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TITLE PAGE

Title

EffectiveNess of a multimodal preHAbilitation program in patieNts with bladder canCEr undergoing radical cystectomy: protocol of the ENHANCE multicenter randomized controlled trial

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ABSTRACT

Introduction Radical cystectomy (RC) is the standard treatment for patients with non-metastatic muscle-invasive bladder cancer, as well as for patients with therapy refractory high-risk non-muscle invasive bladder cancer. However, 50-65% of patients undergoing RC experience perioperative complications. The risk, severity, and impact of these complications is associated with a patient's preoperative cardiorespiratory fitness, nutritional and smoking status, and presence of anxiety and depression. There is emerging evidence supporting multimodal prehabilitation as a strategy to reduce the risk of complications and improve functional recovery after major cancer surgery. However, for bladder cancer the evidence is still limited. The aim of this study is to investigate the superiority of a multimodal prehabilitation program versus standard-of-care in terms of reducing perioperative complications in patients with bladder cancer undergoing RC.

Methods and analysis This multicenter, open label, prospective, randomized controlled trial, will include 154 patients with bladder cancer undergoing RC. Patients are recruited from eight hospitals in The Netherlands and will be randomly (1:1) allocated to the intervention group receiving a structured multimodal prehabilitation program of approximately 4-6 weeks, or to the control group receiving standard-of-care. The primary outcome is the proportion of patients who develop one or more grade ≥2 complications (according to the Clavien-Dindo classification) within 90 days of surgery. Secondary outcomes include cardiorespiratory fitness, length of hospital stay, health-related quality of life, tumor tissue biomarkers of hypoxia, immune cell infiltration, and cost-effectiveness. Data collection will take place at baseline, before surgery, and 4 and 12 weeks after surgery.

Ethics and dissemination Ethical approval for this study was granted by the Medical Ethics Committee NedMec (Amsterdam, The Netherlands) under reference number 22-595/NL78792.031.22. Results of the study will be published in international peer-reviewed journals.

Trial registration number Clinical Trials (NCT05480735). Prospectively registered on 29 July 2022.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This multicenter randomized controlled trial will provide firm empirical evidence regarding the efficacy of multimodal prehabilitation in patients with bladder cancer undergoing radical cystectomy, a population that is currently understudied.
- This is the first prehabilitation study in bladder cancer to include a cost-effectiveness analysis, which will support decisions regarding implementation and reimbursement of prehabilitation in daily clinical practice.
- This is the first study to investigate the effects of prehabilitation on tumor hypoxia and immune cell infiltration in patients with bladder cancer.
- The intervention accounts for heterogeneity in cancer treatment by offering additional support during neoadjuvant treatment when appropriate.
- Due to the two-group design and the multimodal intervention, it will not be possible to disentangle the independent effects of physical exercise training, nutritional support, psychological counseling, and smoking cessation.

INTRODUCTION

Bladder cancer is the 10th most common diagnosed cancer worldwide, with over 573,000 new patients and 213,000 deaths each year [1]. Radical cystectomy (RC) is the standard treatment for patients with non-metastatic muscle-invasive bladder cancer [2, 3], as well as for patients with therapy refractory high-risk non-muscle invasive bladder cancer [4]. RC is a challenging and costly surgical procedure with high morbidity and mortality rates [5]: 50-65% of the patients experience perioperative complications, of which 10-20% are high-grade [6-8]. Low cardiorespiratory fitness [9, 10], poor nutritional status [11], the presence of anxiety and depression [12], and smoking [13] increase the risk of perioperative complications, length of hospital stay, and the associated medical costs [9, 10]. In daily clinical practice, 25% of patients with muscle-invasive bladder cancer receive neoadjuvant treatment, which might further impair preoperative cardiorespiratory fitness and nutritional status [14-17].

Emerging evidence has identified the preoperative period as a window of opportunity to address lifestyle. Multimodal preoperative interventions, including physical exercise training, nutritional support, psychological counseling and smoking cessation, that aim to increase a patient's tolerance to surgery, reduce the incidence, severity, and impact of complications, accelerate and improve the quality of recovery, and improve quality of life have been termed *prehabilitation*.

To date, no adequately powered trial has been performed to establish the effectiveness of a multimodal prehabilitation program for reducing the incidence, severity, and impact of complications and costs associated with RC for bladder cancer. A few studies investigated the impact of a single modal [20, 21] or multimodal [18, 19] prehabilitation program on functional recovery following RC. A phase I/II trial with 54 patients showed improvement in patient-reported quality of life after four weeks of a supervised physical exercise training program before surgery [21]. A feasibility randomized controlled trial with 60 patients provided evidence that a 3- to 6-week supervised vigorous aerobic exercise training program before surgery led to improvements in cardiorespiratory fitness parameters and possibly fewer surgical complications [20]. A randomized controlled trial with 107 patients demonstrated improvement in walking distance during seven days after surgery [18] and improved muscle power [22]. Finally, a randomized controlled trial with 70 patients showed significant better functional capacity in the intervention group that followed a multimodal program compared to the control group, at four weeks after surgery [19]. However, the physical exercise intervention in these studies including patients with bladder cancer had limitations with regard to therapeutic validity [23] due to a short duration of the

intervention [18, 22], relatively low exercise intensity [18, 19, 22], or only patient reported compliance with the exercise intervention [18, 19, 22].

Preclinical studies indicate that exercise may directly affect tumor characteristics such as normalization of tumor vasculature and immune cell infiltration, thereby enhancing tumor perfusion and reducing hypoxia [24, 25]. These factors are associated with treatment efficacy and survival [26-28]. The current study provides a unique opportunity to explore the effects of prehabilitation on tumor inflammation and hypoxia markers, which has not yet been studied in human patients.

Study objectives

The ENHANCE study is designed to investigate the effectiveness of a multimodal prehabilitation program versus standard-of-care in patients approaching RC. The primary aim is to investigate the superiority of a multimodal prehabilitation program in terms of reducing one or more grade ≥2 perioperative complications within 90 days in patients with bladder cancer undergoing RC. Secondary outcomes include changes in preoperative cardiorespiratory fitness, length of hospital stay, health-related quality of life, tumor tissue biomarkers of hypoxia, immune cell infiltration, and cost-effectiveness.

METHODS AND ANALYSIS

The ENHANCE study is a multicenter, open label, two-arm randomized controlled trial. Patient inclusion and data collection started in August 2022. Ethical approval extending to all centers was granted by the Medical Ethical Committee NedMec (Amsterdam, The Netherlands), under reference number 22-595/NL78792.031.22. The trial is prospectively registered in Clinical Trials (NCT05480735) on 29 July 2022.

Study population

The study aims to include 154 patients who meet the following inclusion criteria: aged ≥18 years, histologically confirmed, primary, bladder cancer (cTa-4N0-3M0), and planned to undergo RC. Patients with severe cognitive or psychiatric disorders, patients with a contraindication to perform physical exercise training or a cardiopulmonary exercise test (CPET), patients undergoing surgery within 4 weeks, and patients unable to read or understand the Dutch language will be excluded.

Recruitment and randomization

Patients are recruited from eight academic or teaching hospitals across different regions in The Netherlands (Catharina Hospital, Erasmus Medical Center, Maastricht University Medical Center+, Noordwest Hospital Group, Radboud University Medical Center, Rijnstate Hospital, University Medical Center Groningen, and University Medical Center Utrecht). The Netherlands Cancer Institute is the coordinating center. After establishment of diagnosis and indication for surgery, the urologist or nurse specialist invites patients to participate in the study and provides the patient information letter. The study coordinator contacts these patients to provide further oral information and answer potential questions about the study. When a patient agrees to participate, written informed consent is obtained. After collection of baseline data, patients are randomized in a 1:1 ratio, using a minimization algorithm [29] aimed to achieve optimal balance between the two study arms with regard to the recruiting hospital, neoadjuvant treatment (yes/no), nodal status (N0/N1-3), and type of surgery (open/robot-assisted RC). Minimization is done using the Minirand package in R 4.0.4 [30, 31]. The algorithm includes a random component to ensure blinding of treatment allocation. Due to the nature of the intervention, blinding of participants and research investigators is not possible. After randomization, patients in both the intervention and control groups receive a leaflet with recommendations on physical activity, diet and smoking cessation, according to the latest guidelines for patients with cancer [32, 33]. These recommendations are not further individualised or actively supported.

Patients who do not wish to participate in the study are asked to participate in a one-time questionnaire as described in Table 1. A participant flow diagram is shown in Figure 1.

Control group– standard-of-care

Patients randomized to the standard-of-care arm receive care as usual, which does not include a comprehensive multimodal prehabilitation program. In all participating centers, enhanced recovery after surgery protocols are used to optimize medical conditions to enhance recovery [34]. These protocols include advice on smoking cessation when a patient is smoking and a referral to a dietician when malnutrition is detected. Preoperatively, the urologist determines whether or not the patient is physically fit for surgery. Participants in the control group are not prohibited to be physically active or seek counselling for nutritional advice, psychological support, or smoking cessation.

Intervention group– prehabilitation

Patients randomized to the intervention arm will participate in a multimodal prehabilitation program including supervised physical exercise training, nutritional support, and – when relevant – psychological counseling and professional support for smoking-cessation, to enhance their health status. The intervention starts as soon as possible after baseline measurements and randomization, approximately 4-6 weeks before surgery, and is continued until surgery. Patients who are included before undergoing neoadjuvant treatment (including chemotherapy and immunotherapy) will participate in a physical exercise training program from inclusion until completion of neoadjuvant treatment to prevent the often observed decline in physical fitness throughout neoadjuvant therapy. Subsequently, these patients will participate in the full multimodal prehabilitation program until the date of surgery. Adverse events related to the intervention are monitored.

