BMJ Open

Feasibility of a prehabilitation program dedicated to older cancer patients before complex medico-surgical procedures: the PROADAPT pilot study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042960
Article Type:	Protocol
Date Submitted by the Author:	22-Jul-2020

Complete List of Authors:	Roche, Mélanie; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL Ravot, Christine; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier Lyon Sud Malapert, Amélie; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL Garandeau, Charlène; Hospices Civils de Lyon, Direction à la Recherche Clinique et à l'Innovation Pitiot, Virginie; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL Tomatis, Mélanie; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier Lyon Sud Riche, Benjamin; Hospices Civils de Lyon, Service de Biostatistique - Bioinformatique, Pôle Santé Publique; Université de Lyon, Laboratoire de Biométrie et Biologie Évolutive CNRS UMR 5558, Équipe Biostatistiques Santé Galamand, Béatrice; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier Lyon Sud Granger, Marion; Hospices Civils de Lyon, Geriatrics unit; Centre Hospitalier de Chambery Barbavara, Claire; Hospices Civils de Lyon, Geriatrics unit - Centre Hospitalier Lyon Sud Bourgeois, Chrystelle; Centre Hospitalier Annecy Genevois, Medical Oncology Genest, Evelyne; Hospices Civils de Lyon, Geriatrics unit Stefani, Laetitia; Centre Hospitalier Annecy Genevois, Medical oncology Haïne, Max; L'Hôpital Nord Ouest, Pôle de gérontologie et Médecine de Réadaptation Castel-Kremer, Elisabeth; Hospices Civils de Lyon, Geriatrics unit. Hôpital Edouard Herriot. Morel-Soldner, Isabelle; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier de la Croix Rousse Collange, Vincent; Medipole Lyon-Villeurbanne, Département anesthésie réanimation Le Saux, Olivia; Centre de Recherche en Cancerologie de Lyon, Therapeutic targeting of the tumor cell and its immune microenvironment Dayde, David; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL

	Falandry, Claire; Hospices Civils de Lyon, Geriatrics unit; University of Lyon, CarMeN Laboratory, Inserm U1060, INRA U1397, Université Claude Bernard Lyon 1, INSA Lyon, Charles Mérieux Medical School
Keywords:	Adult oncology < ONCOLOGY, GERIATRIC MEDICINE, REHABILITATION MEDICINE, Adult surgery < SURGERY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Feasibility of a prehabilitation program dedicated to older cancer patients before complex medico-surgical procedures: the PROADAPT pilot study protocol

Roche Mélanie (melanie.roche@chu-lyon.fr)

Ravot Christine (christine.ravot@chu-lyon.fr)

Malapert Amélie (amelie.malapert@chu-lyon.fr)

Charlène Garandeau (charlene.garandeau@chu-lyon.fr)

Pitiot Virginie (virginie.pitiot@chu-lyon.fr)

Tomatis Mélanie (melanie.tomatis@chu-lyon.fr)

Benjamin Riche (benjamin.riche@chu-lyon.fr)

Béatrice Galamand (beatrice.galamand@chu-lyon.fr)

Marion Granger (mariongranger@outlook.fr)

Claire Barbarava (claire.barbavara@gmail.com)

Chrystelle Bourgeois (cbourgeois@ch-annecygenevois.fr)

Evelyne Genest (evelyne.genest@chu-lyon.fr)

Laetitia Stefani (lstefani@ch-annecygenevois.fr)

Max Haïne (mhaine@lhopitalnordouest.fr)

Elisabeth Castel Kremer (Elisabeth.castel-kremer@chu-lyon.fr)

Isabelle Morel-Soldner (isabelle.morel-soldner@chu-lyon.fr)

Vincent Collange (collangev@gmail.com)

Olivia Le Saux (Olivia.LESAUX@lyon.unicancer.fr)

David Dayde (david.dayde@chu-lyon.fr)

Claire Falandry (claire.falandry@chu-lyon.fr) (Corresponding author)

Corresponding email address: claire.falandry@chu-lyon.fr

Abstract

Background: Aging is associated with an increased prevalence of co-morbidities and sarcopenia and with a decline of functional reserve of multiple organ systems, eventually leading in the context of the disease- and/or treatment-related stress to functional deconditioning or organ failure. The multicomponent intervention "PROADAPT" was built multi-professionally to implement prehabilitation in older cancer patients.

Methods: PROADAPT-pilot study is an interventional, non-comparative, prospective, multicenter study. It will include 122 patients oriented to complex medico-surgical curative procedures (major surgery or radiation therapy +/- chemotherapy). After informed consent, patients will undergo a comprehensive geriatric assessment and will be offered a prehabilitation kit "PROADAPT" including an advices booklet with personalized objectives and respiratory rehabilitation devices. Patients will then be called weekly and monitored for physical and respiratory rehabilitation, pre-operative re-nutrition, motivational counseling, and iatrogenic prevention. Six outpatient consultations will be planned at inclusion, few days before the procedure, at 1, 3, 6 and 12 months after the end of the procedure. The main outcome of the study is the feasibility of the intervention, defined as the ability to perform at least one of the components of the program. Clinical data collection will include patient-specific and cancer-specific characteristics.

Discussion: PROADAPT program was designed to be implemented pragmatically in the centers according local habits and in different tumor contexts. Based on the results of this feasibility study, two randomized study are planned, that will evaluate the impact of PRODAPT program after cancer treatment for ovarian cancer (NCT04284969) or susmesocolic cancers.

Ethics and dissemination: Study protocol and several amendments were ethically approved. The results of the primary and secondary objectives will be published in peer-reviewed journals. ClinicalTrials registration: NCT03659123.

Keywords: oncogeriatrics, prehabilitation, motivation, sarcopenia, older cancer patients, care pathway.

Article summary

Strengths and limitations of this study

- PROADAPT program is a prehabilitation program specifically tailored for older cancer patients
- The program was designed according a muldisciplinary analysis of available evidence and according a multistep validation process involving patients.

- PROADAPT pilot trial is a prospective and multicenter trial designed to evaluate the feasibility of the intervention, next leading to future 2 randomised trials
- The construct of the trial includes lots of secondary outcomes, to better adapt the program to patients' specificities

Introduction

Many oncological situations involve complex medical-surgical procedures at risk of patient's deconditioning. Surgery or complex medico-surgical procedures can be considered as one proof-of principle of such risks, since major cancer surgery exposes the older population to a higher risk of morbi-mortality and unplanned hospitalization for geriatric events (1). Outpatient treatments and rapid post-operative rehabilitation strategies are used to decrease post-operative deconditioning but do not take geriatric risk factors into account. The deconditioning of older patients, not anticipated, can thus lead to prolonged and iatrogenic hospitalizations, generating frustration, appeals by patients and their families and additional hospital costs.

In order to reduce complications after surgery, prehabilitation has often been considered, and 71 % of the surgeons would accept a 4 weeks delay before surgery to improve older patients' outcomes if shown to be beneficial (2). However, the actual level of evidence depends on the interventions: high for pre-operative nutrition (3), but low for physical exercise, due to heterogeneous programs with often bad adherence (4). In addition, geriatric validated interventions, in order to prevent iatrogenic event, may be added in a multi-interventional model of intervention.

To date, the interventions likely to prevent geriatric deconditioning include nutritional care, pre-therapeutic (prehabilitation) and post-therapeutic (rehabilitation) physical reconditioning, iatrogenic prevention (drug and care system-related) and hospital-to-home transition to limit the risk of early readmission of patients. Nevertheless, the level of evidence for each of these care segments remains limited, and not specific to the oncogeriatric population. Indeed, studies about more specific care have already been carried out but do not consider all of the above interventions (5). Moreover, cancer in the older patient is often associated with comorbidities, particularly cardiovascular disease (6,7). The older population also has a higher risk of loss of autonomy and cognitive impairment, which can be increased with surgery (8–10). In response to the growing population of older cancer patients, a modification of oncological care and the implementation of specific geriatric interventions have been developed (11–13).

PROADAPT (Prehabilitation & Rehabilitation in Oncogeriatrics: Adaptation to Deconditioning risk and Accompaniment of Patients' Trajectories) is a geriatric intervention program constructed on a multi-professional and multi-disciplinary basis after a systematic analysis of published data. It includes: 1) before surgery: prehabilitation of patients, including nutritional, physical, respiratory and motivational counselling; 2) during hospitalisation for surgery (if performed): optimization of their treatment by pharmaceutical reconciliation, educational interventions, standardization of surgical interventions and improved rehabilitation after surgery; 3) bridging and post-discharge interventions for hospital-to-home transition (table 1).

Methods and analysis

Objectives

Primary objective

The primary objective of the PROADAPT pilot study is to assess the feasibility of the program, defined as the achievement of at least one item of the program during patient's follow up.

Secondary objectives

The secondary objectives of the study are:

1) To assess the achievement of each item of the program independently of each other (rate of achievement of all or part of the instructions);
2) To assess patients' satisfaction with the program;
3) To estimate the rate of adherence to items during the various visits;
4) To appreciate the longitudinal evolution over 1 year.

In addition to these secondary objectives, a series of parameters will be measured and monitored in this order:

5) To assess patients' post treatment complications according Clavien Dindo and NCI-CTC version 4 scoring systems;
6) To estimate the rate and the nature of post-operative complications according to the CCI index at 30 and 90 days;
7) To estimate the post-operative mortality at 30 and 90 days;
8) To estimate the costs of treatments (health system, patients);
9) To study the therapeutic strategies (treatment completion rate);
10) To estimate the progression-free survival rate at one year (PFS);
11) To estimate the overall survival rate at one year (OS);
12) To study the physical performance tests and the evolution of these performances through the proposed exercises;
13) To study the other dimensions of quality of life relating to health at 3 months;
14) To estimate the longitudinal evolution of QoL;
15) To estimate the tolerance of treatments;
16) To estimate the evolution of geriatric covariates.

Study design

PROADAPT - pilot phase is a second category interventional study involving the human person with minimal risks and constraints excluding health products. It is a prospective, non-comparative multicenter opened in different centers of Auvergne-Rhône-Alpes region, France (n=7).

Study sites and participants

The study population will include older patients identified during multidisciplinary consultation meetings and oriented to complex medico-surgical curative procedures in the including centers (Lyon Sud Hospital, Croix Rousse Hospital and Edouard Herriot Hospital from the Hospices Civils de Lyon, Nord-Ouest Villefranche-sur-Saône Hospital, Annecy-Genevois Hospital, Chambery Hospital, Lyon-Villeurbanne Médipôle).

Inclusion criteria are: patient aged 70 and over or 60 and over with significant comorbid condition (modified Charlson index ≥ 3) or disability (ADL score < 6/6), histologically or cytologically proven cancer, life expectancy > 3 months planned for a complex medico-surgical procedure in a curative intent.

Exclusion criteria are: patient with other malignancy within the last 5 years (except for adequately treated carcinoma in situ of the cervix or squamous carcinoma of the skin, or adequately controlled limited basal cell skin cancer), unable to be regularly followed for any reason (geographic, familial, social, psychologic) or with any mental or physical handicap at risk of interfering with the appropriate treatment.

Intervention

PROADAPT intervention program was built according to a multi-dimensional and multidisciplinary basis. From January 2016 to April 2018, nine regional meetings were organized, gathering 40 representatives of the following medical and paramedical specialties: geriatricians, nutritionists, surgeons (subspecialties: gynaecology, digestive surgery, urology), oncologists, anaesthesiologists, nurses, physiotherapists, occupational therapists, adapted physical activity monitors. A systematic review of published data was done in the following axes, in order to provide a graded state-of-the-art: nutrition, physical activity, patient education, medication rationalization, cardiovascular optimization, transition and standardization of surgical procedures. Based on the qualitative grading of existing data, a modified DELPHI method was performed, in order to co-validate the content of the standardized intervention checklist, and the feasibility of the implementation of each point of this checklist (Table 1).

A PROADAPT booklet was built, in order to propose a standardized, adapted and evolutive tool designed to explain physical exercise and nutrition counselling and to insure a follow-up of patients' day-to-day achievements. This first version was tested by candidate patients during two turns of validation before the validation of the current version 3 of the booklet.

PROADAPT standardized geriatric intervention program includes:

- Pre-operative physical activity including strength and endurance exercise +/- group activities during 4 +/-2 weeks. Interventions with high level of evidence were retained, according to an ongoing systematic analysis (http://www.crd.york.ac.uk/PROSPERO Ref CRD42020100110; (14,15));
- Nutrition: nutrition before and after physical activity, pre-postoperative immuno-nutrition +/- artificial nutrition according international guidelines (3);
- Patient (and caregiver) education and coaching (on nutrition, physical exercise) according to a weekly schedule with the activation of integrated supports by hetero- and self-management (16);
- Standardized intervention procedures, according to a checklist established in consensus with surgeons' representatives;
- Enhanced rehabilitation will be promoted according to international guidelines (17);
- Pharmaceutical medication conciliation, treatment optimization, according a centralized process with pharmaceutical expertise;
- Bridging interventions for hospital-to-home transition, according to a proposed standardized procedure including training of dedicated nurses, and post-discharge phone-calls follow-up during 12 weeks after surgery. Interventions with high level of evidence were retained, according to an ongoing systematic analysis (http://www.crd.york.ac.uk/PROSPERO Ref CRD42017055698).

The intervention is designed to be implemented at different times of patients' care (table 1).

During the prehabilitation time:

- A dedicated nurse, trained in patient education ("coaching nurse") presents him/herself to the patient for:
  - Presentation of the program to the patient and his/her caregiver(s)
  - Personalization of the PROADAPT book (see after) to the patient's characteristics
  - Collection of personal data, nutritional and functional habits
  - Evaluation of psycho-cognitive context
  - Gathering of the information needed: comorbidities, comedications (for transmission to the centralized pharmaceutical expertise)
  - Anticipation and organization of the future appointments (anesthesiologist, stomatherapist, …)

- A weekly visit or phone call according to a structured interview for health education and transmission of nutritional and functional advices (see after)

• Nutritional care is based on:
  - A personalized evaluation of nutritional balance and nutritional needs of the patient according to dietician diagnosis based on measured intake and international recommendations
  - A weekly follow-up of weight and nutritional intake
  - Artificial nutrition if needed according ESPEN recommendations (3)
  - Pre-operative immune-nutrition during 7 days before surgery
• Total-body rehabilitation:
  - 2 to 3 times a week: strength exercise (each time with dedicated exercises for upper members, legs and abs, 20 to 45 minutes each sequence)
  - 2 to 3 times a week: endurance exercise (walk or cycle ergometer), 20 to 45 min each sequence
  - 3 times a day: respiratory physiotherapy
  - Once a week (if possible): group activities (according to the center organization and home-hospital distance)
• Pharmaceutical conciliation and optimization according to STOPP/START criteria and international recommendations about peri-operative care (18): to be transmitted to the surgical and anesthesia team without any obligation.

During peri-operative time

• The coaching nurse contacts the surgical team for transmission of:
  o patient's personal data
  o physical (nutritional, functional and/or comorbidities) as well as psychological difficulties
  o medication conciliation results

During rehabilitation time

• The coaching nurse contacts the rehabilitation team for transmission of:
  o patient's personal data and care course
  o physical (nutritional, functional and/or comorbidities) as well as psychological difficulties
  o medication conciliation results
• The rehabilitation program is left at the discretion of the rehabilitation team

- A weekly phone call of the coaching nurse to the rehabilitation team for nutritional and functional follow-up as well as medication conciliation

During hospital-home transition time

- The coaching nurse contacts the patient's general practitioner for transmission of:
  - patient's personal data and care course
  - physical (nutritional, functional and/or comorbidities) as well as psychological difficulties
  - medication conciliation results
- Bi-weekly phone call of the coaching nurse to the patient for nutritional and functional follow-up
- Advices for optimization of symptoms management: abdominal pain, nausea, vomiting…

Participant timeline

Six successive evaluations are planned for the participants.

The inclusion visit is planned during a geriatric consultation planned before the start day of the complex medico-surgical procedure, at least 7 days before start date. If the start date is delayed for any reason or the patient is included into a neo-adjuvant treatment, the prehabilitation time may be prolonged until 9 months. In that case, the frequency of the phone calls is decreased (from 1/week to 1/month) after 4 weeks. During the inclusion visit, lasting about 1 hour, the following steps are planned:

- Clinic (blood pressure, heart rate, WHO score, patient's comorbidities), biologic (albumin, prealbumin, C-reactive protein) and paraclinic (year of birth, gender, weight, height, body mass index, weight evolution over the last 3 and 6 months) data collection
- All concomitant treatments and drug conciliation
- The history of the disease (primitive site, metastasis, histology of the initial tumor, presence of tumor markers)
- Radiological disease assessments (date and nature)
- A standardized geriatric assessment using validated questionnaires with a particular attention on physical activity and nutrition (**Error! Reference source not found.**tables 2 and 3).
- Delivery of the "PROADAPT kit" device during a meeting with a dedicated paramedic (nurse, physiotherapist, ergotherapist…) in order to:
  - Provide to the patient VOLDYNE® and TRIFLO® devices for inspiratory training

- Present the PROADAPT notebook that includes a battery of exercises and nutritional counselling specifically designed for this older population:
  - muscle strengthening of upper limbs (6 exercises, 3 difficulty levels), lower limbs (6 exercises, 3 difficulty levels), abdominal wall (4 exercises, 3 difficulty levels) (objective: 2 to 3 sessions per day for a total time between 20 and 45 minutes)
  - endurance/aerobic activities (7 exercises, 3 difficulty levels with 3 duration objectives, objective: every day)
  - inspiratory training with VOLDYNE® and TRIFLO® devices (objective: 3 sessions per day for a total time of 30 minutes)
  - general nutritional counselling adapted to the older population: food enrichment, inter-meals collations, oral nutritional supplements.
- A fulfilling of 3-day food statement allows, in the 7 days after inclusion, to deliver a dietician-driven personalized nutritional counseling. If needed, in case of unfavorable nutritional parameters, artificial nutrition is introduced.

- Delivery, if needed, of medical prescription:
  - for home physiotherapy according PROADAPT program for respiratory training sessions and physical activity training sessions
  - For oral nutritional supplements
  - For usual medicines, including pharmaceutical review
- For patients requiring inpatient follow-up, hospital admission for a few days in a rehabilitation unit for a physiotherapeutic program and/or artificial nutrition (enteral preferred).

During pre-intervention time, phone calls are planned by a dedicated paramedic (once a week for the first 4 weeks and then once a month until the intervention). Calls are semi-directed interviews focused on the patient's autonomy, physical activity, appetite and sleep over the last period (week/month). A special attention is paid on encouraging patient's motivation and adherence to the program (figure 1)

The pre-therapeutic visit is scheduled when possible between 5 days and the day of the intervention. This visit is performed in the surgery or radiotherapy unit only if the visit is necessary before the intervention still without modifying the standard therapeutic care for:

- Clinic, biologic and paraclinic data collection
- All concomitant treatments and drug conciliation
- Questionnaires about pain, nutrition, fitness and physical tests (table 2 and 3)
- Therapeutic care data collection (date, nature, entitled, reason)

During post-intervention time, paramedics trained in clinical research will resume follow-up calls as before the intervention once a week during 12 weeks after D0 and once a month up to 12 months after D0. The D0 date is determined as the last day of surgery (day of the last resumption of surgery in the limit of 30 days after the first intervention) or the last day of the radiotherapy. For weekly calls, a margin of +/- 2 days is allowed and for monthly calls, a margin of +/- 7 days is allowed.

Visits at 1, 3 and 6 months after the intervention (+/- 7 days): The patient may have started an antineoplastic treatment according to standard of care. The visit could be performed with the surgeon, the radiotherapist or the oncologist according local habits:

- Clinic (blood pressure, heart rate, WHO score), biologic (albumin, prealbumin, C-reactive protein) and paraclinic (weight, body mass index) data collection
- All concomitant treatments and drug conciliation
- Patient care data (surgery and complications, treatment for the cancer)
- Radiological disease assessments (date and nature)
- Questionnaires about quality of life, pain, nutrition, fitness and physical tests (table 2 and 3)
- Socio-economic assessment with patient's care data (date, nature of acts, designation, reason)

The end of study visit is planned at 12 months (per-protocol) or at the date of trial premature discontinuation (+/- 7 days) for a final assessment of the same outcomes as previously listed. When requested, if previous visits were omitted, a final assessment of all the complications during the post-therapeutic period is performed.

Outcomes and measurements

Primary outcome

The main outcome measure will be the percentage of patients who have completed at least one item in the PROADAPT program after 12 months after the start of therapeutic treatment. The start of treatment is defined in this study by the last day of surgery (date of the last recovery within the limit of 30 days after the date of the initial intervention) or the last day of radiotherapy. The workshops of the program are:

- Physical and respiratory rehabilitation
- Re-nutrition session
- Telephone nurse follow-up

Secondary outcomes

The secondary outcomes of the study are:

- To evaluate the feasibility of each stage of the program independently of each other (rate of achievement of all or part of the instructions)
    - Pre-operative physical rehabilitation including (figure 2):
        - Muscle strengthening
        - Respiratory rehabilitation
        - Endurance work
    - Pre-operative nutrition counselling (figure 2)
    - Drug reconciliation / iatrogenic prevention
    - Pre-therapeutic follow-up calls (figure 1)
    - Post-surgery or post-radiotherapy follow-up calls (figure 1)

- To estimate patients' satisfaction with the overall program, at the end of the study (**Error! Reference source not found.**table 2).

- To estimate the rate of adherence to the items (physical activity, nutrition and nursing follow-up) during follow-up time. To evaluate this criterion, various parameters will be recorded: physical activity duration (in h/week), kinetics (duration (% increase), level of difficulty), respiratory activity, food intake during phone calls.

- To assess the longitudinal evolution over 1 year of:
    - patient's physical performance (SPPB, gate speed, TUG test) and functional independence on ADL (19), IADL (20), AIPVQ (21)
    - nutritional parameters of the patient (weight, albuminemia, appetite)
    - health-related quality of life for patients based on QLQ-C30 and ELD14 (5 dimensions: mobility, disease burden, emotional and physical functioning, tiredness) (22,23)
    - pharmaceutical conciliation

In parallel to these secondary objectives, a series of parameters will be measured and monitored in order to:

- Estimate the rate and nature of post-operative complications at 30 days (NCI-CTCAE)
- Estimate the rate and nature of post-operative complications according to the CCI at 30 and 90 days
- Estimate post-operative mortality at 30 and 90 days
- Estimate the overall one-year survival rate (OS)
- Estimate the one-year progression-free survival rate (PFS)

- Estimate the longitudinal evolution of QoL according to QLQ C30, ELD14, EQ-5D
- Estimate treatment costs (health system, patients)
- Study therapeutic strategies (treatment completion rate)
- Estimate the evolution of geriatric covariates.

Sample size calculation

The program will be considered feasible, at the patient level, if all or part of the program is implemented in at least 50 % of the included patients (= alternative hypothesis).

The calculation of the number of subjects needed was done as follows: to reject the null hypothesis of the program feasibility rate lower than 35 %, with a first alpha species risk of 5 % and a power of 90 % (beta=10 %, bilateral test), the number of subjects to be analyzed is 111. Including 10 % non-treatable patients, a total of 122 patients should be included. The included patients will be analyzed with intention-to-treat.

Data management and statistical analyses

Data are monitored by a clinical research associate (CRA). Inconsistencies will be reported to the study investigators in order to decide whether the data should be corrected or considered as missing data. Any changes in the data will be reported.

Data analyses will be performed by the data management and analysis centre. The analyses will be carried out by an independent statistician with the latest version of the R software environment.

All of the characteristics collected will be subjected to a descriptive analysis.

Descriptive analyses

A flow-chart diagram will describe the data available for the patient population at baseline, and during each follow-up visit. Eligibility criteria for treated patients will be verified, as well as follow-up and end of study visits. Reasons for premature end of study will be provided.

Characteristics of the study population and proportions of missing values will be reported. Patient characteristics will be described using mean and standard deviation or median and interquartile range for quantitative variables, and frequencies and distribution for categorical variables. A comparison of baseline characteristics between patients with complete follow-up and those with attrition will be performed. If needed, methods for handling missing data (multiple imputation, mixed model or auxiliary variable) will be used when appropriate.

Primary analysis

The percentage of patients who have completed at least one PROADAPT program activity at the end of 12 months after the start of treatment will be estimated using mean and standard deviation.

Secondary analyses

Time-to-event variables: follow-up, overall survival, progression free survival

The proportion of events at specific measurement times will be estimated according to the Kaplan-Meier curve. Medians of event-free survival will be reported by treatment arm with its 95 % confidence interval (95 % CI), if the number of events allows estimation of the median.

Overall survival rate and progression free survival rate at 12 months (after the day of the last revision of surgery or the last day of radiotherapy) will be provided with 95 % CI.

Quality of life

Analyses of the QoL data will be performed with modified intention to treat (mITT): all included patients, regardless of compliance with the eligibility criteria and whether or not they were followed up and for whom the QoL scores at inclusion will be included in the analysis. Patients' quality of life, linked to health, will be analysed after 3 months through 5 dimensions: mobility, disease burden, emotional and physical functioning, tiredness.

Data monitoring

The successful completion of the database is ensured by the hospital CRA. The hospital CRA also ensures compliance with the study protocol. The sponsor CRA verifies that the rights of the participants are respected.

End of protocol

Patients leave the study either on a per-protocol basis during the "end of study visit" on month 12 after the intervention or at any time during the conduct of the study if they no longer wish to participate. However, as indicated in the information letter to the patients/caregivers, the data collected before exclusion may be used as part of the study.

Confidentiality

Correspondence tables will be kept in a separate file that does not contain clinical data. The access to the nominative information is protected by a password and confidentiality is guaranteed by the study.

Protocol amendments

Any important modifications requiring a new ethics committee approval will be communicated in future publications. Any potential impact of protocol modifications on the results will be discussed as appropriate.

Trial status

Patient enrolment began on July 3, 2018. Data are collecting.

Patients' and public involvement

Patients were involved at different steps of the trial: (i) during PROADAPT booklet conception, several (30) patients were asked to answer an anonymous questionnaire in order to improve its ergonomics; (ii) the information note and consent form of the protocol have been re-read by the patients' review committee of the Ligue Nationale de Lutte contre le Cancer (a French association of cancer patients).

Discussion

Discussion of the intervention

Prehabilitation has long been conceptualized as an effective means of improving the functional capacity of the individual to enable him to resist various stressors. Originally developed in the military as the association of physical training to improve strength and endurance, improving nutritional intake and general education (24), it has been transposed into medicine and major surgery – initially when an ICU admission is planned - at the beginning of this century (25).

Despite a growing interest in the medical community for prehabilitation and particularly cancer prehabilitation, the level of evidence for specific interventions stays too low to be implemented in common care. Among the main disadvantages of published data include the heterogeneity of programs, sometimes poor patient adherence and the fact that most studies were small pilot studies developed for patients more fit and younger than those who should make the best part of prehabilitation. Another point to emphasize is that most programs include only one intervention - physical, nutritional, or psychological rehabilitation - when multimodal interventions are often considered to be more effective in older populations.

Considering these points, the PROADAPT intervention was developed according to an innovative management strategy since it started in 2016 by multi-professional meetings conceived as brainstorming sessions in order to develop a multidisciplinary program dedicated to prehabilitation and follow-up of older patients. The multidisciplinary conception of the intervention, the particular attention paid to older patients' specificities and the previous experience of the participants in as various fields as patients' education, cognition, physiotherapy were hopefully the warrants of the most tailored approach to the target population. For example, the booklet typography was of big character font and the illustrations highly schematic with high contrast. Each sentence was verified by a panel of patients in order to insure proper understanding. Finally, the booklet was evaluated by 30 patients, with a high rate of satisfaction (Ravot et al, PROADAPT Pilot trial: A survey on patients' expectations and satisfaction, unpublished data).

This pilot study is the first step towards an ambitious program, since PROADAPT program will be declined in the future into two randomized studies, PROADAPT-ovary/EWOC-2 (NCT04284969) and PROADAPT sus-mesocolic, designed to evaluate the impact of PROADAPT program on post-treatment complications versus common care. In order to favor patients' compliance and follow-up, an eHealth tool has been developed that will help supervising patients' care courses.

Discussion of the study design

In line with the previous points, this pilot study was designed in order to answer to this critical question: is a multidomain prehabilitation program feasible in an older cancer population? This question encompasses several points: (i) Is the program physically adapted to an older population? (ii) Is such a program appliable in ambulatory care? (iii) How to build pedagogic tools adapted for such ambulatory use? (iv) Are such pedagogic tools understandable? (v) What is the compliance of the patients for each domain of the intervention program?... Another point is to know whether the patient's care team is expected to accept such intervention, but this point was previously evaluated by Ghignone et al. They demonstrated through an international survey that surgeons are generally in favor for such programs since 71 % of them would accept to prehabilitate their elderly patients 4 weeks before surgery, if such intervention is proven to be effective (2). Nevertheless, the participation of surgeons and anesthesiologists during initial brainstorming sessions was of major interest since they enriched a lot the structure of the program.

Thus, the construct of this trial may appear as highly complex with overabundant secondary endpoints, but this design encompasses as much as possible the complexity of prevention care in an older population, which has to mix the adaptation to the target population and the ability to maintain compliance over time.

Ethics and dissemination

The study sponsor is the Hospices Civils de Lyon, responsible for study insurance and pharmacovigilance. The study protocol was approved by the Ile de France 8 Ethics Committee on May 3, 2018 and cover all sites involved in this study. Several amendments have been added to the first version of the protocol. The initial approved version was V2 of May 28, 2018, then the amended versions were as follows: V3 of October 23, 2018 (change in the recruitment period, addition of new investigation centers), V4 of May 17, 2019 (request for an additional 12 months extension, update with the GPDR and update of the patient book). Current version is the V4 of May 17, 2019, authorized on June 27, 2019. The research will be carried out on accordance with the Helsinki Declaration and ICH GCP Guidelines. Trial protocol fulfills SPIRIT 2013 checklist (Supplementary table 1) and World Health Organization Trial Registration Data Set (Supplementary table 2). The study complies with the principles of the data protection act in France and with the General Data Protection Regulations in force in Europe. Each investigator must collect a written consent at the beginning of the procedure. This consent is retained in the patient's medical chart. The patient can stop the study at any time with an oral information at his investigator or clinical research assistant. Patients will be informed on additional amendments according the law in force.

The results of the primary and secondary objectives will be published in peer-reviewed journals. All authors of future publications will have to meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors.

Total words count : 4547

Abbreviations

ADL: Activities of Daily Living; AIPVQ: Physical Instrumental activities of daily living (in French: Activités Instrumentales Physiques de la Vie Quotidienne); CRA: Clinical Research Assistant; ESPEN: European Society for Clinical Nutrition and Metabolism; FSS: Fatigue Severity Scale; GDS: Geriatric Depression Scale; IADL: Instrumental Activities of Daily Living; ICU: Intensive Care Unit; mITT:Modified Intention To Treat; MNA: Mini Nutritional Assessment; QLQ: Quality of Life Questionnaire; QoL: Quality of Life; RAPA: Rapid Assessment of Physical Activity; SF: Short Form; SPPB: Short Physical Performance Battery

Declarations

Acknowledgements

This pilot protocol is part of the PROADAPT initiative for improving care for older people with cancer. The authors wish to thank the professionals who participated to the intervention conception: G. Albrand, D. Barnoud, D. Benayoun. B Billod, J. Bonhomme, A.-L. Bres, C. Brunengo, A. Chanelière, D. Charlety, Y. Chauleur, G. Copaescu, H. Curé, A.-M. Dascalita, B. De La Vigerie, S. Ducoulombier, , O. Ganne, F. Gervais, T. Gilbert, M. Giroud, N. Jomard, C. Lecardonnel, B. Leroy, J.-A. Long, A. Marion, E. Nony, S. Parent, A. Pelisset-Vanhersecke, A. Pirollet, , J.-E. Terrier, J. Trautmann, M.-A. Vincent.

