BMJ Open

Bladder cancer and exeRcise trAining during intraVesical thErapy—the BRAVE trial: a study protocol for a prospective, single-centre, phase II randomised controlled trial

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To cite: Arthuso FZ, Fairey AS, Boulé NG, *et al*. Bladder cancer and exeRcise trAining during intraVesical thErapy—the BRAVE trial: a study protocol for a prospective, single-centre, phase II randomised controlled trial. *BMJ Open* 2021;**11**:e055782. doi:10.1136/bmjopen-2021-055782

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-055782).

Received 26 July 2021
Accepted 15 September 2021

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ABSTRACT

Introduction Non-muscle invasive bladder cancer (NMIBC) accounts for about 75% of newly diagnosed bladder cancers. The treatment for NMIBC involves surgical removal of the tumour followed by 6 weekly instillations of immunotherapy or chemotherapy directly into the bladder (ie, intravesical therapy). NMIBC has a high rate of recurrence (31%–78%) and progression (15%). Moreover, bladder cancer and its treatment may affect patient functioning and quality of life. Exercise is a safe and effective intervention for many patient with cancer groups, however, no studies have examined exercise during intravesical therapy for NMIBC. The primary objective of the Bladder cancer and exeRcise trAining during intraVesical thErapy (BRAVE) trial is to examine the safety and feasibility of an exercise intervention in patients with bladder cancer undergoing intravesical therapy. The secondary objectives are to investigate the preliminary efficacy of exercise on health-related fitness and patient-reported outcomes; examine the social cognitive predictors of exercise adherence; and explore the potential effects of exercise on tumour recurrence and progression.

Methods and analysis BRAVE is a phase II randomised controlled trial that aims to include 66 patients with NMIBC scheduled to receive intravesical therapy. Participants will be randomly assigned to the exercise intervention or usual care. The intervention consists of three supervised, high-intensity interval training sessions per week for 12 weeks. Feasibility will be evaluated by eligibility, recruitment, adherence and attrition rates. Preliminary efficacy will focus on changes in cardiorespiratory fitness and patient-reported outcomes from baseline (prior to intravesical therapy) to pre-cystoscopy (3 months). Cancer outcomes will be tracked at 3 months, and 1-year follow-up by cystoscopy. Analysis of covariance will compare between-group differences at post-intervention (pre-cystoscopy) for all health-related fitness and patient-reported outcomes.

Ethics and dissemination The study was approved by the Health Research Ethics Board of Alberta-Cancer Committee (#20–0184). Dissemination will include publication and presentations at scientific conferences and public channels.

Trial registration number NCT04593862; Pre-results.

Strengths and limitations of this study

- First randomised controlled trial evaluating the safety, feasibility and preliminary efficacy of exercise in patients with non-muscle invasive bladder cancer receiving intravesical therapy.
- The range of secondary outcomes will allow a comprehensive assessment of health-related fitness, patient-reported outcomes, and social cognitive predictors of exercise adherence.
- The study is adequately powered to assess cardiorespiratory fitness, a potential surrogate for improved patient-reported outcomes and cancer outcomes.
- The study is not powered to assess the clinical cancer outcomes of recurrence, progression or survival.
- The modest sample size, the short-term follow-up, and the absence of a tumor-related biological component are limitations.

INTRODUCTION

Bladder cancer is the fifth most common cancer in Canada and most new cases are non-muscle invasive bladder cancer (NMIBC).[1] The treatment for NMIBC initially involves surgical removal of the tumour through a procedure called transurethral resection of the bladder tumour (TURBT). Surgery is usually followed by 6 weeks of intravesical therapy, which consists of weekly instillations of immunotherapy or chemotherapy placed inside the bladder through the urethra.[1 2] Additional intravesical therapy may be offered to the patient depending on the risk profile and initial response to treatments. NMIBC has a high rate of recurrence (31%–78%)[1] and progression (15%),[3] making it one of the most distressing and expensive cancers to treat.[4] Moreover, bladder cancer and its treatments may affect patient functioning

and quality of life,[5] and increase the risk of cardiovascular mortality.[6]

Exercise is generally safe and effective for most patients with cancer and is recommended specifically for improving health-related fitness and some side effects.[7] Few exercise studies, however, have focused on patients with bladder cancer.[8] Limited research has suggested that exercise in patients with bladder cancer may improve health-related quality of life, cardiorespiratory fitness, functional capacity and muscle power[9–15]; however, none of these studies have focused on patients with NMIBC receiving intravesical therapy.[9–15] Currently, it is unclear if exercise is safe and feasible for patients with NMIBC receiving intravesical therapy or whether it has any meaningful benefits (or harms).