Physical exercise training program

The physical exercise training program consists of three training sessions per week under the supervision of a physical therapist. An overview of the training program and training progression is described in Table 2. The program will be delivered at a physical therapy practice near a patient's home to minimize travel time, preferably supervised by a physical therapist affiliated with Onconet, a nationwide network of physical therapists with additional competencies in cancer care. The study coordinator provides the physical therapists instructions via a video call covering the specifics of the training program for the current study.

Training sessions last one hour and consist of individualized aerobic interval training (three times a week), resistance training (two times a week), and relaxation exercises (once a week). Results of the CPET will be used to establish the individual training intensity for aerobic interval training. For the resistance training, six large muscle groups will be targeted, in two sets of a defined maximum number of repetitions. The aim of these training sessions is to improve cardiorespiratory fitness, and muscle strength and mass. Relaxation exercises consist of breathing exercises and progressive muscle relaxation [35], which will be instructed and guided by the physical therapist. The aim of these exercises is to reduce possible anxiety and stress. In addition to the supervised sessions, patients are encouraged to be moderately active on at least two additional days per week for 30 minutes.

Patients who are included before starting neoadjuvant treatment receive additional training sessions during the neoadjuvant treatment period. The supervised sessions aim at preventing loss of physical fitness, and consist of twice-weekly moderate-intensity aerobic and resistance training. Patients receive the physical exercise training program as described above for the remaining 4-6 weeks before surgery.

Nutritional support

Patients receive tailored advice from a registered dietician at the participating hospitals aiming at a total protein intake of 1.9-2.3 g/per kg of fat-free mass as estimated with bioelectrical impedance analysis, to promote an anabolic state. Dietary advice will emphasize the benefit of spreading protein consumption over three meals, with a goal of 25-30 g protein per meal, and includes advice for optimal energy intake. To achieve this, and to increase adaptive responses of the skeletal muscle, participants will receive high-quality protein supplements containing 30 g of whey protein, 20 microgram of vitamin D, and 250 mg of calcium [36] in standardized supplements produced for the purpose of the study (FrieslandCampina, The Netherlands). These supplements are prescribed after each physical exercise training session and daily at least one hour before sleep or in the morning (depending on the patient's preference). The dietician provides intake consultation and one or two follow-up sessions to evaluate nutritional intake. Nutritional support starts at 4-6 weeks before surgery for all patients.

Psychological counseling

Patients are screened for anxiety and depression using the hospital anxiety and depression scale (HADS) questionnaire at baseline [37]. If a patient's score falls between 11 and 18, the option of psychological counselling is discussed and referral is arranged for patients indicating a need for such counselling. Patients who score ≥19 are directly referred to psychological counselling. Referred patients receive an

initial counselling session of 1.5 hours, and additional sessions at the discretion of the psychological counsellor and the patient.

Smoking cessation

Intensive counselling and nicotine replacement therapy is offered to all smoking patients in the 4-6 weeks before surgery. Counselling includes at least one in-person session and one or more telephone or in-person follow-up sessions by trained counsellors. If the patient indicates to be smoking and is willing to quit, the treating physician will refer the patient.

Study outcomes

Data are collected before randomization (T0a), before surgery (T1), and 4 (T2), and 12 (T3) weeks after surgery. If applicable, additional data will be collected after neoadjuvant treatment (T0b). At T0a, clinical data (e.g., treatment, clinical stage) will be abstracted from the medical records and sociodemographic characteristics (e.g., age, sex, education) will be obtained via a questionnaire. In addition, coping mechanisms [38] will be assessed via a questionnaire as this can help understand participation, attendance, and dropouts. Data is collected in CastorEDC and access is restricted to the investigator team. Due to the low-risk of the intervention a data safety monitoring board is not instated.

Primary outcome

The primary outcome is the proportion of patients who develop one or more grade ≥2 perioperative complications within 90 days after surgery. Complications are graded according to the Clavien-Dindo classification system [39] as described in Table 3.

Secondary outcomes

Secondary outcomes are the proportion of patients who develop one or more high-grade (grade ≥3) complications, total number of complications, length of hospital stay, number of readmissions, disease status (progression/recurrence), and additional treatment within 90 days. Secondary outcomes also include the intermediate outcomes of the intervention: cardiorespiratory fitness (measured using the standardized CPET [40]), physical functioning, upper and lower extremity (functional) muscle strength, nutritional intake, nutritional status, body composition, health-related quality of life, bladder cancer-related quality of life, anxiety and depression, fatigue, physical activity, and adherence to the intervention. Direct and indirect costs are collected for the cost-effectiveness analysis. Tumor hypoxia, immune cell infiltration, and pathological response are assessed as explorative outcomes. Participants in the control group will be asked whether they participated in any (structured) lifestyle program during

the preoperative period, to monitor contamination. In both groups, participants will be asked whether they received any postoperative intervention. The timing and type of outcome measures are presented in Table 1.

Compliance

To monitor therapeutic validity, compliance with the physical exercise training program is assessed by attendance rates and compliance to all parts of the training program as scored by the physical therapist on standardized training session forms, as well as by patient self-report via an activity diary. Compliance to nutritional supplement intake is assessed via a diary. Whether smoking cessation has been successful is assessed through questionnaires.

Satisfaction

Patients in the intervention group are asked to complete a short questionnaire at the end of the study about the perceived effectiveness of and satisfaction with the program, whether they would suggest any changes, and whether they would recommend it to other patients with bladder cancer. In addition, patients will be asked if they are willing to be contacted for participation in a focus group where the intervention program and changes that may positively affect implementation will be further discussed.

Sample size calculation

Previous studies in diverse types of cancer reported a reduction of postoperative complications in the intervention group compared to the control group, with odds ratios ranging from 0.11 to 0.88 [41-47]. This study aims to reduce the number of patients with any grade ≥2 perioperative complication within 90 days from 60% [48, 49] to 35% (relative risk 0.58, odds ratio 0.36) [50, 51]. Assuming a two-sided Fisher exact test with a power of 80% and an alpha of 0.05, in total 140 patients will be needed. To account for 10% dropout, including dropout due to cancelling of the planned surgery, 154 patients will be included. Approximately 380 patients with bladder cancer undergo RC in the eight participating hospitals annually. This implies that it is feasible to complete inclusion within two and a half years, if recruitment rate is at least 17%.

Statistical analysis

Primary outcome

All analyses will be performed on an intention-to-treat basis. Descriptive statistics will be calculated to describe and evaluate the comparability of the two groups at baseline on sociodemographic and clinical variables, and to assess the adequacy of the randomization. Patients who do not receive the planned

surgery or have an open-closed procedure, independent of group allocation, will be excluded from the primary analysis. The proportion of patients who develop any grade ≥2 complications will be compared in the two study arms by using Fisher's exact test and a Poisson regression model with a log link, adjusted for the stratification factors and relevant baseline imbalances. The relative risk will be reported with a 95% confidence interval based on robust standard errors [52].

Secondary study outcomes

Between-group differences over time will be evaluated in measures of physical functioning and patient-reported outcomes using linear mixed effects regression analysis. For high-grade complications, length of hospital stay, and number of readmissions, Poisson regression models with an appropriate link function will be used. For continuous outcomes, differences in mean change scores between the two study arms will be accompanied by effect sizes. Standardized effect sizes will be calculated by subtracting the mean change scores of the control group from those of the intervention group, and subsequently dividing this by the pooled standard deviation. Effect sizes of 0.2 are considered small, 0.5 moderate, and 0.8 large [53]. A *p*-value <0.05 will be considered statistically significant.

Intervention fidelity

Descriptive statistics will be used to summarize compliance rates of the supervised exercise sessions as well as home based physical activity, supplement consumption, and smoking cessation. Compliance rates are based on number of completed training sessions, supplementation consumption, and number of patients who stop smoking in the study intervention. Whether the level of compliance is associated with changes over time in primary and secondary study outcomes will be evaluated using generalized linear mixed effects models.

Non-participants

Baseline data of participants will be compared to those of non-participants using chi-squared statistics for categorical variables and analysis of variance for continuous variables.

Exploratory analysis

Exploratory subgroup analyses will be performed to explore a potential difference in effectiveness of the physical exercise training program between those who received neoadjuvant chemotherapy and those who did not. This will be done by adding an interaction term to the model and by performing stratified analyses if the interaction term is statistically significant at $p<0.10$. Exploratory analyses will also be executed to study the relationship of post-intervention/preoperative physical fitness parameters (i.e.,

VO_2peak) and nutritional status, with perioperative outcomes (grade ≥2 complications yes/no and number of days in the hospital). For this analysis, univariable and multivariable Poisson regression analyses will be used.

Economic evaluation

A trial- and model-based economic evaluation will be performed, based on the intention-to-treat analysis. The model-based evaluation will use literature for the potential long-term consequences and parametric survival methods to extrapolate the trial data beyond the included follow-up. The analysis will be approached from a societal perspective of The Netherlands and a lifelong time horizon, using a Markov decision model. Outcomes are 1) the incremental costs per reduced proportion of patients who develop one or more grade ≥2 perioperative complications within 90 days (trial-based), and 2) incremental costs, incremental quality-adjusted life years, and the incremental cost-effectiveness ratio (ICER) (model-based). An estimation of the degree of uncertainty around each input parameter will be included with the use of probabilistic sensitivity analyses. Parameter values will be drawn randomly from the assigned distributions, using Monte Carlo simulations [54]. To capture necessary support regarding adoption and further research, value of information (VOI) analyses will be performed [55]. Where appropriate, Dutch guidelines for costing studies will be used in applying tariffs to units of resource use [56]. Finally, a budget impact analysis will be performed according to the ISPOR guidelines [57].

Patient and public involvement

Patients or the public were not involved in the development of the study design. A patient representative is currently involved in the study and input will be obtained whenever relevant during the trial. Annual consortium meetings with the urologists are organized.