The authors also acknowledge the teams of Lyon Sud Hospital, Edouard Herriot Hospital of Lyon, Croix Rousse Hospital of Lyon, Annecy Genevois Hospital Center, Hôpital Nord Ouest hospital center, Chambéry Hospital Center and Médipôle Lyon-Vileurbanne who contribute to patient enrollment in this study.

The authors would like to thank in particular the patients' review committee of the Ligue Nationale de Lutte contre le Cancer for the valuable editing of the information note and the consent form.

Funding

This work was supported by the Agence Régionale de Santé (ARS) Auvergne Rhône Alpes, through the call for projects "Innovate in health for the Auvergne Rhône Alpes region" jointly organized by the ARS, Bpifrance, the Auvergne Rhône Alpes region, URIOPASS, ORAIDA and Cluster I-care and the decision of the selection committee on June 27, 2016 (Grant N°2016-149 (63)). It provided funding for nurses, dieticians, physiotherapists, and clinical research assistants.

Availability of data and materials

The final dataset of the PROADAPT pilot study will be available on reasonable request after publication of the primary objective. Data requests can be submitted to the corresponding author.

Competing interest

The authors declare that they have no competing interests.

Consent for publication

Not applicable

Author contributions

All authors participated to the PROADAPT intervention conception. Study protocol was conceived by DD, CF, CG, OLS, AM, VP and CR. DD and CF assumed fundraising and grant follow-up. MR led the drafting of the manuscript. All authors critically reviewed and approved the final version of the protocol.

References

1. Tan H-J, Saliba D, Kwan L, Moore AA, Litwin MS. Burden of Geriatric Events Among Older Adults Undergoing Major Cancer Surgery. J Clin Oncol. 2016 Oct 4;34(11):1231–8.

2. Ghignone F, van Leeuwen BL, Montroni I, Huisman MG, Somasundar P, Cheung KL, et al. The assessment and management of older cancer patients: A SIOG surgical task force survey on surgeons' attitudes. Eur J Surg Oncol EJSO. 2016 Feb;42(2):297–302.

3. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr [Internet]. 2016 Aug 6 [cited 2016 Nov 20];0(0). Available from: http://www.clinicalnutritionjournal.com/article/S0261-5614(16)30181-9/abstract

4. Singh F, Newton RU, Galvão DA, Spry N, Baker MK. A systematic review of pre-surgical exercise intervention studies with cancer patients. Surg Oncol. 2013 Jun 1;22(2):92–104.

5. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008 Sep 29;337:a1655.

6. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet] [Internet]. Lyon, France: International Agency for Research on Cancer; 2013 [cited 2016 Sep 4]. Available from: Available from: http://globocan.iarc.fr

7. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared Risk Factors in Cardiovascular Disease and Cancer. Circulation. 2016 Mar 15;133(11):1104–14.

8. Sjölund B-M, Wimo A, Qiu C, Engström M, von Strauss E. Time trends in prevalence of activities of daily living (ADL) disability and survival: Comparing two populations (aged 78+ years) living in a rural area in Sweden. Arch Gerontol Geriatr. 2014 May;58(3):370–5.

9. Sjölund B-M, Wimo A, Engström M, Strauss E von. Incidence of ADL Disability in Older Persons, Physical Activities as a Protective Factor and the Need for Informal and Formal Care – Results from the SNAC-N Project. PLoS ONE [Internet]. 2015 [cited 2016 Sep 4];10(9). Available from: https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pmc/articles/PMC4583409/

10. Jagger C, Gillies C, Moscone F, Cambois E, Van Oyen H, Nusselder W, et al. Inequalities in healthy life years in the 25 countries of the European Union in 2005: a cross-national meta-regression analysis. The Lancet. 2008 Dec 20;372(9656):2124–31.

11. Extermann M, Meyer J, McGinnis M, Crocker TT, Corcoran MB, Yoder J, et al. A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. Crit Rev Oncol Hematol. 2004 Jan;49:69–75.

12. Repetto L, Fratino L, Audisio RA, Venturino A, Gianni W, Vercelli M, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol. 2002 Jan 15;20:494–502.

13. Caillet P, Canoui-Poitrine F, Vouriot J, Berle M, Reinald N, Krypciak S, et al. Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA study. J Clin Oncol. 2011;29:3636–42.

14. Falandry C, Stefani L, Granger M, Momiron C, Habchi H, Bourgeois C, et al. Interventions to improve physical performances of older people with cancer before major surgery: an umbrella review. J Geriatr Oncol. 2018;9(6 suppl 1):S94–5.

15. Falandry C, Stefani L, André L, Granger M, Barbarava C, Habchi H, et al. Interventions to improve physical performances of older people with cancer before complex medico-surgical procedures: protocol for an umbrella review of systematic reviews and meta-analyses. Medicine (Baltimore). 2020;

16. Glasgow RE, Emmons KM. How Can We Increase Translation of Research into Practice? Types of Evidence Needed. Annu Rev Public Health. 2007;28(1):413–33.

17. Colburn JL, Mohanty S, Burton JR. Surgical Guidelines for Perioperative Management of Older Adults: What Geriatricians Need to Know. J Am Geriatr Soc. 2017 Jun 1;65(6):1339–46.

18. Mohanty S, Rosenthal RA, Russell MM, Neuman MD, Ko CY, Esnaola NF. Optimal Perioperative Management of the Geriatric Patient: A Best Practices Guideline from the American College of Surgeons NSQIP and the American Geriatrics Society. J Am Coll Surg. 2016 May 1;222(5):930–47.

19. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of Illness in the Aged. The Index of Adl: A Standardized Measure of Biological and Psychosocial Function. Jama. 1963 Sep 21;185:914–9.

20. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969 Autumn;9:179–86.

21. de Souto Barreto P, Ferrandez A-M. Activités instrumentales physiques de la vie quotidienne chez les personnes âgées: validation d'une échelle. In: L'anthropologie du vivant: objets et méthodes. Chapuis-Lucciani N, Guihard-Costa AM, Boëtsch G. 2010. p. 83–7.

22. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. JNCI J Natl Cancer Inst. 1993 Mar 3;85(5):365–76.

23. Wheelwright S, Darlington A-S, Fitzsimmons D, Fayers P, Arraras JI, Bonnetain F, et al. International validation of the EORTC QLQ-ELD14 questionnaire for assessment of health-related quality of life elderly patients with cancer. Br J Cancer. 2013 Aug 20;109(4):852–8.

24. Prehabilitation, rehabilitation, and revocation in the Army. Br Med J. 1946 Jun 29;1:192–7.

25. Topp R, Ditmyer M, King K, Doherty K, Hornyak J. The effect of bed rest and potential of prehabilitation on patients in the intensive care unit. AACN Clin Issues. 2002 May;13(2):263–76.

Illustrations' legends

Figure 1: PROADAPT program: follow-up visits and phone calls

Figure 2: PROADAPT program: interventions at the patient's level

Table 1: PROADAPT program: tasks according the different domains and the successive chronological steps (before, during and after complex medico-surgical procedure)

Table 2: PROADAPT pilot trial: questionnaires and screening tests

Table 3: PROADAPT pilot trial: flow diagram

Table 1: PROADAPT program: tasks according the different domains and the successive chronological steps (before, during and after complex medico-surgical procedure)

Nurse coaching & education Bridging interventions	Coaching nurse self-presentation Delivery of a personalized patient book Care according best practice guidelines: - Confirm and document patient goals and treatment preferences, including advance directives. - Confirm and document patient's health care proxy or surrogate decision-maker. - In patients with existing advance directives, discuss new risks associated with the surgical procedure and an approach for potentially life-threatening problems consistent with the patient's values and preferences ("required reconsideration"). Weekly phone calls	Coaching nurse visits / phone calls Communication of patient's preference to the staff	Coaching nurse visit in the rehabilitation ward Communication of patient's preference and care difficulties to the staff (checklist): - delirium/cognitive impairment - peri-operative acute pain - pulmonary complications - fall risk - ability to maintain adequate nutrition - urinary tract infection prevention - functional decline monitoring - pressure ulcers prevention	Coaching nurse bi-weekly phone call Communication of patient's care difficulties to the staff
Nutrition	W-4 : nutritional evaluation Nutritional plan based on measured intake W-3 : nutritional follow up - weight W-2 : nutritional follow up-weight W-1 : nutritional follow up-weight + pre-operative immunonutrition	If surgery: Care according best practice guidelines: - Consider shortened fluid fast (clear liquids up to 2 hours before anaesthesia). - Normal food intake or enteral feeding should start as early as possible	Nutritional plan based on - Weight curve - Measured intake Optimal management of - Nausea/vomiting - Abdominal pain	Nutritional plan based on - Weight curve - Measured intake Optimal management of - Nausea/vomiting - Abdominal pain
Physical activity	W-4 : physical performances evaluation Physical activity plan W-3 / W-2 / W-1 \ group physical activity + functional follow-up	If surgery: care according best practice guidelines: - Early physical and/or occupational therapy. - Check for orthostatic hypotension. - Review physical environment to reduce injury risk. - Assistive walking devices (eg walkers) at bedside if used as outpatient	(to the discretion of the rehabilitation unit)	Pursuing of the pre-operative physical activity plan
Medication conciliation	Centralized medication conciliation and treatment optimization (STOPP/START guidelines)	Centralized medication conciliation Advices for care according best practice guidelines (16): - Adhere to existing best practices regarding antibiotic and venous thromboembolism prophylaxis. - Ensure nonessential medications have been stopped and essential medications have been taken.	Centralized medication conciliation	Centralized medication conciliation
Standardization of surgical procedures		If surgery: consider antiseptic toothpaste If surgery: care according best practice Guidelines (16): - Consideration of regional techniques to avoid postoperative complications and improve pain control. - Directed pain history. - Multi-modal or opioid-sparing techniques. - Postoperative nausea risk stratification and prevention strategies. - Strategies to avoid pressure ulcers and nerve damage. - Prevention of postoperative pulmonary complications and hypothermia. - Judicious use ofintravenous fluids. - Appropriate hemodynamic management. - Continuation of indicated cardiac medications. - Daily post-operative roundingchecklist: - delirium/cognitive impairment - peri-operative acute pain - pulmonary complications - fall risk - ability to maintain adequate nutrition - urinary tract infection prevention - functional decline monitoring - Pressure ulcers prevention If surgery: consider IV iron supplementation		

633 Table 2: PROADAPT pilot trial: questionnaires and screening tests

Domain	
Autonomy	Activity of Daily Living Scale (ADL) Instrumental Activities of Daily Living scale (IADL)
Geriatric screening	G8
Physical activity	RAPA (Rapid Assessment of Physical Activity), AIPVQ
Quality of life	QLQ-C30, QLQ-ED14, EQ-5D-3L, SF-36
Locomotion and balance	Time Up and Go, SPPB (Short Physical Performance Battery)
Pain	Pain scale evaluation
Nutrition	Nutrition scale evaluation
Tiredness severity	FSS
Depression/anxiety	MNA, GDS4/GDS15
Cognitive assessment	MINI-COG
Fall risk assessment	Tinetti test
Breathlessness	Borg scale

634

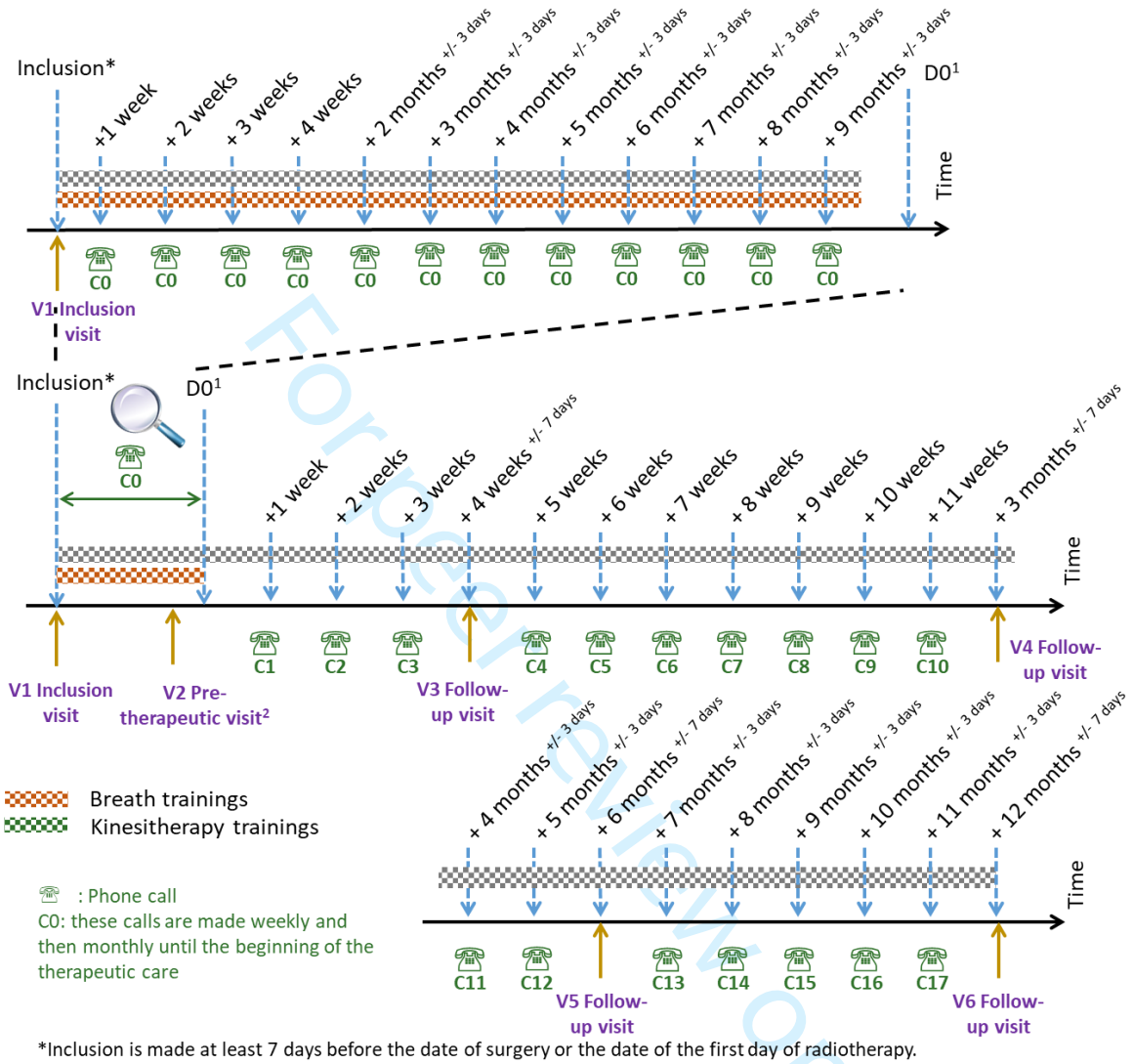
635

636 Table 3: PROADAPT pilot trial: flow diagram

	Baseline	Pre-therapeutic visit (0-5 days before intervention)	M1, M3, M6	M12	End of study visit
Complex geriatric assessment					
G8	X			X	X
ADL/IADL	X			X	X
GDS4/GDS15	X			X	X
MINI COG	X			X	X
MNA	X			X	X
QLQ-C30	X		X	X	X
QLQ-ELD14	X		X	X	X
EQ-5D-3L	X		X	X	X
Pain scale evaluation	X	X	X	X	X
Nutrition scale evaluation	X	X	X	X	X
Socio-economic evaluation	X	X	X	X	X
Physical and respiratory assessments					
FSS	X		X	X	X
SF-36	X		X	X	X
Time and Go	X			X	X
SPPB	X		X	X	X
Borg scale	X			X	X
RAPA questionnaire	X		X	X	X
AIPVQ scale	X		X	X	X
Tinetti test	X			X	X
Equimog evaluation	X			X	X
Triflo	X	X			
Voldyne	X	X			
Physical activity data collection		X	X	X	X
Patients' satisfaction					
Standardized questionnaire					X

637

Figure 1: PROADAPT program: follow-up visits and phone calls



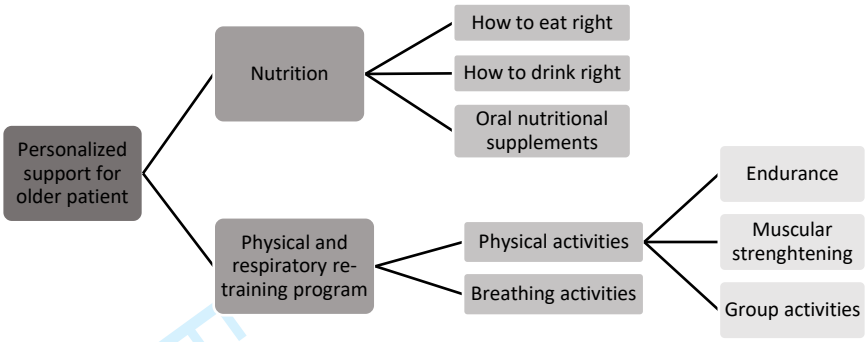
*Inclusion is made at least 7 days before the date of surgery or the date of the first day of radiotherapy. The duration of pre-habilitation may not exceed 9 months after inclusion.

[1] D0 corresponds to the last day of radiotherapy or the last day of the revision of the surgery within 30 days after the initial operation

[2] Visit should be performed between 5 days before and J0

➔ Weekly calls or visits have no margin, monthly calls have a margin of +/- 3 days and visits have a margin of +/- 7 days.

Figure 2: PROADAPT program: interventions at the patient's level



Supplementary table 1: SPIRIT 2013 checklist of the trial

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary table 2 Ref 24
Protocol version	3	Date and version identifier	17 (Ethics and Consent to participate)
Funding	4	Sources and types of financial, material, and other support	17-18 (Funding)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 (Authors' list) 18 (Authors' contributions)
	5b	Name and contact information for the trial sponsor	Supplementary table 2 Ref 24

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	10 (Ethical and legal considerations) 17 (Funding)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13 (Data management and statistical analyses) 14 (Data monitoring)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14 (End of protocol) And N/4 (no dose modifications)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6 (two turns of validations of the PROADAPT booklet by candidate patients)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-13 (Sample size calculation)

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A (no problem for accrual)
Methods: Assignment of interventions (for controlled trials)			**N/A**
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	-
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	-
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Table 3
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13 (Data management and statistical analyses)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14 (Data management and statistical analyses)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14 (Data Monitoring)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11 (Secondary outcomes: NCI CTCAE, QOL)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10 (Ethical and legal considerations)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10 (Ethical and legal considerations) 14 (Protocol amendments)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10-11 (Ethical and legal considerations)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14 (Confidentiality)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17 (Competing interests)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17 (Availability of data and materials)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15 (Dissemination policy)
	31b	Authorship eligibility guidelines and any intended use of professional writers	15 (Dissemination policy), N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Annex 1 (in French)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

Supplementary table 2: All items from the World Health Organization Trial Registration Data Set (SPIRIT item 2b)

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT03659123
Date of registration in primary registry	September 6, 2018
Secondary identifying numbers	69HCL16_0701 ID RCB N° 2018-A001026-49
Source(s) of monetary or material support	Agence Régionale de Santé Auvergne Rhône Alpes
Primary sponsor	Hospices Civils de Lyon
Secondary sponsor(s)	
Contact for public queries	David Dayde, +33.4.78.86.37.74, david.dayde@chu-lyon.fr
Contact for scientific queries	Claire Falandry, +33.4.78.86.66.34, claire.falandry@chu-lyon.fr
Public title	Prehabilitation & Rehabilitation in Oncogeriatrics: Adaptation to Deconditioning Risk and Accompaniment of Patients' With Cancer
Scientific title	Prehabilitation & Rehabilitation in Oncogeriatrics: Adaptation to Deconditioning Risk and Accompaniment of Patients' With Cancer, a Multicenter Pilot Study
Countries of recruitment	France
Health condition(s) or problem(s) studied	Old Injury
Intervention(s)	Behavioral: standardized geriatric intervention Nutritional care is based on: • A personalized evaluation of nutritional balance and nutritional needs of the patient • A weekly follow-up of weight and nutritional intake Total-body rehabilitation is based on: • 2 to 3 times a week: strength exercise • 2 to 3 times a week: endurance exercise, 20 to 45 min each sequence • 2 times a week: respiratory physiotherapy Pharmaceutical conciliation and optimization according STOPP/START criteria During peri-operative time, the nurse contacts the surgical team for transmission of patient's personal data, physical medication conciliation results During rehabilitation time and hospital-home transition time, the nurse contacts

Data category	Information
	the rehabilitation team for transmission of patient's personal data and care course, physical (nutritional, functional and/or comorbidities), medication conciliation results.
Key inclusion and exclusion criteria	Inclusion Criteria: Patient ≥70 year old OR patient ≥60 years with significant comorbid condition (modified Charlson index≥3) or disability (ADL score<6/6); Histologically or cytologically proven cancer. Life expectancy > 3 months. Written informed consent obtained Covered by a Health System where applicable. Exclusion Criteria: Other malignancy within the last 5 years, except for adequately treated carcinoma in situ of the cervix or squamous carcinoma of the skin, or adequately controlled limited basal cell skin cancer. Patient unable to be regularly followed for any reason (geographic, familial, social, psychologic). Any mental or physical handicap at risk of interfering with the appropriate treatment. Any administrative or legal supervision where applicable
Study type	Interventional Allocation: N/A Intervention model: Single Group Assignment Masking: None (Open Label) Primary purpose: Health Services Research Phase II
Date of first enrolment	July 3rd, 2018
Target sample size	122
Recruitment status	Recruiting
Primary outcome(s)	Implementation of at least one item of PROADAPT standardized geriatric intervention of the program PROADAPT pilot study [Time Frame: 12 months]: • Preoperative physical activity including strength and endurance exercise assessed by physical exercises accomplished under the supervision of a physiotherapist. Number of patients with at least 1 intervention achieved in the domain. • Nutrition guidelines before and after physical activity assessed by questionnaires. Number of patients with at least 1 intervention achieved in the domain.

Data category	Information
	• Patient education and coaching assessed by questionnaires and visits. Number of patients with at least 1 intervention achieved in the domain • Achievement of standardized intervention procedures, according to the checklist established in consensus with surgeons. Number of patients with at least 1 intervention achieved in the domain • Rehabilitation assessed by questionnaires. Number of patients with at least 1 intervention achieved in the domain • Accomplishment of pharmaceutical medication conciliation and treatment optimization. Number of patients with at least 1 intervention achieved in the domain • Bridging interventions for hospital-to-home transition. Number of patients with at least 1 intervention achieved in the domain
Key secondary outcomes	• Post operative morbidity [Time Frame: 30 and 90 days] according Clavien-Dindo classification • Post-operative morbidity [Time Frame: 90 days] according to NCI CTC v4.4 • Therapeutic strategy [Time Frame: 12 months]: Treatment plan completion rate: Number of patients for whom the treatment plan was completed. • Progression-free Survival [Time Frame: 12 months] • Post-treatment complication [Time Frame: 12 months]: Post-treatment complication grade≥3 according the National Cancer Institute Common Toxicity Criteria version 4 (NCI-CTC-v4)

Supplementary table 1: SPIRIT 2013checklist of the trial

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary table 2 Ref 24
Protocol version	3	Date and version identifier	17 (Ethics and Consent to participate)
Funding	4	Sources and types of financial, material, and other support	17-18 (Funding)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 (Authors' list) 18 (Authors' contributions)
	5b	Name and contact information for the trial sponsor	Supplementary table 2 Ref 24

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	10 (Ethical and legal considerations) 17 (Funding)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13 (Data management and statistical analyses) 14 (Data monitoring)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14 (End of protocol) And N/4 (no dose modifications)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6 (two turns of validations of the PROADAPT booklet by candidate patients)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-13 (Sample size calculation)

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A (no problem for accrual)
Methods: Assignment of interventions (for controlled trials)			**N/A**
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	-
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	-
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Table 3
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13 (Data management and statistical analyses)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14 (Data management and statistical analyses)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14 (Data Monitoring)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11 (Secondary outcomes: NCI CTCAE, QOL)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10 (Ethical and legal considerations)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10 (Ethical and legal considerations) 14 (Protocol amendments)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10-11 (Ethical and legal considerations)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14 (Confidentiality)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17 (Competing interests)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17 (Availability of data and materials)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15 (Dissemination policy)
	31b	Authorship eligibility guidelines and any intended use of professional writers	15 (Dissemination policy), N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Annex 1 (in French)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Feasibility of a prehabilitation program dedicated to older cancer patients before complex medico-surgical procedures: the PROADAPT pilot study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042960.R1
Article Type:	Protocol
Date Submitted by the Author:	16-Nov-2020
Complete List of Authors:	Roche, Mélanie; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL Ravot, Christine; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier Lyon Sud Malapert, Amélie; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL Garandeau, Charlène; Hospices Civils de Lyon, Direction à la Recherche Clinique et à l'Innovation Pitiot, Virginie; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL Tomatis, Mélanie; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier Lyon Sud Riche, Benjamin; Hospices Civils de Lyon, Service de Biostatistique - Bioinformatique, Pôle Santé Publique; Université de Lyon, Laboratoire de Biométrie et Biologie Évolutive CNRS UMR 5558, Équipe Biostatistiques Santé Galamand, Béatrice; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier Lyon Sud Granger, Marion; Hospices Civils de Lyon, Geriatrics unit; Centre Hospitalier de Chambery Barbavara, Claire; Hospices Civils de Lyon, Geriatrics unit Bourgeois, Chrystelle; Centre Hospitalier Annecy Genevois, Medical Oncology Genest, Evelyne; Hospices Civils de Lyon, Geriatrics unit Stefani, Laetitia; Centre Hospitalier Annecy Genevois, Medical oncology Haïne, Max; Hôpital Nord-Ouest, Pôle de gérontologie et Médecine de Réadaptation Castel-Kremer, Elisabeth; Hospices Civils de Lyon, Geriatrics unit. Hôpital Edouard Herriot. Morel-Soldner, Isabelle; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier de la Croix Rousse Collange, Vincent; Medipole Lyon-Villeurbanne, Département anesthésie réanimation Le Saux, Olivia; Centre de Recherche en Cancerologie de Lyon, Therapeutic targeting of the tumor cell and its immune microenvironment Dayde, David; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL Falandry, Claire; Hospices Civils de Lyon, Geriatrics unit; University of

	Lyon, CarMeN Laboratory, Inserm U1060, INRA U1397, Université Claude Bernard Lyon 1, INSA Lyon, Charles Mérieux Medical School
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Geriatric medicine, Surgery
Keywords:	Adult oncology < ONCOLOGY, GERIATRIC MEDICINE, REHABILITATION MEDICINE, Adult surgery < SURGERY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Feasibility of a prehabilitation program dedicated to older cancer patients before complex medico-surgical procedures: the PROADAPT pilot study protocol

Roche Mélanie (melanie.roche02@chu-lyon.fr)

Ravot Christine (christine.ravot@chu-lyon.fr)

Malapert Amélie (amelie.malapert@chu-lyon.fr)

Charlène Garandeau (charlene.garandeau@chu-lyon.fr)

Pitiot Virginie (virginie.pitiot@chu-lyon.fr)

Tomatis Mélanie (melanie.tomatis@chu-lyon.fr)

Benjamin Riche (benjamin.riche@chu-lyon.fr)

Béatrice Galamand (beatrice.galamand@chu-lyon.fr)

Marion Granger (mariongranger@outlook.fr)

Claire Barbavara (claire.barbavara@gmail.com)

Chrystelle Bourgeois (cbourgeois@ch-annecygenevois.fr)

Evelyne Genest (evelyne.genest@chu-lyon.fr)

Laetitia Stefani (lstefani@ch-annecygenevois.fr)

Max Haïne (mhaine@lhopitalnordouest.fr)

Elisabeth Castel Kremer (Elisabeth.castel-kremer@chu-lyon.fr)

Isabelle Morel-Soldner (isabelle.morel-soldner@chu-lyon.fr)

Vincent Collange (collangev@gmail.com)

Olivia Le Saux (Olivia.LESAUX@lyon.unicancer.fr)

David Dayde (david.dayde@chu-lyon.fr)

Claire Falandry (claire.falandry@chu-lyon.fr) (Corresponding author)

Corresponding email address: claire.falandry@chu-lyon.fr

Abstract

Background: Aging is associated with an increased prevalence of co-morbidities and sarcopenia and with a decline of functional reserve of multiple organ systems, eventually leading in the context of the disease- and/or treatment-related stress to functional deconditioning or organ failure. The multicomponent intervention "PROADAPT" was built multi-professionally to implement prehabilitation in older cancer patients.

Methods: PROADAPT-pilot study is an interventional, non-comparative, prospective, multicenter study. It will include 122 patients oriented to complex medico-surgical curative procedures (major surgery or radiation therapy +/- chemotherapy). After informed consent, patients will undergo a comprehensive geriatric assessment and will be offered a prehabilitation kit "PROADAPT" including an advices booklet with personalized objectives and respiratory rehabilitation devices. Patients will then be called weekly and monitored for physical and respiratory rehabilitation, pre-operative re-nutrition, motivational counseling, and iatrogenic prevention. Six outpatient consultations will be planned at inclusion, few days before the procedure, at 1, 3, 6 and 12 months after the end of the procedure. The main outcome of the study is the feasibility of the intervention, defined as the ability to perform at least one of the components of the program. Clinical data collection will include patient-specific and cancer-specific characteristics.

Ethics and dissemination: Study protocol and several amendments were ethically approved by Ile de France 8 Ethics Committee on May 3, 2018. The results of the primary and secondary objectives will be published in peer-reviewed journals. ClinicalTrials registration: NCT03659123.

Keywords: oncogeriatrics, prehabilitation, motivation, sarcopenia, older cancer patients, care pathway.

Article summary

Strengths and limitations of this study

- PROADAPT program is a prehabilitation program specifically tailored for older cancer patients
- The program was designed according a muldisciplinary analysis of available evidence and according a multistep validation process involving patients
- PROADAPT pilot trial is a prospective and multicenter trial designed to evaluate the feasibility of the intervention
- Different secondary outcomes including quality of life will be collected to better adapt the program to patients' specificities

A specific attention will be paid on program safety and patients' adherence to the program.

Introduction

Many oncological situations involve complex medical-surgical procedures at risk of patient's deconditioning. Surgery or complex medico-surgical procedures can be considered as one proof-of principle of such risks, since major cancer surgery exposes the older population to a higher risk of morbi-mortality and unplanned hospitalization for geriatric events (1). Outpatient treatments and rapid post-operative rehabilitation strategies are used to decrease post-operative deconditioning but do not take geriatric risk factors into account. The deconditioning of older patients, not anticipated, can thus lead to prolonged and iatrogenic hospitalizations such as immobilization syndrome, acute confusion, undernutrition, falls, de novo urinary incontinence and adverse drug events, generating frustration, appeals by patients and their families and additional hospital costs.

In order to reduce complications after surgery, prehabilitation has often been considered, and it can be estimated that a majority of surgeons would accept a 4 weeks delay before surgery to improve older patients' outcomes if shown to be beneficial (2–9). However, the actual level of evidence depends on the interventions: high for pre-operative nutrition (10), but low for physical exercise, due to heterogeneous programs with often bad adherence (11). In addition, geriatric validated interventions, in order to prevent iatrogenic event, may be added in a multi-interventional model of intervention.