Here, we propose the Bladder cancer and exeRcise trAining during intraVesical thErapy (BRAVE) trial, the first phase II randomised controlled trial with the primary objective of determining the safety and feasibility of exercise in patients with bladder cancer scheduled to receive intravesical therapy. The secondary objectives are to examine the preliminary effects of exercise on health-related fitness (cardiorespiratory fitness and physical functioning), patient-reported outcomes (health-related quality of life (HRQoL), fear of cancer recurrence, anxiety, depression, fatigue, perceived stress, self-esteem and sleep quality) and social cognitive predictors of exercise adherence (motivation, perceived benefits, enjoyment, support from others, self-efficacy and barriers). An exploratory objective is to track the short-term bladder cancer recurrence and progression rates for each trial arm. The hypotheses of the BRAVE trial are: (1) exercise will be feasible and safe in this patient population, (2) exercise will significantly improve health-related fitness and patient-reported outcomes, and (3) social cognitive variables from the theory of planned behaviour will predict exercise adherence.

METHODS

Study design

The BRAVE trial will be conducted as a prospective, single-centre, two-armed, phase II randomised controlled trial at the University of Alberta and the Northern Alberta Urology Centre (NAUC) in Edmonton, Alberta, Canada. Participants will be randomly assigned to either the usual care or exercise training group. The proposed participant flow through the study includes (1) enrolment, (2) baseline assessment (before intravesical therapy), (3) allocation, (4) post-intravesical therapy assessment (6-week), (5) pre-cystoscopy (post-intervention) assessment (3-month), and (6) 1-year follow-up assessment (figure 1). The study design is described based on the Standard Protocol Item for Randomised Trials guideline[16] and the Consolidated Standards of Reporting Trials statement for randomised pilot and feasibility trials.[17]

Study population

Eligible participants will include men and women that (1) are ≥18 years old, (2) have a confirmed diagnosis of

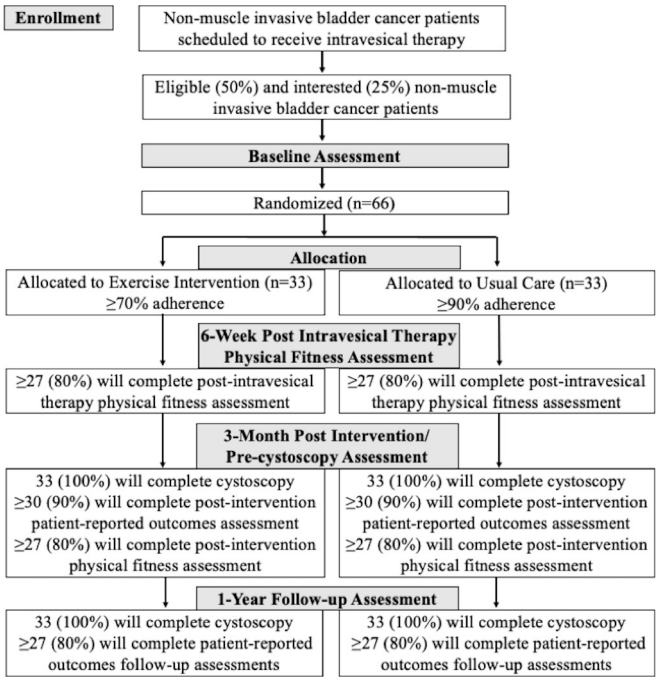

Figure 1 Proposed participant flow diagram for the BRAVE (Bladder cancer and exeRcise trAining during intraVesical thErapy) trial with estimated rates for feasibility.