DISCUSSION

A considerable proportion of patients with bladder cancer scheduled for RC has a poor cardiorespiratory fitness [9, 10], is malnourished [11, 58], and/or is an active smoker at diagnosis [59]. This implies that there is a substantial potential for improving cardiorespiratory fitness and nutritional status in this patient population. Here, the rationale and design of a multimodal prehabilitation program for patients with bladder cancer who are scheduled for RC is presented. It is hypothesized that the program will be effective in reducing the number and severity of perioperative complications.

This study has several strengths, including its multicenter, randomized design, the use of an intention-to-treat basis for the data analysis, and a minimization technique to ensure blinded treatment allocation and comparable groups. Most importantly, the study intervention consists of a tailored program for physical exercise training and nutritional support following current best-practice for prehabilitation. Moreover, a cost-effectiveness analysis will be performed to anticipate smooth implementation and reimbursement, and tumor hypoxia and immune cell infiltration analysis will be performed exploratively. Intervention fidelity will be monitored in detail, as recommended previously [60], as will adverse events related to the intervention. Another notable strength is the additional analysis in non-participants. Selective non-participation is a serious risk for the generalizability of physical exercise training studies. Previous physical exercise training studies in other cancer populations have shown relevant differences between those who participate and those who do not [61, 62]. It has previously been described that patients who were eligible for prehabilitation programs for colon cancer surgery expressed several reservations [63]. It is vital to understand the characteristics of non-participants and reasons for non-participation in bladder cancer prehabilitation. This will not only help judge the generalizability of the results but will also support implementation in a way that will maximize the potential value of the prehabilitation program and achieve equitable health outcomes. Finally, the exploratory subgroup analysis in patients who receive neoadjuvant treatment might be relevant to inform future studies on risk stratification.

To limit barriers to participation and adherence, the exercise program will be delivered as near to the patients' homes as possible, to minimize travel time. This is a very important factor for patients with cancer according to previous studies [51, 64-66]. The availability of and close collaboration with the nationwide Onconet network of physical therapists, who are specifically educated to supervise patients with cancer, is an important advantage. An additional benefit of this approach is that it will facilitate implementation if the intervention proves to be effective.

This study also has some limitations. Patients with bladder cancer will be followed for a period of 90 days after surgery, meaning that longer-term evaluation of outcomes will not be possible. Because up to 60% of patients report complications within 90 days after surgery [67], it is expected that the time frame will be adequate for our primary outcome. A possible limitation is the risk of contamination in the control group. An evaluation questionnaire will be used in the control group to determine whether patients were physically active or received a (structured) lifestyle intervention pre- and postoperatively. Although objective measurements of habitual physical activity may provide a more detailed insight into physical activity levels not prone to recall bias, the collection of physical activity levels will be restricted to using questionnaires for feasibility reasons. This program is designed to maximally improve a patient's health status by including physical exercise training, nutritional support, psychological counseling and smoking cessation. It is not likely that patients who are randomized to the control group would initiate a program consisting of all these components on their own. The multimodal approach prohibits disentangling of the individual effects of each lifestyle component in the prehabilitation program. Considering the number of intervention components and the prevalence of bladder cancer, a larger study using a full factorial design is unlikely to be feasible in this population. Moreover, the current best-practice for other types of cancer supports the use of multimodal interventions over unimodal approaches [68, 69]. Higher levels of physical exercise training have been demonstrated to be beneficial for both cancer prevention and, in some solid tumors, progression of disease and cancer-related mortality [70, 71]. However, the underlying biological mechanism has yet to be demonstrated. It is expected that the prehabilitation program has positive effects on the tumor microenvironment. The hypoxic tumor microenvironment is a common characteristics of a solid tumor when oxygen levels become low, as a result of the rapid proliferation of tumor cells [72] and is linked to poor prognosis in bladder cancer [73]. Physical exercise training has regulatory effects on the angiogenesis of skeletal muscles, which has raised interest in whether these effects might translate to solid tumors [74]. Preclinical research has shown that training may acutely reduce tumor hypoxia through vascular normalization and thereby improve the perfusion of tumor tissue [75-78]. In addition, exercise training has been suggested to alter immune cell infiltration in solid tumors and thereby contribute to enhanced immune surveillance and improved vascular function [25]. However, current evidence is inconsistent and inconclusive [79]. Clinical trials are very limited and this preoperative setting provides an excellent opportunity to investigate the potential role of prehabilitation on tumor hypoxia and immune cell infiltration.

To summarize, this study will provide empirical evidence on the benefits of multimodal prehabilitation for patients with bladder cancer planned for RC who are at high risk of perioperative complications and a long recovery period. When proven (cost-)effective, the study results will support implementation of a multimodal prehabilitation program for patients with bladder cancer in daily clinical practice.

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Authors' contributions
AV, AL, AH, EK, VPR, WH, AM, WG, and MMS conceived the study. AV, WH, AM, WG, MMS, MGS, and EA contributed to the design of the study protocol. RM, AL, AH, VCR, EK, SB, CW, TM, and BB reviewed the study protocol with a clinical perspective. VPR wrote the statistical approach of the economic evaluation. HR composed the protocol of tumor hypoxia and immune cell infiltration analysis. AV, WH, AM, WG, MMS, MGS, and EA wrote the manuscript. All authors read, commented on, and approved the manuscript.

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Competing interests
CW received a research grant from ZonMw and gives courses on robot assisted radical cystectomy during conferences entitied with EAU. TM received consulting fees as member of the advisory board prostate cancer of Janssen-Cilag B.V.. BB participates on a Data Safety Monitoring Board of an international prehabilitation study, is board member of Netherlands Society of Human Movement sciences, member of Exercise is Medicine of Vereniging voor Sportgeneeskunde, and member of the Scientific Committee of Fit4Surgery. RM received research grants from Janssen, Roche and Astellas, an educational grant from Merck, received consulting fees from Merck, MSD, Janssen, Bristol-Myers Squibb Company, received support for attending the 2022 Global Congress on Bladder Cancer, and is EAU Panel member of the Muscle Invasive Bladder Cancer Guideline. MMS is member of the Scientific Committee of Fit4Surgery and board member of Onconet.

Patient consent for publication

Not applicable.

Table 1. Outcome measures in the intervention and control group

Description of outcome	Assessment	Description of measure	T0a	T0b	T1	T2	T3
Primary outcome							
Proportion of patients who develop one or more grade ≥2 perioperative complications within 90 days	Perioperative complications, Grade ≥2 according to Clavien Dindo classification	Number of grade ≥ 2 complication is abstracted from medical records				X	X
Secondary outcomes							
Proportion of patients who develop one or more high-grade (≥3) complications, number of complications, length of hospital stay, and readmissions within 90 days	Perioperative complications, Grade ≥3 according to Clavien Dindo classification, length of hospital stay, readmissions	Number of grade ≥ 3 complications, number of complications, length of hospital stay in days, and readmissions abstracted from medical records				X	X
Cardiorespiratory fitness	Cardiopulmonary exercise test (CPET) on a cycle ergometer using a ramp protocol [40]	Peak oxygen uptake (VO_2peak in ml/kg/min)	X		X		
Physical functioning	Short physical performance battery (SPPB) [80]	5 items organized into three subscales of balance, walking speed, and lower extremity muscle strength	X		X		X
Upper extremity muscle strength	Handgrip strength using a handheld dynamometer [81]	The maximum score of three attempts of both hands in kilogram (kg)					
Lower extremity functional muscle strength	30-second sit-to-stand test [82]	The number of sit to stands within 30 seconds	X		X		X
Nutritional intake	24-h recall	Protein (total gram) and caloric intake (total kcal)	X		X		
Nutritional status	Patient-generated subjective global assessment short form (PG-SGA SF) [83]	4 items assessing weight (status), nutritional intake, symptoms, and physical functioning	X	X	X	X	X
	Nil per mouth consumption during hospitalization	The number of days after RC abstracted from medical records				X	X
Body composition	Bioelectrical impedance analysis	Body mass (kg), body height (cm), (subcutaneous) fat mass (%), and (upper limb) muscle mass (kg) are measured, and BMI (kg/m^2)	X		X		X
Health-related quality of life	EORTC quality of life questionnaire core 30 (QLQ-C30) [84]	30 items, organized into 5 functional scales (physical, role, emotional, cognitive, social), 3 symptom scales (pain, fatigue, and emesis), 6 items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and an overall QoL scale	X	X	X	X	X
Bladder cancer-related quality of life	EORTC muscle-invasive bladder cancer specific module (BLM-30) [85]	30 items, assessing urinary symptoms, bowel symptoms, sexual functioning, urostomy problems, difficulties associated with the use of a catheter and body image	X	X	X	X	X
Anxiety and depression	Hospital anxiety and depression scale (HADS) [37]	7 items assessing anxiety and 7 items assessing depression	X	X	X	X	X
Fatigue	Multidimensional fatigue inventory (MFI) [86]	20 items, categorized into five scales: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue	X	X	X	X	X
Physical activity	Short questionnaire to assess health-enhancing physical activity (SQUASH) [87]	11 items, organized into 4 different physical activities measuring frequency, duration and intensity (physical activity to and from home, household activities, activities at work and physical activities performed during leisure time)	X	X	X	X	X
Tumor hypoxia and immune cell infiltration	Two tumor biopsies: from routine diagnostic investigation and from surgical tumor excision	Immunohistochemistry analysis will be performed for hypoxia and immune cell infiltration biomarkers using the	X		X		

