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Vigorous intensity aerobic interval exercise in bladder cancer patients prior to radical cystectomy: a feasibility randomized controlled trial

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ABSTRACT

Purpose: Strategies to improve pre-operative cardiopulmonary fitness could positively impact recovery after surgery. This study investigated the feasibility of vigorous intensity aerobic interval exercise in bladder cancer patients prior to radical cystectomy (RC). **Methods:** A total of 60 patients were randomised (1:1) to exercise or control following a cardiopulmonary exercise test (CPET). The exercise group was offered twice-weekly pre-operative supervised vigorous intensity aerobic interval exercise in addition to standard treatment. The controls received standard treatment only. A repeat CPET was undertaken before surgery and post-operative recovery outcomes were recorded. **Results:** Over half of the 112 eligible patients approached in the clinic were recruited to the study (53.5%), with recruited patients attending a median of 8 (range: 1-10) exercise sessions over a pre-operative period of 3-6 weeks. Improvements in peak values of oxygen pulse ($P=0.001$), minute ventilation ($P=0.002$) and power output ($P<0.001$) were observed at the follow-up CPET in the exercise group versus controls and there were no adverse events. Although this feasibility study was not powered to detect changes in post-operative recovery outcomes, there were marginal (non-significant) differences in favour of the exercise group in post-operative Clavien-Dindo score and need for High Dependency Unit inotropic support. **Conclusions:** Bladder cancer patients respond well to pre-surgical aerobic interval exercise and the improvements in cardiopulmonary fitness variables could have important implications for post-operative recuperation after RC. These findings provide a strong foundation for an adequately powered randomized controlled trial.

Key words:

Pre-operative care, exercise, urinary bladder neoplasms

INTRODUCTION

Pre-operative cardiopulmonary fitness is increasingly being recognised as an important factor influencing post-operative recovery outcomes. Almost two decades ago, Older *et al.* identified an association between low cardiopulmonary fitness in older people and poor outcome following major surgery [1]. Other studies have since provided further evidence of the utility of pre-operative cardiopulmonary exercise test (CPET) variables for risk stratification of surgical patients, including those undergoing radical cystectomy (RC) [2, 3]. However, the role of pre-operative exercise programs (prehabilitation) for optimising cardiopulmonary fitness prior to surgery has received less attention [4]. Although systematic review evidence suggests that exercise training can improve cardiopulmonary fitness before surgery in older people and can reduce the risk of post-operative complications following major abdominal surgery [5-7], the paucity of high quality clinical trials has been highlighted [5]. Furthermore, studies that have investigated the effects of exercise prehabilitation programs on post-operative recovery outcomes in cancer patients have yielded equivocal results.

Intensive supervised pre-operative exercise programs resulted in modest improvements in pre-operative cardiopulmonary fitness measures in lung cancer patients, including the six-minute walk test [8] and peak aerobic capacity [8, 9], but with no effect on pre-surgical or longer-term quality of life [10]. In addition, a supervised exercise program involving trunk and limb-strengthening exercise improved chemoradiotherapy completion rate in patients with gastrointestinal cancers, but did not improve post-operative recovery outcomes [11]. In contrast, Sekine *et al.* [12] reported a reduction in post-operative pulmonary complications and hospital length of stay in lung cancer patients with chronic obstructive pulmonary disease after daily hospital-based pulmonary exercises and walking (5000 steps/day) in the two weeks prior to lobectomy. Similarly, in prostate cancer patients undergoing radical prostatectomy, there is evidence that home-based pelvic floor muscle exercise has favourable effects on post-operative urinary continence outcomes up to 12 months of follow-up [13-15]. However, home-based exercise programs involving aerobic and resistance exercise have had minimal impact on post-operative hospital length of stay or severity of complications in colorectal or bladder cancer patients [16-19], although Jensen *et al.* [19] reported improved post-operative mobility in the latter.