To date, the interventions likely to prevent geriatric deconditioning include nutritional care, pre-therapeutic (prehabilitation) and post-therapeutic (rehabilitation) physical reconditioning, iatrogenic prevention (drug and care system-related) and hospital-to-home transition to limit the risk of early readmission of patients. Nevertheless, the level of evidence for each of these care segments remains limited, and not specific to the oncogeriatric population. Indeed, studies about more specific care have already been carried out but do not consider all of the above interventions (12). Moreover, cancer in the older patient is often associated with comorbidities, particularly cardiovascular disease (13,14). The older population also has a higher risk of loss of autonomy and cognitive impairment, which can be increased with surgery (15–17). In response to the growing population of older cancer patients, a modification of oncological care and the implementation of specific geriatric interventions have been developed (18–20).

PROADAPT (Prehabilitation & Rehabilitation in Oncogeriatrics: Adaptation to Deconditioning risk and Accompaniment of Patients' Trajectories) is a geriatric intervention program constructed on a multi-professional and multi-disciplinary basis after a systematic analysis of published data. It includes: 1) before surgery: prehabilitation of patients, including nutritional, physical, respiratory and motivational counselling; 2) during hospitalisation for surgery (if performed): optimization of their treatment by pharmaceutical reconciliation, educational interventions, standardization of surgical interventions and

improved rehabilitation after surgery; 3) bridging and post-discharge interventions for hospital-to-home transition (table 1).

Methods and analysis

Objectives

Primary objective

The primary objective of the PROADAPT pilot study is to assess the feasibility of the program, defined as the achievement of at least one item of the program during patient's follow up.

Secondary objectives

The secondary objectives of the study are:

1) To assess the achievement of each item of the program independently of each other (rate of achievement of all or part of the instructions);
2) To assess patients' satisfaction with the program;
3) To estimate the rate of adherence to items during the various visits;
4) To appreciate the longitudinal evolution over 1 year.

In addition to these secondary objectives, a series of parameters will be measured and monitored in this order:

5) To assess patients' post treatment complications according Clavien Dindo and NCI-CTC version 4 scoring systems(21);
6) To estimate the rate and the nature of post-operative complications according to the CCI index at 30 and 90 days;
7) To estimate the post-operative mortality at 30 and 90 days;
8) To estimate the costs of treatments (health system, patients);
9) To study the therapeutic strategies (treatment completion rate);
10) To estimate the progression-free survival rate at one year (PFS);
11) To estimate the overall survival rate at one year (OS);
12) To study the physical performance tests and the evolution of these performances through the proposed exercises;
13) To study the other dimensions of quality of life relating to health at 3 months;
14) To estimate the longitudinal evolution of QoL;
15) To estimate the tolerance of treatments;

16) To estimate the evolution of geriatric covariates.

Study design

PROADAPT - pilot phase is a second category interventional study involving the Human Person with minimal risks and constraints excluding health products. It is a prospective, non-comparative multicenter opened in different centers of Auvergne-Rhône-Alpes region, France (n=7).

Study sites and participants

The study population will include older patients identified during multidisciplinary consultation meetings and oriented to complex medico-surgical curative procedures in the including centers (Lyon Sud Hospital, Croix Rousse Hospital and Edouard Herriot Hospital from the Hospices Civils de Lyon, Nord-Ouest Villefranche-sur-Saône Hospital, Annecy-Genevois Hospital, Chambery Hospital, Lyon-Villeurbanne Médipôle).

Inclusion criteria are: patient aged 70 and over or 60 and over with significant comorbid condition (CIRS-G ≥ 3 (22)) or disability (ADL score < 6/6 (23)), histologically or cytologically proven cancer, life expectancy > 3 months planned for a complex medico-surgical procedure in a curative intent. Complex medico-surgical procedures are defined as major abdominal surgery (breast excluded) either minimally invasive or open.

Exclusion criteria are: patient with other malignancy within the last 5 years (except for adequately treated carcinoma in situ of the cervix or squamous carcinoma of the skin, or adequately controlled limited basal cell skin cancer), unable to be regularly followed for any reason (geographic, familial, social, psychologic) or with any mental or physical handicap at risk of interfering with the appropriate treatment.

A screening of older patients will be systematically performed during multidisciplinary meetings and described in the CONSORT diagram of the study.

Intervention

PROADAPT intervention program was built according to a multi-dimensional and multidisciplinary basis. From January 2016 to April 2018, nine regional meetings were organized, gathering 40 representatives of the following medical and paramedical specialties: geriatricians, nutritionists, surgeons (subspecialties: gynaecology, digestive surgery, urology), oncologists, anaesthesiologists, nurses, physiotherapists, occupational therapists, adapted physical activity monitors. A systematic review of published data was done in the following axes, in order to provide a graded state-of-the-art: nutrition, physical activity, patient education, medication rationalization, cardiovascular optimization, transition and standardization of surgical procedures. Based on the qualitative grading of existing data,

a modified DELPHI method was performed, in order to co-validate the content of the standardized intervention checklist, and the feasibility of the implementation of each point of this checklist (Table 1).

A PROADAPT booklet was built, in order to propose a standardized, adapted and evolutive tool designed to explain physical exercise and nutrition counselling and to insure a follow-up of patients' day-to-day achievements. This first version was tested by candidate patients during two turns of validation before the validation of the current version 3 of the booklet.

PROADAPT standardized geriatric intervention program includes:

- Pre-operative physical activity including strength and endurance exercise +/- group activities during 4 +/-2 weeks. Interventions with high level of evidence were retained, according to an ongoing systematic analysis (http://www.crd.york.ac.uk/PROSPERO Ref CRD42020100110; (24,25));
- Nutrition: nutrition before and after physical activity, pre-postoperative immuno-nutrition +/- artificial nutrition (ie enteral or parenteral nutrition) according international guidelines (10);
- Patient (and caregiver) education and coaching (on nutrition, physical exercise) according to a weekly schedule with the activation of integrated supports by hetero- and self-management (26);
- Standardized intervention procedures, according to a checklist established in consensus with surgeons' representatives;
- Enhanced rehabilitation will be promoted according to international guidelines (27);
- Pharmaceutical medication conciliation, treatment optimization, according a centralized process with pharmaceutical expertise;
- Bridging interventions for hospital-to-home transition, according to a proposed standardized procedure including training of dedicated nurses, and post-discharge phone-calls follow-up during 12 weeks after surgery. In practice, only 2 or 3 people from the coordination team are in charge of coaching for all patients. In the future, a "special nurse coach" will be trained in each center and responsible of patients' coaching. Interventions with high level of evidence were retained, according to an ongoing systematic analysis (http://www.crd.york.ac.uk/PROSPERO Ref CRD42017055698).

The intervention is designed to be implemented at different times of patients' care (table 1).

During the prehabilitation time:

• A dedicated nurse, trained in patient education by the coordination team ("coaching nurse") presents him/herself to the patient for:

- Presentation of the program to the patient and his/her caregiver(s)
- Personalization of the PROADAPT booklet (see after) to the patient's characteristics

- Collection of personal data, nutritional and functional habits
- Evaluation of psycho-cognitive context using questionnaires (GDS4/GDS15, MNA, MINI-COG)
- Gathering of the information needed: comorbidities, comedications (for transmission to the centralized pharmaceutical expertise)
- Anticipation and organization of the future appointments (anesthesiologist, stomatherapist, …)
- A weekly visit or phone call according to a structured interview for health education and transmission of nutritional and functional advices (see after)

• Nutritional care is based on:
- A personalized evaluation of nutritional balance and nutritional needs of the patient according to dietician diagnosis based on measured intake and international recommendations
- A weekly follow-up of weight and nutritional intake. If the coaching nurse identifies an unfavorable nutritional trend, she reports it to the referring physician and nutritionist
- Artificial nutrition if needed according ESPEN recommendations (10,28,29)
- Pre-operative immune-nutrition during 7 days before surgery (29)

• Total-body rehabilitation:
- 2 to 3 times a week: strength exercise (each time with dedicated exercises for upper members, legs and abs, 20 to 45 minutes each sequence)
- 2 to 3 times a week: endurance exercise (walk or cycle ergometer), 20 to 45 min each sequence
- 3 times a day: respiratory physiotherapy
- Once a week (if possible): group activities (according to the center organization and home-hospital distance)

• Pharmaceutical conciliation and optimization according to STOPP/START criteria and international recommendations about peri-operative care (30): to be transmitted to the surgical and anesthesia team without any obligation.

During peri-operative time

• The coaching nurse contacts the surgical team for transmission of:
  o patient's personal data
  o physical (nutritional, functional and/or comorbidities) as well as psychological difficulties
  o medication conciliation results

During rehabilitation time

- The coaching nurse contacts the rehabilitation team for transmission of:
  - patient's personal data and care course
  - physical (nutritional, functional and/or comorbidities) as well as psychological difficulties
  - medication conciliation results
- The rehabilitation program is left at the discretion of the rehabilitation team (standard care and local habits).
- A weekly phone call of the coaching nurse to the rehabilitation team for nutritional and functional follow-up as well as medication conciliation

During hospital-home transition time

- The coaching nurse contacts the patient's general practitioner for transmission of:
  - patient's personal data and care course
  - physical (nutritional, functional and/or comorbidities) as well as psychological difficulties
  - medication conciliation results
- Bi-weekly phone call of the coaching nurse to the patient for nutritional and functional follow-up
- Advices for optimization of symptoms management: abdominal pain, nausea, vomiting…

Participant timeline

Six successive evaluations are planned for the participants.

The inclusion visit is planned during a geriatric consultation planned before the start day of the complex medico-surgical procedure, at least 7 days before start date. If the start date is delayed for any reason or the patient is included into a neo-adjuvant treatment, the prehabilitation time may be prolonged until 9 months. In that case, the frequency of the phone calls is decreased (from 1/week to 1/month) after 4 weeks. During the inclusion visit, lasting about 1 hour, the following steps are planned:

- Clinic (blood pressure, heart rate, ECOG scale(31), patient's comorbidities), biologic (albumin, prealbumin, C-reactive protein) and paraclinic (year of birth, gender, weight, height, body mass index, weight evolution over the last 3 and 6 months) data collection
- All concomitant treatments and drug conciliation

- The history of the disease (primitive site, metastasis, histology of the initial tumor, presence of tumor markers)
- Radiological disease assessments (date and nature)
- A standardized geriatric assessment using validated questionnaires with a particular attention on physical activity and nutrition (ADL(23)/iADL(32), G8 (33), RAPA (34), AIPVQ (35), QLQ-C30 (36), QLQ-ED14 (37), EQ-5D-3L (38), SF-36 (39), SPPB (40), FSS (41), MNA (42), GDS4/GDS15 (43), MINI-COG (44), Tinetti test (45), Borg scale (46), Pain scale (47), Nutrition scale (48)) (**Error! Reference source not found.**tables 2 and 3) .
- Delivery of the "PROADAPT kit" device during a meeting with a dedicated paramedic (nurse, physiotherapist, ergotherapist…) in order to:
    - Provide to the patient VOLDYNE® and TRIFLO® devices for inspiratory training
    - Present the PROADAPT booklet that includes a battery of exercises and nutritional counselling specifically designed for this older population:
        - muscle strengthening of upper limbs (6 exercises, 3 difficulty levels), lower limbs (6 exercises, 3 difficulty levels), abdominal wall (4 exercises, 3 difficulty levels) (objective: 2 to 3 sessions per day for a total time between 20 and 45 minutes)
        - endurance/aerobic activities (7 exercises, 3 difficulty levels with 3 duration objectives, objective: every day)
        - inspiratory training with VOLDYNE® and TRIFLO® devices (objective: 3 sessions per day for a total time of 30 minutes)
        - general nutritional counselling adapted to the older population: food enrichment, inter-meals collations, oral nutritional supplements.
    - A fulfilling of 3-day food statement allows, in the 7 days after inclusion, to deliver a dietician-driven personalized nutritional counseling. If needed, in case of unfavorable nutritional parameters, artificial nutrition is introduced.
- Delivery, if needed, of medical prescription:
    - for home physiotherapy according PROADAPT program for respiratory training sessions and physical activity training sessions
    - For oral nutritional supplements
    - For usual medicines, including pharmaceutical review
- For patients requiring inpatient follow-up, hospital admission for a few days in a rehabilitation unit for a physiotherapeutic program and/or artificial nutrition (enteral preferred).

During pre-intervention time, phone calls are planned by a dedicated paramedic (once a week for the first 4 weeks and then once a month until the intervention). Calls are semi-directed interviews focused on the patient's autonomy, physical activity, appetite and sleep over the last period (week/month). A special attention is paid on encouraging patient's motivation and adherence to the program.

The pre-therapeutic visit is scheduled when possible between 5 days and the day of the intervention. This visit is performed in the surgery or radiotherapy unit only if the visit is necessary before the intervention still without modifying the standard therapeutic care for:

- Clinic, biologic and paraclinic data collection
- All concomitant treatments and drug conciliation
- Questionnaires about pain, nutrition, fitness and physical tests (table 2 and 3)
- Therapeutic care data collection (date, nature, entitled, reason)

During post-intervention time, paramedics trained in clinical research will resume follow-up calls as before the intervention once a week during 12 weeks after D0 and once a month up to 12 months after D0. The D0 date is determined as the last day of surgery (day of the last resumption of surgery in the limit of 30 days after the first intervention) or the last day of the radiotherapy. For weekly calls, a margin of +/- 2 days is allowed and for monthly calls, a margin of +/- 7 days is allowed.

Visits at 1, 3 and 6 months after the intervention (+/- 7 days): The patient may have started an antineoplastic treatment according to standard of care. The visit could be performed with the surgeon, the radiotherapist or the oncologist according local habits:

- Clinic (blood pressure, heart rate, ECOG scale(31)), biologic (albumin, prealbumin, C-reactive protein) and paraclinic (weight, body mass index) data collection
- All concomitant treatments and drug conciliation
- Patient care data (surgery and complications, treatment for the cancer)
- Radiological disease assessments (date and nature)
- Questionnaires about quality of life, pain, nutrition, fitness and physical tests (table 2 and 3)
- Socio-economic assessment with patient's care data (date, nature of acts, designation, reason)

The end of study visit is planned at 12 months (per-protocol) or at the date of trial premature discontinuation (+/- 7 days) for a final assessment of the same outcomes as previously listed. When requested, if previous visits were omitted, a final assessment of all the complications during the post-therapeutic period is performed.

Outcomes and measurements

Primary outcome

The main outcome measure will be the percentage of patients who have completed at least one item in the PROADAPT program after 12 months after the start of therapeutic treatment. The start of treatment is defined in this study by the last day of surgery (date of the last recovery within the limit of 30 days after the date of the initial intervention) or the last day of radiotherapy. The workshops of the program are:

- Physical and respiratory rehabilitation
- Re-nutrition session
- Telephone nurse follow-up

Secondary outcomes

The secondary outcomes of the study are:

- To evaluate the feasibility of each stage of the program independently of each other (rate of achievement of all or part of the instructions)
  - Pre-operative physical rehabilitation including (figure 1):
    - Muscle strengthening
    - Respiratory rehabilitation
    - Endurance work
  - Pre-operative nutrition counselling (figure 1)
  - Drug reconciliation / iatrogenic prevention
  - Pre-therapeutic follow-up calls
  - Post-surgery or post-radiotherapy follow-up calls

- To estimate patients' satisfaction with the overall program, at the end of the study (end of follow-up or study discontinuation) using a questionnaire (Supplemental material).

- To estimate the rate of adherence to the items (physical activity, nutrition and nursing follow-up) during follow-up time. To evaluate this criterion, various parameters will be recorded: physical activity duration (in h/week), kinetics (duration (% increase), level of difficulty), respiratory activity, food intake during phone calls.

- To assess the longitudinal evolution over 1 year of:
  - patient's physical performance (SPPB, gate speed, TUG test) and functional independence on ADL (23), IADL (32), AIPVQ (49)

- nutritional parameters of the patient (weight, albuminemia, appetite)
- health-related quality of life for patients based on QLQ-C30 and ELD14 (5 dimensions: mobility, disease burden, emotional and physical functioning, tiredness) (50,51)
- pharmaceutical conciliation

In parallel to these secondary objectives, a series of parameters will be measured and monitored in order to:

- Estimate the rate and nature of post-operative complications at 30 days (NCI-CTCAE)
- Estimate the rate and nature of post-operative complications according to the CCI at 30 and 90 days
- Estimate post-operative mortality at 30 and 90 days
- Estimate the overall one-year survival rate (OS)
- Estimate the one-year progression-free survival rate (PFS)
- Estimate the longitudinal evolution of QoL according to QLQ C30, ELD14, EQ-5D
- Estimate treatment costs (health system, patients)
- Study therapeutic strategies (treatment completion rate)
- Estimate the evolution of geriatric covariates.

Sample size calculation

The program will be considered feasible, at the patient level, if all or part of the program is implemented in at least 50 % of the included patients (= alternative hypothesis). This threshold was defined in line with previous studies on prehabilitation for older cancer patients, that showed compliance rates between 16 and 95% (52,53). Considering that PROADAPT program is highly complex even if tailored for older patients, we anticipate modest compliance rates.

The calculation of the number of subjects needed was done as follows: to reject the null hypothesis of the program feasibility rate lower than 35 %, with a first alpha species risk of 5 % and a power of 90 % (beta=10 %, bilateral test), the number of subjects to be analyzed is 111. Including 10 % non-treatable patients, a total of 122 patients should be included. The included patients will be analyzed with intention-to-treat.

Data management and statistical analyses

Data are monitored by a clinical research associate (CRA). Inconsistencies will be reported to the study investigators in order to decide whether the data should be corrected or considered as missing data. Any changes in the data will be reported.

Data analyses will be performed by the data management and analysis centre. The analyses will be carried out by an independent statistician with the latest version of the R software environment. All of the characteristics collected will be subjected to a descriptive analysis.

Descriptive analyses

A flow-chart diagram will describe the data available for the patient population at baseline, and during each follow-up visit. Eligibility criteria for treated patients will be verified, as well as follow-up and end of study visits. Reasons for premature end of study will be provided.

Characteristics of the study population and proportions of missing values will be reported. Patient characteristics will be described using mean and standard deviation or median and interquartile range for quantitative variables, and frequencies and distribution for categorical variables. A comparison of baseline characteristics between patients with complete follow-up and those with attrition will be performed. If needed, methods for handling missing data (multiple imputation, mixed model or auxiliary variable) will be used when appropriate.

Primary analysis

The percentage of patients who have completed at least one PROADAPT program activity at the end of 12 months after the start of treatment will be estimated using mean and standard deviation.

Secondary analyses

Time-to-event variables: follow-up, overall survival, progression free survival

The proportion of events at specific measurement times will be estimated according to the Kaplan-Meier curve. Medians of event-free survival will be reported by treatment arm with its 95 % confidence interval (95 % CI), if the number of events allows estimation of the median.

Overall survival rate and progression free survival rate at 12 months (after the day of the last revision of surgery or the last day of radiotherapy) will be provided with 95 % CI.

Quality of life

Analyses of the QoL data will be performed with modified intention to treat (mITT): all included patients, regardless of compliance with the eligibility criteria and whether or not they were followed up and for whom the QoL scores at inclusion will be included in the analysis. Patients' quality of life,

linked to health, will be analysed after 3 months through 5 dimensions: mobility, disease burden, emotional and physical functioning, tiredness.

Data monitoring

The successful completion of the database is ensured by the hospital CRA. The hospital CRA also ensures compliance with the study protocol. The sponsor CRA verifies that the rights of the participants are respected.

End of protocol

Patients leave the study either on a per-protocol basis during the "end of study visit" on month 12 after the intervention or at any time during the conduct of the study if they no longer wish to participate. However, as indicated in the information letter to the patients/caregivers, the data collected before exclusion may be used as part of the study.

Confidentiality

Correspondence tables will be kept in a separate file that does not contain clinical data. The access to the nominative information is protected by a password and confidentiality is guaranteed by the study.

Protocol amendments

Any important modifications requiring a new ethics committee approval will be communicated in future publications. Any potential impact of protocol modifications on the results will be discussed as appropriate.

Trial status

Patient enrolment began on July 3, 2018. Data are collecting.

Patients' and public involvement

Patients were involved at different steps of the trial: (i) during PROADAPT booklet conception, several (30) patients were asked to answer an anonymous questionnaire in order to improve its ergonomics; (ii) the information note and consent form of the protocol have been re-read by the patients' review committee of the Ligue Nationale de Lutte contre le Cancer (a French association of cancer patients).

Discussion

Discussion of the intervention

Prehabilitation has long been conceptualized as an effective means of improving the functional capacity of the individual to enable him to resist various stressors. Originally developed in the military as the association of physical training to improve strength and endurance, improving nutritional intake and general education **(54)**, it has been transposed into medicine and major surgery – initially when an ICU admission is planned - at the beginning of this century **(55)**.

Despite a growing interest in the medical community for prehabilitation and particularly cancer prehabilitation, the level of evidence for specific interventions stays too low to be implemented in common care. Among the main disadvantages of published data include the heterogeneity of programs, sometimes poor patient adherence and the fact that most studies were small pilot studies developed for patients more fit and younger than those who should make the best part of prehabilitation. Another point to emphasize is that most programs include only one intervention - physical, nutritional, or psychological rehabilitation - when multimodal interventions are often considered to be more effective in older populations.

Considering these points, the PROADAPT intervention was developed according to an innovative management strategy since it started in 2016 by multi-professional meetings conceived as brainstorming sessions in order to develop a multidisciplinary program dedicated to prehabilitation and follow-up of older patients. The multidisciplinary conception of the intervention, the particular attention paid to older patients' specificities and the previous experience of the participants in as various fields as patients' education, cognition, physiotherapy were hopefully the warrants of the most tailored approach to the target population. For example, the booklet typography was of big character font and the illustrations highly schematic with high contrast. Each sentence was verified by a panel of patients in order to insure proper understanding. Finally, the booklet was evaluated by 30 patients, with a high rate of satisfaction (Ravot et al, PROADAPT Pilot trial: A survey on patients' expectations and satisfaction, unpublished data).

This pilot study is the first step towards an ambitious program, since PROADAPT program will be declined in the future into two randomized studies, PROADAPT-ovary/EWOC-2 (NCT04284969) and PROADAPT sus-mesocolic, designed to evaluate the impact of PROADAPT program on post-treatment complications versus common care. In order to favor patients' compliance and follow-up, an eHealth tool has been developed that will help supervising patients' care courses.

Discussion of the study design

In line with the previous points, this pilot study was designed in order to answer to this critical question: is a multidomain prehabilitation program feasible in an older cancer population? This question encompasses several points: (i) Is the program physically adapted to an older population? (ii) Is such a program appliable in ambulatory care? (iii) How to build pedagogic tools adapted for such ambulatory use? (iv) Are such pedagogic tools understandable? (v) What is the compliance of the patients for each domain of the intervention program?... Another point is to know whether the patient's care team is expected to accept such intervention, but this point was previously evaluated by Ghignone et al. They demonstrated through an international survey that surgeons are generally in favor for such programs since 71 % of them would accept to prehabilitate their elderly patients 4 weeks before surgery, if such intervention is proven to be effective (2). Nevertheless, the participation of surgeons and anesthesiologists during initial brainstorming sessions was of major interest since they enriched a lot the structure of the program.

Thus, the construct of this trial may appear as highly complex with overabundant secondary endpoints, but this design encompasses as much as possible the complexity of prevention care in an older population, which has to mix the adaptation to the target population and the ability to maintain compliance over time.

Ethics and dissemination

The study sponsor is the Hospices Civils de Lyon, responsible for study insurance and pharmacovigilance. The study protocol was approved by the Ile de France 8 Ethics Committee on May 3, 2018 and cover all sites involved in this study. Several amendments have been added to the first version of the protocol. The initial approved version was V2 of May 28, 2018, then the amended versions were as follows: V3 of October 23, 2018 (change in the recruitment period, addition of new investigation centers), V4 of May 17, 2019 (request for an additional 12 months extension, update with the GPDR and update of the patient booklet), V5 of July 17, 2020 (addition of a cohort of 30 patients to test the follow-up program with an e-health interface, request for an additional 8 months extension). Current version is the V5 of July 17, 2020, authorized on September 10, 2020. The research will be carried out on accordance with the Helsinki Declaration and ICH GCP Guidelines. Trial protocol fulfills SPIRIT 2013 checklist (Supplementary table 1) and World Health Organization Trial Registration Data Set (Supplementary table 2). The study complies with the principles of the data protection act in France and with the General Data Protection Regulations in force in Europe. Each investigator must collect a written consent at the beginning of the procedure. This consent is retained in the patient's medical chart. The patient can stop the study at any time with an oral information at his investigator

or clinical research assistant. Patients will be informed on additional amendments according the law in force.

The results of the primary and secondary objectives will be published in peer-reviewed journals. All authors of future publications will have to meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors.

Total words count : 4791

Abbreviations

ADL: Activities of Daily Living; AIPVQ: Physical Instrumental activities of daily living (in French: Activités Instrumentales Physiques de la Vie Quotidienne); CRA: Clinical Research Assistant; ESPEN: European Society for Clinical Nutrition and Metabolism; FSS: Fatigue Severity Scale; GDS: Geriatric Depression Scale; IADL: Instrumental Activities of Daily Living; ICU: Intensive Care Unit; mITT:Modified Intention To Treat; MNA: Mini Nutritional Assessment; QLQ: Quality of Life Questionnaire; QoL: Quality of Life; RAPA: Rapid Assessment of Physical Activity; SF: Short Form; SPPB: Short Physical Performance Battery

Declarations

Acknowledgements

This pilot protocol is part of the PROADAPT initiative for improving care for older people with cancer. The authors wish to thank the professionals who participated to the intervention conception: G. Albrand, D. Barnoud, D. Benayoun. B Billod, J. Bonhomme, A.-L. Bres, C. Brunengo, A. Chanelière, D. Charlety, Y. Chauleur, G. Copaescu, H. Curé, A.-M. Dascalita, B. De La Vigerie, S. Ducoulombier, , O. Ganne, F. Gervais, T. Gilbert, M. Giroud, N. Jomard, C. Lecardonnel, B. Leroy, J.-A. Long, A. Marion, E. Nony, S. Parent, A. Pelisset-Vanhersecke, A. Pirollet, , J.-E. Terrier, J. Trautmann, M.-A. Vincent.

The authors also acknowledge the teams of Lyon Sud Hospital, Edouard Herriot Hospital of Lyon, Croix Rousse Hospital of Lyon, Annecy Genevois Hospital Center, Hôpital Nord Ouest hospital center, Chambéry Hospital Center and Médipôle Lyon-Vileurbanne who contribute to patient enrollment in this study.

The authors would like to thank in particular the patients' review committee of the Ligue Nationale de Lutte contre le Cancer for the valuable editing of the information note and the consent form.

Funding

This work was supported by the Agence Régionale de Santé (ARS) Auvergne Rhône Alpes, through the call for projects "Innovate in health for the Auvergne Rhône Alpes region" jointly organized by the ARS, Bpifrance, the Auvergne Rhône Alpes region, URIOPASS, ORAIDA and Cluster I-care and the decision of the selection committee on June 27, 2016 (Grant N°2016-149 (63)). It provided funding for nurses, dieticians, physiotherapists, and clinical research assistants.

Availability of data and materials

The final dataset of the PROADAPT pilot study will be available on reasonable request after publication of the primary objective. Data requests can be submitted to the corresponding author.

Competing interest

The authors declare that they have no competing interests.

Consent for publication

Not applicable

Author contributions

All authors participated to the PROADAPT intervention conception. Study protocol was conceived by DD, CF, CG, OLS, AM, VP and CR. DD and CF assumed fundraising and grant follow-up. MR led the drafting of the manuscript. All authors (MR, CR, AM, CG, VP, MT, BR, BG, MG, CBa, CBo, EG, LS, MH, ECK, IMS, VC, OLS, DD and CF) critically reviewed and approved the final version of the protocol.

References

1. Tan H-J, Saliba D, Kwan L, Moore AA, Litwin MS. Burden of Geriatric Events Among Older Adults Undergoing Major Cancer Surgery. J Clin Oncol. 2016 Oct 4;34(11):1231–8.

2. Ghignone F, van Leeuwen BL, Montroni I, Huisman MG, Somasundar P, Cheung KL, et al. The assessment and management of older cancer patients: A SIOG surgical task force survey on surgeons' attitudes. Eur J Surg Oncol EJSO. 2016 Feb;42(2):297–302.

3. Thomas G, Tahir MR, Bongers BC, Kallen VL, Slooter GD, van Meeteren NL. Prehabilitation before major intra-abdominal cancer surgery: A systematic review of randomised controlled trials. Eur J Anaesthesiol. 2019;36(12):933–45.

4. Carli FMMp, Bousquet-Dion G, Awasthi R, Elsherbini N, Liberman S, Boutros M, et al. Effect of Multimodal Prehabilitation vs Postoperative Rehabilitation on 30-Day Postoperative Complications for Frail Patients Undergoing Resection of Colorectal Cancer: A Randomized Clinical Trial. JAMA Surg. 2020 Mar;155(3):233–42.

5. Bongers BC, Klaase JM, Meeteren NLU van. Prehabilitation vs Postoperative Rehabilitation for Frail Patients. JAMA Surg. 2020 Sep 1;155(9):896–7.

6. Cooper L, Frain L, Jaklitsch MT. Prehabilitation vs Postoperative Rehabilitation for Frail Patients. JAMA Surg. 2020 Sep 1;155(9):898–9.

7. Kako JMhsRO, Kajiwara K, Tatematsu N. Prehabilitation vs Postoperative Rehabilitation for Frail Patients. [Letter]. JAMA Surg.

8. Keller DS, Carter B, Moug SJ. Prehabilitation vs Postoperative Rehabilitation for Frail Patients. JAMA Surg. 2020 Sep 1;155(9):896–896.

9. Carli F, Bousquet-Dion G, Fiore JF. Prehabilitation vs Postoperative Rehabilitation for Frail Patients. JAMA Surg. 2020 Sep 1;155(9):899–900.

10. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr [Internet]. 2016 Aug 6 [cited 2016 Nov 20];0(0). Available from: http://www.clinicalnutritionjournal.com/article/S0261-5614(16)30181-9/abstract

11. Singh F, Newton RU, Galvão DA, Spry N, Baker MK. A systematic review of pre-surgical exercise intervention studies with cancer patients. Surg Oncol. 2013 Jun 1;22(2):92–104.

12. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008 Sep 29;337:a1655.

13. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet] [Internet]. Lyon, France: International Agency for Research on Cancer; 2013 [cited 2016 Sep 4]. Available from: Available from: http://globocan.iarc.fr

14. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared Risk Factors in Cardiovascular Disease and Cancer. Circulation. 2016 Mar 15;133(11):1104–14.

15. Sjölund B-M, Wimo A, Qiu C, Engström M, von Strauss E. Time trends in prevalence of activities of daily living (ADL) disability and survival: Comparing two populations (aged 78+ years) living in a rural area in Sweden. Arch Gerontol Geriatr. 2014 May;58(3):370–5.

16. Sjölund B-M, Wimo A, Engström M, Strauss E von. Incidence of ADL Disability in Older Persons, Physical Activities as a Protective Factor and the Need for Informal and Formal Care – Results from the SNAC-N Project. PLoS ONE [Internet]. 2015 [cited 2016 Sep 4];10(9). Available from: https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pmc/articles/PMC4583409/

17. Jagger C, Gillies C, Moscone F, Cambois E, Van Oyen H, Nusselder W, et al. Inequalities in healthy life years in the 25 countries of the European Union in 2005: a cross-national meta-regression analysis. The Lancet. 2008 Dec 20;372(9656):2124–31.