		laboratory of the Karolinska Institutet (Sweden) and their according protocols					
Cost-effectiveness	EuroQol 5-dimension (EQ-5D-5L) [88]	5 items (dimensions) multi-attribute utility questionnaire that measures mobility, self-care, usual activities, pain/discomfort and anxiety/depression in 5 levels	X	X	X	X	X
	iMTA medical consumption questionnaire (iMCQ) [89] and productivity costs questionnaire (iPCQ) [90]	Patient reported productivity losses and medical consumption		X	X	X	X
	Health care costs	Medical activities abstracted from the management systems of the hospitals					X
Other outcomes							
Sociodemographic and clinical data	Sociodemographic data, disease, and treatment characteristics will be abstracted from medical records or reported by the patient	Patient reported: place of birth, sex, marital status, living and work situation, education, lifestyle variables, and the self-administrated comorbidity questionnaire [91] Medical records: birth month and year, date of diagnosis, date and type of treatment, tumor characteristics, ASA score, WHO score	X				
		Patient reported: smoking status	X	X	X	X	X
Coping mechanism	Sense of coherence questionnaire [92]	13 items, categorized into three scales: comprehensibility, manageability, meaningfulness	X				
Compliance to the intervention	Adherence rates	Patient reported: self-composed (activity) diary Physical therapist: adherence of the physical exercise training intervention on standardized training session forms	X	X	X		
Patient evaluation	Self-composed questionnaire	Patients in the intervention group: satisfaction with the program and willingness to participate in focus group Patients in the control group: evaluate contamination Both groups: evaluation of possible post-surgical intervention					X
Non-participation	Self-composed questionnaire	Patient reported outcomes: sociodemographic, health- and bladder cancer-related quality of life, anxiety and depression, fatigue, physical activity, coping mechanism, and reason(s) for not participating Medical records: birth month and year, date of diagnosis, date and type of treatment, tumor characteristics, ASA score, WHO score	X				

Table 2. Content of the supervised physical exercise training program in the intervention group

Frequency	**I**ntensity	**T**ime	**T**ype
Three times a week	Aerobic interval training, consisting of 4 intervals of alternating effort performed on a cycle ergometer: - 4 min of low-intensity exercise, defined as 30% of the workload achieved at VO_2peak - 2-3 min of high-intensity exercise, defined as 90% of the workload achieved at VO_2peak[a]	24-28 min	Aerobic interval training
Two times a week	During neoadjuvant treatment: **Week 1 – 3**: consisting of 20 minutes on a cycle ergometer and 10 minutes on a different aerobic machine, corresponding to 30% of the heart rate reserve **Week 4 – 6:** consisting of 20 minutes on a cycle ergometer and 10 minutes on a different aerobic machine, corresponding to 40% of the heart rate reserve **Week 7 – 9:** consisting of 20 minutes on a cycle ergometer and 10 minutes on a different aerobic machine, corresponding to 50% of the heart rate reserve **Week 10 – 12 (and further):** consisting of 20 minutes on a cycle ergometer and 10 minutes on a different aerobic machine, corresponding to 60% of the heart rate reserve	30 min	Aerobic training
Two times a week	Resistance training, consisting of training six large muscle groups (leg press, bench press or chest press, abdominal crunch, pull over, low row, and step up)[b] in 2 sets: - Week 1: maximal 15 repetitions at ~65% of 1RM per set - Week 2: maximal 12 repetitions at ~70% of 1RM per set (weight week 1 +10%) - Week 3: maximal 10 repetitions at ~75% of 1RM per set (weight week 2 +10%) - From week 4 maximal 10 repetitions per set[c]	~20 min	Resistance training
Once a week	Progressive muscle relaxation techniques [35]	~20 min	Relaxation exercises

Abbreviations: 1RM=one-repetition maximum; CPET=cardiopulmonary exercise test; VO_2peak=oxygen uptake at peak exercise.

[a] Further tailoring is done by the physical therapists: if a patient is not able to complete the high-intensity interval, the intensity will be reduced by 10%. The intensity can be reduced further in steps of 10% until the patient can complete all four high-intensity intervals. If a patient is able to complete all high-intensity intervals, moderate and high intensity will be increased by 10% [93]. During neoadjuvant treatment [94]: if a patient scores below a Borg score of 12 intensity is increased, if a patient scores above a Borg score of 15 intensity is decreased.

[b] Physical therapists can offer alternative resistance exercises targeting the same muscle group to accommodate a patient's abilities and preferences.

[c] If the patient is able to do two repetitions more than planned, the load will be increased by 10%. The load will be decreased by 10% if the patient is not able to achieve the planned number of repetitions.

Table 3. The Clavien-Dindo classification of surgical complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physical therapy This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusionsand total parenteral nutritionare also included
Grade III	Requiring surgical, endoscopic, or radiological intervention
-IIIa	Intervention not under general anesthesia
-IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)[a] requiring IC/ICU-management
-IVa	Single organ dysfunction (including dialysis)
-IVb	Multiorgan dysfunction
Grade V	Death of a patient

Adapted from [39].

Abbreviations: CNS=central nervous system; IC=intermediate care; ICU=intensive care unit.

[a] brain hemorrhage, ischemic stroke, subarrachnoidalbleeding, but excluding transient ischemic attacks (TIA)

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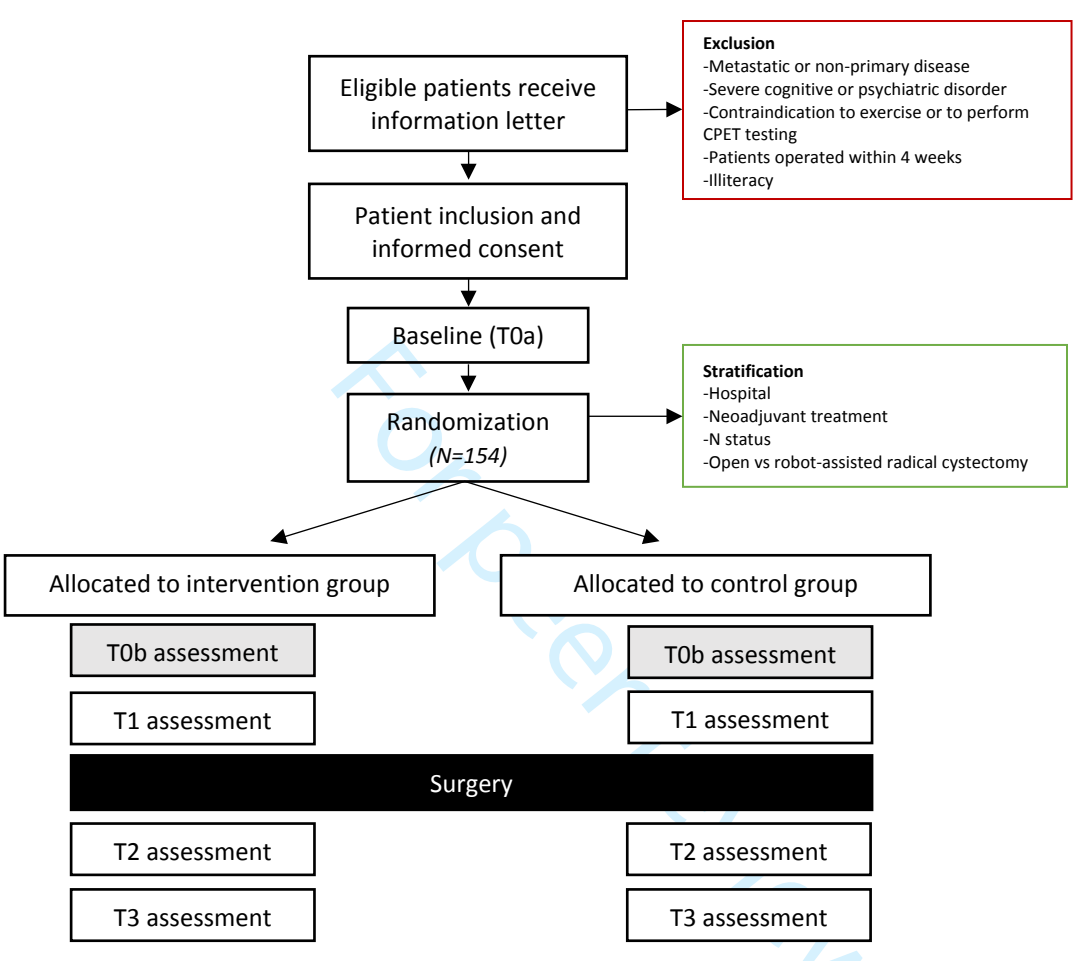
Figure 1. Study flow chart



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

Section/item	Item No	Description	Addressed on page number
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	3, 7
	2b	All items from the World Health Organization Trial Registration Data Set	3, 7
Protocol version	3	Date and version identifier	N.A.
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 2, 17
	5b	Name and contact information for the trial sponsor	17
	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	17
	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)	7

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	5, 6
	6b	Explanation for choice of comparators	8
Objectives	7	Specific objectives or hypotheses	6
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)	7
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	7
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)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10, Table 2
	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)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10,11, 14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	10, 11
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)	7, 8, Figure 1, Table 1

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	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
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	7
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	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N.A.
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	10, 11, Table 1
	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	Table 2

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	10
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	11-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12, 13
	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)	12
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	10
	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	8, 14
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	7
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)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
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	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
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	10
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	3
	31b	Authorship eligibility guidelines and any intended use of professional writers	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	N.A.
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.

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EffectiveNess of a multimodal preHAbilitation program in patieNts with bladder canCEr undergoing radical cystectomy: protocol of the ENHANCE multicenter randomized controlled trial

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Primary Subject Heading:	Oncology
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Keywords:	Urological tumours < ONCOLOGY, REHABILITATION MEDICINE, Nutritional support < ONCOLOGY, SURGERY

TITLE PAGE

Title

EffectiveNess of a multimodal preHAbilitation program in patieNts with bladder canCEr undergoing radical cystectomy: protocol of the ENHANCE multicenter randomized controlled trial

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ABSTRACT

Introduction Radical cystectomy (RC) is the standard treatment for patients with non-metastatic muscle-invasive bladder cancer, as well as for patients with therapy refractory high-risk non-muscle invasive bladder cancer. However, 50-65% of patients undergoing RC experience perioperative complications. The risk, severity, and impact of these complications is associated with a patient's preoperative cardiorespiratory fitness, nutritional and smoking status, and presence of anxiety and depression. There is emerging evidence supporting multimodal prehabilitation as a strategy to reduce the risk of complications and improve functional recovery after major cancer surgery. However, for bladder cancer the evidence is still limited. The aim of this study is to investigate the superiority of a multimodal prehabilitation program versus standard-of-care in terms of reducing perioperative complications in patients with bladder cancer undergoing RC.