Jensen *et al.* [20] showed that a 2-week home-based program of pre-operative muscle strengthening exercises and endurance training was feasible and resulted in improvements in muscle power in bladder cancer patients prior to RC. However, because of the short time-window between decision for surgery and RC, there is a need to optimise the exercise stimulus for cardiopulmonary adaptations and the potential advantages of vigorous

intensity interval exercise in this respect, were recently highlighted [21]. Interval training enables patients to undertake aerobic (endurance) exercise at a higher intensity than would be possible for continuous exercise at the same intensity but the feasibility of this exercise modality in bladder cancer patients awaiting RC is unknown. Hence, the main purpose of this study was to investigate the feasibility of randomizing bladder cancer patients to a short-term program of pre-operative vigorous intensity aerobic interval exercise versus standard care prior to elective RC. A secondary aim was to collect and report preliminary data on CPET and post-operative recovery outcomes before and after the exercise prehabilitation program.

METHODS

Patient recruitment, randomization and sample size

Patients were recruited from the Urology Department at the Norfolk and Norwich University Hospitals National Health Service (NHS) Foundation Trust, United Kingdom, between 2012 and 2014, and were randomized to standard treatment or pre-operative exercise training. Medical clearance to participate in the study was given by one of four consultant urologists, who were blind to treatment allocation. Randomization was undertaken using a pre-generated random sequence (nQuery Advisor 6.1; Statistical Solutions) which was held by a research administrator not involved in the day to day running of the study. Upon completion of the baseline assessments, the study urologist (SB) phoned the administrator for group allocation (exercise or standard care). As the main purpose was to assess the feasibility of the exercise program, there was no formal sample size calculation but we aimed to recruit 60 patients (30 in each group) in accordance with published recommendations [22, 23]. Written informed consent was obtained prior to study participation and ethical approval was granted by the East of England Regional Ethics Committee.

Inclusion and exclusion criteria

The aim was to be as inclusive as possible so that the results of the study would have broad applicability. Bladder cancer patients listed for RC via the multi-disciplinary team were included in the study and eligibility was not limited by choice of surgical technique. Patients undergoing neo-adjuvant chemotherapy before RC were also included but entered the trial at least 2 weeks after completion of treatment. Patients offered urinary diversion for benign disease were excluded from the study. None of the patients recruited to the study were meeting current physical activity guidelines of a minimum of 150 minutes of moderate intensity physical activity per week [24].

Standard treatment

Patients are treated according to targets set by NHS England, i.e. following general practitioner referral for a suspected cancer, patients are to be investigated by 31 days and treated by 62 days, resulting in a time-window between decision to operate and RC of 31 days (though this can vary due to medical decisions and availability of operating slots). Pre- and post-operatively, patients in both groups received the same level of standard treatment, which included pre-planned admission to the same High Dependency Unit (HDU) in the immediate post-operative period and subsequent step down to a urology ward. Patients were cared for by the same group of nurses and doctors who were blinded to group allocation. Patients in the control group were advised to carry on with their lifestyles in the 'usual way'.

Supervised exercise intervention

Twice-weekly exercise training sessions were supervised by a small team of exercise science staff working closely with the study urologist (SB) in an exercise facility at the University of East Anglia, UK, which is close to the treating hospital. A consistent approach to setting the exercise intensity and monitoring physiological responses was used throughout the study. Sessions comprised vigorous intensity aerobic interval exercise on a cycle ergometer (Monark 824E; Varberg, Sweden) using the Borg Ratings of Perceived Exertion (RPE) Scale to control intensity [25]. The Borg RPE Scale is a psychophysiological scale, ranging from "No exertion" to "Maximal Exertion". Following a 5-10 min warm-up against light resistance (50 W), the aim was for patients to perform 6 x 5 min intervals at a target perceived exertion of 13-15 ('somewhat hard' to 'hard', equating to 70-85% predicted maximum heart rate based on $220 - \text{age}$), with 2.5 min interpolated active rest intervals against light resistance (50 W). They were instructed to maintain a steady pedalling cadence of 50-60 rev·min⁻¹ during the aerobic intervals and the exercise program was progressed by gradually adding more load to the flywheel to maintain the target perceived exertion (Figure 2). Immediately following the aerobic intervals, patients performed a 'cool-down' against low resistance (50 W).