18. Extermann M, Meyer J, McGinnis M, Crocker TT, Corcoran MB, Yoder J, et al. A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. Crit Rev Oncol Hematol. 2004 Jan;49:69–75.

19. Repetto L, Fratino L, Audisio RA, Venturino A, Gianni W, Vercelli M, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol. 2002 Jan 15;20:494–502.

20. Caillet P, Canoui-Poitrine F, Vouriot J, Berle M, Reinald N, Krypciak S, et al. Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA study. J Clin Oncol. 2011;29:3636–42.

21. Website: http://www.cepd.fr/CUSTOM/CEPD_toxicite.pdf.

22. Linn BS, Linn MW, Gurel L. CUMULATIVE ILLNESS RATING SCALE. J Am Geriatr Soc. 1968 May;16(5):622–6.

23. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of Illness in the Aged. The Index of Adl: A Standardized Measure of Biological and Psychosocial Function. Jama. 1963 Sep 21;185:914–9.

24. Falandry C, Stefani L, Granger M, Momiron C, Habchi H, Bourgeois C, et al. Interventions to improve physical performances of older people with cancer before major surgery: an umbrella review. J Geriatr Oncol. 2018;9(6 suppl 1):S94–5.

25. Falandry C, Stefani L, André L, Granger M, Barbarava C, Habchi H, et al. Interventions to improve physical performances of older people with cancer before complex medico-surgical procedures: protocol for an umbrella review of systematic reviews and meta-analyses. Medicine (Baltimore). 2020;

26. Glasgow RE, Emmons KM. How Can We Increase Translation of Research into Practice? Types of Evidence Needed. Annu Rev Public Health. 2007;28(1):413–33.

27. Colburn JL, Mohanty S, Burton JR. Surgical Guidelines for Perioperative Management of Older Adults: What Geriatricians Need to Know. J Am Geriatr Soc. 2017 Jun 1;65(6):1339–46.

28. Arends J, Bodoky G, Bozzetti F, Fearon K, Muscaritoli M, Selga G, et al. ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology. Clin Nutr. 2006 Apr;25(2):245–59.

29. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, et al. ESPEN Guidelines on Enteral Nutrition: Surgery including Organ Transplantation. Clin Nutr. 2006 Apr;25(2):224–44.

30. Mohanty S, Rosenthal RA, Russell MM, Neuman MD, Ko CY, Esnaola NF. Optimal Perioperative Management of the Geriatric Patient: A Best Practices Guideline from the American College of Surgeons NSQIP and the American Geriatrics Society. J Am Coll Surg. 2016 May 1;222(5):930–47.

31. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649–55.

32. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969 Autumn;9:179–86.

33. Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol. 2012 Aug;23(8):2166–72.

34. Topolski TD, LoGerfo J, Patrick DL, Williams B, Walwick J, Patrick MB. The Rapid Assessment of Physical Activity (RAPA) among older adults. Prev Chronic Dis. 2006 Oct;3(4):A118.

35. Gill TM, Baker DI, Gottschalk M, Peduzzi PN, Allore H, Van Ness PH. A prehabilitation program for the prevention of functional decline: effect on higher-level physical function. Arch Phys Med Rehabil. 2004 Jul;85(7):1043–9.

36. Quinten C, Coens C, Ghislain I, Zikos E, Sprangers MAG, Ringash J, et al. The effects of age on health-related quality of life in cancer populations: A pooled analysis of randomized controlled trials using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 involving 6024 cancer patients. Eur J Cancer. 2015 Dec;51(18):2808–19.

37. Wheelwright S, Darlington A-S, Fitzsimmons D, Fayers P, Arraras JI, Bonnetain F, et al. International validation of the EORTC QLQ-ELD14 questionnaire for assessment of health-related quality of life elderly patients with cancer. Br J Cancer. 2013 Aug;109(4):852–8.

38. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013 Sep;22(7):1717–27.

39. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473–83.

40. Fish J. Short Physical Performance Battery. In: Kreutzer JS, DeLuca J, Caplan B, editors. Encyclopedia of Clinical Neuropsychology [Internet]. New York, NY: Springer New York; 2011 [cited 2020 Nov 4]. p. 2289–91. Available from: http://link.springer.com/10.1007/978-0-387-79948-3_1832

41. Goo A-J, Song Y-M, Shin J, Ko H. Factors Associated with Depression Assessed by the Patient Health Questionnaire-2 in Long-Term Cancer Survivors. Korean J Fam Med. 2016;37(4):228.

42. Guigoz Y, Vellas B, Garry PJ. Assessing the Nutritional Status of the Elderly: The Mini Nutritional Assessment as Part of the Geriatric Evaluation. Nutr Rev. 2009 Apr 27;54(1):S59–65.

43. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiatr Res. 1982 Jan;17(1):37–49.

44. McCarten JR, Anderson P, Kuskowski MA, McPherson SE, Borson S. Screening for Cognitive Impairment in an Elderly Veteran Population: Acceptability and Results Using Different Versions of the Mini-Cog: SCREENING ELDERLY VETERANS USING THE MINI-COG. J Am Geriatr Soc. 2011 Feb;59(2):309–13.

45. Tinetti ME, Baker DI, McAvay G, Claus EB, Garrett P, Gottschalk M, et al. A Multifactorial Intervention to Reduce the Risk of Falling among Elderly People Living in the Community. N Engl J Med. 1994 Sep 29;331(13):821–7.

46. Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med. 1970;2(2):92–8.

47. Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES). Assessment and follow-up of chronic pain in adults in ambulatory medicine. 1999 Feb;

48. Société Francophone Nutrition Clinique et Métabolisme (SFNCM). Evaluation of food intake.

49. de Souto Barreto P, Ferrandez A-M. Activités instrumentales physiques de la vie quotidienne chez les personnes âgées: validation d'une échelle. In: L'anthropologie du vivant: objets et méthodes. Chapuis-Lucciani N, Guihard-Costa AM, Boëtsch G. 2010. p. 83–7.

50. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. JNCI J Natl Cancer Inst. 1993 Mar 3;85(5):365–76.

51. Wheelwright S, Darlington A-S, Fitzsimmons D, Fayers P, Arraras JI, Bonnetain F, et al. International validation of the EORTC QLQ-ELD14 questionnaire for assessment of health-related quality of life elderly patients with cancer. Br J Cancer. 2013 Aug 20;109(4):852–8.

52. Boereboom C, Doleman B, Lund JN, Williams JP. Systematic review of pre-operative exercise in colorectal cancer patients. Tech Coloproctology. 2016 Feb 1;20(2):81–9.

53. Sun V, Raz DJ, Kim JY, Melstrom L, Hite S, Varatkar G, et al. Barriers and facilitators of adherence to a perioperative physical activity intervention for older adults with cancer and their family caregivers. J Geriatr Oncol. 2020 Mar 1;11(2):256–62.

54. Prehabilitation, rehabilitation, and revocation in the Army. Br Med J. 1946 Jun 29;1:192–7.

55. Topp R, Ditmyer M, King K, Doherty K, Hornyak J. The effect of bed rest and potential of prehabilitation on patients in the intensive care unit. AACN Clin Issues. 2002 May;13(2):263–76.

Illustrations' legends

Figure 1: PROADAPT program: interventions at the patient's level

Table 1: PROADAPT program: tasks according the different domains and the successive chronological steps (before, during and after complex medico-surgical procedure)

Table 2: PROADAPT pilot trial: questionnaires and screening tests

Table 3: PROADAPT pilot trial: flow diagram

712 Table 1: PROADAPT program: tasks according the different domains and the successive chronological
713 steps (before, during and after complex medico-surgical procedure)

Nurse coaching & education Bridging interventions	Coaching nurse self-presentation Delivery of a personalized patient booklet Care according best practice guidelines: - Confirm and document patient goals and treatment preferences, including advance directives. - Confirm and document patient's health care proxy or surrogate decision-maker. - In patients with existing advance directives, discuss new risks associated with the surgical procedure and an approach for potentially life-threatening problems consistent with the patient's values and preferences ("required reconsideration"). Weekly phone calls	Coaching nurse visits / phone calls Communication of patient's preference to the staff	Coaching nurse visit in the rehabilitation ward Communication of patient's preference and care difficulties to the staff (checklist): - delirium/cognitive impairment - peri-operative acute pain - pulmonary complications - fall risk - ability to maintain adequate nutrition - urinary tract infection prevention - functional decline monitoring - pressure ulcers prevention	Coaching nurse bi-weekly phone call Communication of patient's care difficulties to the staff
Nutrition	W-4 : nutritional evaluation Nutritional plan based on measured intake W-3 : nutritional follow up - weight W-2 : nutritional follow up-weight W-1 : nutritional follow up-weight + pre-operative immunonutrition	If surgery: Care according best practice guidelines: - Consider shortened fluid fast (clear liquids up to 2 hours before anaesthesia).(29) - Normal food intake or enteral feeding should start as early as possible	Nutritional plan based on - Weight curve - Measured intake Optimal management of - Nausea/vomiting - Abdominal pain	Nutritional plan based on - Weight curve - Measured intake Optimal management of - Nausea/vomiting - Abdominal pain
Physical activity	W-4 : physical performances evaluation Physical activity plan W-3 \ group physical activity W-2 + W-1 \ functional follow-up	If surgery: care according best practice guidelines: - Early physical and/or occupational therapy. - Check for orthostatic hypotension. - Review physical environment to reduce injury risk. - Assistive walking devices (eg walkers) at bedside if used as outpatient	(to the discretion of the rehabilitation unit)	Pursuing of the pre-operative physical activity plan
Medication conciliation	Centralized medication conciliation and treatment optimization (STOPP/START guidelines)	Centralized medication conciliation Advices for care according best practice guidelines (16): - Adhere to existing best practices regarding antibiotic and venous thromboembolism prophylaxis. - Ensure nonessential medications have been stopped and essential medications have been taken.	Centralized medication conciliation	Centralized medication conciliation
Standardization of surgical procedures		If surgery: consider antiseptic toothpaste If surgery: care according best practice Guidelines (16): - Consideration of regional techniques to avoid postoperative complications and improve pain control. - Directed pain history. - Multi-modal or opioid-sparing techniques. - Postoperative nausea risk stratification and prevention strategies. - Strategies to avoid pressure ulcers and nerve damage. - Prevention of postoperative pulmonary complications and hypothermia. - Judicious use ofintravenous fluids. - Appropriate hemodynamic management. - Continuation of indicated cardiac medications. - Daily post-operative roundingchecklist: - delirium/cognitive impairment - peri-operative acute pain - pulmonary complications - fall risk - ability to maintain adequate nutrition - urinary tract infection prevention - functional decline monitoring - Pressure ulcers prevention If surgery: consider IV iron supplementation		

714

715

716 Table 2: PROADAPT pilot trial: questionnaires and screening tests

Domain	
Autonomy	Activity of Daily Living Scale (ADL) Instrumental Activities of Daily Living scale (IADL)
Geriatric screening	G8
Physical activity	RAPA (Rapid Assessment of Physical Activity), AIPVQ
Quality of life	QLQ-C30, QLQ-ED14, EQ-5D-3L, SF-36
Locomotion and balance	Time Up and Go, SPPB (Short Physical Performance Battery)
Pain	Pain scale evaluation
Nutrition	Nutrition scale evaluation
Tiredness severity	FSS
Depression/anxiety	MNA, GDS4/GDS15
Cognitive assessment	MINI-COG
Fall risk assessment	Tinetti test
Breathlessness	Borg scale

717

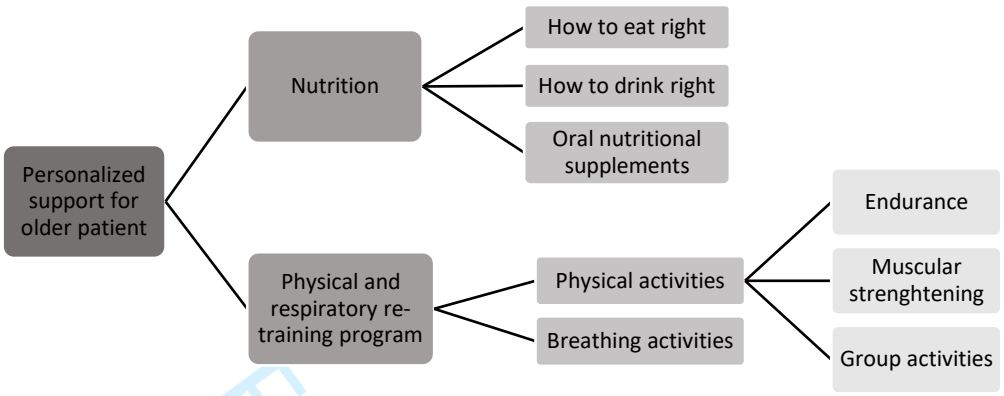
718

719 Table 3: PROADAPT pilot trial: flow diagram

	Baseline	Pre-therapeutic visit (0-5 days before intervention)	M1, M3, M6	M12	End of study visit
Complex geriatric assessment					
G8	X			X	X
ADL/IADL	X			X	X
GDS4/GDS15	X			X	X
MINI COG	X			X	X
MNA	X			X	X
QLQ-C30	X		X	X	X
QLQ-ELD14	X		X	X	X
EQ-5D-3L	X		X	X	X
Pain scale evaluation	X	X	X	X	X
Nutrition scale evaluation	X	X	X	X	X
Socio-economic evaluation	X				
Physical and respiratory assessments					
FSS	X		X	X	X
SF-36	X		X	X	X
Time and Go	X			X	X
SPPB	X		X	X	X
Borg scale	X			X	X
RAPA questionnaire	X		X	X	X
AIPVQ scale	X		X	X	X
Tinetti test	X			X	X
Equimog evaluation	X			X	X
Triflo	X	X			
Voldyne	X	X			
Physical activity data collection		X	X	X	X
Patients' satisfaction					
Standardized questionnaire					X

720

Figure 1 : PROADAPT program : interventions at the patient's level



Supplementary table 1 : Satisfaction questionnaire

Hospices Civils de Lyon **Direction de la Recherche Clinique et de l'Innovation**	**PATIENT ASSESSMENT OF THE PROADAPT PILOT PHASE PROGRAM**

Mrs, Mr,

You have been part of the PROADAPT - pilot phase study and we thank you for your involvement. In order to assess and improve this study, we would like to collect your opinion. This opinion is anonymous and does not affect your healthcare.

The following questions concern the patient booklet that was given to you as part of the study

If you consider the booklet globally

- The explanations seem appropriate to you ? Not at all ☐ A little ☐ Absolutely ☐
- The information seem clear to you ? Not at all ☐ A little ☐ Absolutely ☐
- The pages seem readable enough ? Not at all ☐ A little ☐ Absolutely ☐
- The illustrations seem clear to you ? Not at all ☐ A little ☐ Absolutely ☐

How would you rate the booklet ? (useless = 0 ; very useful = 10) 0 1 2 3 4 5 6 7 8 9 10

The following questions concern the PROADAPT pilot phase program globally (breathing and physical exercises, booklet, calls and follow-up visits)

Did you have difficulty to understand the explanations given by the medical staff and the physician

- for breathing exercises ? Not at all ☐ A little ☐ A lot ☐
- for physical exercises ? Not at all ☐ A little ☐ A lot ☐
- for nutritional advices ? Not at all ☐ A little ☐ A lot ☐
- during the assessment with the physician on the different drugs you are taking ? Not at all ☐ A little ☐ A lot ☐

Did you encounter any difficulties

- for the realization of breathing exercises ? Not at all ☐ A little ☐ A lot ☐
- for the realization of physical exercises ? Not at all ☐ A little ☐ A lot ☐

- for the setting up of nutritional advice ? Not at all ☐ A little ☐ A lot ☐
- for the filling of activities ? Not at all ☐ A little ☐ A lot ☐

How do you estimate nursing phone calls

- at the beginning of your healthcare before your surgery / radiothery Useless ☐ Little important ☐ Needed ☐
- after your surgery/radiotherapy Useless ☐ Little important ☐ Needed ☐

Would you like to get more information ? No ☐ Yes ☐
If yes, which ones,……
……

What would be your propositions to make the program more suitable for patients?
……
……
……

Thank you for your time, we will use your advice to improve the PROADAPT program and the patient booklet.

Pr Claire Falandry, study coordinator

Supplementary table 2: All items from the World Health Organization Trial Registration Data Set (SPIRIT item 2b)

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT03659123
Date of registration in primary registry	September 6, 2018
Secondary identifying numbers	69HCL16_0701 ID RCB N° 2018-A001026-49
Source(s) of monetary or material support	Agence Régionale de Santé Auvergne Rhône Alpes
Primary sponsor	Hospices Civils de Lyon
Secondary sponsor(s)	
Contact for public queries	David Dayde, +33.4.78.86.37.74, david.dayde@chu-lyon.fr
Contact for scientific queries	Claire Falandry, +33.4.78.86.66.34, claire.falandry@chu-lyon.fr
Public title	Prehabilitation & Rehabilitation in Oncogeriatrics: Adaptation to Deconditioning Risk and Accompaniment of Patients' With Cancer
Scientific title	Prehabilitation & Rehabilitation in Oncogeriatrics: Adaptation to Deconditioning Risk and Accompaniment of Patients' With Cancer, a Multicenter Pilot Study
Countries of recruitment	France
Health condition(s) or problem(s) studied	Old Injury
Intervention(s)	Behavioral: standardized geriatric intervention Nutritional care is based on: • A personalized evaluation of nutritional balance and nutritional needs of the patient • A weekly follow-up of weight and nutritional intake Total-body rehabilitation is based on: • 2 to 3 times a week: strength exercise • 2 to 3 times a week: endurance exercise, 20 to 45 min each sequence • 2 times a week: respiratory physiotherapy Pharmaceutical conciliation and optimization according STOPP/START criteria During peri-operative time, the nurse contacts the surgical team for transmission of patient's personal data, physical medication conciliation results During rehabilitation time and hospital-home transition time, the nurse contacts

Data category	Information
	the rehabilitation team for transmission of patient's personal data and care course, physical (nutritional, functional and/or comorbidities), medication conciliation results.
Key inclusion and exclusion criteria	Inclusion Criteria: Patient ≥70 year old OR patient ≥60 years with significant comorbid condition (modified Charlson index≥3) or disability (ADL score<6/6); Histologically or cytologically proven cancer. Life expectancy > 3 months. Written informed consent obtained Covered by a Health System where applicable. Exclusion Criteria: Other malignancy within the last 5 years, except for adequately treated carcinoma in situ of the cervix or squamous carcinoma of the skin, or adequately controlled limited basal cell skin cancer. Patient unable to be regularly followed for any reason (geographic, familial, social, psychologic). Any mental or physical handicap at risk of interfering with the appropriate treatment. Any administrative or legal supervision where applicable
Study type	Interventional Allocation: N/A Intervention model: Single Group Assignment Masking: None (Open Label) Primary purpose: Health Services Research Phase II
Date of first enrolment	July 3rd, 2018
Target sample size	122
Recruitment status	Recruiting
Primary outcome(s)	Implementation of at least one item of PROADAPT standardized geriatric intervention of the program PROADAPT pilot study [Time Frame: 12 months]: • Preoperative physical activity including strength and endurance exercise assessed by physical exercises accomplished under the supervision of a physiotherapist. Number of patients with at least 1 intervention achieved in the domain. • Nutrition guidelines before and after physical activity assessed by questionnaires. Number of patients with at least 1 intervention achieved in the domain.

Data category	Information
	• Patient education and coaching assessed by questionnaires and visits. Number of patients with at least 1 intervention achieved in the domain • Achievement of standardized intervention procedures, according to the checklist established in consensus with surgeons. Number of patients with at least 1 intervention achieved in the domain • Rehabilitation assessed by questionnaires. Number of patients with at least 1 intervention achieved in the domain • Accomplishment of pharmaceutical medication conciliation and treatment optimization. Number of patients with at least 1 intervention achieved in the domain • Bridging interventions for hospital-to-home transition. Number of patients with at least 1 intervention achieved in the domain
Key secondary outcomes	• Post operative morbidity [Time Frame: 30 and 90 days] according Clavien-Dindo classification • Post-operative morbidity [Time Frame: 90 days] according to NCI CTC v4.4 • Therapeutic strategy [Time Frame: 12 months]: Treatment plan completion rate: Number of patients for whom the treatment plan was completed. • Progression-free Survival [Time Frame: 12 months] • Post-treatment complication [Time Frame: 12 months]: Post-treatment complication grade≥3 according the National Cancer Institute Common Toxicity Criteria version 4 (NCI-CTC-v4)

Supplementary table 1: SPIRIT 2013checklist of the trial

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary table 2 Ref 24
Protocol version	3	Date and version identifier	17 (Ethics and Consent to participate)
Funding	4	Sources and types of financial, material, and other support	17-18 (Funding)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 (Authors' list) 18 (Authors' contributions)
	5b	Name and contact information for the trial sponsor	Supplementary table 2 Ref 24

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	10 (Ethical and legal considerations) 17 (Funding)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13 (Data management and statistical analyses) 14 (Data monitoring)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14 (End of protocol) And N/4 (no dose modifications)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6 (two turns of validations of the PROADAPT booklet by candidate patients)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-13 (Sample size calculation)

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A (no problem for accrual)
Methods: Assignment of interventions (for controlled trials)			**N/A**
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	-
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	-
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Table 3
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13 (Data management and statistical analyses)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14 (Data management and statistical analyses)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14 (Data Monitoring)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11 (Secondary outcomes: NCI CTCAE, QOL)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10 (Ethical and legal considerations)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10 (Ethical and legal considerations) 14 (Protocol amendments)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10-11 (Ethical and legal considerations)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14 (Confidentiality)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17 (Competing interests)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17 (Availability of data and materials)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15 (Dissemination policy)
	31b	Authorship eligibility guidelines and any intended use of professional writers	15 (Dissemination policy), N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Annex 1 (in French)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Feasibility of a prehabilitation program dedicated to older cancer patients before complex medico-surgical procedures: the PROADAPT pilot study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042960.R2
Article Type:	Protocol
Date Submitted by the Author:	08-Jan-2021

Complete List of Authors:	Roche, Mélanie; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL Ravot, Christine; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier Lyon Sud Malapert, Amélie; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL Paget-Bailly, Sophie; University Hospital Centre Besancon, Methodology and Quality of Life Unit in Oncology; Université Bourgogne Franche-Comté, INSERM, EFS BFC, UMR1098, Interactions Hôte-Greffon-Tumeur/Ingénierie Cellulaire Et Génique Garandeau, Charlène; Hospices Civils de Lyon, Direction à la Recherche Clinique et à l'Innovation Pitiot, Virginie; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL Tomatis, Mélanie; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier Lyon Sud Riche, Benjamin; Hospices Civils de Lyon, Service de Biostatistique - Bioinformatique, Pôle Santé Publique; Université de Lyon, Laboratoire de Biométrie et Biologie Évolutive CNRS UMR 5558, Équipe Biostatistiques Santé Galamand, Béatrice; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier Lyon Sud Granger, Marion; Hospices Civils de Lyon, Geriatrics unit; Centre Hospitalier de Chambery Barbavara, Claire; Hospices Civils de Lyon, Geriatrics unit Bourgeois, Chrystelle; Centre Hospitalier Annecy Genevois, Medical Oncology Genest, Evelyne; Hospices Civils de Lyon, Geriatrics unit Stefani, Laetitia; Centre Hospitalier Annecy Genevois, Medical oncology Haïne, Max; Hôpital Nord-Ouest, Pôle de gérontologie et Médecine de Réadaptation Castel-Kremer, Elisabeth; Hospices Civils de Lyon, Geriatrics unit. Hôpital Edouard Herriot. Morel-Soldner, Isabelle; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier de la Croix Rousse Collange, Vincent; Medipole Lyon-Villeurbanne, Département anesthésie réanimation Le Saux, Olivia; Centre de Recherche en Cancerologie de Lyon, Therapeutic targeting of the tumor cell and its immune

	microenvironment Dayde, David; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL Falandry, Claire; Hospices Civils de Lyon, Geriatrics unit; University of Lyon, CarMeN Laboratory, Inserm U1060, INRA U1397, Université Claude Bernard Lyon 1, INSA Lyon, Charles Mérieux Medical School
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Geriatric medicine, Surgery
Keywords:	Adult oncology < ONCOLOGY, GERIATRIC MEDICINE, REHABILITATION MEDICINE, Adult surgery < SURGERY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Feasibility of a prehabilitation program dedicated to older cancer patients before complex medico-surgical procedures: the PROADAPT pilot study protocol

Mélanie Roche (melanie.roche02@chu-lyon.fr)

Christine Ravot (christine.ravot@chu-lyon.fr)

Amélie Malapert (amelie.malapert@chu-lyon.fr)

Sophie Paget-Bailly (spaget@chu-besancon.fr)

Charlène Garandeau (charlene.garandeau@chu-lyon.fr)

Virginie Pitiot (virginie.pitiot@chu-lyon.fr)

Mélanie Tomatis (melanie.tomatis@chu-lyon.fr)

Benjamin Riche (benjamin.riche@chu-lyon.fr)

Béatrice Galamand (beatrice.galamand@chu-lyon.fr)

Marion Granger (mariongranger@outlook.fr)

Claire Barbavara (claire.barbavara@gmail.com)

Chrystelle Bourgeois (cbourgeois@ch-annecygenevois.fr)

Evelyne Genest (evelyne.genest@chu-lyon.fr)

Laetitia Stefani (lstefani@ch-annecygenevois.fr)

Max Haïne (mhaine@lhopitalnordouest.fr)

Elisabeth Castel Kremer (Elisabeth.castel-kremer@chu-lyon.fr)

Isabelle Morel-Soldner (isabelle.morel-soldner@chu-lyon.fr)

Vincent Collange (collangev@gmail.com)

Olivia Le Saux (Olivia.LESAUX@lyon.unicancer.fr)

David Dayde (david.dayde@chu-lyon.fr)

Claire Falandry (claire.falandry@chu-lyon.fr) (Corresponding author)

Corresponding email address: claire.falandry@chu-lyon.fr

Abstract

Background: Aging is associated with an increased prevalence of co-morbidities and sarcopenia and with a decline of functional reserve of multiple organ systems, eventually leading in the context of the disease and/or treatment-related stress to functional deconditioning or organ failure. The multicomponent intervention "PROADAPT" was built multi-professionally to implement prehabilitation in older cancer patients.

Methods: PROADAPT-pilot study is an interventional, non-randomized, prospective, multicenter study. It will include 122 patients oriented to complex medico-surgical curative procedures (major surgery or radiation therapy +/- chemotherapy). After informed consent, patients will undergo a comprehensive geriatric assessment and will be offered a prehabilitation kit "PROADAPT" including an advices booklet with personalized objectives and respiratory rehabilitation devices. Patients will then be called weekly and monitored for physical and respiratory rehabilitation, pre-operative re-nutrition, motivational counseling, and iatrogenic prevention. Six outpatient consultations will be planned at inclusion, few days before the procedure, at 1, 3, 6 and 12 months after the end of the procedure. The main outcome of the study is the feasibility of the intervention, defined as the ability to perform at least one of the components of the program. Clinical data collection will include patient-specific and cancer-specific characteristics.

Ethics and dissemination: Study protocol and several amendments were ethically approved by Ile de France 8 Ethics Committee on May 3, 2018. The results of the primary and secondary objectives will be published in peer-reviewed journals. ClinicalTrials registration: NCT03659123.

Keywords: oncogeriatrics, prehabilitation, motivation, sarcopenia, older cancer patients, care pathway.

Article summary

Strengths and limitations of this study

- PROADAPT program is a prehabilitation intervention specifically tailored for older cancer patients
- PROADAPT pilot trial is a prospective and multicentre trial designed to evaluate the feasibility of the intervention
- Different secondary outcomes including quality of life will be collected to better adapt the program to patients' specificities

- The main limitation of such an intervention is the risk of poor adherence of the patients to the program
- This non comparative study will appeal, if satisfactory, to randomized studies in the future.

Introduction

Many oncological situations involve complex medical-surgical procedures at risk of patient's deconditioning. Surgery or complex medico-surgical procedures can be considered as one proof-of principle of such risks, since major cancer surgery exposes the older population to a higher risk of morbi-mortality and unplanned hospitalization for geriatric events (1). Outpatient treatments and rapid post-operative rehabilitation strategies are used to decrease post-operative deconditioning but do not take geriatric risk factors into account. The deconditioning of older patients, not anticipated, can thus lead to prolonged and iatrogenic hospitalizations such as immobilization syndrome, acute confusion, undernutrition, falls, de novo urinary incontinence and adverse drug events, generating frustration, appeals by patients and their families and additional hospital costs.

In order to reduce complications after surgery, prehabilitation has often been considered, and it can be estimated that a majority of surgeons would accept a 4 weeks delay before surgery to improve older patients' outcomes if shown to be beneficial (2–9). However, the actual level of evidence depends on the interventions: high for pre-operative nutrition (10), but low for physical exercise, due to heterogeneous programs with often bad adherence (11). In addition, geriatric validated interventions, in order to prevent iatrogenic event, may be added in a multi-interventional model of intervention.

To date, the interventions likely to prevent geriatric deconditioning include nutritional care, pre-therapeutic (prehabilitation) and post-therapeutic (rehabilitation) physical reconditioning, iatrogenic prevention (drug and care system-related) and hospital-to-home transition to limit the risk of early readmission of patients. Nevertheless, the level of evidence for each of these care segments remains limited, and not specific to the oncogeriatric population. Indeed, studies about more specific care have already been carried out but do not consider all of the above interventions (12). Moreover, cancer in the older patient is often associated with comorbidities, particularly cardiovascular disease (13,14). The older population also has a higher risk of loss of autonomy and cognitive impairment, which can be increased with surgery (15–17). In response to the growing population of older cancer patients, a modification of oncological care and the implementation of specific geriatric interventions have been developed (18–20).

PROADAPT (Prehabilitation & Rehabilitation in Oncogeriatrics: Adaptation to Deconditioning risk and Accompaniment of Patients' Trajectories) is a geriatric intervention program constructed on a multi-professional and multi-disciplinary basis after a systematic analysis of published data. It includes: 1) before surgery: prehabilitation of patients, including nutritional, physical, respiratory and motivational counselling; 2) during hospitalisation for surgery (if performed): optimization of their treatment by pharmaceutical reconciliation, educational interventions, standardization of surgical interventions and

improved rehabilitation after surgery; 3) bridging and post-discharge interventions for hospital-to-home transition (table 1).

Methods and analysis

Objectives

Primary objective

The primary objective of the PROADAPT pilot study is to assess the feasibility of the program, defined as the achievement of at least one item of the program during patient's follow up.

Secondary objectives

The secondary objectives of the study are:

1) To assess the achievement of each item of the program independently of each other (rate of achievement of all or part of the instructions);
2) To assess patients' satisfaction with the program;
3) To estimate the rate of adherence to each item of the program during the various visits;
4) To appreciate the longitudinal evolution of health-related quality of life over 1 year.
5) To assess patients' post treatment complications according Clavien Dindo and NCI-CTC version 4 scoring systems (21);
6) To estimate the rate and the nature of post-operative complications at 30 and 90 days;
7) To estimate the post-operative mortality at 30 and 90 days;
8) To estimate the costs of treatments (health system, patients);
9) To study the therapeutic strategies (treatment completion rate);
10) To estimate the progression-free survival rate at one year (PFS);
11) To estimate the overall survival rate at one year (OS);
12) To study the physical performance tests and the evolution of these performances through the proposed exercises;
13) To study the other dimensions of quality of life relating to health at 3 months;
14) To estimate the longitudinal evolution of QoL;
15) To estimate the tolerance of treatments;
16) To estimate the evolution of geriatric covariates.

