program in isolation. Nutritional and psychological intervention and a geriatric assessment, especially among patients who undergo systemic treatment, will be essential. This will be the first RCT investigating the feasibility and effectiveness of a MPP during preoperative CT in patients affected by CRLM. We expect less decrease in physical fitness in patients where the MPP is implemented during CT and a consequent improvement in function during the four weeks before surgery, compared with those following the MPP only during this short period. This will allow us to determine the optimum period to develop a MPP which improves better patient functional capacity before surgery.

Likewise, the present study aims to evaluate the impact of a MPP on postoperative outcomes. Postoperative complications will be recorded by Clavien-Dindo classification and CCI, along with LOS and re-admissions. Previous studies have demonstrated that the implementation of a prehabilitation program that includes a structured exercise training intervention can improve physical fitness before surgery [32,37], though only a few studies have evaluated this benefit in terms of postoperative outcomes.

Prehabilitation programs are increasing in patients undergoing liver resection. Dunne et al. [16] published a RCT showing that the implementation of 12 high-intensity exercise sessions (during 4 weeks) before liver surgery for CRLM was associated with preoperative improvements in physical fitness and HRQoL. Another recent prospective study conducted by Wang et al. [17], showed a reduction in overall complication rate (52.9 *vs.* 30%, p=0.02) and a gain in HRQoL in patients undergoing a prehabilition program before elective liver resection. This improvement resulted in a shortening of LOS by 2.5 days and a median cost reduction of 16.5% (p=0.07) in the prehabilitation group compared with control patients. Although this study was non-randomized and included non-homogeneous patients in both groups in terms of Charlson comorbidity index, it indicates that prehabilitation program may have a role before planned liver surgery. Therefore, we expect that the implementation of a MPP, if capable of improving the patient's preoperative physical fitness, may result in more favorable postoperative outcomes.

The main outcome will be measured by the 6MWT and this will show changes in patient functional capacity due to the MPP. Although specific measures of each intervention will be performed, it will not be possible to discriminate which of these contributes more. Conversely, analysis of basal patient characteristics and measures obtained during the program, will allow us to discriminate which patients will benefit the most from the MPP, with the aim of promoting an efficient health care service addressed to those who need it most.

One of the limits of the study is that it is not designed as a multicenter trial. The authors are aware that implementing

prehabilitation interventions in patients who are undergoing CT may be complex. However, if this MPP demonstrates promising results, it could be put forward to be implemented in other centers. Due to the nature of the study, both research staff and patient will not be blinded to group allocation.

In summary, we aim to show that a MPP implemented during and following CT in CRLM patients, including an in-hospital high-moderate intensive exercise training, nutritional and psychological intervention, smoking cessation and frailty assessment, will improve patients' functional capacity before liver resection, with a subsequent improvement in postoperative outcomes.

Acknowledgement

The authors would like to thank Miss Gemma Falcó, medical librarian, for her valuable help provided to perform the literature search.

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