Feasibility outcomes

Feasibility was assessed in terms of recruitment and attrition, willingness to be randomized, acceptability of the outcome measures, adherence to the intervention, safety and suitability of the exercise dose and adverse events.

Cardiopulmonary exercise test and post-operative recovery outcomes

CPETs and post-operative recovery outcomes were blindly assessed by an exercise physiologist who was not directly involved in the supervision of exercise sessions and clinical staff at the treating hospital who were unaware of group allocation, respectively.

All patients performed a baseline incremental CPET to maximum exercise tolerance on an electronically-braked cycle ergometer (Excalibur Sport, Lode, Netherlands). Following a 2-min warm-up against no resistance (0 W), work rate was increased using a ramp protocol (10-20 W·min⁻¹) to maximum exercise tolerance. Heart rate was recorded continuously by ECG (Cardioperfect, Cardioperfect, Welch Allyn, USA). Pulmonary gas exchange variables (oxygen uptake [$\dot{V}O_2$]; carbon dioxide production:[$\dot{V}CO_2$]; minute ventilation [$\dot{V}E$]) and other respiratory variables) were measured breath-by-breath with an on-line expired gas analysis system (Ultima, CardioO2; Medical Graphics Corporation). Anaerobic threshold (AT) was determined from 30 s averaged data by two experienced exercise physiologists (JS and GC) using the V-slope method and confirmed by analysing the ventilatory equivalents [26]. Peak values for all variables were recorded as the highest value over any 30-s averaged period, with peak oxygen pulse calculated as the amount of oxygen consumed per heartbeat.

Post-operative recovery outcomes

Clavien-Dindo grading was used to score post-surgical complications [27, 28]. Post-operative ileus and pneumonia prevalence, time spent in HDU, need for inotropic support and hospital length of stay (LoS) were used as other post-operative recovery outcomes.

Data analysis

All statistical analyses were undertaken using SPSS (SPSS Inc., Chicago, Illinois, USA). CPET and post-operative recovery outcomes were tested for normality of distribution using Kolmogorov-Smirnov test. Body mass index (BMI) and CPET variables were normally distributed and analysed using Analysis of Covariance (ANCOVA), with baseline values as the covariate [29], to compare differences between the groups at follow-up (prior to surgery). Post-operative recovery outcomes were not normally distributed and non-parametric statistical tests were used. The Chi -Square test was used to compare categorical data. The Spearman's rank correlation coefficient was used to investigate bivariate associations between CPET variables and post-operative recovery outcomes in pooled baseline data (independent of group assignment). Normally distributed

data are presented as mean \pm SD and non-normally distributed data as medians and range (unless otherwise stated). The significance level was set at $P < 0.05$.

RESULTS

Feasibility

Of the 112 eligible patients who were approached to take part in the study, 60 (53.5%) agreed to participate (53 males; 7 females). All recruited patients were willing to be randomized and none withdrew consent following randomization. The groups were well-matched for demographic variables, surgical treatment, comorbidities and smoking habits, though more patients in the control group had a history of ischemic heart disease and more patients in the exercise group had undergone neoadjuvant chemotherapy prior to the study (Table 1). Travel distance to the exercise facility was cited as the reason for non-participation in 38 (73%) of 52 eligible patients who declined to take part. Three eligible patients (5.8%) refused to take part because they felt they would be unable to undertake the CPET or comply with the exercise regimen. A further four patients (7.6%) refused to take part as they had an indwelling urethral catheter or a nephrostomy which they thought might prevent them from undertaking exercise. Seven patients (13.4%) did not specify their reasons for not participating. Only five of the 60 recruited patients dropped out of the study, two were deemed unfit for surgery following randomization and three opted for radiotherapy after the follow-up CPET. Recruitment and patient flow through the study is shown in Figure 1.