Study design

PROADAPT - pilot phase is a second category interventional study involving the Human Person with minimal risks and constraints excluding health products. It is a prospective, non-randomized multicenter opened in different centers of Auvergne-Rhône-Alpes region, France (n=7).

Study sites and participants

The study population will include older patients identified during multidisciplinary consultation meetings and oriented to complex medico-surgical curative procedures in the including centers (Lyon Sud Hospital, Croix Rousse Hospital and Edouard Herriot Hospital from the Hospices Civils de Lyon, Nord-Ouest Villefranche-sur-Saône Hospital, Annecy-Genevois Hospital, Chambery Hospital, Lyon-Villeurbanne Médipôle).

Inclusion criteria are: patient aged 70 and over or 60 and over with significant comorbid condition (Cumulative Illness Rating Scale (CIRS-G) ≥ 3 (22)) or disability (ADL score < 6/6 (23)), histologically or cytologically proven cancer, life expectancy > 3 months planned for a complex medico-surgical procedure in a curative intent. Complex medico-surgical procedures are defined as major abdominal surgery (breast excluded) either minimally invasive or open.

Exclusion criteria are: patient with other malignancy within the last 5 years (except for adequately treated carcinoma in situ of the cervix or squamous carcinoma of the skin, or adequately controlled limited basal cell skin cancer), unable to be regularly followed for any reason (geographic, familial, social, psychologic) or with any mental or physical handicap at risk of interfering with the appropriate treatment.

A screening of older patients will be systematically performed during multidisciplinary meetings and described in the CONSORT diagram of the study.

Intervention

PROADAPT intervention program was built according to a multi-dimensional and multidisciplinary basis. From January 2016 to April 2018, nine regional meetings were organized, gathering 40 representatives of the following medical and paramedical specialties: geriatricians, nutritionists, surgeons (subspecialties: gynaecology, digestive surgery, urology), oncologists, anaesthesiologists, nurses, physiotherapists, occupational therapists, adapted physical activity monitors. A systematic review of published data was done in the following axes, to provide a graded state-of-the-art: nutrition, physical activity, patient education, medication rationalization, cardiovascular optimization, transition and standardization of surgical procedures. Based on the qualitative grading of existing data, a modified DELPHI method was performed, to co-validate the content of the standardized intervention checklist, and the feasibility of the implementation of each point of this checklist (Table 1).

A PROADAPT booklet was built, to propose a standardized, adapted and evolutive tool designed to explain physical exercise and nutrition counselling and to insure a follow-up of patients' day-to-day achievements. This first version was tested by candidate patients during two turns of validation before the validation of the current version 3 of the booklet.

PROADAPT standardized geriatric intervention program includes:

- Pre-operative physical activity including strength and endurance exercise +/- group activities during 4 +/-2 weeks. Interventions with high level of evidence were retained, according to an ongoing systematic analysis (http://www.crd.york.ac.uk/PROSPERO Ref CRD42020100110; (24,25)). Since the intervention is expected to be performed in any health system context, with a vast majority of the intervention to be performed at home, the content of the intervention was standardized and presented in the booklet, but the conditions of the implementation were left to the investigator's decision (physiotherapist intervention at home, group activities when available, etc…).
- Nutrition: nutrition before and after physical activity, pre-postoperative immuno-nutrition +/- artificial nutrition (ie enteral or parenteral nutrition) according international guidelines (10);
- Patient (and caregiver) education and coaching (on nutrition, physical exercise) according to a weekly schedule with the activation of integrated supports by hetero- and self-management (26);
- Standardized intervention procedures, according to a checklist established in consensus with surgeons' representatives;
- Enhanced rehabilitation will be promoted according to international guidelines (27);
- Pharmaceutical medication conciliation, treatment optimization, according to a centralized process with pharmaceutical expertise.
- Bridging interventions for hospital-to-home transition, according to a proposed standardized procedure including training of dedicated nurses, and post-discharge phone-calls follow-up during 12 weeks after surgery. In practice, only 2 or 3 people from the coordination team are in charge of coaching for all patients. In the future, a "special nurse coach" will be trained in each center and responsible for patients' coaching. Interventions with high level of evidence were retained, according to an ongoing systematic analysis (http://www.crd.york.ac.uk/PROSPERO Ref CRD42017055698).

The intervention is designed to be implemented at different times of patients' care (table 1).

During the prehabilitation time:

- A dedicated nurse, trained in patient education by the coordination team ("coaching nurse") presents him/herself to the patient for:
  - Presentation of the program to the patient and his/her caregiver(s)
  - Personalization of the PROADAPT booklet (see after) to the patient's characteristics

- Collection of personal data, nutritional and functional habits
- Evaluation of psycho-cognitive context using questionnaires (GDS4/GDS15, MNA, MINI-COG)
- Gathering of the information needed: comorbidities, comedications (for transmission to the centralized pharmaceutical expertise)
- Anticipation and organization of the future appointments (anesthesiologist, stomatherapist, …)
- A weekly visit or phone call according to a structured interview for health education and transmission of nutritional and functional advices (see after)

• Nutritional care is based on:
- A personalized evaluation of nutritional balance and nutritional needs of the patient according to dietician diagnosis based on measured intake and international recommendations
- A weekly follow-up of weight and nutritional intake. If the coaching nurse identifies an unfavorable nutritional trend, she reports it to the referring physician and nutritionist.
- Artificial nutrition if needed according ESPEN recommendations (10,28,29)
- Pre-operative immune-nutrition during 7 days before surgery (29)

• Total-body rehabilitation:
- 2 to 3 times a week: strength exercise (each time with dedicated exercises for upper members, legs and abs, 20 to 45 minutes each sequence)
- 2 to 3 times a week: endurance exercise (walk or cycle ergometer), 20 to 45 min each sequence
- 3 times a day: respiratory physiotherapy
- Once a week (if possible): group activities (according to the center organization and home-hospital distance)

• Pharmaceutical conciliation and optimization according to STOPP/START criteria and international recommendations about peri-operative care (30): to be transmitted to the surgical and anesthesia team without any obligation.

During peri-operative time

• The coaching nurse contacts the surgical team for transmission of:
  o patient's personal data
  o physical (nutritional, functional and/or comorbidities) as well as psychological difficulties
  o medication conciliation results

During rehabilitation time

- The coaching nurse contacts the rehabilitation team for transmission of:
  - patient's personal data and care course
  - physical (nutritional, functional and/or comorbidities) as well as psychological difficulties
  - medication conciliation results
- The rehabilitation program is left at the discretion of the rehabilitation team (standard care and local habits).
- A weekly phone call of the coaching nurse to the rehabilitation team for nutritional and functional follow-up as well as medication conciliation

During hospital-home transition time

- The coaching nurse contacts the patient's general practitioner for transmission of:
  - patient's personal data and care course
  - physical (nutritional, functional and/or comorbidities) as well as psychological difficulties
  - medication conciliation results
- Bi-weekly phone call of the coaching nurse to the patient for nutritional and functional follow-up
- Advices for optimization of symptoms management: abdominal pain, nausea, vomiting…

Participant timeline

Six successive evaluations are planned for the participants.

The inclusion visit is planned during a geriatric consultation planned before the start day of the complex medico-surgical procedure, at least 7 days before start date. If the start date is delayed for any reason or the patient is included into a neo-adjuvant treatment, the prehabilitation time may be prolonged until 9 months. In that case, the frequency of the phone calls is decreased (from 1/week to 1/month) after 4 weeks. During the inclusion visit, lasting about 1 hour, the following steps are planned:

- Clinic (blood pressure, heart rate, ECOG scale(31), patient's comorbidities), biologic (albumin, prealbumin, C-reactive protein) and paraclinic (year of birth, gender, weight, height, body mass index, weight evolution over the last 3 and 6 months) data collection
- All concomitant treatments and drug conciliation

- The history of the disease (primitive site, metastasis, histology of the initial tumor, presence of tumor markers)
- Radiological disease assessments (date and nature)
- A standardized geriatric assessment using validated questionnaires with a particular attention on physical activity and nutrition (ADL(23)/IADL(32), G8 (33), Rapid Assessment of Physical Activity (RAPA) (34), AIPVQ (35), EORTC QLQ-C30 (36), EORTC QLQ-ED14 (37), EQ-5D-3L (38), Short Form Health Survey in 36-items (SF-36) (39), Short Physical Performance Battery (SPPB) (40), Fatigue Severity Scale (FSS) (41), Mini-Nutritional Assessment (MNA) (42), Geriatric Depression Scale (GDS4/GDS15) (43), MINI-COG (44), Tinetti test (45), Borg scale (46), Pain scale (47), Nutrition scale (48)) (**Error! Reference source not found.**tables 2 and 3).
- Delivery of the "PROADAPT kit" device during a meeting with a dedicated paramedic (nurse, physiotherapist, ergotherapist…) in order to:
    - Provide to the patient VOLDYNE® and TRIFLO® devices for inspiratory training
    - Present the PROADAPT booklet that includes a battery of exercises and nutritional counselling specifically designed for this older population:
        - muscle strengthening of upper limbs (6 exercises, 3 difficulty levels), lower limbs (6 exercises, 3 difficulty levels), abdominal wall (4 exercises, 3 difficulty levels) (objective: 2 to 3 sessions per day for a total time between 20 and 45 minutes)
        - endurance/aerobic activities (7 exercises, 3 difficulty levels with 3 duration objectives, objective: every day)
        - inspiratory training with VOLDYNE® and TRIFLO® devices (objective: 3 sessions per day for a total time of 30 minutes)
        - general nutritional counselling adapted to the older population: food enrichment, inter-meals collations, oral nutritional supplements.
    - A fulfilling of 3-day food statement allows, in the 7 days after inclusion, to deliver a dietician-driven personalized nutritional counseling. If needed, in case of unfavorable nutritional parameters, artificial nutrition is introduced.
- Delivery, if needed, of medical prescription:
    - for home physiotherapy according PROADAPT program for respiratory training sessions and physical activity training sessions
    - For oral nutritional supplements
    - For usual medicines, including pharmaceutical review
- For patients requiring inpatient follow-up, hospital admission for a few days in a rehabilitation unit for a physiotherapeutic program and/or artificial nutrition (enteral preferred).

During pre-intervention time, phone calls are planned by a dedicated paramedic (once a week for the first 4 weeks and then once a month until the intervention). Calls are semi-directed interviews focused on the patient's autonomy, physical activity, appetite and sleep over the last period (week/month). A special attention is paid on encouraging patient's motivation and adherence to the program.

The pre-therapeutic visit is scheduled when possible between 5 days and the day of the intervention. This visit is performed in the surgery or radiotherapy unit only if the visit is necessary before the intervention still without modifying the standard therapeutic care for:

- Clinic, biologic and paraclinic data collection
- All concomitant treatments and drug conciliation
- Questionnaires about pain, nutrition, fitness and physical tests (table 2 and 3)
- Therapeutic care data collection (date, nature, entitled, reason)

During post-intervention time, paramedics trained in clinical research will resume follow-up calls as before the intervention once a week during 12 weeks after D0 and once a month up to 12 months after D0. The D0 date is determined as the last day of surgery (day of the last resumption of surgery in the limit of 30 days after the first intervention) or the last day of the radiotherapy. For weekly calls, a margin of +/- 2 days is allowed and for monthly calls, a margin of +/- 7 days is allowed.

Visits at 1, 3 and 6 months after the intervention (+/- 7 days): The patient may have started an antineoplastic treatment according to standard of care. The visit could be performed with the surgeon, the radiotherapist or the oncologist according local habits:

- Clinic (blood pressure, heart rate, ECOG scale(31)), biologic (albumin, prealbumin, C-reactive protein) and paraclinic (weight, body mass index) data collection
- All concomitant treatments and drug conciliation
- Patient care data (surgery and complications, treatment for the cancer)
- Radiological disease assessments (date and nature)
- Questionnaires about quality of life, pain, nutrition, fitness and physical tests (table 2 and 3)
- Socio-economic assessment with patient's care data (date, nature of acts, designation, reason)

The end of study visit is planned at 12 months (per-protocol) or at the date of trial premature discontinuation (+/- 7 days) for a final assessment of the same outcomes as previously listed. When requested, if previous visits were omitted, a final assessment of all the complications during the post-therapeutic period is performed.

Outcomes and measurements

Primary outcome

The main outcome measure will be the percentage of patients who have completed at least one item in the PROADAPT program after 12 months after the start of therapeutic treatment. The start of treatment is defined in this study by the last day of surgery (date of the last recovery within the limit of 30 days after the date of the initial intervention) or the last day of radiotherapy. The workshops of the program are:

- Physical and respiratory rehabilitation
- Re-nutrition session
- Telephone nurse follow-up

Secondary outcomes

The secondary outcomes of the study are:

- To evaluate the feasibility of each stage of the program independently of each other (rate of achievement of all or part of the instructions)
  - Pre-operative physical rehabilitation including (figure 1):
    - Muscle strengthening
    - Respiratory rehabilitation
    - Endurance work
  - Pre-operative nutrition counselling (figure 1)
  - Drug reconciliation / iatrogenic prevention
  - Pre-therapeutic follow-up calls
  - Post-surgery or post-radiotherapy follow-up calls

- To estimate patients' satisfaction with the overall program, at the end of the study (end of follow-up or study discontinuation) using a questionnaire (Supplemental material).

- To estimate the rate of adherence to the items (physical activity, nutrition and nursing follow-up) during follow-up time. To evaluate this criterion, various parameters will be recorded: physical activity duration (in h/week), kinetics (duration (% increase), level of difficulty), respiratory activity, food intake during phone calls.

- To assess the longitudinal evolution over 1 year of:
  - patient's physical performance (SPPB, gate speed, TUG test) and functional independence on ADL (23), IADL (32), AIPVQ (49)
  - nutritional parameters of the patient (weight, albuminemia, appetite)

- health-related quality of life for patients based on QLQ-C30 and ELD14 (5 dimensions: mobility, disease burden, emotional and physical functioning, tiredness) (50,51)
- pharmaceutical conciliation

In parallel to these secondary objectives, a series of parameters will be measured and monitored in order to:

- Estimate the rate and nature of post-operative complications at 30 days (NCI-CTCAE)
- Estimate the rate and nature of post-operative complications according to the CCI at 30 and 90 days
- Estimate post-operative mortality at 30 and 90 days
- Estimate the overall one-year survival rate (OS)
- Estimate the one-year progression-free survival rate (PFS)
- Estimate the longitudinal evolution of QoL according to QLQ C30, ELD14, EQ-5D
- Estimate treatment costs (health system, patients)
- Study therapeutic strategies (treatment completion rate)
- Estimate the evolution of geriatric covariates.

Sample size calculation

The program will be considered feasible, at the patient level, if all or part of the program is implemented in at least 50 % of the included patients (= alternative hypothesis). This threshold was defined in line with previous studies on prehabilitation for older cancer patients, that showed compliance rates between 16 and 95% (52,53). Considering that PROADAPT program is highly complex even if tailored for older patients, we anticipate modest compliance rates.

The calculation of the required sample size was done as follows: to reject the null hypothesis of the program feasibility rate lower than 35 %, with a bilateral alpha error risk of 5 % and a statistical power of 90 % (beta=10 %), the number of required patients to be analyzed is 111. Including 10 % non-treatable patients, a total of 122 patients should be included.

Data management and statistical analyses

Data are monitored by a clinical research associate (CRA). Inconsistencies will be reported to the study investigators in order to decide whether the data should be corrected or considered as missing data. Any changes in the data will be reported.

Data analyses will be performed by the data management and analysis centre. The analyses will be carried out by an independent statistician with the latest version of the R software environment and SAS software version 9.4.

All of the characteristics collected will be subjected to a descriptive analysis.

Descriptive analyses

A flow-chart diagram will describe the data available for the patient population at baseline, and during each follow-up visit. Eligibility criteria for treated patients will be verified, as well as follow-up and end of study visits. Reasons for premature end of study will be provided.

Characteristics of the study population and proportions of missing values will be reported. Patient characteristics will be described using mean and standard deviation or median and interquartile range for quantitative variables, and frequencies and distribution for categorical variables. A comparison of baseline characteristics between patients with complete follow-up and those with attrition will be performed. If needed, methods for handling missing data (multiple imputation, mixed model or auxiliary variable) will be used when appropriate.

Primary analysis

The number and percentage of patients who have completed at least one PROADAPT program activity at the end of 12 months after the start of treatment will be reported. All included patients will be analysed in the primary analysis as intention to treat, defined as all included patients with or without the respect of the eligibility criteria and whatever the respect or not of the intervention.

Secondary analyses

Time-to-event variables: follow-up, overall survival, progression free survival

The proportion of events at specific measurement times will be estimated according to the Kaplan-Meier curve. Medians of event-free survival will be reported by treatment arm with its 95 % confidence interval (95 % CI), if the number of events allows estimation of the median.

Overall survival rate and progression free survival rate at 12 months (after the day of the last revision of surgery or the last day of radiotherapy) will be provided with 95 % CI.

Quality of life

Analyses of the QoL data will be performed with modified intention to treat (mITT) population, i.e. including all included patients with at least a QoL score available at baseline. Patients' quality of life, linked to health, will be analysed after 3 months through 4 targeted dimensions: mobility, disease burden, emotional and physical functioning. All other dimensions will be analysed as exploratory

purpose only. QoL scores will be described at baseline and at 3 months using the mean and standard deviation or median and range. Mean difference between baseline and 3 months will be reported with its 95% confidence interval. A 10-point difference will be considered as the minimal important difference for each score of the EORTC questionnaires.

Longitudinal follow-up

Covariates planned to be repeatedly tested during entire 1-year follow up will help analysing the resilience concept ie the ability and the celerity with which one individual will recover to his baseline level (54). Will be included in such analyses the covariates evaluating functional and physical performance levels (SPPB, gate speed, TUG test, ADL, IADL, AIPVQ), nutritional parameters (weight, albuminemia, appetite), and health-related quality of life. The longitudinal changes of these variables will be analysed using linear mixed models (55). A "time-to-recovery" composite endpoint will be also proposed as exploratory, defined as the time to complete functional and nutritional recovery of the patients, a construction similar to the "Time to deterioration" composite endpoint proposed in the oncologic field (56)."

Data monitoring

The successful completion of the database is ensured by the hospital CRA. The hospital CRA also ensures compliance with the study protocol. The sponsor CRA verifies that the rights of the participants are respected.

End of protocol

Patients leave the study either on a per-protocol basis during the "end of study visit" on month 12 after the intervention or at any time during the conduct of the study if they no longer wish to participate. However, as indicated in the information letter to the patients/caregivers, the data collected before exclusion may be used as part of the study.

Confidentiality

Correspondence tables will be kept in a separate file that does not contain clinical data. The access to the nominative information is protected by a password and confidentiality is guaranteed by the study.

Protocol amendments

Any important modifications requiring a new ethics committee approval will be communicated in future publications. Any potential impact of protocol modifications on the results will be discussed as appropriate.

Trial status

Patient enrolment began on July 3, 2018. Data are collecting.

Patients' and public involvement

Patients were involved at different steps of the trial: (i) during PROADAPT booklet conception, several (30) patients were asked to answer an anonymous questionnaire in order to improve its ergonomics; (ii) the information note and consent form of the protocol have been re-read by the patients' review committee of the Ligue Nationale de Lutte contre le Cancer (a French association of cancer patients).

Discussion

Discussion of the intervention

Prehabilitation has long been conceptualized as an effective means of improving the functional capacity of the individual to enable him to resist various stressors. Originally developed in the military as the association of physical training to improve strength and endurance, improving nutritional intake and general education (57), it has been transposed into medicine and major surgery – initially when an ICU admission is planned - at the beginning of this century (58).

Despite a growing interest in the medical community for prehabilitation and particularly cancer prehabilitation, the level of evidence for specific interventions stays too low to be implemented in common care. Among the main disadvantages of published data include the heterogeneity of programs, sometimes poor patient adherence and the fact that most studies were small pilot studies developed for patients more fit and younger than those who should make the best part of prehabilitation. Another point to emphasize is that most programs include only one intervention - physical, nutritional, or psychological rehabilitation - when multimodal interventions are often considered to be more effective in older populations.

Considering these points, the PROADAPT intervention was developed according to an innovative management strategy since it started in 2016 by multi-professional meetings conceived as brainstorming sessions in order to develop a multidisciplinary program dedicated to prehabilitation and follow-up of older patients. The multidisciplinary conception of the intervention, the particular

attention paid to older patients' specificities and the previous experience of the participants in as various fields as patients' education, cognition, physiotherapy were hopefully the warrants of the most tailored approach to the target population. For example, the booklet typography was of big character font and the illustrations highly schematic with high contrast. Each sentence was verified by a panel of patients in order to insure proper understanding. Finally, the booklet was evaluated by 30 patients, with a high rate of satisfaction (Ravot et al, PROADAPT Pilot trial: A survey on patients' expectations and satisfaction, unpublished data).

The fact that the PROADAPT intervention was constructed as an outpatient program may be considered as at risk of poor and heterogeneous supervision of the physical exercises. However, this limitation is balanced by a weekly phone calls to the patients, able to evaluate partially patients' skills and motivation for the program. In addition, such design allows to neutralize somehow the consequences of any inequalities or heterogeneity arising from the health system. As an example, PROADAPT pilot study was able, during the last months, to maintain accrual and patients' coaching and follow up, despite sudden closing of geriatric wards and surgical rooms during COVID pandemic.

This pilot study is the first step towards an ambitious program, since PROADAPT program will be declined in the future into two randomized studies, PROADAPT-ovary/EWOC-2 (NCT04284969) and PROADAPT sus-mesocolic, designed to evaluate the impact of PROADAPT program on post-treatment complications versus common care. In order to favor patients' compliance and follow-up, an eHealth tool has been developed that will help supervising patients' care courses.

Discussion of the study design

In line with the previous points, this pilot study was designed in order to answer to this critical question: is a multidomain prehabilitation program feasible in an older cancer population? This question encompasses several points: (i) Is the program physically adapted to an older population? (ii) Is such a program appliable in ambulatory care? (iii) How to build pedagogic tools adapted for such ambulatory use? (iv) Are such pedagogic tools understandable? (v) What is the compliance of the patients for each domain of the intervention program?... Another point is to know whether the patient's care team is expected to accept such intervention, but this point was previously evaluated by Ghignone et al. They demonstrated through an international survey that surgeons are generally in favor for such programs since 71 % of them would accept to prehabilitate their elderly patients 4 weeks before surgery, if such intervention is proven to be effective (2). Nevertheless, the participation of surgeons and anesthesiologists during initial brainstorming sessions was of major interest since they enriched a lot the structure of the program.

Thus, the construct of this trial may appear as highly complex with overabundant secondary endpoints, but this design encompasses as much as possible the complexity of prevention care in an older population, which has to mix the adaptation to the target population and the ability to maintain compliance over time.

Ethics and dissemination

The study sponsor is the Hospices Civils de Lyon, responsible for study insurance and pharmacovigilance. The study protocol was approved by the Ile de France 8 Ethics Committee on May 3, 2018 and cover all sites involved in this study. Several amendments have been added to the first version of the protocol. The initial approved version was V2 of May 28, 2018, then the amended versions were as follows: V3 of October 23, 2018 (change in the recruitment period, addition of new investigation centers), V4 of May 17, 2019 (request for an additional 12 months extension, update with the GPDR and update of the patient booklet), V5 of July 17, 2020 (addition of a cohort of 30 patients to test the follow-up program with an e-health interface, request for an additional 8 months extension). Current version is the V5 of July 17, 2020, authorized on September 10, 2020. The research will be carried out in accordance with the Helsinki Declaration and ICH GCP Guidelines. Trial protocol fulfills SPIRIT 2013 checklist (Supplementary table 1) and World Health Organization Trial Registration Data Set (Supplementary table 2). The study complies with the principles of the data protection act in France and with the General Data Protection Regulations in force in Europe. Each investigator must collect a written consent at the beginning of the procedure. This consent is retained in the patient's medical chart. The patient can stop the study at any time with an oral information at his investigator or clinical research assistant. Patients will be informed on additional amendments according the law in force.

The results of the primary and secondary objectives will be published in peer-reviewed journals. All authors of future publications will have to meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors.

Total words count : 5161

Abbreviations

ADL: Activities of Daily Living; AIPVQ: Physical Instrumental activities of daily living (in French: Activités Instrumentales Physiques de la Vie Quotidienne); CRA: Clinical Research Assistant; ESPEN: European Society for Clinical Nutrition and Metabolism; FSS: Fatigue Severity Scale; GDS: Geriatric Depression Scale; IADL: Instrumental Activities of Daily Living; ICU: Intensive Care Unit; mITT:Modified Intention To Treat; MNA: Mini Nutritional Assessment; QLQ: Quality of Life Questionnaire; QoL: Quality of Life; RAPA: Rapid Assessment of Physical Activity; SF: Short Form Health Survey in 36 items; SPPB: Short Physical Performance Battery

Declarations

Acknowledgements

This pilot protocol is part of the PROADAPT initiative for improving care for older people with cancer and takes part to the FHU-OncoAge consortium (www.oncoage.org). The authors wish to thank the professionals who participated to the intervention conception: G. Albrand, D. Barnoud, D. Benayoun. B Billod, J. Bonhomme, A.-L. Bres, C. Brunengo, A. Chanelière, D. Charlety, Y. Chauleur, G. Copaescu, H. Curé, A.-M. Dascalita, B. De La Vigerie, S. Ducoulombier, O. Ganne, F. Gervais, T. Gilbert, M. Giroud, N. Jomard, C. Lecardonnel, B. Leroy, J.-A. Long, A. Marion, E. Nony, S. Parent, A. Pelisset-Vanhersecke, A. Pirollet, J.-E. Terrier, J. Trautmann, M.-A. Vincent.

The authors also acknowledge the teams of Lyon Sud Hospital, Edouard Herriot Hospital of Lyon, Croix Rousse Hospital of Lyon, Annecy Genevois Hospital Center, Hôpital Nord Ouest hospital center, Chambéry Hospital Center and Médipôle Lyon-Villeurbanne who contribute to patient enrollment in this study and Thomas Gilbert for a friendly reviewing of the manuscript.

The authors would like to thank the patients' review committee of the Ligue Nationale de Lutte contre le Cancer for the valuable editing of the information note and the consent form.

Funding

This work was supported by the Agence Régionale de Santé (ARS) Auvergne Rhône Alpes, through the call for projects "Innovate in health for the Auvergne Rhône Alpes region" jointly organized by the ARS, Bpifrance, the Auvergne Rhône Alpes region, URIOPASS, ORAIDA and Cluster I-care and the decision of the selection committee on June 27, 2016 (Grant N°2016-149). It provided funding for nurses, dieticians, physiotherapists, and clinical research assistants.

Availability of data and materials

The final dataset of the PROADAPT pilot study will be available on reasonable request after publication of the primary objective. Data requests can be submitted to the corresponding author.

Competing interest

The authors declare that they have no competing interests.

Consent for publication

Not applicable

Author contributions

All authors participated to the PROADAPT intervention conception. Study protocol was conceived by DD, CF, CG, SPB, OLS, AM, VP and CR. DD and CF assumed fundraising and grant follow-up. MR led the drafting of the manuscript. All authors (MR, CR, AM, SPB, CG, VP, MT, BR, BG, MG, Cba, CBo, EG, LS, MH, ECK, IMS, VC, OLS, DD and CF) critically reviewed and approved the final version of the protocol.

References

1. Tan H-J, Saliba D, Kwan L, Moore AA, Litwin MS. Burden of Geriatric Events Among Older Adults Undergoing Major Cancer Surgery. J Clin Oncol. 2016 Oct 4;34(11):1231–8.

2. Ghignone F, van Leeuwen BL, Montroni I, Huisman MG, Somasundar P, Cheung KL, et al. The assessment and management of older cancer patients: A SIOG surgical task force survey on surgeons' attitudes. Eur J Surg Oncol EJSO. 2016 Feb;42(2):297–302.

3. Thomas G, Tahir MR, Bongers BC, Kallen VL, Slooter GD, van Meeteren NL. Prehabilitation before major intra-abdominal cancer surgery: A systematic review of randomised controlled trials. Eur J Anaesthesiol. 2019;36(12):933–45.

4. Carli FMMp, Bousquet-Dion G, Awasthi R, Elsherbini N, Liberman S, Boutros M, et al. Effect of Multimodal Prehabilitation vs Postoperative Rehabilitation on 30-Day Postoperative Complications for Frail Patients Undergoing Resection of Colorectal Cancer: A Randomized Clinical Trial. JAMA Surg. 2020 Mar;155(3):233–42.

5. Bongers BC, Klaase JM, Meeteren NLU van. Prehabilitation vs Postoperative Rehabilitation for Frail Patients. JAMA Surg. 2020 Sep 1;155(9):896–7.

6. Cooper L, Frain L, Jaklitsch MT. Prehabilitation vs Postoperative Rehabilitation for Frail Patients. JAMA Surg. 2020 Sep 1;155(9):898–9.

7. Kako JMhsRO, Kajiwara K, Tatematsu N. Prehabilitation vs Postoperative Rehabilitation for Frail Patients. [Letter]. JAMA Surg.

8. Keller DS, Carter B, Moug SJ. Prehabilitation vs Postoperative Rehabilitation for Frail Patients. JAMA Surg. 2020 Sep 1;155(9):896–896.

9. Carli F, Bousquet-Dion G, Fiore JF. Prehabilitation vs Postoperative Rehabilitation for Frail Patients. JAMA Surg. 2020 Sep 1;155(9):899–900.

10. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr [Internet]. 2016 Aug 6 [cited 2016 Nov 20];0(0). Available from: http://www.clinicalnutritionjournal.com/article/S0261-5614(16)30181-9/abstract

11. Singh F, Newton RU, Galvão DA, Spry N, Baker MK. A systematic review of pre-surgical exercise intervention studies with cancer patients. Surg Oncol. 2013 Jun 1;22(2):92–104.

12. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008 Sep 29;337:a1655.

13. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet] [Internet]. Lyon, France: International Agency for Research on Cancer; 2013 [cited 2016 Sep 4]. Available from: Available from: http://globocan.iarc.fr

14. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared Risk Factors in Cardiovascular Disease and Cancer. Circulation. 2016 Mar 15;133(11):1104–14.

15. Sjölund B-M, Wimo A, Qiu C, Engström M, von Strauss E. Time trends in prevalence of activities of daily living (ADL) disability and survival: Comparing two populations (aged 78+ years) living in a rural area in Sweden. Arch Gerontol Geriatr. 2014 May;58(3):370–5.

16. Sjölund B-M, Wimo A, Engström M, Strauss E von. Incidence of ADL Disability in Older Persons, Physical Activities as a Protective Factor and the Need for Informal and Formal Care – Results from the SNAC-N Project. PLoS ONE [Internet]. 2015 [cited 2016 Sep 4];10(9). Available from: https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pmc/articles/PMC4583409/

17. Jagger C, Gillies C, Moscone F, Cambois E, Van Oyen H, Nusselder W, et al. Inequalities in healthy life years in the 25 countries of the European Union in 2005: a cross-national meta-regression analysis. The Lancet. 2008 Dec 20;372(9656):2124–31.

18. Extermann M, Meyer J, McGinnis M, Crocker TT, Corcoran MB, Yoder J, et al. A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. Crit Rev Oncol Hematol. 2004 Jan;49:69–75.

