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EffectiveNess of a multimodal preHAbilitation program in patieNts with bladder canCEr undergoing radical cystectomy: protocol of the ENHANCE multicentre randomised 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 programme versus standard-of-care in terms of reducing perioperative complications in patients with bladder cancer undergoing RC.

Methods and analysis This multicentre, open label, prospective, randomised 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 programme 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, tumour 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.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a multicentre randomised 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 tumour 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 counselling and smoking cessation.

Trial registration number NCT05480735.

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 counselling 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 programme 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 programme on functional recovery following RC. A phase I/II trial with 54 patients showed improvement in patient-reported quality of life after 4 weeks of a supervised physical exercise training programme before surgery.[19] A feasibility randomised controlled trial with 60 patients provided evidence that a 3–6 weeks supervised vigorous aerobic exercise training programme before surgery led to improvements in cardiorespiratory fitness parameters and possibly fewer surgical complications.[18] A randomised controlled trial with 107 patients demonstrated improvement in walking distance during 7 days after surgery[20] and improved muscle power.[22] Finally, a randomised controlled trial with 70 patients showed significantly better functional capacity in the intervention group that followed a multimodal programme compared with the control group, at 4 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 tumour characteristics such as normalisation of tumour vasculature and immune cell infiltration, thereby enhancing tumour 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 tumour 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 programme versus standard-of-care in patients approaching RC. The primary aim is to investigate the superiority of a multimodal prehabilitation programme 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, tumour tissue biomarkers of hypoxia, immune cell infiltration and cost-effectiveness.

METHODS AND ANALYSIS

The ENHANCE study is a multicentre, open label, two-arm randomised controlled trial. Patient inclusion and data collection started in August 2022. Ethical approval, extending to all participating centres, 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 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 favour 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 programme regardless of randomisation 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 randomisation

Patients are recruited from eight academic or teaching hospitals across different regions in The Netherlands (Catharina Hospital, Erasmus University 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 centre. 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 randomised in a 1:1 ratio, using a minimisation 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). Minimisation is done using the Minirand package in R V.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 randomisation, 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 randomised to the standard-of-care arm receive care as usual, which does not include a comprehensive multimodal prehabilitation programme. In all participating centres, enhanced recovery after surgery protocols are used to optimise 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 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 randomised to the intervention arm will participate in a multimodal prehabilitation programme including supervised physical exercise training, nutritional support and—when relevant—psychological counselling and professional support for smoking-cessation, to enhance their health status. The intervention starts as soon as possible after baseline measurements and randomisation, 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 programme 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 programme until the date of surgery. Adverse events related to the intervention are monitored.

Physical exercise training programme

The physical exercise training programme consists of three training sessions per week under the supervision of a physical therapist. An overview of the training programme and training progression is described in table 2. The programme will be delivered at a physical therapy practice near a patient's home to minimise 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 programme for the current study.

Training sessions last 1 hour and consist of individualised aerobic interval training (three times a week), resistance training (two times a week) and relaxation exercises (one time 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.[35] 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 min.

The supervised sessions during neoadjuvant treatment consist of twice-weekly moderate-intensity aerobic and resistance training. Patients receive the physical exercise training programme 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 emphasise 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 µg of vitamin D and 250 mg of calcium[36] in standardised 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 1 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 advice will be provided to reduce nutritional protein intake. Nutritional support starts at 3–6 weeks before surgery for all patients.

Psychological counselling

Patients are screened for anxiety and depression using the Hospital Anxiety and Depression Scale 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

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 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[84]	Five items organised 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[85]	The maximum score of three attempts of both hands in kilogram (kg)	X		X		X
Lower extremity functional muscle strength	30-s sit-to-stand test[86]	The number of sit to stands within 30 s	X		X		X
Nutritional intake	24-hour recall	Protein (total gram) and caloric intake (total kcal)	X		X		
Nutritional status	Patient-generated subjective global assessment short form[87]	Four items assessing weight (status), nutritional intake, symptoms and physical functioning	X	X	X	X	X
	Nil per mouth consumption during hospitalisation	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[88]	Thirty items, organised into five functional scales (physical, role, emotional, cognitive and social), three symptom scales (pain, fatigue and emesis), six items (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact), and an overall quality of life scale	X	X	X	X	X
Bladder cancer-related quality of life	EORTC muscle-invasive bladder cancer specific module[89]	Thirty 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