NMIBC (clinical stage cis, Ta or T1), and (3) are scheduled to begin or have received only one induction intravesical therapy with chemotherapy (eg, gemcitabine or mitomycin) or immunotherapy (ie, BCG) agents. In the face of a slower-than-expected recruitment rate, eligibility criteria may be extended to patients in the maintenance phases of treatment for NMIBC, where patients receive 3 weekly instillations of intravesical therapy. Exclusion criteria for participants include: (1) not medically cleared to participate in the exercise intervention by their treating urologist and a certified exercise physiologist using the Physical Activity Readiness Questionnaire for Everyone,[18] (2) contraindications for cardiopulmonary stress and/or physical fitness tests (eg, resting hypertension, mental impairment with limited ability to cooperate, physical disability that precludes safe and adequate testing),[19] (3) already meeting the exercise guidelines for cancer survivors,[7 20] assessed by the Godin Leisure-Time Exercise Questionnaire (GLTEQ),[21] (4) unable to read and comprehend English and (5) not willing to be randomised to a supervised exercise training programme or usual care (no exercise) for 12 weeks.

The target accrual number is 66 patients over 24 months (May 2021 to April 2023). According to Cancer Control Alberta,[22] 1040 bladder cancers were diagnosed in 2020 in Alberta of which 75% (780) were NMIBC.[1] Approximately one-third of these cases (n=260) will be in the Edmonton region. Considering approximately 520 available patients over 2 years, we anticipate a 50% eligibility rate (n=260) and a 25% recruitment rate (n=66) will achieve our target sample size.

Recruitment and screening

Recruitment will be conducted through NAUC medical records and check-up visits at the Kaye Edmonton Clinic, Alberta, Canada. Specifically, the study coordinator will verify if the patients are ≥18 years old and have a confirmed diagnosis of NMIBC. The study coordinator will then notify the urologist about a potential eligible participant prior to the appointment. If the patient is scheduled to begin or has received one intravesical therapy, the urologist will hand out the study brochure and ask for consent for contact by the study coordinator. The study coordinator will then contact the patient to provide further details about the study, clarify any questions, document enrolment data and screen for current physical activity readiness and participation level. Using the GLTEQ, patients will be asked to recall their average weekly frequency and duration of light, moderate and vigorous exercise that lasted 10 min or longer and was done during free time in the past month. The total minutes of exercise per week will be calculated as moderate minutes plus two times the vigorous minutes. Eligibility will be confirmed if the total minutes of exercise per week is <150 min. Eligible patients will be scheduled for baseline testing.

Randomisation and blinding

After completing baseline assessments, patients will be randomly assigned to either the exercise training group or usual care group in a 1:1 ratio using a computer-generated programme with random blocks of 4 or 6. The allocation sequence will be generated independently by a research assistant, not otherwise involved in the trial, and concealed from the study coordinator. The results of the randomisation will be reported in person to the patient immediately after the baseline assessment. Participants and investigators will not be blinded to group assignment given the nature of the intervention. Outcome assessors will be blinded to group assignment for the clinical outcomes of tumour recurrence and progression. Fitness outcome assessors will not be blinded to group assignment but will follow a detailed protocol and be trained in the importance of standardising outcome assessments.

Intervention

Exercise group: In addition to standard medical care, which includes offer of a smoking cessation programme for current smokers, the exercise group will be asked to perform 36 high-intensity interval training sessions over a 12-week period. The exercise frequency will be three times per week during the 6 weeks of intravesical therapy and the 6 weeks of recovery (total 12 weeks) prior to the 3-month surveillance cystoscopy. Figure 2 shows the intervention within the treatment timeline. The intervention will be performed on a treadmill and will include a warm-up and cool-down at 50%–60% and 40% of the peak oxygen consumption (VO_{2peak}), respectively, for 5 min. The high-intensity interval training (HIIT) protocol will be 4×4, which consists of four bouts of 4 min at a workload corresponding to vigorous intensity (75%–95% of the baseline and 6-week VO_{2peak}) alternating with 3 min of recovery intervals at 40% of the VO_{2peak} (figure 3). The exercise session will last 35 min and include 16 min of high intensity exercise. The exercise programme will be personalised to patients: the intensity of the exercise will be modified by changing the speed and/or grade of the treadmill following a standardised equation[23] based on 75%–95% of VO_{2peak} measured at baseline and updated at post-intravesical therapy (6-week). Moreover, a gradual approach for progression will be used to enhance adherence and reduce risk of cardiovascular events and injuries (figure 4).[24] To address safety concerns, prior to the beginning of each exercise session, the participants will have resting blood pressure, resting heart rate and overall symptoms screened. Participants will be asked to wear a heart monitor while exercising. Heart rate will be registered at the last minute of each session component (warm-up, high-intensity interval, recovery interval, and cool-down). The average heart rate and the highest heart rate of the entire HIIT session will be monitored. Exercise