Methods and analysis This multicenter, open label, prospective, randomized controlled trial, will include 154 patients with bladder cancer undergoing RC. Patients are recruited from eight hospitals in The Netherlands and will be randomly (1:1) allocated to the intervention group receiving a structured multimodal prehabilitation program of approximately 3-6 weeks, or to the control group receiving standard-of-care. The primary outcome is the proportion of patients who develop one or more grade ≥2 complications (according to the Clavien-Dindo classification) within 90 days of surgery. Secondary outcomes include cardiorespiratory fitness, length of hospital stay, health-related quality of life, tumor tissue biomarkers of hypoxia, immune cell infiltration, and cost-effectiveness. Data collection will take place at baseline, before surgery, and 4 and 12 weeks after surgery.

Ethics and dissemination Ethical approval for this study was granted by the Medical Ethics Committee NedMec (Amsterdam, The Netherlands) under reference number 22-595/NL78792.031.22. Results of the study will be published in international peer-reviewed journals.

Trial registration number Clinical Trials (NCT05480735). Prospectively registered on 29 July 2022.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a multicenter randomized controlled trial investigating the effects of multimodal prehabilitation in an understudied group of patients with bladder cancer undergoing radical cystectomy.
- This data collected in this study enables exploration of the effects of prehabilitation on tumor hypoxia and immune cell infiltration.
- The intervention accounts for heterogeneity in cancer treatment by offering additional support during neoadjuvant treatment when appropriate.
- This study includes a cost-effectiveness analysis from a societal perspective.
- Due to the two-group design and the multimodal intervention, it will not be possible to disentangle the independent effects of physical exercise training, nutritional support, psychological counseling, and smoking cessation.

INTRODUCTION

Bladder cancer is the 10th most common diagnosed cancer worldwide, with over 573,000 new patients and 213,000 deaths each year [1]. Radical cystectomy (RC) is the standard treatment for patients with non-metastatic muscle-invasive bladder cancer [2, 3], as well as for patients with therapy refractory high-risk non-muscle invasive bladder cancer [4]. RC is a challenging and costly surgical procedure with high morbidity and mortality rates [5]: 50-65% of the patients experience perioperative complications, of which 10-20% are high-grade [6-8]. Low cardiorespiratory fitness [9, 10], poor nutritional status [11], the presence of anxiety and depression [12], and smoking [13] increase the risk of perioperative complications, length of hospital stay, and the associated medical costs [9, 10]. In daily clinical practice, 25% of patients with muscle-invasive bladder cancer receive neoadjuvant treatment, which might further impair preoperative cardiorespiratory fitness and nutritional status [14-17].

Emerging evidence has identified the preoperative period as a window of opportunity to address lifestyle. Multimodal preoperative interventions, including physical exercise training, nutritional support, psychological counseling, and smoking cessation, that aim to increase a patient's tolerance to surgery, reduce the incidence, severity, and impact of complications, accelerate and improve the quality of recovery, and improve quality of life have been termed *prehabilitation*.

To date, no adequately powered trial has been performed to establish the effectiveness of a multimodal prehabilitation program for reducing the incidence, severity, and impact of complications and costs associated with RC for bladder cancer. A few studies investigated the impact of a single modal [18, 19] or multimodal [20, 21] prehabilitation program on functional recovery following RC. A phase I/II trial with 54 patients showed improvement in patient-reported quality of life after four weeks of a supervised physical exercise training program before surgery [19]. A feasibility randomized controlled trial with 60 patients provided evidence that a 3- to 6-week supervised vigorous aerobic exercise training program before surgery led to improvements in cardiorespiratory fitness parameters and possibly fewer surgical complications [18]. A randomized controlled trial with 107 patients demonstrated improvement in walking distance during seven days after surgery [20] and improved muscle power [22]. Finally, a randomized controlled trial with 70 patients showed significant better functional capacity in the intervention group that followed a multimodal program compared to the control group, at four weeks after surgery [21]. However, the physical exercise intervention in these studies including patients with bladder cancer had limitations with regard to therapeutic validity [23] due to a short duration of the

intervention [20, 22], relatively low exercise intensity [20-22], or only patient reported compliance with the exercise intervention [20-22].

Preclinical studies indicate that exercise may directly affect tumor characteristics such as normalization of tumor vasculature and immune cell infiltration, thereby enhancing tumor perfusion and reducing hypoxia [24, 25]. These factors are associated with treatment efficacy and survival [26-28]. The current study provides a unique opportunity to explore the effects of prehabilitation on tumor inflammation and hypoxia markers, which has not yet been studied in human patients.

Study objectives

The ENHANCE study is designed to investigate the effectiveness of a multimodal prehabilitation program versus standard-of-care in patients approaching RC. The primary aim is to investigate the superiority of a multimodal prehabilitation program in terms of reducing one or more grade ≥2 perioperative complications within 90 days in patients with bladder cancer undergoing RC. Secondary outcomes include changes in preoperative cardiorespiratory fitness, length of hospital stay, health-related quality of life, tumor tissue biomarkers of hypoxia, immune cell infiltration, and cost-effectiveness.

METHODS AND ANALYSIS

The ENHANCE study is a multicenter, open label, two-arm randomized controlled trial. Patient inclusion and data collection started in August 2022. Ethical approval, extending to all participating centers, was granted by the Medical Ethical Committee NedMec (Amsterdam, The Netherlands), under reference number 22-595/NL78792.031.22. The trial is prospectively registered in Clinical Trials (NCT05480735) on 29 July 2022.

Study population

The study aims to include 154 patients who meet the following inclusion criteria: aged ≥18 years, histologically confirmed, primary, bladder cancer (cTa-4N0-3M0), and planned to undergo RC. Surgery will not be delayed in favor of prehabilitation. Hence, patients who are scheduled for surgery within 3 weeks are not eligible for the trial. Patients who express the intention to follow a similar exercise training program regardless of randomization outcome, patients with severe cognitive or psychiatric disorders, patients with a contraindication to perform physical exercise training or a cardiopulmonary exercise test (CPET), and patients unable to read or understand the Dutch language will also be excluded.

Recruitment and randomization

Patients are recruited from eight academic or teaching hospitals across different regions in The Netherlands (Catharina Hospital, Erasmus Medical Center, Maastricht University Medical Center+, Noordwest Hospital Group, Radboud University Medical Center, Rijnstate Hospital, University Medical Center Groningen, and University Medical Center Utrecht). The Netherlands Cancer Institute is the coordinating center. After establishment of diagnosis and indication for surgery, the urologist or nurse specialist invites patients to participate in the study and provides the patient information letter. The study coordinator contacts these patients to provide further oral information and answer potential questions about the study. When a patient agrees to participate, written informed consent is obtained. After collection of baseline data, patients are randomized in a 1:1 ratio, using a minimization algorithm [29] aimed to achieve optimal balance between the two study arms with regard to the recruiting hospital, neoadjuvant treatment (yes/no), nodal status (N0/N1-3), and type of surgery (open/robot-assisted RC). Minimization is done using the Minirand package in R 4.0.4 [30, 31]. The algorithm includes a random component to ensure blinding of treatment allocation. Due to the nature of the intervention, blinding of participants and research investigators is not possible. After randomization, patients in both the intervention and control groups receive a leaflet with recommendations on physical activity, diet

and smoking cessation, according to the latest guidelines for patients with cancer [32, 33]. These recommendations are not further individualised or actively supported.

Patients who do not wish to participate in the study are asked to participate in a one-time questionnaire as described in Table 1. A participant flow diagram is shown in Figure 1.

Table 1. Outcome measures in the intervention and control group

Description of outcome	Assessment	Description of measure	T0a	T0b	T1	T2	T3
Primary outcome							
Proportion of patients who develop one or more grade ≥2 perioperative complications within 90 days	Perioperative complications, Grade ≥2 according to Clavien Dindo classification	Number of grade ≥ 2 complication is abstracted from medical records				X	X
Secondary outcomes							
Proportion of patients who develop one or more high-grade (≥3) complications, number of complications, length of hospital stay, and readmissions within 90 days	Perioperative complications, Grade ≥3 according to Clavien Dindo classification, length of hospital stay, readmissions	Number of grade ≥ 3 complications, number of complications, length of hospital stay in days, and readmissions abstracted from medical records				X	X
Cardiorespiratory fitness	Cardiopulmonary exercise test (CPET) on a cycle ergometer using a ramp protocol [34]	Peak oxygen uptake (VO_2peak in ml/kg/min)	X		X		
Physical functioning	Short physical performance battery (SPPB) [35]	5 items organized into three subscales of balance, walking speed, and lower extremity muscle strength	X		X		X
Upper extremity muscle strength	Handgrip strength using a handheld dynamometer [36]	The maximum score of three attempts of both hands in kilogram (kg)					
Lower extremity functional muscle strength	30-second sit-to-stand test [37]	The number of sit to stands within 30 seconds	X		X		X
Nutritional intake	24-h recall	Protein (total gram) and caloric intake (total kcal)	X		X		
Nutritional status	Patient-generated subjective global assessment short form (PG-SGA SF) [38]	4 items assessing weight (status), nutritional intake, symptoms, and physical functioning	X	X	X	X	X
	Nil per mouth consumption during hospitalization	The number of days after RC abstracted from medical records				X	X
Body composition	Bioelectrical impedance analysis	Body mass (kg), body height (cm), (subcutaneous) fat mass (%), and (upper limb) muscle mass (kg) are measured, and BMI (kg/m^2)	X		X		X
Health-related quality of life	EORTC quality of life questionnaire core 30 (QLQ-C30) [39]	30 items, organized into 5 functional scales (physical, role, emotional, cognitive, social), 3 symptom scales (pain, fatigue, and emesis), 6 items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and an overall QoL scale	X	X	X	X	X
Bladder cancer-related quality of life	EORTC muscle-invasive bladder cancer specific module (BLM-30) [40]	30 items, assessing urinary symptoms, bowel symptoms, sexual functioning, urostomy problems, difficulties associated with the use of a catheter and body image	X	X	X	X	X
Anxiety and depression	Hospital anxiety and depression scale (HADS) [41]	7 items assessing anxiety and 7 items assessing depression	X	X	X	X	X
Fatigue	Multidimensional fatigue inventory (MFI) [42]	20 items, categorized into five scales: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue	X	X	X	X	X