Most patients completed all assessments, demonstrating the acceptability of the pre-operative CPET and post-operative recovery outcomes. One patient from each group dropped out of the study before the follow-up CPET. Another two patients from the exercise group and four controls did not complete the follow-up CPET but their post-operative outcomes were included in the analysis (Figure 1). The latter patients did not drop out of the study, rather they were unable to attend the follow-up (pre-operative) CPET. This means that a total of 27/30 (90%) of patients in the exercise group and 25/30 (83%) patients in the control group completed both CPET assessments (Figure 1), with no adverse events, and with AT data being available for 24 and 23 patients, respectively. There were no post-operative recovery outcomes for three other patients in the exercise group (one dropped out before the follow-up CPET and the others after the follow-up CPET) and two other patients in the control group (one dropped out before the follow-up CPET and the other after the follow-up CPET). This means that 10% of patients in the exercise group and 7% in the control group dropped out of the study (Figure 1).

The median number of supervised exercise sessions attended by patients in the exercise arm was 8 (range: 1-10) over a pre-operative period of 3 - 6 weeks. Three exercise patients underwent RC <4 weeks after recruitment and consequently attended <8 sessions. Between the first and fourth week, patients exercised at an average of 85-87% predicted maximum heart rate (based on $220 - \text{age}$) and 90-92% of the measured peak heart rate during the CPET (Figure 2), demonstrating the safety and suitability of the exercise dose. Flywheel load (power output) was gradually increased from 111 ± 5.5 W to 122 ± 5.8 W during this time to ensure target heart rates for vigorous intensity exercise were maintained as patients adapted to the exercise program (Figure 2). The average number of aerobic intervals achieved in the first week of exercise was 5.5 (range: 3.5-6.0), whereas all patients were achieving 6 intervals per session in the fourth week. There were no adverse events resulting from the supervised exercise sessions.

CPET and post-operative recovery outcomes

CPET variables at baseline and follow-up are presented in Table 2. The time between baseline and follow-up CPET was 32 (6.5) days (range: 20-45 days) for the exercise group and 29 (4.2) days (range: 21-37 days) for the controls. Improvements in peak values of oxygen pulse ($P=0.001$), $\dot{V}E$ ($P=0.002$) and power output ($P<0.001$) but not peak $\dot{V}O_2$ ($P=0.057$) or AT ($P=0.637$) were observed at the follow-up CPET in the exercise group versus controls (Table 2). Although this feasibility study was not powered to detect changes in post-operative recovery outcomes, four patients (15%) in the exercise group versus 10 controls (36%) had some deviation from the normal post-operative course of recovery (Clavien-Dindo Grade ≥ 1 ; $P=0.075$), whereas one patient (4%) in the exercise group and four controls (14%) had a Clavien-Dindo Grade ≥ 3 ; ($P=0.172$). The prevalence of post-operative ileus ($P=0.808$) and pneumonia ($P=0.609$) were similar between the exercise and control groups (6 versus 7 patients and 3 versus 2 patients, respectively). Median time spent in HDU was 1 day in both the exercise and control group (range 1-10 and 1-7 days, respectively; $P=0.938$), although fewer patients in the exercise group needed HDU inotropic support, reaching borderline statistical significance (2 versus 7 patients; $P=0.078$). The median hospital LoS was 7 days in both the exercise and control groups (range 4-78 and 5-107 days, respectively; $P=0.865$). When the pre-operative data were pooled and considered independent of group assignment, inverse associations were observed between LoS (HDU and hospital) and pre-operative CPET variables ($P<0.05$; Table 3).