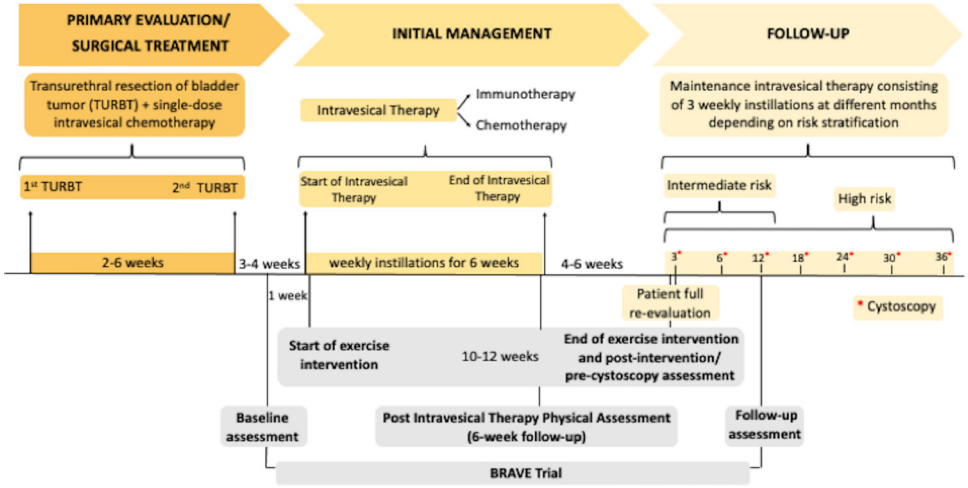

Figure 2 The BRAVE (Bladder cancer and exeRcise trAining during intraVesical thErapy) trial within non-muscle invasive bladder cancer treatment timeline.

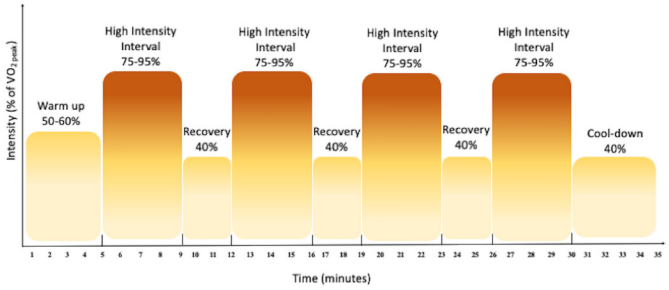

Figure 3 High-intensity interval training protocol in the BRAVE (Bladder cancer and exeRcise trAining during intraVesical thErapy) trial. VO_{2peak}: peak oxygen consumption

tolerance will be assessed at the end of the session using the 0–10 Borg's ratio of perceived exertion scale.[25] After the post-intervention assessments and 3-month cystoscopy, patients will be provided with an updated exercise prescription and encouraged to continue the exercise programme on their own.

Usual care: The usual care group will receive standard medical care, which does not include any exercise programme or recommendations, only a smoking cessation programme for current smokers. Patients in the usual care group will be asked not to initiate an exercise programme or to increase their exercise level from baseline during the 12-week study. After the post-intervention assessments and 3-month cystoscopy, patients in the usual care group will be offered a 4-week supervised exercise programme.

Feasibility measures

Feasibility will be evaluated by tracking the eligibility rate (and reasons for ineligibility), recruitment rate (and reasons for declining), exercise adherence rate (including reasons for dose modification and exercise interruption) and follow-up assessment rate (and reasons for drop out). The eligibility rate will be the number of patients with NMIBC scheduled for intravesical induction therapy divided by the number of patients deemed eligible. The recruitment rate will be the number of patients with NMIBC randomised in the study divided by the number of eligible patients. Adherence to the programme will be measured by the number of exercise sessions completed with and without dose modifications. Reasons for not completing the exercise session or for dose adjustments will be recorded. The follow-up assessment rate will be determined by the number of participants who complete the post-intervention or follow-up assessments for each of the outcomes.