Continued

Table 1 Continued

Description of outcome	Assessment	Description of measure	T0a	T0b	T1	T2	T3
Anxiety and depression	Hospital Anxiety and Depression Scale[37]	Seven items assessing anxiety and seven items assessing depression	X	X	X	X	X
Fatigue	Multidimensional fatigue inventory[90]	Twenty items, categorised 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[91]	Eleven items, organised into four 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
Tumour hypoxia and immune cell infiltration	Two tumour biopsies: from routine diagnostic investigation and from surgical tumour 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-5 levels[44]	Five items (dimensions) multiattribute utility questionnaire that measures mobility, self-care, usual activities, pain/discomfort and anxiety/depression in five levels	X	X	X	X	X
	iMTA Medical Consumption Questionnaire[42] and Productivity Costs Questionnaire[43]	Patient-reported productivity losses and medical consumption		X	X	X	X
	Healthcare costs	Medical activities abstracted from the management systems of the hospitals					X
Other outcomes							
Socio-demographic and clinical data	Socio-demographic 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[92] Medical records: birth month and year, date of diagnosis, date and type of treatment, type of urinary diversion, tumour characteristics, ASA score, WHO score	X				
		Patient reported: smoking status	X	X	X	X	X
Coping mechanism	Sense of coherence questionnaire[93]	Thirteen items, categorised into three scales: comprehensibility, manageability and meaningfulness	X				
Compliance to the intervention	Adherence rates	Patient reported: self-composed (activity) diary. Physical therapist: adherence of the physical exercise training intervention on standardised training session forms	X	X	X		
Patient evaluation	Self-composed questionnaire	Patients in the intervention group: satisfaction with the programme and willingness to participate in focus group Patients in the control group: evaluate contamination Both groups: evaluation of possible post-surgical intervention					X

Continued

Table 1 Continued

Description of outcome	Assessment	Description of measure	T0a	T0b	T1	T2	T3
Non-participation	Self-composed questionnaire	Patient-reported outcomes: socio-demographic, health-related 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, tumour characteristics, ASA score, WHO score	X				

ASA, American Society of Anesthesiologists; BMI, body mass index; EORTC, European Organisation for Research and Treatment of Cancer; RC, radical cystectomy; VO$_2$peak, oxygen uptake at peak exercise.