DISCUSSION

This is the first study to show that vigorous intensity aerobic interval exercise is feasible in bladder cancer patients awaiting RC. Patients adapted to the program quickly and all were able to perform six aerobic intervals per exercise session at the vigorous intensity target heart rate by the fourth week of exercise. The recruitment rate of eligible patients was very good (53.5%), with the main reason for non-participation being distance between the exercise facility and their home. As the hospital serves a large rural community, with some patients living >80 km away, twice-weekly travel to the supervised exercise sessions was too onerous for some participants. We also observed excellent retention over the course of the study (8.3% attrition), which is likely to be at least in part due to flexible exercise scheduling. In addition, most patients (87%) were able to attend both CPET assessments prior to RC and there were no adverse events. The time between baseline and follow-up CPET assessments was in the range of 20-45 days across both groups. This provided an opportunity for all patients in the exercise arm to attend a minimum of six supervised exercise sessions prior to RC.

Because of the short time-window between decision for surgery and RC, there is a need for pre-surgical exercise programs to be effective and time efficient and the potential advantages of vigorous interval exercise were recently highlighted [21]. Supervised pre-operative exercise programs also need to be pragmatic, taking into account the need for extra hospital visits, and the challenges this presents for some patients. Our exercise program involved twice-weekly aerobic interval exercise training at “somewhat hard” to “hard” intensity (Borg RPE 13-15), equating to ~70-85% predicted maximum heart rate [30], which is reported to be optimal for inducing improvements in cardiopulmonary fitness in previously sedentary older people [31]. Improvements in peak values of oxygen pulse, $\dot{V}E$ and power output suggests the exercise program could be an effective stimulus for inducing cardiopulmonary adaptations. Furthermore, the improvement in peak oxygen pulse and progressive increase in power output needed to maintain the vigorous intensity target heart rate (Figure 2) are indicative of adaptations in cardiac stroke volume, which commonly result from endurance training [32]. These improvements were accompanied by a marginal (non-significant) increase in peak $\dot{V}O_2$, which in conjunction with enhanced pedalling efficiency, probably account for the increase in peak power output observed in the exercise group. In contrast, AT was unchanged, suggesting metabolic adaptations influencing oxygen utilisation within active skeletal muscles were negligible. In the exercise group, the ability of skeletal muscle to utilise additional oxygen resulting from enhanced delivery may have been compromised to a greater degree because a

higher proportion of participants had undergone neoadjuvant chemotherapy (33% versus 17% in the control group).

Neoadjuvant chemotherapy was previously shown to adversely affect skeletal muscle mitochondrial oxidative phosphorylation in patients with locally advanced rectal cancer, probably influencing the reported decline in peak $\dot{V}O_2$ and AT prior to surgery [33]. Furthermore, cisplatin (commonly used in neoadjuvant chemotherapy) causes skeletal muscle atrophy and alterations in metabolic signalling pathways that were only partially reversed by exercise training in healthy mice [34]. As improvements in AT following endurance training are strongly influenced by adaptations in metabolic pathways that enhance fat utilization and oxidative ATP production [32], a higher volume of pre-operative exercise and/or longer period of recovery may be needed to overcome the adverse effects of neoadjuvant chemotherapy on skeletal muscle mitochondria and signalling pathways prior to RC. In this respect, a 6-week program of thrice-weekly cycle ergometer interval training was needed to restore AT to pre-neoadjuvant chemotherapy levels in patients with locally advanced rectal cancer [35]. Hence, programs which offer additional weekly sessions might be needed to enhance the stimulus for metabolic adaptations in patients who have undergone neoadjuvant chemotherapy.

Systematic reviews support the positive impact of pre-operative exercise on post-operative recovery outcomes in patients undergoing cardiac and abdominal surgery but there has been significant heterogeneity in study design and a paucity of high quality studies [36, 37]. Our results are to be considered with caution as adequately powered clinical trials are needed to establish whether improvements in pre-operative cardiopulmonary fitness are associated with enhanced recovery following RC. Nevertheless, these preliminary data show marginal (non-significant) differences in favour of the exercise group in post-operative Clavien-Dindo score (≥ 1) and need for HDU inotropic support. It has been proposed that pre-operative exercise has the potential to improve physiological reserve, thereby helping to counter the physical challenges of surgery and enhancing post-operative recuperation [4]. However, the magnitude of change necessary to positively influence surgical outcomes is unclear and previous research suggests that improvements of 2-3 ml·kg⁻¹·min⁻¹ in pre-operative peak $\dot{V}O_2$ following exercise programs [8, 9] might not translate into quality of life enhancements in lung cancer patients before or after surgery [10]. Other exercise prehabilitation studies in lung, colorectal and bladder cancer patients have not reported changes in cardiopulmonary fitness following exercise prehabilitation programs that resulted in improvements [12] or no improvements [16-19] in post-operative recovery outcomes. Observational