Physical activity	Short questionnaire to assess health-enhancing physical activity (SQUASH) [43]	11 items, organized into 4 different physical activities measuring frequency, duration and intensity (physical activity to and from home, household activities, activities at work and physical activities performed during leisure time)	X	X	X	X	X
Tumor hypoxia and immune cell infiltration	Two tumor biopsies: from routine diagnostic investigation and from surgical tumor excision	Immunohistochemistry analysis will be performed for hypoxia and immune cell infiltration biomarkers using the laboratory of the Karolinska Institutet (Sweden) and their according protocols	X		X		
Cost-effectiveness	EuroQol 5-dimension (EQ-5D-5L) [44]	5 items (dimensions) multi-attribute utility questionnaire that measures mobility, self-care, usual activities, pain/discomfort and anxiety/depression in 5 levels	X	X	X	X	X
	iMTA medical consumption questionnaire (iMCQ) [45] and productivity costs questionnaire (iPCQ) [46]	Patient reported productivity losses and medical consumption		X	X	X	X
	Health care costs	Medical activities abstracted from the management systems of the hospitals					X
Other outcomes							
Sociodemographic and clinical data	Sociodemographic data, disease, and treatment characteristics will be abstracted from medical records or reported by the patient	Patient reported: place of birth, sex, marital status, living and work situation, education, lifestyle variables, and the self-administrated comorbidity questionnaire [47] Medical records: birth month and year, date of diagnosis, date and type of treatment, type of urinary diversion, tumor characteristics, ASA score, WHO score	X				
		Patient reported: smoking status	X	X	X	X	X
Coping mechanism	Sense of coherence questionnaire [48]	13 items, categorized into three scales: comprehensibility, manageability, meaningfulness	X				
Compliance to the intervention	Adherence rates	Patient reported: self-composed (activity) diary Physical therapist: adherence of the physical exercise training intervention on standardized training session forms	X	X	X		
Patient evaluation	Self-composed questionnaire	Patients in the intervention group: satisfaction with the program and willingness to participate in focus group Patients in the control group: evaluate contamination Both groups: evaluation of possible post-surgical intervention					X
Non-participation	Self-composed questionnaire	Patient reported outcomes: sociodemographic, health- and bladder cancer-related quality of life, anxiety and depression, fatigue, physical activity, coping mechanism, and reason(s) for not participating Medical records: birth month and year, date of diagnosis, date and type of treatment, tumor characteristics, ASA score, WHO score	X				

Control group– standard-of-care

Patients randomized to the standard-of-care arm receive care as usual, which does not include a comprehensive multimodal prehabilitation program. In all participating centers, enhanced recovery after surgery protocols are used to optimize medical conditions to enhance recovery [49]. These protocols include advice on smoking cessation when a patient is smoking and a referral to a dietician when malnutrition is detected. Preoperatively, the urologist determines whether the patient is physically fit for surgery. Patients in the control group are not prohibited to be physically active or seek counselling for nutritional advice, psychological support, or smoking cessation.

Intervention group– prehabilitation

Patients randomized to the intervention arm will participate in a multimodal prehabilitation program including supervised physical exercise training, nutritional support, and – when relevant – psychological counseling and professional support for smoking-cessation, to enhance their health status. The intervention starts as soon as possible after baseline measurements and randomization, approximately 3-6 weeks before surgery, and is continued until surgery. Patients who are included before undergoing neoadjuvant treatment (including chemotherapy and immunotherapy) will participate in a physical exercise training program from inclusion until completion of neoadjuvant treatment to prevent the often observed decline in physical fitness throughout neoadjuvant therapy. Subsequently, these patients will participate in the full multimodal prehabilitation program until the date of surgery. Adverse events related to the intervention are monitored.

Physical exercise training program

The physical exercise training program consists of three training sessions per week under the supervision of a physical therapist. An overview of the training program and training progression is described in Table 2. The program will be delivered at a physical therapy practice near a patient's home to minimize travel time, preferably supervised by a physical therapist affiliated with Onconet, a nationwide network of physical therapists with additional competencies in cancer care. The study coordinator provides the physical therapists instructions via a video call covering the specifics of the training program for the current study.

Table 2. Content of the supervised physical exercise training program in the intervention group

Frequency	**I**ntensity	**T**ime	**T**ype
Three times a week	Aerobic interval training, consisting of 4 intervals of alternating effort performed on a cycle ergometer: - 4 min of low-intensity exercise, defined as 30% of the workload achieved at VO_2peak - 2-3 min of high-intensity exercise, defined as 90% of the workload achieved at VO_2peak[a]	24-28 min	Aerobic interval training
Two times a week	During neoadjuvant treatment: **Week 1 – 3**: consisting of 20 minutes on a cycle ergometer and 10 minutes on a different aerobic machine, corresponding to 30% of the heart rate reserve **Week 4 – 6:** consisting of 20 minutes on a cycle ergometer and 10 minutes on a different aerobic machine, corresponding to 40% of the heart rate reserve **Week 7 – 9:** consisting of 20 minutes on a cycle ergometer and 10 minutes on a different aerobic machine, corresponding to 50% of the heart rate reserve **Week 10 – 12 (and further):** consisting of 20 minutes on a cycle ergometer and 10 minutes on a different aerobic machine, corresponding to 60% of the heart rate reserve	30 min	Aerobic training
Two times a week	Resistance training, consisting of training six large muscle groups (leg press, bench press or chest press, abdominal crunch, pull over, low row, and step up)[b] in 2 sets: - Week 1: maximal 15 repetitions at ~65% of 1RM per set - Week 2: maximal 12 repetitions at ~70% of 1RM per set (weight week 1 +10%) - Week 3: maximal 10 repetitions at ~75% of 1RM per set (weight week 2 +10%) - From week 4 maximal 10 repetitions per set[c]	~20 min	Resistance training
Once a week	Progressive muscle relaxation techniques [50]	~20 min	Relaxation exercises

Abbreviations: 1RM=one-repetition maximum; CPET=cardiopulmonary exercise test; VO_2peak=oxygen uptake at peak exercise.

[a] Further tailoring is done by the physical therapists: if a patient is not able to complete the high-intensity interval, the intensity will be reduced by 10%. The intensity can be reduced further in steps of 10% until the patient can complete all four high-intensity intervals. If a patient is able to complete all high-intensity intervals, moderate and high intensity will be increased by 10% [51]. During neoadjuvant treatment [52]: if a patient scores below a Borg score of 12 intensity is increased, if a patient scores above a Borg score of 15 intensity is decreased.

[b] Physical therapists can offer alternative resistance exercises targeting the same muscle group to accommodate a patient's abilities and preferences.

[c] If the patient is able to do two repetitions more than planned, the load will be increased by 10%. The load will be decreased by 10% if the patient is not able to achieve the planned number of repetitions.

Training sessions last one hour and consist of individualized aerobic interval training (three times a week), resistance training (two times a week), and relaxation exercises (once a week). Results of the CPET will be used to establish the individual training intensity for aerobic interval training. For the resistance training, six large muscle groups will be targeted, in two sets of a defined maximum number of repetitions. The aim of these training sessions is to improve cardiorespiratory fitness, and muscle strength and mass. Relaxation exercises consist of guided breathing exercises and progressive muscle relaxation [50]. The aim of these exercises is to reduce possible anxiety and stress. In addition to the supervised sessions, patients are encouraged to be moderately active on at least two additional days per week for 30 minutes.

The supervised sessions during neoadjuvant treatment consist of twice-weekly moderate-intensity aerobic and resistance training. Patients receive the physical exercise training program as described above for the remaining 3-6 weeks before surgery.

Nutritional support

Patients receive tailored advice from a registered dietician at the participating hospitals aiming at a total protein intake of 1.9-2.3 g/per kg of fat-free mass as estimated with bioelectrical impedance analysis, to promote an anabolic state. Dietary advice will emphasize the benefit of spreading protein consumption over three meals, with a goal of 25-30 g protein per meal, and includes advice for optimal energy intake. To achieve this, and to increase adaptive responses of the skeletal muscle, participants will receive high-quality protein supplements containing 30 g of whey protein, 20 microgram of vitamin D, and 250 mg of calcium [53] in standardized supplements produced for the purpose of the study (FrieslandCampina, The Netherlands). These supplements are prescribed after each physical exercise training session and daily at least one hour before sleep or in the morning (depending on the patient's preference). The dietician provides intake consultation and one or two follow-up sessions to evaluate nutritional intake. Protein intake will be restricted according to the severity of renal impairment. Depending on the patient's protein intake, patients will be advised to either reduce or drop the intake of protein supplements. If necessary, additional dietary advices will be provided to reduce nutritional protein intake. Nutritional support starts at 3-6 weeks before surgery for all patients.