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 randomisation (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 (eg, treatment, clinical stage) will be abstracted from the medical records and socio-demographic characteristics (eg, age, sex and 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 Castor EDC and access is restricted to the investigator team. Due to the low risk of the intervention a data safety monitoring board is not instated.
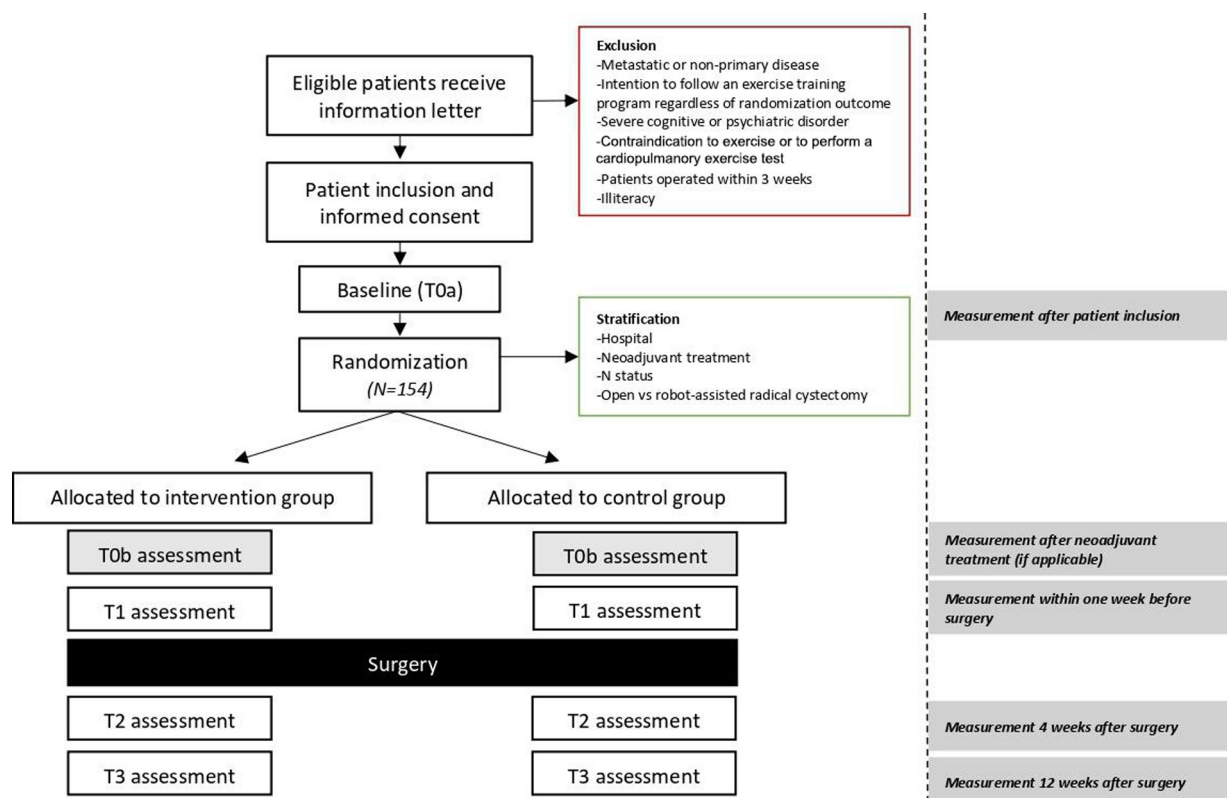

Figure 1 Study flow chart.

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

Frequency	Intensity	Time	Type
Three times a week	Aerobic interval training, consisting of four 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.*	24–28 min	Aerobic interval training
Two times a week	During neoadjuvant treatment: ▶ Week 1–3: consisting of 20 min on a cycle ergometer and 10 min on a different aerobic machine, corresponding to 30% of the heart rate reserve. ▶ Week 4–6: consisting of 20 min on a cycle ergometer and 10 min on a different aerobic machine, corresponding to 40% of the heart rate reserve. ▶ Week 7–9: consisting of 20 min on a cycle ergometer and 10 min on a different aerobic machine, corresponding to 50% of the heart rate reserve. ▶ Week 10–12 (and further): consisting of 20 min on a cycle ergometer and 10 min 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)† in two 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.‡	~20 min	Resistance training
One time a week	Progressive muscle relaxation techniques.[35]	~20 min	Relaxation exercises

*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%.[94] During neoadjuvant treatment[95]: 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.
†Physical therapists can offer alternative resistance exercises targeting the same muscle group to accommodate a patient's abilities and preferences.
‡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 number of repetitions the patient achieves is two less than the planned number of repetitions.
1RM, one-repetition maximum; CPET, cardiopulmonary exercise test; VO_2peak, oxygen uptake at peak exercise.

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 standardised 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. Tumour 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 programme 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 programme, including physical exercise training, nutritional support, psychological counselling and smoking cessation, will be determined by means of the activity-based costing[41] method. Costs for neoadjuvant 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)[42] will be used to gather data on medical consumption outside the hospital. The iMCQ includes

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 transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention.
Grade-IIIa	Intervention not under general anaesthesia.
Grade-IIIb	Intervention under general anaesthesia.
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management.
Grade-IVa	Single organ dysfunction (including dialysis).
Grade-IVb	Multiorgan dysfunction.
Grade V	Death of a patient.