studies suggest that an AT of less than 11-12 ml·kg⁻¹·min⁻¹ is associated with major post-operative complications (Clavien Class ≥3) and poorer recovery outcomes (including hospital length of stay) in bladder cancer patients undergoing RC [2, 38] and this is consistent with evidence from a large-scale study of patients (N=843) undergoing intra-abdominal surgery [39]. AT was >11 ml·kg⁻¹·min⁻¹ in >50% of our participants prior to surgery and when our data were pooled and considered independent of group assignment, higher scores for pre-operative peak $\dot{V}O_2$, peak $\dot{V}E$, peak power output and AT were associated with improved recovery outcomes (Table 3). This raises the question of whether cardiopulmonary fitness gains that fail to reach a given AT or peak $\dot{V}O_2$ threshold could positively influence post-operative recovery outcomes in this patient group. In addition, the relative importance of cardiopulmonary fitness versus other factors in optimising post-operative recovery, e.g. adequate nutrition, mental preparation, etc. [4], is an important avenue for future research.

This study had some limitations. The sample size was insufficient to draw definitive conclusions about the effects of improved pre-operative cardiopulmonary fitness on post-operative recovery outcomes and we have no data on the long-term maintenance of intervention effects. Furthermore, because we aimed to be as inclusive as possible, broad variability in participant characteristics at baseline (comorbidities, physical fitness levels, etc.) and differences in the number of exercise sessions attended are likely to have had some bearing on the results. In addition, the mean age of our sample population (>70 years) and recruitment of patients from a single centre serving a large rural community may limit the generalization of our results. Regarding the latter, our recruitment rate and reasons for non-participation may be less representative of patients living closer to treating hospitals. Travel distance to the exercise facility was cited as the main reason for non-participation in the study but this is likely to be less of an issue in patients living in closer proximity. Nevertheless, other reasons (including physical limitations or a lack of confidence to engage in the exercise program) prevented >26% of eligible patients from taking part. This suggests that a program of hospital supervised vigorous intensity aerobic interval exercise is unlikely to be feasible for all bladder cancer patients. For this reason, other forms of pre-operative exercise, particularly exercise that can be undertaken in the home or community environment, should be evaluated in future research.

LIST OF ABBREVIATIONS

ANCOVA: Analysis of Covariance

AT: Anaerobic threshold

BMI: Body mass index

CPET: Cardiopulmonary exercise test

HDU: High Dependency Unit

LoS: Length of Stay

NHS: National Health Service

RC: Radical Cystectomy

RPE: Ratings of Perceived Exertion

\dot{V}_E : Minute ventilation

$\dot{V}O_2$: Oxygen consumption per minute

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest. The corresponding author has full control of all primary data and agrees to allow the journal to review the data if requested.

REFERENCES

1. Older P, Hall A, Hader R (1999) Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly. *Chest* 116:355-362.
2. Prentis JM, Trenell MI, Vasdev N, French R, Dines G et al (2013) Impaired cardiopulmonary reserve in an elderly population is related to postoperative morbidity and length of hospital stay after radical cystectomy. *BJU Int* 112:E13-19.
3. Stringer W, Casaburi R, Older P (2012) Cardiopulmonary exercise testing: does it improve perioperative care and outcome? *Curr Opin Anaesthesiol* 25:178-184.
4. Carli FG, Scheede-Bergdahl C (2017) Promoting a culture of prehabilitation for the surgical cancer patient. *Acta Oncologica*; Published online: 09 Jan 2017.
5. Jack S, West M, Grocott MP (2011) Perioperative exercise training in elderly subjects. *Best Pract Res Clin Anaesthesiol* 25:461-472.