Psychological counseling

Patients are screened for anxiety and depression using the hospital anxiety and depression scale (HADS) questionnaire at baseline [41]. If a patient's score falls between 11 and 18, the option of psychological counselling is discussed, and referral is arranged for patients indicating a need for such counselling. Patients who score ≥19 are directly referred to psychological counselling. Referred patients receive an initial counselling session of 1.5 hours, and additional sessions at the discretion of the psychological counsellor and the patient.

Smoking cessation

Intensive counselling and nicotine replacement therapy is offered to all smoking patients in the 3-6 weeks before surgery. Counselling includes at least one in-person session and one or more telephone or in-person follow-up sessions by trained counsellors. If the patient indicates to be smoking and is willing to quit, the treating physician will refer the patient.

Study outcomes

Data are collected before randomization (T0a), before surgery (T1), and 4 (T2), and 12 (T3) weeks after surgery. If applicable, additional data will be collected after neoadjuvant treatment (T0b). At T0a, clinical data (e.g., treatment, clinical stage) will be abstracted from the medical records and sociodemographic characteristics (e.g., age, sex, education) will be obtained via a questionnaire. In addition, coping mechanisms [54] will be assessed via a questionnaire as this can help understand participation, attendance, and dropouts. Data is collected in CastorEDC and access is restricted to the investigator team. Due to the low risk of the intervention a data safety monitoring board is not instated.

Primary outcome

The primary outcome is the proportion of patients who develop one or more grade ≥2 perioperative complications within 90 days after surgery. Complications are graded according to the Clavien-Dindo classification system [55] as described in Table 3.

Table 3. The Clavien-Dindo classification of surgical complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physical therapy This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusionsand total parenteral nutritionare also included
Grade III	Requiring surgical, endoscopic, or radiological intervention
-IIIa	Intervention not under general anesthesia
-IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)[a] requiring IC/ICU-management
-IVa	Single organ dysfunction (including dialysis)
-IVb	Multiorgan dysfunction
Grade V	Death of a patient

Adapted from [55].

Abbreviations: CNS=central nervous system; IC=intermediate care; ICU=intensive care unit.

[a] brain hemorrhage, ischemic stroke, subarrachnoidalbleeding, but excluding transient ischemic attacks (TIA)

Secondary outcomes

Secondary outcomes are the proportion of patients who develop one or more high-grade (grade ≥3) complications, total number of complications, length of hospital stay, number of readmissions, disease status (progression/recurrence), and additional treatment within 90 days. Secondary outcomes also include the intermediate outcomes of the intervention: cardiorespiratory fitness (measured using the standardized CPET [34]), physical functioning, upper and lower extremity (functional) muscle strength, nutritional intake, nutritional status, body composition, health-related quality of life, bladder cancer-related quality of life, anxiety and depression, fatigue, physical activity, and adherence to the intervention. Direct and indirect costs are collected for the cost-effectiveness analysis. Tumor hypoxia, immune cell infiltration, and pathological response are assessed as explorative outcomes. Participants in the control group will be asked whether they participated in any (structured) lifestyle program during the preoperative period, to monitor contamination. In both groups, participants will be asked whether they received any postoperative intervention. The timing and type of outcome measures are presented in Table 1.

Costs

For direct costs in both groups, medical records will be used to gather data on treatment, complications, length of hospital stay and number of readmissions, follow up, and diagnostics. For the intervention group, the costs for the prehabilitation program, including physical exercise training, nutritional support, psychological counseling, and smoking cessation, will be determined by means of the activity-based costing (ABC) [56] method. Costs for neo-adjuvant treatment are expected to be equal for both arms and will therefore not be included in the calculation. For indirect costs, the iMTA medical consumption questionnaire (iMCQ) [45] will be used, to gather data on medical consumption outside the hospital. The iMCQ includes questions related to frequently occurring contacts with health care providers. For patients who currently have remunerative employment, productivity losses will be obtained through the iMTA productivity costs questionnaire (iPCQ) [46]. To calculate quality-adjusted life years, utilities will be derived from the EuroQoL 5-dimension (EQ-5D-5L) questionnaire [44].

Compliance

To monitor therapeutic validity, compliance with the physical exercise training program is assessed by attendance rates and compliance to all parts of the training program as scored by the physical therapist on standardized training session forms, as well as by patient self-report via an activity diary. Compliance

to nutritional supplement intake is assessed via a diary. Whether smoking cessation has been successful is assessed through questionnaires.

Satisfaction

Patients in the intervention group are asked to complete a short questionnaire at the end of the study about the perceived effectiveness of and satisfaction with the program, whether they would suggest any changes, and whether they would recommend it to other patients with bladder cancer. In addition, patients will be asked if they are willing to be contacted for participation in a focus group where the intervention program and changes that may positively affect implementation will be further discussed.

Sample size calculation

Previous studies in diverse types of cancer reported a reduction of postoperative complications in the intervention group compared to the control group, with odds ratios ranging from 0.11 to 0.88 [57-63]. This study aims to reduce the number of patients with any grade ≥2 perioperative complication within 90 days from 60% [64, 65] to 35% (relative risk 0.58, odds ratio 0.36) [66, 67]. Assuming a two-sided Fisher exact test with a power of 80% and an alpha of 0.05, in total 140 patients will be needed. To account for 10% dropout, including dropout due to cancelling of the planned surgery, 154 patients will be included. Approximately 380 patients with bladder cancer undergo RC in the eight participating hospitals annually. This implies that it is feasible to complete inclusion within two and a half years, if recruitment rate is at least 17%.

Statistical analysis

Primary outcome

All analyses will be performed on an intention-to-treat basis. Descriptive statistics will be calculated to describe and evaluate the comparability of the two groups at baseline on sociodemographic and clinical variables, and to assess the adequacy of the randomization. Patients who do not receive the planned surgery or have an open-closed procedure, independent of group allocation, will be excluded from the primary analysis. The proportion of patients who develop any grade ≥2 complications will be compared in the two study arms by using Fisher's exact test and a Poisson regression model with a log link, adjusted for the stratification factors and relevant baseline imbalances. The relative risk will be reported with a 95% confidence interval based on robust standard errors [68].

Secondary study outcomes

Between-group differences over time will be evaluated in measures of physical functioning and patient-

reported outcomes using linear mixed effects regression analysis. For high-grade complications, length of hospital-stay, and number of readmissions, Poisson regression models with an appropriate link function will be used. For continuous outcomes, differences in mean change scores between the two study arms will be accompanied by effect sizes. Standardized effect sizes will be calculated by subtracting the mean change scores of the control group from those of the intervention group, and subsequently dividing this by the pooled standard deviation. Effect sizes of 0.2 are considered small, 0.5 moderate, and 0.8 large [69]. A *p*-value <0.05 will be considered statistically significant.

Intervention fidelity

Descriptive statistics will be used to summarize compliance rates of the supervised exercise sessions as well as home based physical activity, supplement consumption, and smoking cessation. Compliance rates are based on number of completed training sessions, supplementation consumption, and number of patients who stop smoking in the study intervention. Whether the level of compliance is associated with changes over time in primary and secondary study outcomes will be evaluated using generalized linear mixed effects models.

Non-participants

Baseline data of participants will be compared to those of non-participants using chi-squared statistics for categorical variables and analysis of variance for continuous variables.

Exploratory analysis

Exploratory analyses will be performed to explore the moderating effect of intervention duration, and differences in effectiveness of the physical exercise training program between those who received neoadjuvant chemotherapy and those who did not. This will be done by adding interaction terms to the model and by performing stratified analyses if the interaction term is statistically significant at $p<0.10$. Exploratory analyses will also be executed to study the relationship of post-intervention/preoperative physical fitness parameters (i.e., VO_2peak) and nutritional status, with perioperative outcomes (grade ≥2 complications yes/no and number of days in the hospital. For this analysis, univariable and multivariable Poisson regression analyses will be used.

Economic evaluation

A trial- and model-based economic evaluation will be performed, based on the intention-to-treat analysis. The model-based evaluation will use literature for the potential long-term consequences and parametric survival methods to extrapolate the trial data beyond the included follow-up. The analysis

will be approached from a societal perspective of The Netherlands and a lifelong time horizon. A Markov decision model will be built, with relevant health states derived from the EQ-5D-5L questionnaire. Outcomes are 1) the incremental costs per reduced proportion of patients who develop one or more grade ≥2 perioperative complications within 90 days (trial-based), and 2) incremental costs, incremental quality-adjusted life years, and the incremental cost-effectiveness ratio (ICER) (model-based). An estimation of the degree of uncertainty around each input parameter will be included with the use of probabilistic sensitivity analyses. Parameter values will be drawn randomly from the assigned distributions, using Monte Carlo simulations [70]. To capture necessary support regarding adoption and further research, value of information (VOI) analyses will be performed [71]. Where appropriate, Dutch guidelines for costing studies will be used in applying tariffs to units of resource use [72]. Finally, a budget impact analysis will be performed according to the ISPOR guidelines [73].

Patient and public involvement

Patients or the public were not involved in the development of the study design. A patient representative is currently involved in the study and input will be obtained whenever relevant during the trial. Annual consortium meetings with the urologists are organized.

DISCUSSION

A considerable proportion of patients with bladder cancer scheduled for RC has a poor cardiorespiratory fitness [9, 10], is malnourished [11, 74], and/or is an active smoker at diagnosis [75]. This implies that there is a substantial potential for improving cardiorespiratory fitness and nutritional status in this patient population. Here, the rationale and design of a multimodal prehabilitation program for patients with bladder cancer who are scheduled for RC is presented. It is hypothesized that the program will be effective in reducing the number and severity of perioperative complications.