19. Repetto L, Fratino L, Audisio RA, Venturino A, Gianni W, Vercelli M, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol. 2002 Jan 15;20:494–502.

20. Caillet P, Canoui-Poitrine F, Vouriot J, Berle M, Reinald N, Krypciak S, et al. Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA study. J Clin Oncol. 2011;29:3636–42.

21. Website: http://www.cepd.fr/CUSTOM/CEPD_toxicite.pdf.

22. Linn BS, Linn MW, Gurel L. CUMULATIVE ILLNESS RATING SCALE. J Am Geriatr Soc. 1968 May;16(5):622–6.

23. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of Illness in the Aged. The Index of Adl: A Standardized Measure of Biological and Psychosocial Function. Jama. 1963 Sep 21;185:914–9.

24. Falandry C, Stefani L, Granger M, Momiron C, Habchi H, Bourgeois C, et al. Interventions to improve physical performances of older people with cancer before major surgery: an umbrella review. J Geriatr Oncol. 2018;9(6 suppl 1):S94–5.

25. Falandry C, Stefani L, André L, Granger M, Barbarava C, Habchi H, et al. Interventions to improve physical performances of older people with cancer before complex medico-surgical procedures: protocol for an umbrella review of systematic reviews and meta-analyses. Medicine (Baltimore). 2020;in press.

26. Glasgow RE, Emmons KM. How Can We Increase Translation of Research into Practice? Types of Evidence Needed. Annu Rev Public Health. 2007;28(1):413–33.

27. Colburn JL, Mohanty S, Burton JR. Surgical Guidelines for Perioperative Management of Older Adults: What Geriatricians Need to Know. J Am Geriatr Soc. 2017 Jun 1;65(6):1339–46.

28. Arends J, Bodoky G, Bozzetti F, Fearon K, Muscaritoli M, Selga G, et al. ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology. Clin Nutr. 2006 Apr;25(2):245–59.

29. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, et al. ESPEN Guidelines on Enteral Nutrition: Surgery including Organ Transplantation. Clin Nutr. 2006 Apr;25(2):224–44.

30. Mohanty S, Rosenthal RA, Russell MM, Neuman MD, Ko CY, Esnaola NF. Optimal Perioperative Management of the Geriatric Patient: A Best Practices Guideline from the American College of Surgeons NSQIP and the American Geriatrics Society. J Am Coll Surg. 2016 May 1;222(5):930–47.

31. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649–55.

32. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969 Autumn;9:179–86.

33. Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol. 2012 Aug;23(8):2166–72.

34. Topolski TD, LoGerfo J, Patrick DL, Williams B, Walwick J, Patrick MB. The Rapid Assessment of Physical Activity (RAPA) among older adults. Prev Chronic Dis. 2006 Oct;3(4):A118.

35. Gill TM, Baker DI, Gottschalk M, Peduzzi PN, Allore H, Van Ness PH. A prehabilitation program for the prevention of functional decline: effect on higher-level physical function. Arch Phys Med Rehabil. 2004 Jul;85(7):1043–9.

36. Quinten C, Coens C, Ghislain I, Zikos E, Sprangers MAG, Ringash J, et al. The effects of age on health-related quality of life in cancer populations: A pooled analysis of randomized controlled trials using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 involving 6024 cancer patients. Eur J Cancer. 2015 Dec;51(18):2808–19.

37. Wheelwright S, Darlington A-S, Fitzsimmons D, Fayers P, Arraras JI, Bonnetain F, et al. International validation of the EORTC QLQ-ELD14 questionnaire for assessment of health-related quality of life elderly patients with cancer. Br J Cancer. 2013 Aug;109(4):852–8.

38. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013 Sep;22(7):1717–27.

39. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473–83.

40. Fish J. Short Physical Performance Battery. In: Kreutzer JS, DeLuca J, Caplan B, editors. Encyclopedia of Clinical Neuropsychology [Internet]. New York, NY: Springer New York; 2011 [cited 2020 Nov 4]. p. 2289–91. Available from: http://link.springer.com/10.1007/978-0-387-79948-3_1832

41. Goo A-J, Song Y-M, Shin J, Ko H. Factors Associated with Depression Assessed by the Patient Health Questionnaire-2 in Long-Term Cancer Survivors. Korean J Fam Med. 2016;37(4):228.

42. Guigoz Y, Vellas B, Garry PJ. Assessing the Nutritional Status of the Elderly: The Mini Nutritional Assessment as Part of the Geriatric Evaluation. Nutr Rev. 2009 Apr 27;54(1):S59–65.

43. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiatr Res. 1982 Jan;17(1):37–49.

44. McCarten JR, Anderson P, Kuskowski MA, McPherson SE, Borson S. Screening for Cognitive Impairment in an Elderly Veteran Population: Acceptability and Results Using Different Versions of the Mini-Cog: SCREENING ELDERLY VETERANS USING THE MINI-COG. J Am Geriatr Soc. 2011 Feb;59(2):309–13.

45. Tinetti ME, Baker DI, McAvay G, Claus EB, Garrett P, Gottschalk M, et al. A Multifactorial Intervention to Reduce the Risk of Falling among Elderly People Living in the Community. N Engl J Med. 1994 Sep 29;331(13):821–7.

46. Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med. 1970;2(2):92–8.

47. Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES). Assessment and follow-up of chronic pain in adults in ambulatory medicine. 1999 Feb;

48. Société Francophone Nutrition Clinique et Métabolisme (SFNCM). Evaluation of food intake.

49. de Souto Barreto P, Ferrandez A-M. Activités instrumentales physiques de la vie quotidienne chez les personnes âgées: validation d'une échelle. In: L'anthropologie du vivant: objets et méthodes. Chapuis-Lucciani N, Guihard-Costa AM, Boëtsch G. 2010. p. 83–7.

50. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. JNCI J Natl Cancer Inst. 1993 Mar 3;85(5):365–76.

51. Wheelwright S, Darlington A-S, Fitzsimmons D, Fayers P, Arraras JI, Bonnetain F, et al. International validation of the EORTC QLQ-ELD14 questionnaire for assessment of health-related quality of life elderly patients with cancer. Br J Cancer. 2013 Aug 20;109(4):852–8.

52. Boereboom C, Doleman B, Lund JN, Williams JP. Systematic review of pre-operative exercise in colorectal cancer patients. Tech Coloproctology. 2016 Feb 1;20(2):81–9.

53. Sun V, Raz DJ, Kim JY, Melstrom L, Hite S, Varatkar G, et al. Barriers and facilitators of adherence to a perioperative physical activity intervention for older adults with cancer and their family caregivers. J Geriatr Oncol. 2020 Mar 1;11(2):256–62.

54. Gijzel SMW, Whitson HE, Leemput IA, Scheffer M, Asselt D, Rector JL, et al. Resilience in Clinical Care: Getting a Grip on the Recovery Potential of Older Adults. J Am Geriatr Soc. 2019 Dec;67(12):2650–7.

55. Cnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. Stat Med. 1997 Oct 30;16(20):2349–80.

56. Bonnetain F, Fiteni F, Efficace F, Anota A. Statistical Challenges in the Analysis of Health-Related Quality of Life in Cancer Clinical Trials. J Clin Oncol. 2016 Jan 6;34(16):1953–6.

57. Prehabilitation, rehabilitation, and revocation in the Army. Br Med J. 1946 Jun 29;1:192–7.

58. Topp R, Ditmyer M, King K, Doherty K, Hornyak J. The effect of bed rest and potential of prehabilitation on patients in the intensive care unit. AACN Clin Issues. 2002 May;13(2):263–76.

Illustrations' legends

Figure 1: PROADAPT program: interventions at the patient's level

Table 1: PROADAPT program: tasks according the different domains and the successive chronological steps (before, during and after complex medico-surgical procedure)

Table 2: PROADAPT pilot trial: questionnaires and screening tests

Table 3: PROADAPT pilot trial: flow diagram

Table 1: PROADAPT program: tasks according the different domains and the successive chronological steps (before, during and after complex medico-surgical procedure)

Nurse coaching & education Bridging interventions	Coaching nurse self-presentation Delivery of a personalized patient booklet Care according best practice guidelines: - Confirm and document patient goals and treatment preferences, including advance directives. - Confirm and document patient's health care proxy or surrogate decision-maker. - In patients with existing advance directives, discuss new risks associated with the surgical procedure and an approach for potentially life-threatening problems consistent with the patient's values and preferences ("required reconsideration"). Weekly phone calls	Coaching nurse visits / phone calls Communication of patient's preference to the staff	Coaching nurse visit in the rehabilitation ward Communication of patient's preference and care difficulties to the staff (checklist): - delirium/cognitive impairment - peri-operative acute pain - pulmonary complications - fall risk - ability to maintain adequate nutrition - urinary tract infection prevention - functional decline monitoring - pressure ulcers prevention	Coaching nurse bi-weekly phone call Communication of patient's care difficulties to the staff
Nutrition	W-4 : nutritional evaluation Nutritional plan based on measured intake W-3 : nutritional follow up - weight W-2 : nutritional follow up-weight W-1 : nutritional follow up-weight + pre-operative immunonutrition	If surgery: Care according best practice guidelines: - Consider shortened fluid fast (clear liquids up to 2 hours before anaesthesia).(29) - Normal food intake or enteral feeding should start as early as possible	Nutritional plan based on - Weight curve - Measured intake Optimal management of - Nausea/vomiting - Abdominal pain	Nutritional plan based on - Weight curve - Measured intake Optimal management of - Nausea/vomiting - Abdominal pain
Physical activity	W-4 : physical performances evaluation Physical activity plan W-3 \ group physical activity W-2 + W-1 \ functional follow-up	If surgery: care according best practice guidelines: - Early physical and/or occupational therapy. - Check for orthostatic hypotension. - Review physical environment to reduce injury risk. - Assistive walking devices (eg walkers) at bedside if used as outpatient	(to the discretion of the rehabilitation unit)	Pursuing of the pre-operative physical activity plan
Medication conciliation	Centralized medication conciliation and treatment optimization (STOPP/START guidelines)	Centralized medication conciliation Advices for care according best practice guidelines (16): - Adhere to existing best practices regarding antibiotic and venous thromboembolism prophylaxis. - Ensure nonessential medications have been stopped and essential medications have been taken.	Centralized medication conciliation	Centralized medication conciliation
Standardization of surgical procedures		If surgery: consider antiseptic toothpaste If surgery: care according best practice Guidelines (16): - Consideration of regional techniques to avoid postoperative complications and improve pain control. - Directed pain history. - Multi-modal or opioid-sparing techniques. - Postoperative nausea risk stratification and prevention strategies. - Strategies to avoid pressure ulcers and nerve damage. - Prevention of postoperative pulmonary complications and hypothermia. - Judicious use ofintravenous fluids. - Appropriate hemodynamic management. - Continuation of indicated cardiac medications. - Daily post-operative roundingchecklist: - delirium/cognitive impairment - peri-operative acute pain - pulmonary complications - fall risk - ability to maintain adequate nutrition - urinary tract infection prevention - functional decline monitoring - Pressure ulcers prevention If surgery: consider IV iron supplementation		

759 Table 2: PROADAPT pilot trial: questionnaires and screening tests

Domain	
Autonomy	Activity of Daily Living Scale (ADL) Instrumental Activities of Daily Living scale (IADL)
Geriatric screening	G8
Physical activity	RAPA (Rapid Assessment of Physical Activity), AIPVQ
Quality of life	QLQ-C30 cancer specific QoL questionnaire, QLQ-ED14 older cancer patients questionnaire, EQ-5D-3L utility questionnaire, SF-36 general QoL questionnaire
Locomotion and balance	Timed Up and Go test, SPPB (Short Physical Performance Battery)
Pain	Pain scale evaluation
Nutrition	Nutrition scale evaluation
Tiredness severity	FSS
Depression/anxiety	MNA, GDS4/GDS15
Cognitive assessment	MINI-COG
Fall risk assessment	Tinetti test
Breathlessness	Borg scale

760

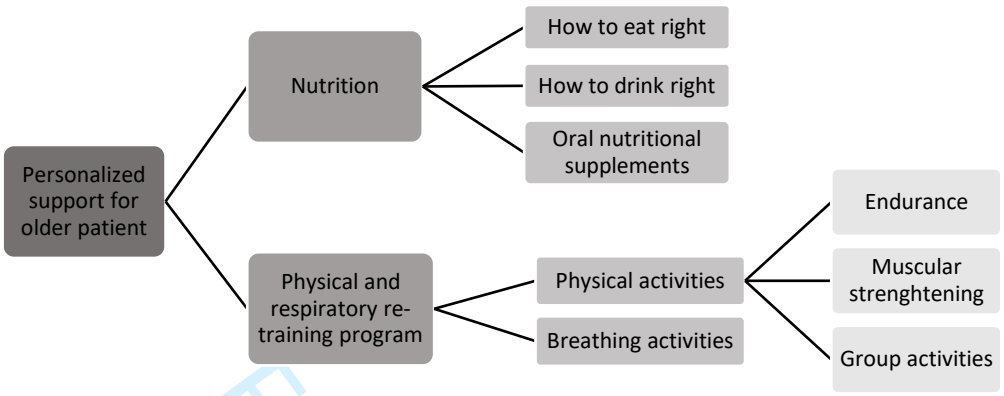
761

762 Table 3: PROADAPT pilot trial: flow diagram

	Baseline	Pre-therapeutic visit (0-5 days before intervention)	M1, M3, M6	M12	End of study visit
Complex geriatric assessment					
G8	X			X	X
ADL/IADL	X			X	X
GDS4/GDS15	X			X	X
MINI COG	X			X	X
MNA	X			X	X
QLQ-C30	X		X	X	X
QLQ-ELD14	X		X	X	X
EQ-5D-3L	X		X	X	X
Pain scale evaluation	X	X	X	X	X
Nutrition scale evaluation	X	X	X	X	X
Socio-economic evaluation	X				
Physical and respiratory assessments					
FSS	X		X	X	X
SF-36	X		X	X	X
Timed Up and Go test	X			X	X
SPPB	X		X	X	X
Borg scale	X			X	X
RAPA questionnaire	X		X	X	X
AIPVQ scale	X		X	X	X
Tinetti test	X			X	X
Equimog evaluation	X			X	X
Triflo	X	X			
Voldyne	X	X			
Physical activity data collection		X	X	X	X
Patients' satisfaction					
Standardized questionnaire					X

763

Figure 1 : PROADAPT program : interventions at the patient's level



Supplementary table 1 : Satisfaction questionnaire

Hospices Civils de Lyon **Direction de la Recherche Clinique et de l'Innovation**	**PATIENT ASSESSMENT OF THE PROADAPT PILOT PHASE PROGRAM**

Mrs, Mr,

You have been part of the PROADAPT - pilot phase study and we thank you for your involvement. In order to assess and improve this study, we would like to collect your opinion. This opinion is anonymous and does not affect your healthcare.

The following questions concern the patient booklet that was given to you as part of the study

If you consider the booklet globally

- The explanations seem appropriate to you ? Not at all ☐ A little ☐ Absolutely ☐
- The information seem clear to you ? Not at all ☐ A little ☐ Absolutely ☐
- The pages seem readable enough ? Not at all ☐ A little ☐ Absolutely ☐
- The illustrations seem clear to you ? Not at all ☐ A little ☐ Absolutely ☐

How would you rate the booklet ? (useless = 0 ; very useful = 10) 0 1 2 3 4 5 6 7 8 9 10

The following questions concern the PROADAPT pilot phase program globally (breathing and physical exercises, booklet, calls and follow-up visits)

Did you have difficulty to understand the explanations given by the medical staff and the physician

- for breathing exercises ? Not at all ☐ A little ☐ A lot ☐
- for physical exercises ? Not at all ☐ A little ☐ A lot ☐
- for nutritional advices ? Not at all ☐ A little ☐ A lot ☐
- during the assessment with the physician on the different drugs you are taking ? Not at all ☐ A little ☐ A lot ☐

Did you encounter any difficulties

- for the realization of breathing exercises ? Not at all ☐ A little ☐ A lot ☐
- for the realization of physical exercises ? Not at all ☐ A little ☐ A lot ☐

- for the setting up of nutritional advice ? Not at all ☐ A little ☐ A lot ☐
- for the filling of activities ? Not at all ☐ A little ☐ A lot ☐

How do you estimate nursing phone calls

- at the beginning of your healthcare before your surgery / radiothery Useless ☐ Little important ☐ Needed ☐
- after your surgery/radiotherapy Useless ☐ Little important ☐ Needed ☐

Would you like to get more information ? No ☐ Yes ☐
If yes, which ones,……
……

What would be your propositions to make the program more suitable for patients?
……
……
……

Thank you for your time, we will use your advice to improve the PROADAPT program and the patient booklet.

Pr Claire Falandry, study coordinator

Supplementary table 2: All items from the World Health Organization Trial Registration Data Set (SPIRIT item 2b)

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT03659123
Date of registration in primary registry	September 6, 2018
Secondary identifying numbers	69HCL16_0701 ID RCB N° 2018-A001026-49
Source(s) of monetary or material support	Agence Régionale de Santé Auvergne Rhône Alpes
Primary sponsor	Hospices Civils de Lyon
Secondary sponsor(s)	
Contact for public queries	David Dayde, +33.4.78.86.37.74, david.dayde@chu-lyon.fr
Contact for scientific queries	Claire Falandry, +33.4.78.86.66.34, claire.falandry@chu-lyon.fr
Public title	Prehabilitation & Rehabilitation in Oncogeriatrics: Adaptation to Deconditioning Risk and Accompaniment of Patients' With Cancer
Scientific title	Prehabilitation & Rehabilitation in Oncogeriatrics: Adaptation to Deconditioning Risk and Accompaniment of Patients' With Cancer, a Multicenter Pilot Study
Countries of recruitment	France
Health condition(s) or problem(s) studied	Old Injury
Intervention(s)	Behavioral: standardized geriatric intervention Nutritional care is based on: • A personalized evaluation of nutritional balance and nutritional needs of the patient • A weekly follow-up of weight and nutritional intake Total-body rehabilitation is based on: • 2 to 3 times a week: strength exercise • 2 to 3 times a week: endurance exercise, 20 to 45 min each sequence • 2 times a week: respiratory physiotherapy Pharmaceutical conciliation and optimization according STOPP/START criteria During peri-operative time, the nurse contacts the surgical team for transmission of patient's personal data, physical medication conciliation results During rehabilitation time and hospital-home transition time, the nurse contacts

Data category	Information
	the rehabilitation team for transmission of patient's personal data and care course, physical (nutritional, functional and/or comorbidities), medication conciliation results.
Key inclusion and exclusion criteria	Inclusion Criteria: Patient ≥70 year old OR patient ≥60 years with significant comorbid condition (modified Charlson index≥3) or disability (ADL score<6/6); Histologically or cytologically proven cancer. Life expectancy > 3 months. Written informed consent obtained Covered by a Health System where applicable. Exclusion Criteria: Other malignancy within the last 5 years, except for adequately treated carcinoma in situ of the cervix or squamous carcinoma of the skin, or adequately controlled limited basal cell skin cancer. Patient unable to be regularly followed for any reason (geographic, familial, social, psychologic). Any mental or physical handicap at risk of interfering with the appropriate treatment. Any administrative or legal supervision where applicable
Study type	Interventional Allocation: N/A Intervention model: Single Group Assignment Masking: None (Open Label) Primary purpose: Health Services Research Phase II
Date of first enrolment	July 3rd, 2018
Target sample size	122
Recruitment status	Recruiting
Primary outcome(s)	Implementation of at least one item of PROADAPT standardized geriatric intervention of the program PROADAPT pilot study [Time Frame: 12 months]: • Preoperative physical activity including strength and endurance exercise assessed by physical exercises accomplished under the supervision of a physiotherapist. Number of patients with at least 1 intervention achieved in the domain. • Nutrition guidelines before and after physical activity assessed by questionnaires. Number of patients with at least 1 intervention achieved in the domain.

Data category	Information
	• Patient education and coaching assessed by questionnaires and visits. Number of patients with at least 1 intervention achieved in the domain • Achievement of standardized intervention procedures, according to the checklist established in consensus with surgeons. Number of patients with at least 1 intervention achieved in the domain • Rehabilitation assessed by questionnaires. Number of patients with at least 1 intervention achieved in the domain • Accomplishment of pharmaceutical medication conciliation and treatment optimization. Number of patients with at least 1 intervention achieved in the domain • Bridging interventions for hospital-to-home transition. Number of patients with at least 1 intervention achieved in the domain
Key secondary outcomes	• Post operative morbidity [Time Frame: 30 and 90 days] according Clavien-Dindo classification • Post-operative morbidity [Time Frame: 90 days] according to NCI CTC v4.4 • Therapeutic strategy [Time Frame: 12 months]: Treatment plan completion rate: Number of patients for whom the treatment plan was completed. • Progression-free Survival [Time Frame: 12 months] • Post-treatment complication [Time Frame: 12 months]: Post-treatment complication grade≥3 according the National Cancer Institute Common Toxicity Criteria version 4 (NCI-CTC-v4)

Supplementary table 1: SPIRIT 2013checklist of the trial

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary table 2 Ref 24
Protocol version	3	Date and version identifier	17 (Ethics and Consent to participate)
Funding	4	Sources and types of financial, material, and other support	17-18 (Funding)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 (Authors' list) 18 (Authors' contributions)
	5b	Name and contact information for the trial sponsor	Supplementary table 2 Ref 24

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	10 (Ethical and legal considerations) 17 (Funding)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13 (Data management and statistical analyses) 14 (Data monitoring)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14 (End of protocol) And N/4 (no dose modifications)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6 (two turns of validations of the PROADAPT booklet by candidate patients)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-13 (Sample size calculation)

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A (no problem for accrual)
Methods: Assignment of interventions (for controlled trials)			**N/A**
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	-
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	-
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Table 3
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13 (Data management and statistical analyses)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14 (Data management and statistical analyses)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14 (Data Monitoring)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11 (Secondary outcomes: NCI CTCAE, QOL)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10 (Ethical and legal considerations)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10 (Ethical and legal considerations) 14 (Protocol amendments)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10-11 (Ethical and legal considerations)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14 (Confidentiality)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17 (Competing interests)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17 (Availability of data and materials)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15 (Dissemination policy)
	31b	Authorship eligibility guidelines and any intended use of professional writers	15 (Dissemination policy), N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Annex 1 (in French)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Feasibility of a prehabilitation programme dedicated to older cancer patients before complex medical-surgical procedures: the PROADAPT pilot study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042960.R3
Article Type:	Protocol
Date Submitted by the Author:	20-Feb-2021
Complete List of Authors:	Roche, Mélanie; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL Ravot, Christine; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier Lyon Sud Malapert, Amélie; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL Paget-Bailly, Sophie; University Hospital Centre Besancon, Methodology and Quality of Life Unit in Oncology; Université Bourgogne Franche-Comté, INSERM, EFS BFC, UMR1098, Interactions Hôte-Greffon-Tumeur/Ingénierie Cellulaire Et Génique Garandeau, Charlène; Hospices Civils de Lyon, Direction à la Recherche Clinique et à l'Innovation Pitiot, Virginie; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL Tomatis, Mélanie; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier Lyon Sud Riche, Benjamin; Hospices Civils de Lyon, Service de Biostatistique - Bioinformatique, Pôle Santé Publique; Université de Lyon, Laboratoire de Biométrie et Biologie Évolutive CNRS UMR 5558, Équipe Biostatistiques Santé Galamand, Béatrice; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier Lyon Sud Granger, Marion; Hospices Civils de Lyon, Geriatrics unit; Centre Hospitalier de Chambery Barbavara, Claire; Hospices Civils de Lyon, Geriatrics unit Bourgeois, Chrystelle; Centre Hospitalier Annecy Genevois, Medical Oncology Genest, Evelyne; Hospices Civils de Lyon, Geriatrics unit Stefani, Laetitia; Centre Hospitalier Annecy Genevois, Medical oncology Haïne, Max; Hôpital Nord-Ouest, Pôle de gérontologie et Médecine de Réadaptation Castel-Kremer, Elisabeth; Hospices Civils de Lyon, Geriatrics unit. Hôpital Edouard Herriot. Morel-Soldner, Isabelle; Hospices Civils de Lyon, Geriatrics unit. Centre Hospitalier de la Croix Rousse Collange, Vincent; Medipole Lyon-Villeurbanne, Département anesthésie réanimation Le Saux, Olivia; Centre de Recherche en Cancerologie de Lyon, Therapeutic targeting of the tumor cell and its immune

	microenvironment Dayde, David; Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL Falandry, Claire; Hospices Civils de Lyon, Geriatrics unit, Centre Hospitalier Lyon Sud; University of Lyon, CarMeN Laboratory, Inserm U1060, INRA U1397, Université Claude Bernard Lyon 1, INSA Lyon, Charles Mérieux Medical School
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Geriatric medicine, Surgery
Keywords:	Adult oncology < ONCOLOGY, GERIATRIC MEDICINE, REHABILITATION MEDICINE, Adult surgery < SURGERY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Feasibility of a prehabilitation programme dedicated to older cancer patients before complex medical-surgical procedures: the PROADAPT pilot study protocol

Mélanie Roche (melanie.roche02@chu-lyon.fr)

Christine Ravot (christine.ravot@chu-lyon.fr)

Amélie Malapert (amelie.malapert@chu-lyon.fr)

Sophie Paget-Bailly (spaget@chu-besancon.fr)

Charlène Garandeau (charlene.garandeau@chu-lyon.fr)

Virginie Pitiot (virginie.pitiot@chu-lyon.fr)

Mélanie Tomatis (melanie.tomatis@chu-lyon.fr)

Benjamin Riche (benjamin.riche@chu-lyon.fr)

Béatrice Galamand (beatrice.galamand@chu-lyon.fr)

Marion Granger (mariongranger@outlook.fr)

Claire Barbavara (claire.barbavara@gmail.com)

Chrystelle Bourgeois (cbourgeois@ch-annecygenevois.fr)

Evelyne Genest (evelyne.genest@chu-lyon.fr)

Laetitia Stefani (lstefani@ch-annecygenevois.fr)

Max Haïne (mhaine@lhopitalnordouest.fr)

Elisabeth Castel Kremer (Elisabeth.castel-kremer@chu-lyon.fr)

Isabelle Morel-Soldner (isabelle.morel-soldner@chu-lyon.fr)

Vincent Collange (collangev@gmail.com)

Olivia Le Saux (Olivia.LESAUX@lyon.unicancer.fr)

David Dayde (david.dayde@chu-lyon.fr)

Claire Falandry (claire.falandry@chu-lyon.fr) (Corresponding author)

Corresponding email address: claire.falandry@chu-lyon.fr

on behalf of PROADAPT working group

Mélanie Roche, Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL, Pierre-Bénite, France

Christine Ravot, Hospices Civils de Lyon, Service de gériatrie, Centre Hospitalier Lyon Sud Pierre-Bénite, France

Amélie Malapert, Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL, Pierre-Bénite, France

Sophie Paget-Bailly, University Hospital Centre Besancon, Unité de Méthodologie et de Qualité de Vie en Cancérologie, Université Bourgogne Franche-Comté, INSERM, EFS BFC, UMR1098, Interactions Hôte-Greffon-Tumeur/Ingénierie Cellulaire Et Génique, Besançon, France

Charlène Garandeau, Hospices Civils de Lyon, Direction de la Recherche Clinique et de l'Innovation, Lyon, France

Virginie Pitiot, Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL, Pierre-Bénite, France

Mélanie Tomatis, Hospices Civils de Lyon, Service de Gériatrie. Centre Hospitalier Lyon Sud, Pierre-Bénite, France

Benjamin Riche, Hospices Civils de Lyon, Service de Biostatistique -Bioinformatique, Pôle Santé Publique; Université de Lyon, Laboratoire de Biométrie et Biologie Évolutive CNRS UMR 5558, Équipe Biostatistiques Santé, Lyon, France

Béatrice Galamand, Hospices Civils de Lyon, Service de Gériatrie. Centre Hospitalier Lyon Sud, Pierre-Bénite, France

Marion Granger, Hospices Civils de Lyon, Service de Gériatrie; Centre Hospitalier de Chambery, Chambéry, France, Pierre-Bénite, France

Claire Barbavara, Hospices Civils de Lyon, Service de Gériatrie, Centre Hospitalier Lyon Sud, Pierre-Bénite, France

Chrystelle Bourgeois, Centre Hospitalier Annecy Genevois, Service d'Oncologie médicale, Pringy, France

Evelyne Genest, Hospices Civils de Lyon, Service de Gériatrie, Centre Hospitalier Lyon Sud, Pierre-Bénite, France

Laetitia Stefani, Centre Hospitalier Annecy Genevois, Service d'oncologie médicale, Pringy, France

Max Haïne, Hôpital Nord-Ouest, Pôle de gérontologie et Médecine de Réadaptation, Gleizé, France

Elisabeth Castel-Kremer, Hospices Civils de Lyon, Service de Gériatrie. Hôpital Edouard Herriot, Lyon, France

Isabelle Morel-Soldner,; Hospices Civils de Lyon, Service de Gériatrie, Centre Hospitalier de la Croix Rousse

Vincent Collange, Medipole Lyon-Villeurbanne, Département anesthésie réanimation, Villeurbanne, France

Olivia Le Saux, Centre de Recherche en Cancérologie de Lyon, Ciblage de la tumeur et de son environnement immunitaire, Lyon, France

David Dayde, Hospices Civils de Lyon, Plateforme Transversale de Recherche de l'ICHCL, Pierre-Bénite, France

Claire Falandry, Hospices Civils de Lyon, Service de Gériatrie, Centre Hospitalier Lyon Sud, Pierre-Bénite, France and Université de Lyon, CarMeN Laboratory, Inserm U1060, INRA

U1397, Université Claude Bernard Lyon 1, INSA Lyon, Faculté de Médecine et de Maïeutique Charles Mérieux, Pierre-Bénite, France

Abstract

Background: Aging is associated with an increased prevalence of co-morbidities and sarcopenia as well as a decline of functional reserve of multiple organ systems, which may lead, in the context of the disease- and/or treatment-related stress, to functional deconditioning. The multicomponent "PROADAPT" intervention was developed multi-professionally to implement prehabilitation in older cancer patients.

Methods: The PROADAPT pilot study is an interventional, non-comparative, prospective, multicentre study. It will include 122 patients oriented to complex medical-surgical curative procedures (major surgery or radiation therapy with or without chemotherapy). After informed consent, patients will undergo a comprehensive geriatric assessment and will be offered a prehabilitation kit that includes an advice booklet with personalised objectives and respiratory rehabilitation devices. Patients will then be called weekly and monitored for physical and respiratory rehabilitation, pre-operative re-nutrition, motivational counselling, and iatrogenic prevention. Six outpatient visits will be planned: at inclusion, a few days before the procedure, and at 1, 3, 6 and 12 months after the end of the procedure. The main outcome of the study is the feasibility of the intervention, defined as the ability to perform at least one of the components of the programme. Clinical data collected will include patient- and cancer-specific characteristics.

Ethics and dissemination: The study protocol was approved by the Ile de France 8 ethics committee on 5 June 2018. The results of the primary and secondary objectives will be published in peer-reviewed journals. ClinicalTrials registration: NCT03659123.

Keywords: oncogeriatrics; prehabilitation; motivation; sarcopenia; older cancer patients; care pathway.

Article summary

Strengths and limitations of this study

- The PROADAPT programme is a prehabilitation programme specifically tailored for older cancer patients
- The programme was designed according to a multidisciplinary analysis of available evidence and according to a multistep validation process involving patients
- The PROADAPT pilot study is a prospective and multicentre trial designed to evaluate the feasibility of the intervention
- Different secondary outcomes, including quality of life, will be evaluated to better adapt the programme to patient specificities

A specific attention will be paid to programme safety and patient compliance to the programme.