To evaluate the safety of the programme, any adverse events during the physical fitness assessments or exercise sessions will be recorded. Once the event has been evaluated, a decision will be made regarding the avoidance of future events, and whether the participant can return to the intervention. If the adverse event requires medical attention, the participant will need to be cleared by a physician before returning to the study. The research team will forward all adverse event report forms to the ethics board.

Outcome measures

There will be four assessment time points: baseline (pre-intravesical therapy), post-intravesical therapy (6 weeks), pre-cystoscopy/post-intervention (12 weeks) and 1-year follow-up (table 1). Health-related fitness will be assessed at baseline, post-intravesical therapy and post-intervention. Patient-reported outcomes and social cognitive predictors of exercise adherence will be assessed at baseline, pre-cystoscopy (post-intervention) and 1-year follow-up. Tumour recurrence and progression will be assessed at post-intervention (3-month surveillance cystoscopy) and 1-year follow-up (1-year surveillance cystoscopy). No follow-up research visits are required. All the information needed for the follow-up assessments will be collected via medical records and by mail or email, as preferred by the participant.

Cardiorespiratory fitness will be assessed through direct measurement of VO_{2peak} (mL/kg/min) by the modified Bruce treadmill protocol exercise test, using a metabolic measurement system (Parvo Medics TrueOne 2400; Sandy, Utah, USA).[26] This protocol was chosen because it was originally designed for high-risk and elderly individuals, it is widely used in the clinical setting and because of its specificity with the exercise intervention for this study, which will be on a treadmill. Overall, the test consist of stages that are 3 min long starting at 0% grade and a speed of 1.7 mph, with a gradual increase of intensity by changing first the incline, then both incline and speed. The test will terminate when the patient achieves volitional exhaustion or in the presence of any test termination criteria.[23] VO_{2peak} will be determined as the highest value obtained over a 30 s average.[27] The ventilatory threshold, defined as an increase in ventilation without a corresponding increase in VO_2, will be determined by the V-slope method.[28] Physical functioning will be assessed by the Senior Fitness Test (SFT) which is used to evaluate health-related physical fitness and functional capacity among older adults.[23] The SFT includes: (1) 30-second

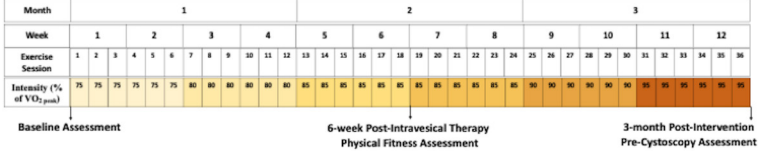

Figure 4 The 12-week high-intensity interval training periodisation scheme and the assessment time points in the BRAVE (Bladder cancer and exeRcise trAining during intraVesical thErapy) trial. VO_{2peak}: peak oxygen consumption

Table 1 Outcomes measures and assessment time points of the BRAVE trial

Outcome	Instrument	Pre-intravesical therapy (baseline)	Post-intravesical therapy (6 weeks)	Post-intervention/pre-cystoscopy (3 months)	Follow-up (12 months)
Cardiorespiratory fitness	Cardiopulmonary exercise test	X	X	X	
Physical functioning					
Lower body strength	30-second chair stand	X	X	X	
Upper body strength	Arm curl	X	X	X	
Flexibility	Chair sit-and-reach and back scratch	X	X	X	
Agility	8-foot up-and-go	X	X	X	
Aerobic endurance	6-minute walk	X	X	X	
Anthropometry and body composition	BMI and circumferences	X	X	X	
Patient reported-outcomes					
Health-related quality of life	EORTC QLQ-C30 and EORTC NMIBC C24	X		X	X
Fear of cancer recurrence	9-item fear of cancer recurrence inventory	X		X	X
Anxiety	10-item state-trait anxiety inventory	X		X	X
Depression	10-item CES-D	X		X	X
Fatigue	FACIT—fatigue scale	X		X	X
Stress	14-item Perceived Stress Scale	X		X	X
Self-esteem	Rosenberg Self-esteem Scale	X		X	X
Sleep quality	Insomnia Severity Index	X		X	X
Behavioural outcomes					
Social cognitive variables	Theory of planned behaviour constructs	X		X	X
Physical activity level	Godin Leisure-time questionnaire	X		X	X
Cancer-related outcomes					
Intravesical therapy adherence	Medical records		X		
Intravesical therapy toxicity	Medical records		X		
Tumour recurrence and progression	Cystoscopy			X	X
Baseline descriptive variables					
Sociodemographic details	Participant self-report	X			
Medical information	Medical records	X			