This study has several strengths, including its multicenter, randomized design, the use of an intention-to-treat basis for the data analysis, and a minimization technique to ensure blinded treatment allocation and comparable groups. Most importantly, the study intervention consists of a tailored program for physical exercise training and nutritional support following current best-practice for prehabilitation. Moreover, a cost-effectiveness analysis will be performed to anticipate smooth implementation and reimbursement, and tumor hypoxia and immune cell infiltration analysis will be performed exploratively. Intervention fidelity will be monitored in detail, as recommended previously [76], as will adverse events related to the intervention. Another notable strength is the additional analysis in non-participants. Selective non-participation is a serious risk for the generalizability of physical exercise training studies. Previous physical exercise training studies in other cancer populations have shown relevant differences between those who participate and those who do not [77, 78]. It has previously been described that patients who were eligible for prehabilitation programs for colon cancer surgery expressed several reservations [79]. It is vital to understand the characteristics of non-participants and reasons for non-participation in bladder cancer prehabilitation. This will not only help judge the generalizability of the results but will also support implementation in a way that will maximize the potential value of the prehabilitation program and achieve equitable health outcomes. Finally, the exploratory subgroup analysis in patients who receive neoadjuvant treatment might be relevant to inform future studies on risk stratification.

To limit barriers to participation and adherence, the exercise program will be delivered as near to the patients' homes as possible, to minimize travel time. This is a very important factor for patients with cancer according to previous studies [67, 80-82]. The availability of and close collaboration with the nationwide Onconet network of physical therapists, who are specifically educated to supervise patients with cancer, is an important advantage. An additional benefit of this approach is that it will facilitate implementation if the intervention proves to be effective.

This study also has some limitations. Patients with bladder cancer will be followed for a period of 90 days after surgery, meaning that longer-term evaluation of outcomes will not be possible. Because up to 60% of patients report complications within 90 days after surgery [83], it is expected that the time frame will be adequate for our primary outcome. A possible limitation is the risk of contamination in the control group. An evaluation questionnaire will be used in the control group to determine whether patients were physically active or received a (structured) lifestyle intervention pre- and postoperatively. Although objective measurements of habitual physical activity may provide a more detailed insight into physical activity levels not prone to recall bias, the collection of physical activity levels will be restricted to using questionnaires for feasibility reasons. This program is designed to maximally improve a patient's health status by including physical exercise training, nutritional support, psychological counseling and smoking cessation. It is not likely that patients who are randomized to the control group would initiate a program consisting of all these components on their own. The multimodal approach prohibits disentangling of the individual effects of each lifestyle component in the prehabilitation program. Considering the number of intervention components and the prevalence of bladder cancer, a larger study using a full factorial design is unlikely to be feasible in this population. Moreover, the current best-practice for other types of cancer supports the use of multimodal interventions over unimodal approaches [84, 85]. Higher levels of physical exercise training have been demonstrated to be beneficial for both cancer prevention and, in some solid tumors, progression of disease and cancer-related mortality [86, 87]. However, the underlying biological mechanism has yet to be demonstrated. It is expected that the prehabilitation program has positive effects on the tumor microenvironment. The hypoxic tumor microenvironment is a common characteristics of a solid tumor when oxygen levels become low, as a result of the rapid proliferation of tumor cells [88] and is linked to poor prognosis in bladder cancer [89]. Physical exercise training has regulatory effects on the angiogenesis of skeletal muscles, which has raised interest in whether these effects might translate to solid tumors [90]. Preclinical research has shown that training may acutely reduce tumor hypoxia through vascular normalization and thereby improve the perfusion of tumor tissue [91-94]. In addition, exercise training has been suggested to alter immune cell infiltration in solid tumors and thereby contribute to enhanced immune surveillance and improved vascular function [25]. However, current evidence is inconsistent and inconclusive [95]. Clinical trials are very limited and this preoperative setting provides an excellent opportunity to investigate the potential role of prehabilitation on tumor hypoxia and immune cell infiltration.

To summarize, this study will provide empirical evidence on the benefits of multimodal prehabilitation for patients with bladder cancer planned for RC who are at high risk of perioperative complications and a long recovery period. When proven (cost-)effective, the study results will support implementation of a multimodal prehabilitation program for patients with bladder cancer in daily clinical practice.

Figure caption

Figure 1. Study flow chart

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Authors' contributions
AV, AL, AH, EK, VPR, WH, AM, WG, and MMS conceived the study. AV, WH, AM, WG, MMS, MGS, and EA contributed to the design of the study protocol. RM, AL, AH, VCR, EK, SB, CW, TM, and BB reviewed the study protocol with a clinical perspective. VPR wrote the statistical approach of the economic evaluation. HR composed the protocol of tumor hypoxia and immune cell infiltration analysis. AV, WH, AM, WG, MMS, MGS, and EA wrote the manuscript. All authors read, commented on, and approved the manuscript.

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Competing interests
CW received a research grant from ZonMw and gives courses on robot assisted radical cystectomy during conferences entitied with EAU. TM received consulting fees as member of the advisory board prostate cancer of Janssen-Cilag B.V.. BB participates on a Data Safety Monitoring Board of an international prehabilitation study, is board member of Netherlands Society of Human Movement sciences, member of Exercise is Medicine of Vereniging voor Sportgeneeskunde, and member of the Scientific Committee of Fit4Surgery. RM received research grants from Janssen, Roche and Astellas, an educational grant from Merck, received consulting fees from Merck, MSD, Janssen, Bristol-Myers Squibb Company, received support for attending the 2022 Global Congress on Bladder Cancer, and is EAU Panel member of the Muscle Invasive Bladder Cancer Guideline. MMS is member of the Scientific Committee of Fit4Surgery and board member of Onconet.

Patient consent for publication
Not applicable.

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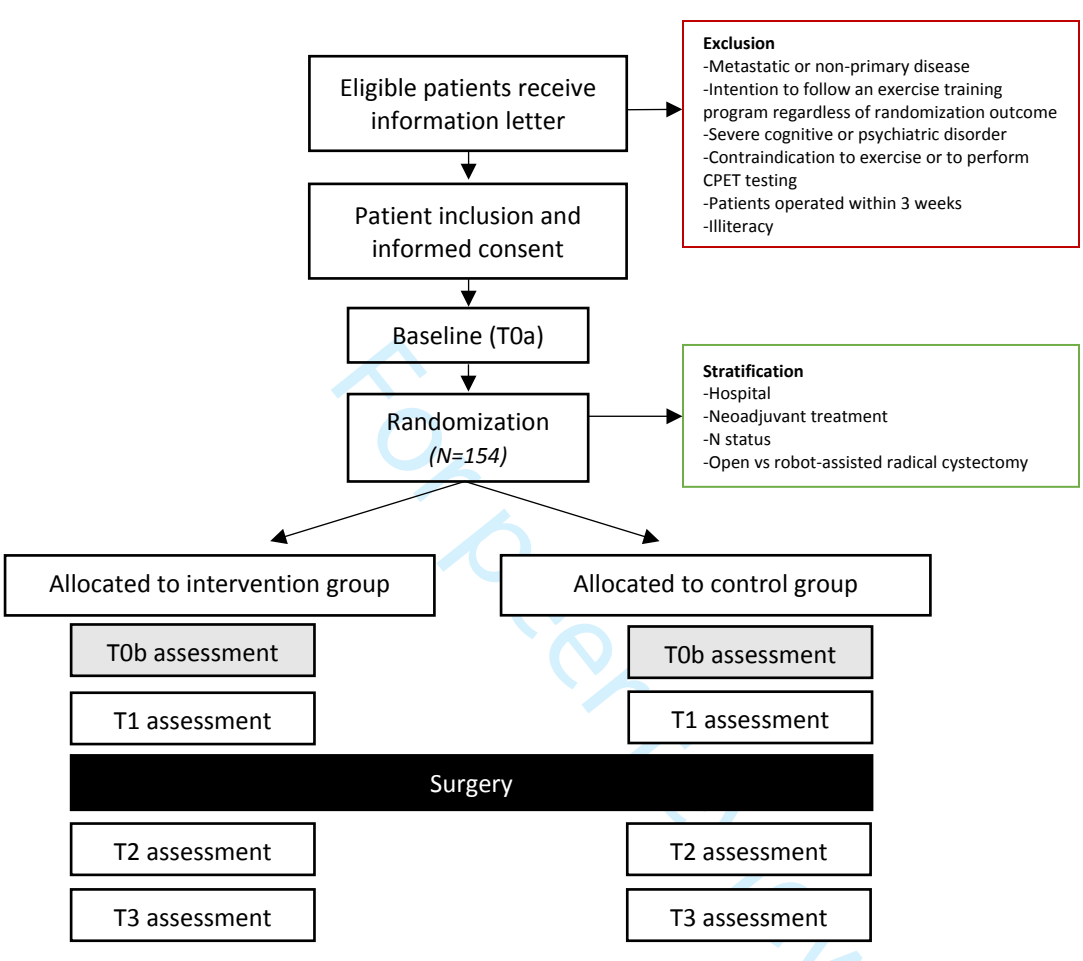
Figure 1. Study flow chart



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

Section/item	Item No	Description	Addressed on page number
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	3, 7
	2b	All items from the World Health Organization Trial Registration Data Set	3, 7
Protocol version	3	Date and version identifier	N.A.
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 2, 17
	5b	Name and contact information for the trial sponsor	17
	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	17
	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)	7

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	5, 6
	6b	Explanation for choice of comparators	8
Objectives	7	Specific objectives or hypotheses	6
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)	7
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	7
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)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10, Table 2
	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)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10,11, 14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	10, 11
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)	7, 8, Figure 1, Table 1

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	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
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	7
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	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N.A.
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	10, 11, Table 1
	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	Table 2

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	10
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	11-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12, 13
	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)	12
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	10
	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	8, 14
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	7
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)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
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	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
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	10
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	3
	31b	Authorship eligibility guidelines and any intended use of professional writers	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	N.A.
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.