Introduction

Many oncological situations involve complex medical-surgical procedures that increase the risk of patient deconditioning in older and/or sarcopenic patients (1). This may lead to a disabling cascade, a "domino effect", defined as the succession of adverse events in response to a primary stress (2). This is illustrated by increased morbidity and mortality (3), but also a higher risk of unplanned hospitalisations for geriatric events, defined as immobilisation syndrome, acute confusion, undernutrition, falls, *de novo* urinary incontinence, and adverse drug events (4). These generate frustration, appeals by patients and their families, additional hospital costs (5), and more importantly, a reduced duration of life without disability (6). One of the responses to this situation is enhanced rehabilitation after surgery (7).

In order to reduce complications after surgery, pre-operative rehabilitation (or prehabilitation) has often been considered for the general population (8). The majority of the programmes include nutrition, physical activity, motivational coaching, and, for some tobacco cessation (8); the level of evidence is high for pre-operative nutrition (9), but it is low for physical exercise, due to heterogeneous programmes with often poor compliance (10), and is deemed insufficient considering psychological preparation (11). Some programmes adapted interventions on nutrition, physical activity, and motivational coaching to geriatric patients but conclusions as to the effectiveness of these are difficult to draw (12). It is also of note that Carli et al. did not report any significant difference in the efficacy of prehabilitation versus post-operative rehabilitation only in 110 frail patients aged 65 years or above operated on for colon cancer (13), questioning the ability of standard prehabilitation to improve outcomes for frail older patients.

It would, therefore, potentially be of interest to widen the spectrum of interventions included in prehabilitation of older patients. To date, the other interventions known to prevent hospital-related geriatric deconditioning include comprehensive geriatric assessment (14,15), iatrogenic

prevention (drug and care system-related) (16,17), and hospital-to-home transition to limit the risk of early readmission of patients (18). In addition, some degree of individualization is also needed since cancer in the older patient is often associated with comorbidities, particularly cardiovascular disease (19,20), and the older population also has a higher risk of loss of autonomy and cognitive impairment, which can be increased with surgery (21–23).

In this context, and after a systematic analysis of published data, we developed the Prehabilitation & Rehabilitation in Oncogeriatrics: Adaptation to Deconditioning risk and Accompaniment of Patients' Trajectories (PROADAPT), a geriatric multi-professional intervention programme. Such a multi-domain intervention should be evaluated according the methodology of complex interventions evaluation (24). Hence, we designed the PROADAPT pilot study to evaluate the feasibility of such a complex intervention. This manuscript describes both PROADAPT multi-domain intervention and PROADAPT pilot study.

Methods and analysis

Objectives

Primary objective

The primary objective of the PROADAPT pilot study is to assess the feasibility of the programme, defined as the achievement of at least one item of the programme during patient follow-up.

Secondary objectives

The secondary objectives of the study are:

1) To assess the achievement of each item of the programme independently of each other (rate of achievement of all or part of the instructions);

2) To assess patient satisfaction with the programme (Supplementary file 1);
3) To estimate the rate of compliance to items during the various visits;
4) To evaluate the functional status and quality of life (QoL) over one year following surgery (health-related QoL, other dimensions)
5) To assess post-treatment complications, their rates, and their severity at 30 and 90 days according to the Clavien-Dindo and National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4 classification systems (25);
6) To estimate the post-operative mortality at 30 and 90 days;
7) To estimate the costs of treatments (health system);
8) To study the therapeutic strategies (treatment completion rate);
9) To estimate the progression-free survival (PFS) rate at one year;
10) To estimate the overall survival (OS) at one year;
11) To estimate the tolerance of treatments;
12) To assess the change in geriatric covariates over one year.

Study design

PROADAPT - pilot study is a prospective, non-comparative multicentre conducted in seven centres of the Auvergne-Rhône-Alpes region of France.

Study sites and participants

The study population will include older patients identified during multidisciplinary consultation meetings and oriented to complex medical-surgical curative procedures in the study centres (Lyon Sud hospital, Croix Rousse hospital and Edouard Herriot hospital from the Hospices Civils de Lyon, Nord-Ouest Villefranche-sur-Saône hospital, Annecy-Genevois hospital, Chambery hospital, Lyon-Villeurbanne Médipôle).

Inclusion criteria are: age ≥70 years, or ≥60 years with significant comorbidity (Cumulative Illness Rating Scale for Geriatrics (CIRS-G) ≥ 3 (26)) or disability (Activities of Daily Living (ADL) score < 6/6 (27)), histologically or cytologically proven cancer, life expectancy > 3 months, planned complex medical-surgical procedure with curative intent. Complex medical-surgical procedures are defined as major abdominal surgery (breast excluded), either minimally invasive or open.

Exclusion criteria are: other malignancy within the previous 5 years (except for adequately treated carcinoma *in situ* of the cervix or squamous carcinoma of the skin, or adequately controlled limited basal cell skin cancer), unable to be regularly followed for any reason (geographic, familial, social, psychological), or with any mental or physical handicap at risk of interfering with the appropriate treatment.

A screening of older patients will be systematically performed during multidisciplinary meetings and described in the CONSORT flow diagram of the article reporting the study.

Intervention

The PROADAPT intervention programme was developed on a multi-dimensional and multidisciplinary basis. From January 2016 to April 2018, nine regional meetings were organised, gathering 40 representatives of the following medical and paramedical specialties: geriatricians, nutritionists, surgeons (subspecialties: gynaecology, digestive surgery, urology), oncologists, anaesthesiologists, nurses, physiotherapists, occupational therapists, adapted physical activity monitors. A systematic review of published data was conducted in the following axes, to provide a graded state-of-the-art: nutrition, physical activity, patient education, medication rationalisation, cardiovascular optimisation, transition, and standardisation of surgical procedures. Based on the qualitative grading of existing data, a

modified Delphi method was used to co-validate the content of the standardised intervention checklist, and the feasibility of the implementation of each point of this checklist (Table 1).

A PROADAPT booklet was developed; it is a standardised, adapted, and evolutive tool designed to explain physical exercise and nutrition counselling, and to ensure the collection of patients' day-to-day achievements. The first version was tested by candidate patients before the validation of the current (version 3) of the booklet.

PROADAPT standardised geriatric intervention programme includes:

- Pre-operative physical activity, including strength and endurance exercise ± group activities over 4 ±2 weeks. Interventions with a high level of evidence were retained, according to an ongoing umbrella review of systematic reviews (http://www.crd.york.ac.uk/PROSPERO Ref CRD42020100110; (28,29));
- Nutrition: nutrition before and after physical activity, pre-postoperative immuno-nutrition ± artificial nutrition (*i.e.* enteral or parenteral nutrition) according international guidelines (9);
- Patient (and caregiver) education and coaching (on nutrition and physical exercise) according to a weekly schedule with the activation of integrated supports (30);
- Standardised intervention procedures, according to a checklist established in consensus with surgeons;
- Enhanced rehabilitation will be promoted according to international guidelines (31);
- Pharmaceutical medication conciliation and treatment optimisation, according to a centralised process with pharmaceutical expertise;
- Bridging interventions for hospital-to-home transition, according to a proposed standardised procedure including training of dedicated nurses, and post-discharge phone calls follow-up over the 12 weeks after surgery. In practice, only 2 or 3 people from the coordination

centre team are in charge of coaching for all patients. In the future, a nurse coach will be trained in each centre and will be responsible for patient coaching. Interventions with a high level of evidence were retained, according to an ongoing umbrella review of systematic reviews (http://www.crd.york.ac.uk/PROSPERO Ref CRD42017055698).

The intervention is designed to be implemented at different moments of patient care (Table 1).

During the prehabilitation period:

- A dedicated nurse, trained in patient education by the coordinating centre team ("coaching nurse") presents him/herself to the patient for:
  - Presentation of the programme to the patient and his/her caregiver(s)
  - Personalisation of the PROADAPT booklet (see below) to the patient's characteristics
  - Collection of personal data, nutritional, and functional habits
  - Geriatric assessment using standardised scores (cognition using the Mini-COG screening tool (32), depression using the geriatric depression scale in 4 and 15 items [GDS4/GDS15] (33), nutrition using the mini-nutritional assessment [MNA] (34))
  - Collection of the information to be sent to the pharmacist: comorbidities, comedications
  - Anticipation and organisation of the future appointments (anaesthetists, stomatherapist, …)
  - A weekly visit or phone call according to a structured interview for health education and transmission of nutritional and functional advice (see below)
- Nutritional care is based on:

- A personalised evaluation of nutritional balance and nutritional needs of the patient according to dietician diagnosis based on measured intake and international recommendations
- A weekly follow-up of weight and nutritional intake. If the coaching nurse identifies an unfavourable nutritional trend, s/he reports it to the referring physician and nutritionist
- Artificial nutrition if needed according European Society for Clinical Nutrition and Metabolism (ESPEN) recommendations (9,35,36)
- Pre-operative immunonutrition during 7 days before surgery (36)

• Total-body rehabilitation:

- 2 to 3 times a week: strength exercise (each time with dedicated exercises for upper and lower limbs, as well as abdominal muscles; 20 to 45 minutes each sequence)
- 2 to 3 times a week: endurance exercise (walking or cycle ergometer), 20 to 45 minutes each sequence
- 3 times a day: respiratory physiotherapy
- Once a week (if possible): group activities (according to the centre organisation and home-hospital distance)

• Pharmaceutical conciliation and optimisation according to Screening Tool of Older Persons' Prescriptions and Screening Tool to Alert to Right Treatment (STOPP/START) criteria version 2 (37) and international recommendations concerning peri-operative care (7): to be transmitted to the surgical and anaesthesia team without any obligation to change patient care.

During peri-operative period

• The coaching nurse contacts the surgical team for transmission of:

- patient's personal data
- physical (nutritional, functional, and/or comorbidities) as well as psychological difficulties
- results of medication conciliation

During rehabilitation period

- The coaching nurse contacts the rehabilitation team for transmission of:
  - patient's personal data and care course
  - physical (nutritional, functional, and/or comorbidities) as well as psychological difficulties
  - results of medication conciliation
- The rehabilitation programme is left to the discretion of the rehabilitation team (standard care and local habits).
- A weekly phone call from the coaching nurse to the rehabilitation team for nutritional and functional follow-up, as well as medication conciliation

During hospital-home transition period

- The coaching nurse contacts the patient's general practitioner for transmission of:
  - patient's personal data and care course
  - physical (nutritional, functional, and/or comorbidities) as well as psychological difficulties
  - results of medication conciliation
- Bi-weekly phone call of the coaching nurse to the patient for nutritional and functional follow-up
- Advice for optimisation of symptom management: abdominal pain, nausea, vomiting…

Participant timeline

Six successive evaluations are planned for the participants.

The inclusion visit is planned during a geriatric consultation planned at least 7 days before the start day of the complex medical-surgical procedure. If the complex medical-surgical procedure is delayed for any reason or the patient receives a neo-adjuvant treatment, the prehabilitation period may be prolonged up to 9 months. In such cases, the frequency of the phone calls is decreased (from 1/week to 1/month) after 4 weeks. During the inclusion visit, lasting about 1 hour, the following data are collected:

- Clinical (blood pressure, heart rate, Eastern Cooperative Oncology Group (ECOG) score (38), comorbidities), laboratory (albumin, prealbumin, C-reactive protein), and paraclinic (year of birth, sex, weight, height, body mass index, change in weight over the last 3 and 6 months)
- All concomitant treatments and drug conciliation
- The history of the disease (primitive site, metastases, histology of the initial tumour, presence of tumour markers)
- Radiological disease assessments (date and nature)
- Results of a standardised geriatric assessment using validated questionnaires with a particular attention on physical activity and nutrition (ADL(27)/instrumental ADL (IADL) (39), G8 (40), Rapid Assessment of Physical Activity (RAPA) (41), daily physical instrumental activities (AIPVQ) (42), European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (43) and Elderly specific questionnaire in 14 items, (QLQ-ELD14) (44), the EUROQOL EQ-5D-3L evaluating five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression in three levels (45), fatigue short form inventory (SF-36) (46), Short

physical performance battery (SPPB) (47), Timed up and go (TUG) test (48), 9-item Fatigue Severity Scale (FSS) (49), MNA (34), GDS4/GDS15 (33), Mini-COG (32), Tinetti test (50), Borg scale (51), Pain scale (52), Nutrition scale (53)) (**Error! Reference source not found.**Tables 2 and 3).

- Delivery of the "PROADAPT kit" during a meeting with a dedicated paramedic (nurse, physiotherapist, ergotherapist…) to:
    - Provide to the patient Voldyne® (Hudson RCI, Temecula, CA, USA) and Triflo II® (Tyco Healthcare, Mansfield, MA, USA) incentive spirometry devices for inspiratory muscle training
    - Present the PROADAPT booklet that includes a battery of exercises and nutritional counselling specifically designed for this older population:
        - muscle strengthening of the upper limbs (6 exercises, 3 difficulty levels), lower limbs (6 exercises, 3 difficulty levels), abdominal wall (4 exercises, 3 difficulty levels); objective: 2 to 3 sessions per day for a total duration of between 20 and 45 minutes
        - endurance/aerobic activities (7 exercises, 3 difficulty levels with 3 duration objectives); objective: every day
        - inspiratory muscle training with Voldyne® and Triflo II® devices; objective: 3 sessions per day for a total duration of 30 minutes
        - general nutritional counselling adapted to the older population: food enrichment, inter-meal collations, oral nutritional supplements.
    - Fulfil a 3-day food statement that allows, in the 7 days after inclusion, to deliver a dietician-driven personalised nutritional counselling. If needed, in case of unfavourable nutritional parameters, artificial nutrition is introduced.
- Prescription, if needed:

    - of home physiotherapy according to the PROADAPT programme for respiratory training sessions and physical activity training sessions
    - of oral nutritional supplements
    - of usual medicines, adapted following pharmaceutical review
- For patients requiring inpatient follow-up, hospital admission for a few days in a rehabilitation unit for a physiotherapeutic programme and/or artificial nutrition (enteral preferred).

During the pre-intervention period, phone calls by a dedicated paramedic are planned (once a week for the first 4 weeks and then once a month until the intervention). Calls are semi-directed interviews focused on the patient's autonomy, physical activity, appetite, and sleep over the last period (week/month). A special attention is paid to encouraging patient motivation and compliance to the programme.

The pre-therapeutic visit is scheduled when possible within the 5 days before the day of the intervention. This visit is performed in the surgery or radiotherapy unit only if the visit is necessary before the intervention and does not modify standard therapeutic care; it collects:

- Clinical, laboratory, and paraclinic data
- All concomitant treatments and drug conciliation
- Data concerning pain, nutrition, fitness, and physical tests (Table 2 and 3)

During the post-intervention period, paramedics trained in clinical research will resume follow-up phone calls as before the intervention once a week for 12 weeks after day 0 (D0), and once a month up to 12 months after D0. D0 is defined as the last day of surgery (day of the last resumption of surgery in the limit of 30 days after the first intervention) or the last day of radiotherapy. For weekly calls, a margin of ± 2 days is allowed, and for monthly calls a margin of ± 7 days is allowed.

Visits at 1, 3, and 6 months after the intervention (± 7 days): The patient may have started an antineoplastic treatment according to standard of care. The visit could be with the surgeon, the radiotherapist, or the oncologist according local habits. The data to be collected are:

- Clinical (blood pressure, heart rate, ECOG scale (38)), laboratory (albumin, prealbumin, C-reactive protein), and patient characteristics (weight, body mass index)
- All concomitant treatments and drug conciliation
- Patient care (surgery and complications, treatment for the cancer)
- Radiological disease assessments (date and nature)
- Quality of life, pain, nutrition, fitness, physical performance through questionnaires and tests regarding (Table 2 and 3)
- Hospital costs related to complications

The end of study visit is planned at 12 months (per-protocol) or at the date of trial premature discontinuation (± 7 days) for the collection of the data listed above. In addition, and in case of omission of one or more of the intermediate visits, data relating to complications occurring during the post-therapeutic period are collected.

Outcomes and measurements

Primary outcome

The main outcome measure will be the proportion of patients who have completed at least one item in the PROADAPT programme after 12 months after D0. The workshops of the programme are:

- Physical and respiratory rehabilitation
- Re-nutrition session
- Telephone nurse follow-up

Secondary outcomes

The secondary outcomes of the study are:

- The feasibility of each stage of the programme independently of each other (rate of achievement of all or part of the instructions)
    - Pre-operative physical rehabilitation including (Figure 1):
        - Muscle strengthening
        - Respiratory rehabilitation
        - Endurance work
    - Pre-operative nutrition counselling (Figure 1)
    - Drug reconciliation / iatrogenic prevention
    - Pre-therapeutic follow-up calls
    - Post-surgery or post-radiotherapy follow-up calls

- Patient satisfaction with the overall programme at the end of the study (end of follow-up or study discontinuation) estimated using a questionnaire (Supplementary file 1).
- To assess the change over time before surgery of: physical parameters and exercises, inspiratory parameters and exercises (Voldyne®, Triflo®), as well as weight and food intake (qualitative and quantitative assessments).
- To assess the change over 1 year of:
    - physical performance (SPPB, gate speed, TUG test) and functional independence on ADL (27), IADL (39), AIPVQ (42)
    - nutritional parameters of the patient (weight, albuminemia, appetite)
    - health-related QoL for patients based on QLQ-C30 and ELD14 (5 dimensions: mobility, disease burden, emotional and physical functioning, tiredness) (54,55)
    - pharmaceutical conciliation

- Estimate the rate and nature of post-operative complications at 30 days (NCI-CTCAE)
- Estimate the rate and nature of post-operative complications according to the CCI at 30 and 90 days
- Estimate post-operative mortality at 30 and 90 days
- Estimate the one-year overall survival (OS) rate
- Estimate the one-year progression-free survival (PFS) rate
- Estimate the longitudinal change of QoL according to QLQ C30, ELD14, and EQ-5D
- Estimate treatment costs (health system)
- Study therapeutic strategies (treatment completion rate)
- Estimate the change of geriatric covariates over 1 year.

Sample size calculation

The programme will be considered feasible, at the patient level, if all or part of the programme is implemented in at least 50% of the included patients (= alternative hypothesis). This threshold was defined in line with previous studies on prehabilitation for older cancer patients, that reported compliance rates between 16 and 95% (56,57). Considering that the PROADAPT programme is complex even if tailored to older patients, we anticipate modest compliance rates. To reject the null hypothesis of programme feasibility in less than 35% of patients, with an alpha risk of 5% and a power of 90% (beta=10%, bilateral test), the number of subjects required is 111; accounting for 10% non-treatable patients, a total of 122 patients should be included. The included patients will be analysed according to the intention-to-treat principle.

Data management and statistical analyses

Data are monitored by a clinical research assistant (CRA). Inconsistencies will be reported to the study investigators in order to decide whether the data should be corrected or considered as missing. Any changes in the data will be reported.

Data analyses will be performed by the data management and analysis centre. The analyses will be carried out by an independent statistician with the latest version of the R software environment (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). All of the characteristics collected will be subjected to a descriptive analysis.

Descriptive analyses

A flow diagram will describe the data available for the patient population at baseline, and during each follow-up visit. Eligibility criteria for treated patients will be verified, as well as follow-up and end of study visits. Reasons for premature end of study will be provided.

Characteristics of the study population, numbers and proportions of missing values will be reported. Patient characteristics will be described using mean and standard deviation or median and interquartile range for quantitative variables, and frequencies and distribution for categorical variables. A comparison of baseline characteristics between patients with complete follow-up and those with attrition will be performed. If needed, methods for handling missing data (multiple imputation, mixed model, or auxiliary variable) will be used when appropriate.

Primary analysis

The proportion of patients who have completed at least one PROADAPT programme activity 12 months after the start of treatment will be estimated using mean and standard deviation.

Secondary analyses

Time-to-event variables: follow-up, overall survival, progression-free survival

The probabilities of events at specific measurement times will be estimated according to the Kaplan-Meier method. Medians of event-free survival will be reported by treatment arm with its 95 % confidence interval [95% CI], if the number of events allows estimation of the median. OS and PFS probabilities at 12 months (after the day of the last revision of surgery or the last day of radiotherapy) will be provided with 95% CI.

Quality of life

Analyses of the QoL data will be performed according to the modified intention-to-treat (mITT) principle: all included patients, regardless of compliance with the eligibility criteria and whether or not they were followed-up, and for whom the QoL scores are available at inclusion will be included in the analysis. Patient QoL, linked to health, will be analysed after 3 months through 5 dimensions: mobility, disease burden, emotional and physical functioning, and fatigue.

Data monitoring

The successful completion of the database is ensured by the hospital CRA. The hospital CRA also ensures compliance with the study protocol. The sponsor CRA verifies that the rights of the participants are respected.

End of study

Patients leave the study either on a per-protocol basis during the "end of study visit" on month 12 after the intervention or at any time during the conduct of the study if they no longer wish to participate. However, as indicated in the information letter to the patients/caregivers, the data collected before exclusion may be used as part of the study.

Confidentiality

Correspondence tables will be kept in a separate file that does not contain clinical data. The access to the nominative information is protected by a password and confidentiality is guaranteed by the study.

Protocol amendments

Any important modification requiring a new ethics committee approval will be communicated in future publications. Any potential impact of protocol modifications on the results will be discussed as appropriate.

Trial status

Patient enrolment began on 3 July 2018. Data are currently being collected.

Patient and public involvement

Patients were involved at different steps of the trial: during the development of the PROADAPT booklet, several (n=30) patients were asked to answer an anonymous questionnaire in order to improve its ergonomics; the information letter and consent form for the study were reviewed by the patients committee of the *Ligue Nationale de Lutte contre le Cancer* (a French association of cancer patients).

Discussion

Discussion of the intervention

Prehabilitation has long been conceptualised as an effective means of improving the functional capacity of the individual to enable them to resist various stressors. Originally developed in the military as the association of physical training to improve strength and endurance, improvement

of nutritional intake, and general education (58), it has been transposed into medicine and major surgery – initially when an ICU admission is planned – at the beginning of the century (59).

Despite a growing interest in the medical community for prehabilitation, and particularly cancer prehabilitation, the level of evidence for specific interventions remains too low for it to be implemented in everyday practice. Among the main limitations include the heterogeneity of programmes, sometimes poor patient compliance, and the fact that most studies were small pilot studies developed for patients fitter and younger than those who are likely to benefit the most from prehabilitation. Another point to emphasise is that most programmes include only one intervention – physical, nutritional, or psychological rehabilitation – while multimodal interventions are often considered to be more effective in older populations.

Considering these points, the PROADAPT intervention was developed according to an innovative management strategy since it started in 2016 by multi-professional meetings conceived as brainstorming sessions in order to develop a multidisciplinary programme dedicated to prehabilitation and follow-up of older patients. The multidisciplinary conception of the intervention, the particular attention paid to older patients' specificities and the previous experience of the participants in various fields, including patient education, cognition, and physiotherapy, are hopefully the warrants of the most tailored approach to the target population. For example, a large font was used in the booklet and the illustrations highly schematic and highly contrasted, and, furthermore, each sentence was verified by a panel of patients in order to ensure correct understanding. This resulted in high rate of satisfaction regarding the booklet that was evaluated by 30 patients (unpublished data).

This pilot study is the first step towards an ambitious programme, since the PROADAPT programme will be evaluated in the future in two randomized studies, PROADAPT-ovary/EWOC-2 (NCT04284969) and PROADAPT sus-mesocolic, designed to evaluate the impact of the PROADAPT programme on post-treatment complications versus usual practice.

In order to favour patient compliance and follow-up, an eHealth tool, ID-PROADAPT®, has been developed that will help supervise the course of patients' care.

Discussion of the study design

In line with the previous points, this pilot study was designed to answer the critical question: is a multidomain prehabilitation programme feasible in an older cancer population? This question encompasses several points: Is the programme physically adapted to an older population? Is such a program applicable in ambulatory care? How to build pedagogical tools adapted for such ambulatory use? Are such pedagogical tools understandable? What is the compliance of the patients to each domain of the intervention programme?... Another point is to understand is whether the patient's care team accepts such intervention; however, this point was previously evaluated by Ghignone *et al*. who demonstrated through an international survey that surgeons are generally in favour for such programmes since 71% of them would accept to prehabilitate their elderly patients four weeks before surgery, if such intervention is proven to be effective (60). Nevertheless, the participation of surgeons and anaesthetists during initial brainstorming sessions was of major interest since they greatly enriched the structure of the programme.

Thus, the construct of this trial may appear as highly complex with overabundant secondary endpoints, but this design encompasses as much as possible the complexity of preventive care in an older population, which has to mix adaptation to the target population and the ability to maintain compliance over time.

Ethics and dissemination

The study sponsor is the Hospices Civils de Lyon, responsible for study insurance and pharmacovigilance. The study protocol (V2) was approved by the Ile de France 8 ethics committee on 5 June 2018 and cover all sites involved in this study. The amended versions were as follows: V3 dated 23 October 2018 (change in the recruitment period, addition of new

investigation centres), V4 dated 17 May 2019 (request for an additional 12 months extension, update with the General Data Protection Regulations (GPDR) and update of the patient booklet), V5 dated 17 July 2020 (addition of a cohort of 30 patients to test the follow-up programme with the ID-PROADAPT® eHealth tool, Supplementary file 2, request for an additional 8 months extension). The current version is the V5 dated 17 July 2020, authorised on 10 September 2020. The research will be carried out in accordance with the Helsinki Declaration and ICH GCP (International Conference on Harmonisation-Good Clinical Practice) Guidelines. The trial protocol fulfils the SPIRIT 2013 checklist (Supplementary table 1) and World Health Organization trial registration data set (Supplementary table 2). The study complies with the principles of the data protection act in France and with the GPRD in force in Europe. Each investigator must collect a written informed consent at the beginning of the procedure. This consent is retained in the patient's medical chart. The patient can stop participation in the study at any time with an oral instruction given to the investigator or CRA. Patients will be informed of additional amendments according to the law in force.

The results of the primary and secondary objectives will be published in peer-reviewed journals. All authors of future publications will have to meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors.

Total words count: 4771

Abbreviations

ADL: Activities of Daily Living; AIPVQ: Physical Instrumental activities of daily living (in French: Activités Instrumentales Physiques de la Vie Quotidienne); CRA: Clinical Research Assistant; EORTC: European organisation for research and treatment of cancer; ESPEN:

European Society for Clinical Nutrition and Metabolism; FSS: Fatigue Severity Scale; GDS: Geriatric Depression Scale; IADL: Instrumental Activities of Daily Living; ICU: Intensive Care Unit; mITT: Modified Intention To Treat; MNA: Mini Nutritional Assessment; QLQ-C30: quality of life questionnaire core 30 of the EORTC; QLQ-ELD14: Older patients- specific quality of life questionnaire in 14 items of the EORTC; RAPA: Rapid Assessment of Physical Activity; SF-36: short form 36 health survey questionnaire; SPPB: Short Physical Performance Battery

Declarations

Acknowledgements

This pilot protocol is part of the PROADAPT working group initiative for improving care for older people with cancer.

PROADAPT working group

Coordinator: C. Falandry; physicians: G. Albrand, D. Barnoud, D. Benayoun. B Billod, J. Bonhomme, A.-L. Bres, C. Brunengo, E. Castel-Kremer, A. Chanelière, Y. Chauleur, V. Collange, G. Copaescu, H. Curé, A.-M. Dascalita, B. De La Vigerie, S. Ducoulombier, O. Ganne, F. Gervais, T. Gilbert, M. Giroud, R. Guyot, H. Habchi, M. Haïne, N. Jomard, O. Le Saux, C. Lecardonnel, B. Leroy, J.-A. Long, A. Marion, I. Morel-Soldner, E. Nony, S. Parent, A. Pelisset-Vanhersecke, A. Pirollet, L. Stefani, J.-E. Terrier, J. Trautmann, M.-A. Vincent ; pharmacists: D. Charlety; statisticians: S. Paget-Bailly, B. Riche; paramedics: C. Barbarava, C. Bourgeois, M. Granger, A. Laurent, M. Tomatis; clinical research teams: D. Dayde, C. El Khoury, B. Galamand, E. Genest, C. Garandeau, E. Gadéa-Deschamps, S. Goutte, A. Malapert, V. Pitiot, M. Roche.

The authors also acknowledge the teams of Lyon Sud Hospital, Edouard Herriot Hospital of Lyon, Croix Rousse Hospital of Lyon, Annecy Genevois Hospital Center, Hôpital Nord Ouest hospital center, Chambéry Hospital Center and Médipôle Lyon-Villeurbanne who contribute to patient enrolment in this study. They also thank Philip Robinson (DRCI, Hospices Civils de Lyon) for help in manuscript preparation.

The authors would like to thank the patients' review committee of the Ligue Nationale de Lutte contre le Cancer for the valuable editing of the information note and the consent form.

Funding

This work was supported by the Agence Régionale de Santé (ARS) Auvergne Rhône Alpes, through the call for projects "Innovate in health for the Auvergne Rhône Alpes region" jointly organized by the ARS, Bpifrance, the Auvergne Rhône Alpes region, URIOPASS, ORAIDA and Cluster I-care and the decision of the selection committee on June 27, 2016 (Grant N°2016-149 (63)). It provided funding for nurses, dieticians, physiotherapists, and clinical research assistants.

Availability of data and materials

The final dataset of the PROADAPT pilot study will be available on reasonable request after publication of the primary objective. Data requests can be submitted to the corresponding author.

Competing interest

The authors declare that they have no competing interests.

Consent for publication

Not applicable

Author contributions

All authors participated to the PROADAPT intervention conception. Study protocol was conceived by DD, CF, CG, SPB, OLS, AM, VP and CR. DD and CF assumed fundraising and grant follow-up. MR led the drafting of the manuscript. All authors (MR, CR, AM, SPB, CG, VP, MT, BR, BG, MG, CBa, CBo, EG, LS, MH, ECK, IMS, VC, OLS, DD and CF) critically reviewed and approved the final version of the protocol.

References

1. Wagner D. Role of frailty and sarcopenia in predicting outcomes among patients undergoing gastrointestinal surgery. World J Gastrointest Surg. 2016;8(1):27.

2. Heppenstall CP, Wilkinson TJ, Hanger HC, Keeling S. Frailty: dominos or deliberation? N Z Med J. 2009 Jul 24;122(1299):42–53.

3. Lopez-Lopez V, Gómez-Ruiz AJ, Eshmuminov D, Cascales-Campos PA, Alconchel F, Arevalo-Perez J, et al. Surgical oncology in patients aged 80 years and older is associated with increased postoperative morbidity and mortality: A systematic review and meta-analysis of literature over 25 years. Surg Oncol. 2020 Jun;33:81–95.

4. Tan H-J, Saliba D, Kwan L, Moore AA, Litwin MS. Burden of Geriatric Events Among Older Adults Undergoing Major Cancer Surgery. J Clin Oncol. 2016 Oct 4;34(11):1231–8.

5. Akushevich I, Kravchenko J, Akushevich L, Ukraintseva S, Arbeev K, Yashin AI, et al. Medical Cost Trajectories and Onsets of Cancer and NonCancer Diseases in US Elderly Population, Medical Cost Trajectories and Onsets of Cancer and NonCancer Diseases in US Elderly Population. Comput Math Methods Med Comput Math Methods Med. 2011 Jun 1;2011, 2011:e857892.

6. De Roo AC, Li Y, Abrahamse PH, Regenbogen SE, Suwanabol PA. Long-term Functional Decline After High-Risk Elective Colorectal Surgery in Older Adults. Dis Colon Rectum. 2020 Jan;63(1):75–83.