BMI, body mass index; BRAVE, Bladder cancer and exeRcise trAining during intraVesical thErapy; CES-D, Center for Epidemiologic Studies Depression Scale; EORTC NMIBC C24, European Organization for Research and Treatment of Cancer for non-muscle invasive bladder cancer 24-item; EORTC QLQ-C 30, European Organization for Research and Treatment of Cancer core 30-item questionnaire; FACIT, Functional Assessment of Cancer Therapy.

chair stand, (2) arm curl, (3) chair sit-and-reach, (4) back scratch, 5) 8-foot up-and-go and (6) 6-minute walk. These tests are used to assess, respectively, lower and upper body strength, lower and upper body flexibility, agility/dynamic balance and aerobic endurance.[29]

Anthropometry and body composition measurements will include height, weight, waist, hip, and calf circumferences.[19 30]

Patient-reported outcomes will include the assessment of HRQoL using the European Organization for Research and Treatment of Cancer (EORTC) core 30-item questionnaire (QLQ-C30) V.3.0.[31] The EORTC QLQ-C30 is designed to cover a range of quality of life issues relevant to patients with cancer, including functional scales (physical, cognitive, role, emotional and social), symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation and diarrhoea), perceived financial impact scale and a global health status/QoL scale.[31] The assessment of HRQoL will be complemented by the EORTC QLQ NMIBC C24,[32] which evaluates urinary symptoms, intravesical treatment issues, future perspective, fever and feeling ill, abdominal bloating and flatulence and sexual functioning.[32] Patient-reported outcome evaluation will also include fear of cancer recurrence/progression assessed by the Fear of Cancer Recurrence Inventory,[33] anxiety using the 10-item state-trait anxiety inventory,[34] depression using the 10-item Center for Epidemiologic Studies Depression Scale,[35] fatigue using the Functional Assessment of Cancer Therapy–Fatigue,[36] perceived stress using the 14-item Perceived Stress Scale,[37] self-esteem using the Rosenberg self-esteem scale[38] and sleep quality using the Insomnia Severity Index.[39] Social cognitive predictors of exercise adherence: motivation, perceived benefits, enjoyment, support from others, self-efficacy and barriers will be assessed using standard scales for the Theory of Planned Behavior.[40] Patient-reported outcomes and social cognitive predictors will be assessed using email or mail delivery format.

Intravesical therapy adherence will be tracked by medical records of attendance and self-report drug retention time. Treatment toxicities will be abstracted from medical records. Bladder cancer recurrence and progression will be assessed by cystoscopy. Specifically, the outcome of interest will be complete response (CR), defined as negative cytology, imaging and cystoscopy and, when the TURBT is indicated, a negative biopsy. CR will be assessed at 3-month and 1-year follow-up.

Sociodemographic information will be obtained through baseline questionnaire and will include age, sex, ethnicity, marital status, education, income, smoking status and comorbidities. Medical information will be assessed via medical records and will include date of cystoscopy, date of the surgical resection (TURBT), tumour histology, grade, stage and intravesical therapy protocol.