Adapted from the study by Dindo et al.[39]
*Brain haemorrhage, ischaemic stroke, subarachnoidal bleeding, but excluding transient ischaemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

questions related to frequently occurring contacts with healthcare providers. For patients who currently have remunerative employment, productivity losses will be obtained through the iMTA Productivity Costs Questionnaire.[43] To calculate quality-adjusted life years, utilities will be derived from the EuroQol 5-dimension-5 levels (EQ-5D-5L) questionnaire.[44]

Compliance
To monitor therapeutic validity, compliance with the physical exercise training programme is assessed by attendance rates and compliance to all parts of the training programme as scored by the physical therapist on standardised 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 programme, 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 programme 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 with the control group, with ORs ranging from 0.11 to 0.88.[45–51] This study aims to reduce the number of patients with any grade ≥2 perioperative complication within 90 days from 60%[52 53] to 35% (relative risk 0.58, OR 0.36).[54 55] Assuming a two-sided Fisher's 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 socio-demographic and clinical variables, and to assess the adequacy of the randomisation. 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% CI based on robust SEs.[56]

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. Standardised 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 SD. Effect sizes of 0.2 are considered small, 0.5 moderate and 0.8 large.[57] A p value<0.05 will be considered statistically significant.

Intervention fidelity

Descriptive statistics will be used to summarise 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 generalised linear mixed effects models.

Non-participants

Baseline data of participants will be compared with those of non-participants using χ^2 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 programme 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 (ie, oxygen uptake at peak exercise) 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-based 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 (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.[58] To capture necessary support regarding adoption and further research, value of information analyses will be performed.[59] Where appropriate, Dutch guidelines for costing studies will be used in applying tariffs to units of resource use.[60] Finally, a budget impact analysis will be performed according to the International Society for Pharmacoeconomics and Outcomes Research guidelines.[61]

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 organised.

DISCUSSION

A considerable proportion of patients with bladder cancer scheduled for RC has a poor cardiorespiratory fitness,[9 10] is malnourished[11 62] and/or is an active smoker at diagnosis.[63] 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 programme for patients with bladder cancer who are scheduled for RC is presented. It is hypothesised that the programme will be effective in reducing the number and severity of perioperative complications.

This study has several strengths, including its multicentre, randomised design, the use of an intention-to-treat basis for the data analysis and a minimisation technique to ensure blinded treatment allocation and comparable groups. Most importantly, the study intervention consists of a tailored programme 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 tumour hypoxia and immune cell infiltration analysis will be performed exploratively. Intervention fidelity will be monitored in detail, as recommended previously,[64] 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 generalisability 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.[65 66] It has previously been described that patients who were eligible for prehabilitation programmes for colon cancer surgery expressed several reservations.[67] 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 generalisability of the results but will also support implementation in a way that will maximise the potential value of the prehabilitation programme 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 programme will be delivered as near to the patients' homes as possible, to minimise travel time. This is a very important factor for patients with cancer according to previous studies.[55 68–70] 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,[71] 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 preoperatively 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 programme is designed to maximally improve a patient's health status by including physical exercise training, nutritional support, psychological counselling and smoking cessation. It is not likely that patients who are randomised to the control group would initiate a programme consisting of all these components on their own. The multimodal approach prohibits disentangling of the individual effects of each lifestyle component in the prehabilitation programme. 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.[72 73] Higher levels of physical exercise training have been demonstrated to be beneficial for both cancer prevention and, in some solid tumours, progression of disease and cancer-related mortality.[74 75] However, the underlying biological mechanism has yet to be demonstrated. It is expected that the prehabilitation programme has positive effects on the tumour microenvironment. The hypoxic tumour microenvironment is a common characteristic of a solid tumour when oxygen levels become low, as a result of the rapid proliferation of tumour cells[76] and is linked to poor prognosis in bladder cancer.[77] Physical exercise training has regulatory effects on the angiogenesis of skeletal muscles, which has raised interest in whether these effects might translate to solid tumours.[78] Preclinical research has shown that training may acutely reduce tumour hypoxia through vascular normalisation and thereby improve the perfusion of tumour tissue.[79–82] In addition, exercise training has been suggested to alter immune cell infiltration in solid tumours and thereby contribute to enhanced immune surveillance and improved vascular function.[25] However, current evidence is inconsistent and inconclusive.[83] Clinical trials are very limited and this preoperative setting provides an excellent opportunity to investigate the potential role of prehabilitation on tumour hypoxia and immune cell infiltration.

To summarise, 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 programme for patients with bladder cancer in daily clinical practice.

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