7. Mohanty S, Rosenthal RA, Russell MM, Neuman MD, Ko CY, Esnaola NF. Optimal Perioperative Management of the Geriatric Patient: A Best Practices Guideline from the American College of Surgeons NSQIP and the American Geriatrics Society. J Am Coll Surg. 2016 May 1;222(5):930–47.

8. Treanor C, Kyaw T, Donnelly M. An international review and meta-analysis of prehabilitation compared to usual care for cancer patients. J Cancer Surviv Res Pract. 2018 Feb;12(1):64–73.

9. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr [Internet]. 2016 Aug 6 [cited 2016 Nov 20];0(0). Available from: http://www.clinicalnutritionjournal.com/article/S0261-5614(16)30181-9/abstract

10. Singh F, Newton RU, Galvão DA, Spry N, Baker MK. A systematic review of pre-surgical exercise intervention studies with cancer patients. Surg Oncol. 2013 Jun 1;22(2):92–104.

11. Powell R, Scott NW, Manyande A, Bruce J, Vögele C, Byrne-Davis LM, et al. Psychological preparation and postoperative outcomes for adults undergoing surgery under general anaesthesia. Cochrane Anaesthesia, Critical and Emergency Care Group, editor. Cochrane Database Syst Rev [Internet]. 2016 May 26 [cited 2021 Feb 8]; Available from: http://doi.wiley.com/10.1002/14651858.CD008646.pub2

12. Santa Mina D, Alibhai SMH. Prehabilitation in geriatric oncology. J Geriatr Oncol. 2020 May 1;11(4):731–4.

13. Carli F, Bousquet-Dion G, Fiore JF. Prehabilitation vs Postoperative Rehabilitation for Frail Patients. JAMA Surg. 2020 Sep 1;155(9):899–900.

14. Ellis G, Whitehead MA, O'Neill D, Langhorne P, Robinson D. Comprehensive geriatric assessment for older adults admitted to hospital. Cochrane Database Syst Rev. 2011;7:CD006211.

15. Ellis G, Gardner M, Tsiachristas A, Langhorne P, Burke O, Harwood RH, et al. Comprehensive geriatric assessment for older adults admitted to hospital. Cochrane Database Syst Rev. 2017 12;9:CD006211.

16. Meid AD, Lampert A, Burnett A, Seidling HM, Haefeli WE. The impact of pharmaceutical care interventions for medication underuse in older people: a systematic review and meta-analysis. Br J Clin Pharmacol. 2015;80(4):768–76.

17. Royal S, Smeaton L, Avery AJ, Hurwitz B, Sheikh A. Interventions in primary care to reduce medication related adverse events and hospital admissions: systematic review and meta-analysis. Qual Saf Health Care. 2006 Feb;15(1):23–31.

18. Rennke S, Nguyen OK, Shoeb MH, Magan Y, Wachter RM, Ranji SR. Hospital-initiated transitional care interventions as a patient safety strategy: a systematic review. Ann Intern Med. 2013 Mar 5;158(5 Pt 2):433–40.

19. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet] [Internet]. Lyon, France: International Agency for Research on Cancer; 2013 [cited 2016 Sep 4]. Available from: Available from: http://globocan.iarc.fr

20. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared Risk Factors in Cardiovascular Disease and Cancer. Circulation. 2016 Mar 15;133(11):1104–14.

21. Sjölund B-M, Wimo A, Qiu C, Engström M, von Strauss E. Time trends in prevalence of activities of daily living (ADL) disability and survival: Comparing two populations (aged 78+ years) living in a rural area in Sweden. Arch Gerontol Geriatr. 2014 May;58(3):370–5.

22. Sjölund B-M, Wimo A, Engström M, Strauss E von. Incidence of ADL Disability in Older Persons, Physical Activities as a Protective Factor and the Need for Informal and Formal Care – Results from the SNAC-N Project. PLoS ONE [Internet]. 2015 [cited 2016 Sep 4];10(9). Available from: https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pmc/articles/PMC4583409/

23. Jagger C, Gillies C, Moscone F, Cambois E, Van Oyen H, Nusselder W, et al. Inequalities in healthy life years in the 25 countries of the European Union in 2005: a cross-national meta-regression analysis. The Lancet. 2008 Dec 20;372(9656):2124–31.

24. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008 Sep 29;337:a1655.

25. Website: http://www.cepd.fr/CUSTOM/CEPD_toxicite.pdf.

26. Linn BS, Linn MW, Gurel L. CUMULATIVE ILLNESS RATING SCALE. J Am Geriatr Soc. 1968 May;16(5):622–6.

27. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of Illness in the Aged. The Index of Adl: A Standardized Measure of Biological and Psychosocial Function. Jama. 1963 Sep 21;185:914–9.

28. Falandry C, Stefani L, Granger M, Momiron C, Habchi H, Bourgeois C, et al. Interventions to improve physical performances of older people with cancer before major surgery: an umbrella review. J Geriatr Oncol. 2018;9(6 suppl 1):S94–5.

29. Falandry C, Stefani L, Andre L, Granger M, Barbavara C, Habchi H, et al. Interventions to improve physical performances of older people with cancer before complex medico-surgical procedures: Protocol for an umbrella review of systematic reviews and meta-analyses. Medicine (Baltimore). 2020 Sep 25;99(39):e21780.

30. Glasgow RE, Emmons KM. How Can We Increase Translation of Research into Practice? Types of Evidence Needed. Annu Rev Public Health. 2007;28(1):413–33.

31. Colburn JL, Mohanty S, Burton JR. Surgical Guidelines for Perioperative Management of Older Adults: What Geriatricians Need to Know. J Am Geriatr Soc. 2017 Jun 1;65(6):1339–46.

32. McCarten JR, Anderson P, Kuskowski MA, McPherson SE, Borson S. Screening for Cognitive Impairment in an Elderly Veteran Population: Acceptability and Results Using Different Versions of the Mini-Cog: SCREENING ELDERLY VETERANS USING THE MINI-COG. J Am Geriatr Soc. 2011 Feb;59(2):309–13.

33. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiatr Res. 1982 Jan;17(1):37–49.

34. Guigoz Y, Vellas B, Garry PJ. Assessing the Nutritional Status of the Elderly: The Mini Nutritional Assessment as Part of the Geriatric Evaluation. Nutr Rev. 2009 Apr 27;54(1):S59–65.

35. Arends J, Bodoky G, Bozzetti F, Fearon K, Muscaritoli M, Selga G, et al. ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology. Clin Nutr. 2006 Apr;25(2):245–59.

36. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, et al. ESPEN Guidelines on Enteral Nutrition: Surgery including Organ Transplantation. Clin Nutr. 2006 Apr;25(2):224–44.

37. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015 Mar;44(2):213–8.

38. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649–55.

39. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969 Autumn;9:179–86.

40. Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol. 2012 Aug;23(8):2166–72.

41. Topolski TD, LoGerfo J, Patrick DL, Williams B, Walwick J, Patrick MB. The Rapid Assessment of Physical Activity (RAPA) among older adults. Prev Chronic Dis. 2006 Oct;3(4):A118.

42. de Souto Barreto P, Ferrandez A-M. Activités instrumentales physiques de la vie quotidienne chez les personnes âgées: validation d'une échelle. In: L'anthropologie du vivant: objets et méthodes. Chapuis-Lucciani N, Guihard-Costa AM, Boëtsch G. 2010. p. 83–7.

43. Quinten C, Coens C, Ghislain I, Zikos E, Sprangers MAG, Ringash J, et al. The effects of age on health-related quality of life in cancer populations: A pooled analysis of randomized controlled trials using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 involving 6024 cancer patients. Eur J Cancer. 2015 Dec;51(18):2808–19.

44. Wheelwright S, Darlington A-S, Fitzsimmons D, Fayers P, Arraras JI, Bonnetain F, et al. International validation of the EORTC QLQ-ELD14 questionnaire for assessment of health-related quality of life elderly patients with cancer. Br J Cancer. 2013 Aug;109(4):852–8.

45. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013 Sep;22(7):1717–27.

46. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473–83.

47. Fish J. Short Physical Performance Battery. In: Kreutzer JS, DeLuca J, Caplan B, editors. Encyclopedia of Clinical Neuropsychology [Internet]. New York, NY: Springer New York; 2011 [cited 2020 Nov 4]. p. 2289–91. Available from: http://link.springer.com/10.1007/978-0-387-79948-3_1832

48. Podsiadlo D, Richardson S. The timed 'Up & Go': a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991 Feb;39:142–8.

49. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989 Oct;46(10):1121–3.

50. Tinetti ME, Baker DI, McAvay G, Claus EB, Garrett P, Gottschalk M, et al. A Multifactorial Intervention to Reduce the Risk of Falling among Elderly People Living in the Community. N Engl J Med. 1994 Sep 29;331(13):821–7.

51. Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med. 1970;2(2):92–8.

52. Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES). Assessment and follow-up of chronic pain in adults in ambulatory medicine. 1999 Feb;

53. Société Francophone Nutrition Clinique et Métabolisme (SFNCM). Evaluation of food intake.

54. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. JNCI J Natl Cancer Inst. 1993 Mar 3;85(5):365–76.

55. Wheelwright S, Darlington A-S, Fitzsimmons D, Fayers P, Arraras JI, Bonnetain F, et al. International validation of the EORTC QLQ-ELD14 questionnaire for assessment of health-related quality of life elderly patients with cancer. Br J Cancer. 2013 Aug 20;109(4):852–8.

56. Boereboom C, Doleman B, Lund JN, Williams JP. Systematic review of pre-operative exercise in colorectal cancer patients. Tech Coloproctology. 2016 Feb 1;20(2):81–9.

57. Sun V, Raz DJ, Kim JY, Melstrom L, Hite S, Varatkar G, et al. Barriers and facilitators of adherence to a perioperative physical activity intervention for older adults with cancer and their family caregivers. J Geriatr Oncol. 2020 Mar 1;11(2):256–62.

58. Prehabilitation, rehabilitation, and revocation in the Army. Br Med J. 1946 Jun 29;1:192–7.

59. Topp R, Ditmyer M, King K, Doherty K, Hornyak J. The effect of bed rest and potential of prehabilitation on patients in the intensive care unit. AACN Clin Issues. 2002 May;13(2):263–76.

60. Ghignone F, van Leeuwen BL, Montroni I, Huisman MG, Somasundar P, Cheung KL, et al. The assessment and management of older cancer patients: A SIOG surgical task force survey on surgeons' attitudes. Eur J Surg Oncol EJSO. 2016 Feb;42(2):297–302.

Illustrations' legends

Figure 1: PROADAPT program: interventions at the patient's level

Table 1: PROADAPT programme: tasks according to the different domains and the successive chronological steps (before, during, and after complex medical-surgical procedures)

Table 2: PROADAPT pilot trial: questionnaires and screening tests

Table 3: PROADAPT pilot trial study: flow diagram

Table 1: PROADAPT programme: tasks according to the different domains and the successive chronological steps (before, during, and after complex medical-surgical procedures)

Nurse coaching & education Bridging interventions	Coaching nurse self-presentation Delivery of a personalised patient booklet Care according to best practice guidelines: - Confirm and document patient goals and treatment preferences, including advance directives. - Confirm and document patient's healthcare proxy or surrogate decision-maker. - In patients with existing advance directives, discuss new risks associated with the surgical procedure and an approach for potentially life-threatening problems consistent with the patient's values and preferences ("required reconsideration"). Weekly phone calls	Coaching nurse visits / phone calls Communication of patient's preference to the staff	Coaching nurse visit in the rehabilitation ward Communication of patient's preference and care difficulties to the staff (checklist): - delirium/cognitive impairment - peri-operative acute pain - pulmonary complications - fall risk - ability to maintain adequate nutrition - urinary tract infection prevention - functional decline monitoring - pressure ulcers prevention	Coaching nurse bi-weekly phone call Communication of patient's care difficulties to the staff
Nutrition	W-4: nutritional evaluation Nutritional plan based on measured intake W-3: nutritional follow up - weight W-2: nutritional follow up- weight W-1: nutritional follow up- weight + pre-operative immunonutrition	If surgery: care according to best practice guidelines: - Consider shortened fluid fastin (clear liquids up to 2 hours before anaesthesia).(36) - Normal food intake or enteral feeding should start as early as possible	Nutritional plan based on - Weight curve - Measured intake Optimal management of - Nausea/vomiting - Abdominal pain	Nutritional plan based on - Weight curve - Measured intake Optimal management of - Nausea/vomiting - Abdominal pain
Physical activity	W-4: physical performance evaluation Physical activity plan W-3 \ group physical activity W-2 + W-1 functional follow-up	If surgery: care according best practice guidelines: - Early physical and/or occupational therapy. - Check for orthostatic hypotension. - Review physical environment to reduce injury risk. - Assistive walking devices (e.g. walkers) at bedside if used as outpatient	(to the discretion of the rehabilitation unit)	Pursuing of the pre-operative physical activity plan
Medication conciliation	Centralised medication conciliation and treatment optimisation (STOPP/START guidelines)	Centralised medication conciliation Advices for care according best practice guidelines (16): - Adhere to existing best practices regarding antibiotic and venous thromboembolism prophylaxis. - Ensure nonessential medications have been stopped and essential medications have been taken.	Centralised medication conciliation	Centralised medication conciliation
Standardisation of surgical procedures		If surgery: consider antiseptic toothpaste If surgery: care according to best practice guidelines (16): - Consideration of regional techniques to avoid postoperative complications and improve pain control. - Directed pain history. - Multi-modal or opioid-sparing techniques. - Postoperative nausea risk stratification and prevention strategies. - Strategies to avoid pressure ulcers and nerve damage. - Prevention of postoperative pulmonary complications and hypothermia. - Judicious use of intravenous fluids. - Appropriate haemodynamic management. - Continuation of indicated cardiac medications. - Daily post-operative rounding checklist: - delirium/cognitive impairment - peri-operative acute pain - pulmonary complications - fall risk - ability to maintain adequate nutrition - urinary tract infection prevention - functional decline monitoring - Pressure ulcers prevention If surgery: consider IV iron supplementation		

Table 2: PROADAPT pilot trial: questionnaires and screening tests

Domain	
Autonomy	ADL, IADL
Geriatric screening	G8
Physical activity	RAPA, AIPVQ
Quality of life	QLQ-C30, QLQ-ED14, EQ-5D-3L, SF-36
Locomotion and balance	TUG test, SPPB
Pain	Pain scale
Nutrition	Nutrition scale
Tiredness severity	FSS
Depression/anxiety	MNA, GDS4/GDS15
Cognitive assessment	Mini-COG
Fall risk assessment	Tinetti test
Breathlessness	Borg scale

Abbreviations: Abbreviations: ADL: Activities of Daily Living; AIPVQ: Physical Instrumental activities of daily living (in French: Activités Instrumentales Physiques de la Vie Quotidienne); EQ-5D-3L: EUROQOL evaluation of quality of life in five dimensions and three levels; FSS: Fatigue Severity Scale; GDS: Geriatric Depression Scale; IADL: Instrumental Activities of Daily Living; MNA: Mini Nutritional Assessment; QLQ-C30: quality of life questionnaire core 30 of the European organisation for research and treatment of cancer (EORTC); QLQ-ELD14: Older patients- specific quality of life questionnaire in 14 items of the EORTC; RAPA: Rapid Assessment of Physical Activity; SF-36: Short Form 36 Health Survey Questionnaire; SPPB: Short Physical Performance Battery

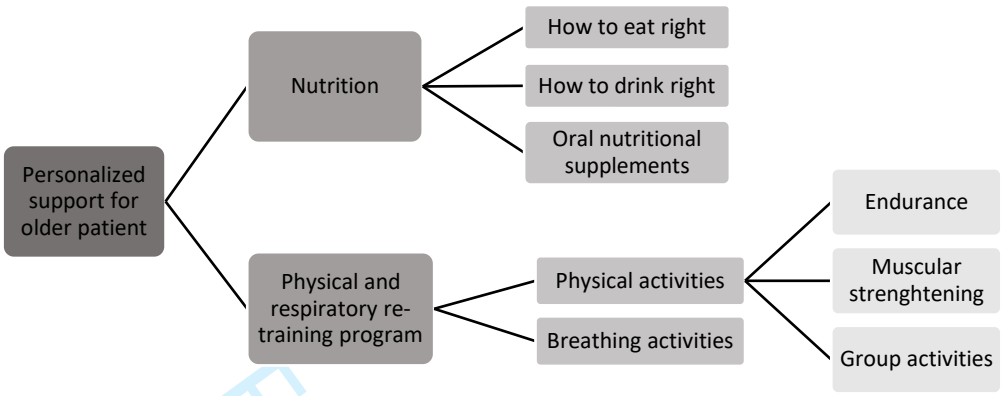
Table 3: PROADAPT pilot study: flow diagram

	Baseline	Pre-therapeutic visit (0-5 days before intervention)	M1, M3, M6	M12	End of study visit
Comprehensive geriatric assessment					
G8	X			X	X
ADL/IADL	X			X	X
GDS4/GDS15	X			X	X
Mini COG	X			X	X
MNA	X			X	X
QLQ-C30	X		X	X	X
QLQ-ELD14	X		X	X	X
EQ-5D-3L	X		X	X	X
Pain scale	X	X	X	X	X
Nutrition scale	X	X	X	X	X
Socio-economic evaluation	X				
Physical and respiratory assessments					
FSS	X		X	X	X
SF-36	X		X	X	X
Timed Up and Go	X			X	X
SPPB	X		X	X	X
Borg scale	X			X	X
RAPA questionnaire	X		X	X	X
AIPVQ scale	X		X	X	X
Tinetti test	X			X	X
Equimog evaluation	X			X	X
Triflo II	X	X			
Voldyne	X	X			
Physical activity data collection		X	X	X	X
Patient satisfaction					
Standardised questionnaire					X

Abbreviations: ADL: Activities of Daily Living; AIPVQ: Physical Instrumental activities of daily living (in French: Activités Instrumentales Physiques de la Vie Quotidienne); EQ-5D-3L: EUROQOL evaluation of quality of life in five dimensions and three levels; FSS: Fatigue Severity Scale; GDS: Geriatric Depression Scale; IADL: Instrumental Activities of Daily Living; MNA: Mini Nutritional Assessment; QLQ-C30: quality of life questionnaire core 30 of the European organisation for research and treatment of cancer (EORTC); QLQ-ELD14: Older patients- specific quality of life questionnaire in 14 items of the EORTC; RAPA: Rapid Assessment of Physical Activity; SF-36: Short Form 36 Health Survey Questionnaire; SPPB: Short Physical Performance Battery

886

Figure 1 : PROADAPT program : interventions at the patient's level



Supplementary file 1: Patient satisfaction assessment of the PROADAPT programme

Hospices Civils de Lyon **Direction de la Recherche Clinique et de l'Innovation**	**PATIENT ASSESSMENT OF THE PROADAPT PROGRAMME**

Dear Sir or Madam,

You have been part of the PROADAPT - pilot study and we thank you for your involvement. In order to assess and improve this study, we would like to collect your opinion. This opinion is anonymous and does not affect your healthcare.

The following questions are concerning the patient booklet that was given to you as part of the study

If you consider the booklet overall

• Did the explanations seem appropriate to you?	Not at all ☐	A little ☐	Absolutely ☐
• Did the information seem clear to you?	Not at all ☐	A little ☐	Absolutely ☐
• Did the pages seem readable enough?	Not at all ☐	A little ☐	Absolutely ☐
• Did the illustrations seem clear to you?	Not at all ☐	A little ☐	Absolutely ☐

How would you rate the booklet?
(useless = 0 ; very useful = 10) 0 1 2 3 4 5 6 7 8 9 10

The following questions are concerning the overall PROADAPT programme (breathing and physical exercises, booklet, calls, and follow-up visits)

Did you have difficulty in understanding the explanations given by the medical staff

• for breathing exercises?	Not at all ☐	A little ☐	A lot ☐
• for physical exercises?	Not at all ☐	A little ☐	A lot ☐
• for nutritional advices?	Not at all ☐	A little ☐	A lot ☐
• during the assessment with the physician of the different drugs you are taking?	Not at all ☐	A little ☐	A lot ☐

Did you encounter any difficulties

- for the realisation of breathing exercises ? Not at all ☐ A little ☐ A lot ☐
- for the realisation of physical exercises ? Not at all ☐ A little ☐ A lot ☐
- for the application of nutritional advice? Not at all ☐ A little ☐ A lot ☐
- for the recording of activities? Not at all ☐ A little ☐ A lot ☐

How do you estimate nursing phone calls

- at the beginning of your healthcare before your surgery / radiotherapy Useless ☐ Of little importance ☐ Needed ☐
- after your surgery / radiotherapy Useless ☐ Of little importance ☐ Needed ☐

Would you have liked to have more information? No ☐ Yes ☐
If yes, on which aspect
……
……
……
……

What would you propose to make the programme more suitable for patients?
……
……
……
……
……

Thank you for your time, we will use your opinions to improve the PROADAPT programme and the patient booklet.

Prof Claire Falandry, study coordinator

Supplementary file 2: Patient satisfaction assessment of ID-PROADAPT® eHealth device

Hospices Civils de Lyon **Direction de la Recherche Clinique et de l'Innovation**	**ASSESSMENT OF THE ID-PROADAPT® DEVICE, COMPANION OF THE PROADAPT PROGRAMME**

Dear Sir or Madam,

You have been part of the PROADAPT-pilot study and we thank you for your involvement. In order to assess and improve this study, we would like to collect your opinion. This opinion is anonymous and does not affect your healthcare.

The following questions are concerning your experience with the PROADAPT programme as proposed in the ID-PROADAPT® device

If you consider the PROADAPT programme provided using ID-PROADAPT® device overall

• Did the font appear easy to read?	Not at all ☐	A little ☐	Absolutely ☐
• Did you manage to use the stylus easily?	Not at all ☐	A little ☐	Absolutely ☐
• Did you experience any visual fatigue after watching the program?	Not at all ☐	A little ☐	Absolutely ☐
• Were you tired at the end of filling out the various questionnaires?	Not at all ☐	A little ☐	Absolutely ☐
• Have you encountered connection problems?	Not at all ☐	A little ☐	Absolutely ☐
• Were you bothered by certain colors?	Not at all ☐	A little ☐	Absolutely ☐
If yes: which ones?	……	……	……

The following questions concern the overall PROADAPT programme (breathing and physical exercises, booklet, calls, and follow-up visits)

Did you have difficulty in understanding the explanations given proposed in the ID-PROADAPT® device?

• for breathing exercises?	Not at all ☐	A little ☐	A lot ☐
• for physical exercises?	Not at all ☐	A little ☐	A lot ☐
• for nutritional advices?	Not at all ☐	A little ☐	A lot ☐

Ergonomics evaluation of the ID-PROADAPT® device

We now ask you to focus on your ergonomics (ease of use) of the PROADAPT program that was proposed on the provided tablet. Please indicate on this scale how you rate each statement.

	Not agree at all	Somewhat agree	Neither agree nor disagree	Somewhat agree	Totally agree
I have used the **PROADAPT program regularly**	☐	☐	☐	☐	☐
I find the PROADAPT program **unnecessarily complex**	☐	☐	☐	☐	☐
I find the PROADAPT program **easy to use**	☐	☐	☐	☐	☐
I regularly **needed help from technical support** to be able to use the PROADAPT program	☐	☐	☐	☐	☐
I find that the **different functions** of the PROADAPT program have been well integrated	☐	☐	☐	☐	☐
I find there are **too many inconsistencies** in the PROADAPT program	☐	☐	☐	☐	☐
I find the PROADAPT program **very restrictive to use**	☐	☐	☐	☐	☐
I feel **very confident** using the PROADAPT program	☐	☐	☐	☐	☐
I needed to **learn a lot** before I could use the PROADAPT program effectively	☐	☐	☐	☐	☐

User experience evaluation

We now ask you to focus on your overall experience with the PROADAPT interface. We offer two opposite terms and a 7-point scale. Please indicate on this scale where your impression is located.

Annoying	○	○	○	○	○	○	○	**Cheering**
Incomprehensible	○	○	○	○	○	○	○	**Understandable**
Creative	○	○	○	○	○	○	○	**Monotone**
Easy to use	○	○	○	○	○	○	○	**Difficult to use**
Precious	○	○	○	○	○	○	○	**Poor**
Boring	○	○	○	○	○	○	○	**Captivating**
Uninteresting	○	○	○	○	○	○	○	**Interesting**
Unpredictable	○	○	○	○	○	○	○	**Predictable**

Fast	○	○	○	○	○	○	○	**Slow**
Original	○	○	○	○	○	○	○	**Conventional**
Handicapping	○	○	○	○	○	○	○	**Helping**
Good	○	○	○	○	○	○	○	**Bad**
Complicated	○	○	○	○	○	○	○	**Simple**
Repulsive	○	○	○	○	○	○	○	**Attractive**
Common	○	○	○	○	○	○	○	**Unpublished**
Unpleasant	○	○	○	○	○	○	○	**Pleasant**

Would you have liked to have more information? No ☐ Yes ☐
If yes, on which aspect?
……
……
……
……

What would you propose to make the programme more suitable for patients?
……
……
……
……
……

How would you rate the contents of the tablet? (not adapted = 0 ; very suitable = 10)	0	1	2	3	4	5	6	7	8	9	10
How would you rate the overall organisation of the program? (not adapted = 0 ; very suitable = 10)	0	1	2	3	4	5	6	7	8	9	10
How would you rate the intuitive nature of the tablet? (not adapted = 0 ; very suitable = 10)	0	1	2	3	4	5	6	7	8	9	10
How would you rate the videos on the tablet? (not adapted = 0 ; very suitable = 10)	0	1	2	3	4	5	6	7	8	9	10

Thank you for your time, we will use your opinions to improve the ID-PROADAPT® device and the PROADAPT programme.

Prof Claire Falandry, study coordinator

Supplementary table 1: SPIRIT 2013 checklist of the trial

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary table 2 Ref 24
Protocol version	3	Date and version identifier	17 (Ethics and Consent to participate)
Funding	4	Sources and types of financial, material, and other support	17-18 (Funding)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 (Authors' list) 18 (Authors' contributions)
	5b	Name and contact information for the trial sponsor	Supplementary table 2 Ref 24
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	10 (Ethical and legal considerations) 17 (Funding)

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13 (Data management and statistical analyses) 14 (Data monitoring)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14 (End of protocol) And N/4 (no dose modifications)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6 (two turns of validations of the PROADAPT booklet by candidate patients)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-13 (Sample size calculation)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A (no problem for accrual)
Methods: Assignment of interventions (for controlled trials)			**N/A**
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	-
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	-
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Table 3
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13 (Data management and statistical analyses)

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14 (Data management and statistical analyses)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14 (Data Monitoring)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11 (Secondary outcomes: NCI CTCAE, QOL)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10 (Ethical and legal considerations)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10 (Ethical and legal considerations) 14 (Protocol amendments)

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10-11 (Ethical and legal considerations)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14 (Confidentiality)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17 (Competing interests)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17 (Availability of data and materials)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15 (Dissemination policy)
	31b	Authorship eligibility guidelines and any intended use of professional writers	15 (Dissemination policy), N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Annex 1 (in French)

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

Supplementary table 2: All items from the World Health Organization Trial Registration Data Set (SPIRIT item 2b)

Data category	**Information**
Primary registry and trial identifying number	ClinicalTrials.gov NCT03659123
Date of registration in primary registry	6 September 2018
Secondary identifying numbers	69HCL16_0701 ID RCB N° 2018-A001026-49
Source(s) of monetary or material support	Agence Régionale de Santé Auvergne Rhône Alpes
Primary sponsor	Hospices Civils de Lyon
Secondary sponsor(s)	
Contact for public queries	David Dayde, +33.4.78.86.37.74, david.dayde@chu-lyon.fr
Contact for scientific queries	Claire Falandry, +33.4.78.86.66.34, claire.falandry@chu-lyon.fr
Public title	Prehabilitation & Rehabilitation in Oncogeriatrics: Adaptation to Deconditioning Risk and Accompaniment of Patients' With Cancer
Scientific title	Prehabilitation & Rehabilitation in Oncogeriatrics: Adaptation to Deconditioning Risk and Accompaniment of Patients' With Cancer, a Multicentre Pilot Study
Countries of recruitment	France
Health condition(s) or problem(s) studied	Old Injury
Intervention(s)	Behavioural: standardised geriatric intervention Nutritional care is based on: • A personalised evaluation of nutritional balance and nutritional needs of the patient • A weekly follow-up of weight and nutritional intake Total-body rehabilitation is based on: • 2 to 3 times a week: strength exercise • 2 to 3 times a week: endurance exercise, 20 to 45 min each sequence • 2 times a week: respiratory physiotherapy Pharmaceutical conciliation and optimisation according to the STOPP/START criteria During peri-operative time, the nurse contacts the surgical team for transmission of the patient's personal data, physical medication conciliation results During rehabilitation time and hospital-home transition time, the nurse contacts the rehabilitation team for transmission of the patient's personal data and care course, physical (nutritional, functional, and/or comorbidities), medication conciliation results.

Data category	Information
Key inclusion and exclusion criteria	Inclusion criteria: Patient aged ≥70 years OR patient aged ≥60 years with significant comorbid condition (modified Charlson index ≥3) or disability (ADL score <6/6); Histologically or cytologically proven cancer. Life expectancy > 3 months. Written informed consent obtained Covered by a Health System where applicable. Exclusion Criteria: Other malignancy within the previous 5 years, except for adequately treated carcinoma *in situ* of the cervix or squamous carcinoma of the skin, or adequately controlled limited basal cell skin cancer. Patient unable to be regularly followed for any reason (geographical, familial, social, psychological). Any mental or physical handicap at risk of interfering with the appropriate treatment. Any administrative or legal supervision where applicable
Study type	Interventional Allocation: N/A Intervention model: Single Group Assignment Masking: None (Open Label) Primary purpose: Health Services Research Phase II
Date of first enrolment	3 July 2018
Target sample size	122
Recruitment status	Recruiting
Primary outcome(s)	Implementation of at least one item of PROADAPT standardised geriatric intervention of the PROADAPT programme pilot study [Time Frame: 12 months]: • Preoperative physical activity including strength and endurance exercise assessed by physical exercises accomplished under the supervision of a physiotherapist. Number of patients with at least 1 intervention achieved in the domain. • Nutrition guidelines before and after physical activity assessed by questionnaires. Number of patients with at least 1 intervention achieved in the domain. • Patient education and coaching assessed by questionnaires and visits. Number of patients with at least 1 intervention achieved in the domain • Achievement of standardized intervention procedures, according to the checklist established in consensus with surgeons. Number of patients with at least 1 intervention achieved in the domain • Rehabilitation assessed by questionnaires. Number of patients with at least 1 intervention achieved in the domain

Data category	Information
	• Accomplishment of pharmaceutical medication conciliation and treatment optimisation. Number of patients with at least 1 intervention achieved in the domain • Bridging interventions for hospital-to-home transition. Number of patients with at least 1 intervention achieved in the domain
Key secondary outcomes	• Post-operative morbidity [Time Frame: 30 and 90 days] according to the Clavien-Dindo classification • Post-operative morbidity [Time Frame: 90 days] according to NCI CTC v4.4 • Therapeutic strategy [Time Frame: 12 months]: Treatment plan completion rate: Number of patients for whom the treatment plan was completed. • Progression-free survival [Time Frame: 12 months] • Post-treatment complication [Time Frame: 12 months]: Post-treatment complication grade ≥3 according the National Cancer Institute Common Toxicity Criteria version 4 (NCI-CTC-v4)