Sample size

Given the descriptive nature of the primary objectives (safety and feasibility), we selected VO_{2peak} for the sample size calculation because improvement in cardiorespiratory fitness (ie, VO_{2peak}) is the intended immediate effect of the intervention. Moreover, VO_{2peak} may be considered a 'bridge'' between feasibility and efficacy because it reflects the patient's ability and willingness to do the exercise programme (feasibility) and is a potential surrogate for improved patient-reported outcomes and cancer outcomes (efficacy). If we reach the accrual of 66 participants (33 per group), it provides 80% power using a two-tailed alpha <0.05 to detect a clinically meaningful difference of one metabolic equivalent (MET=3.5 mL/kg/min) in VO_{2peak} assuming a SD of 5.6 mL/kg/min, 10% missing data and adjustment for baseline value and other prognostic covariates.[41] This power may also be sufficient for detecting differences in some patient-reported outcomes if the effects exceed standardised effect sizes of approximately ≥d=0.60. This power is unlikely sufficient for detecting differences in any of the cancer outcomes (recurrence and progression). Given that the purpose of this trial is to inform larger phase II and phase III trials, the patient-reported and clinical outcomes will be interpreted for clinical significance based on the direction and the magnitude of the numerical differences.

Data collection and management

All data will be recorded on case report forms (CRFs) and stored anonymised in the Behavioural Medicine Laboratory at the University of Alberta. The investigators will provide access to the data file on reasonable request. The investigator is ultimately responsible for the collection and timely reporting of all applicable data entered in CRFs and ensuring they are accurate, original, attributable, complete, legible, contemporaneous, and available when required.

Statistical considerations

All randomised participants will be included in the analyses using the intention-to-treat approach. If missing data is <10% we will conduct a complete case analysis. If missing data is >10%, we will employ a multiple imputation missing data strategy.[42 43] There will be no interim analyses. Continuous variables will be described using mean (SD) or median (IQR), while categorical variables will be described using frequencies (percentages) and CIs. Descriptive analyses will be performed for participant characteristics, feasibility outcomes and disease recurrence and progression. Analysis of covariance will be conducted for health-related fitness outcomes and patient-reported outcomes to compare the between-group differences at post-intervention (pre-cystoscopy) after adjustment for the baseline value of the outcome as well as other potential covariates. All analyses will be performed using SPSS. The level of statistical significance will be set at 0.05 and all hypotheses tests will be two-sided.

Strategies to minimise drop-outs and protocol deviations will include: (1) reducing the intensity of the exercise session, (2) reducing the number of high-intensity intervals, and/or (3) reducing the frequency of visits to the exercise facility by offering home-based unsupervised exercise sessions when necessary and feasible. All patients who drop out of the intervention will be invited

to complete the follow-up assessments in order to keep a low rate of missing data for the intention-to-treat analysis.

Patient and public involvement

A patient and public involvement panel were not specifically conducted to inform the research question, study design, recruitment or dissemination plan for this study.

Ethics and dissemination

The BRAVE trial was approved by the Health Research Ethics Board of Alberta-Cancer Committee (#20–0184). All patients will provide written informed consent prior to the beginning of the study. The outcomes of the BRAVE trial will be disseminated through peer-reviewed academic journals, conferences, via the webpage www.bravestudy.ca and monthly newsletter for stakeholders.

DISCUSSION

Exercise is recommended to many patients with cancer in different clinical settings, however, there are no studies examining the effects of exercise in patients with NMIBC receiving intravesical therapy.[44] The patient with NMIBC group is older and has significant comorbidities that may make exercise more unsafe or less feasible compared with other patient with cancer groups. Moreover, no study to date has examined exercise during intravesical therapy. Feasibility studies are important for understanding if further investigation should be conducted considering the sustainability and relevance of the research and findings.[45] The primary focus of the BRAVE trial will be safety and feasibility because it is the first exercise trial in this patient population.

To date, only four randomised controlled trials have been conducted exclusively among patients with bladder cancer and all four have been in the prehabilitation setting (ie, prior to radical cystectomy).[9–15] These studies have provided promising evidence that exercise interventions prior to radical cystectomy may be associated with improvements in specific domains of HRQoL, including the physical domain[12] and disease-specific symptoms.[10] In addition, these studies have reported benefits in cardiorespiratory fitness,[9 11] functional capacity[12 13 15] and muscle power.[14] These studies have limitations, however, because they lack important information about the exercise intervention,[9 12] do not report recruitment and eligibility rates,[14] include variability in disease invasiveness,[10–14] have small sample sizes (18–107) and have substantial loss to follow-up (8%–44%). As noted earlier, however, the most critical issue from our perspective is that these studies were conducted in the preoperative setting and focused on preparation for radical cystectomy.[8–15] To our knowledge, no studies have examined the feasibility, safety and efficacy of exercise during intravesical therapy for NMIBC.

HIIT was selected as the exercise intervention in the BRAVE trial for several reasons. First, HIIT seems to be safe and efficient for improving cardiovascular and metabolic function in both healthy[46] and chronic illness population,[47–50] including a variety types of cancers such as lung,[51] colorectal with liver metastasis,[52] testicular,[53] prostate,[54 55] colorectal,[56 57] breast,[58] bladder[11] and mixed cancers.[59 60] Second, HIIT is a good option to increase the amount of time spent in vigorous intensity during an exercise session,[23] resulting in comparable or greater improvements in cardiorespiratory fitness when compared with traditional moderate continuous endurance training.[46 49 61–64] The evidence suggests a dose-response relationship between the physical activity intensity and cancer risk reduction[65 66] and cancer mortality.[67] Exercise intensity mediates physiological adaptations related to the aerobic energy metabolism, such as metabolic signal and mitochondrial protein synthesis rate, that are greater at higher intensities of exercise when training volumes are equal to moderate continuous training, or similar when the volume of the interval training is inferior.[68] When compared with moderate-intensity continuous training, HIIT has the ability to maximise the benefits on cardiorespiratory fitness with larger improvements in the volume of oxygen consumption,[68 69] and higher levels of cardiorespiratory fitness are strongly related with a reduced risk of cancer mortality.[70] In addition, HIIT may be perceived to be as enjoyable or more enjoyable than moderate intensity continuous training due to the changing stimulus.[71 72]

Moreover, HIIT may play a therapeutic role in tumour recurrence and progression, attenuating inflammatory processes and modifying the tumour microenvironment.[73] Changes at the tumour microenvironment level may contribute to an optimal therapeutic response.[74] Lastly, HIIT may protect against treatment-related cardiotoxicity and cardiometabolic disease.[73 75] For instance, in animal models with urothelial carcinoma and disease-related cardiac dysfunction, HIIT induced biological processes related to cardiac regenerative ability (eg, adenosine triphosphate metabolism), highlighting the exercise-related protective effect on cardiac function and providing insights on the beneficial effects of exercise training after bladder cancer diagnosis.[76]

The BRAVE trial has several limitations including the modest sample size, the short-term follow-up and the absence of a correlative (biological) component such as gene expression alterations potentially associated with bladder cancer recurrence and progression. The study is principally aimed at establishing safety and feasibility, and is underpowered to determine the efficacy of exercise on the most important clinical outcomes of tumour progression and recurrence. Moreover, the progression rate in this clinical setting is only 5% at 1 year, and the recurrence rate is 10%–30% depending on the treatment and disease stage.[77] We have included tumour recurrence and progression as an exploratory outcome in our trial primarily to demonstrate the feasibility of collecting such data at our site. We will also determine if there is any signal in the hypothesised direction (numerically superior) although we acknowledge that the likelihood of demonstrating a statistically significant effect is very low. This information will help inform the objectives

and design of larger exercise trials in this clinical setting, should they be warranted.

The BRAVE trial has several strengths including the novel patient population, the randomised controlled trial design, the supervised exercise and the comprehensive and valid assessment of important outcomes. It will be the first randomised controlled trial to test the safety and feasibility of any exercise intervention in patients with NMIBC receiving intravesical therapy. The BRAVE trial will also provide preliminary evidence on whether exercise may improve health-related fitness and patient-reported outcomes during intravesical therapy. Finally, the BRAVE trial will establish if social cognitive variables from the theory of planned behaviour predict exercise adherence during intravesical therapy, which will inform strategies to maximise adherence in future trials. The BRAVE trial may inform larger phase II and III trials designed to test the efficacy of exercise on important clinical outcomes in this setting including quality of life, symptom management, progression, recurrence and overall survival.

Contributors FZA, ASF, NB and KC contributed to the design and development of the study. All authors will oversee the implementation of the protocol and contribute to the acquisition, analysis or interpretation of data. FZA and KC wrote the manuscript. All authors revised the manuscript critically for important intellectual content and approved the final manuscript.

Funding This work is supported by a grant from the Alberta Cancer Foundation/ Alberta Cancer Clinical Trials - Provincial Investigator-Initiated Trial Competition. Grant number N/A.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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