6. Singh F, Newton RU, Galvao DA, Spry N, Baker MK (2013) A systematic review of pre-surgical exercise intervention studies with cancer patients. *Surg Oncol* 22:92-104.
7. Santa Mina D, Clarke H, Ritvo P, Leung YW, Matthew AG et al (2014) Effect of total-body prehabilitation on postoperative outcomes: a systematic review and meta-analysis. *Physiotherapy* 100:196-207.
8. Jones LW, Peddle CJ, Eves ND, Haykowsky MJ, Courneya KS et al (2007) Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. *Cancer* 110:590-598.
9. Stefanelli F, Meoli I, Cobuccio R, Curcio C, Amore D et al (2013) High-intensity training and cardiopulmonary exercise testing in patients with chronic obstructive pulmonary disease and non-small-cell lung cancer undergoing lobectomy. *Eur J Cardiothorac Surg* 44:e260-265.
10. Peddle CJ, Jones LW, Eves ND, Reiman T, Sellar CM et al (2009) Effects of presurgical exercise training on quality of life in patients undergoing lung resection for suspected malignancy: a pilot study. *Cancer Nurs* 32:158-165.
11. Chevile AL, Alberts SR, Rummans TA, Basford JR, Lapid MI et al (2015) Improving Adherence to Cancer Treatment by Addressing Quality of Life in Patients With Advanced Gastrointestinal Cancers. *J Pain Symptom Manage* 50:321-327.
12. Sekine Y, Chiyo M, Iwata T, Yasufuku K, Furukawa S et al (2005) Perioperative rehabilitation and physiotherapy for lung cancer patients with chronic obstructive pulmonary disease. *Jpn J Thorac Cardiovasc Surg* 53:237-243.
13. Sueppel C, Kreder K, See W (2001) Improved continence outcomes with preoperative pelvic floor muscle strengthening exercises. *Urol Nurs* 21:201-210.
14. Burgio KL, Goode PS, Urban DA, Umlauf MG, Locher JL et al (2006) Preoperative biofeedback assisted behavioral training to decrease post-prostatectomy incontinence: a randomized, controlled trial. *J Urol* 175:196-201.
15. Centemero A, Rigatti L, Giraud D, Lazzeri M, Lughezzani G et al (2010) Preoperative pelvic floor muscle exercise for early continence after radical prostatectomy: a randomised controlled study. *Eur Urol* 57:1039-1043.
16. Li C, Carli F, Lee L, Charlebois P, Stein B et al (2013) Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. *Surg Endosc* 27:1072-1082.

17. Gillis C, Li C, Lee L, Awasthi R, Augustin B et al (2014) Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. *Anesthesiology* 121:937-947.
18. Jensen BT, Jensen JB, Laustsen S, Petersen AK, Sondergaard I et al (2014) Multidisciplinary rehabilitation can impact on health-related quality of life outcome in radical cystectomy: secondary reported outcome of a randomized controlled trial. *J Multidiscip Healthc* 7:301-311.
19. Jensen BT, Petersen AK, Jensen JB, Laustsen S, Borre M (2015) Efficacy of a multiprofessional rehabilitation programme in radical cystectomy pathways: a prospective randomized controlled trial. *Scand J Urol* 49:133-141.
20. Jensen BE, Laustsen S, Jensen JB, Borre M, Petersen AK (2016). Exercise-based pre-habilitation is feasible and effective in radical cystectomy pathways—secondary results from a randomized controlled trial. *Support Care Cancer* 24: 3325-3331.
21. Weston M, Weston KL, Prentis JM, Snowden CP (2016) High-intensity interval training (HIT) for effective and time-efficient pre-surgical exercise interventions. *Perioper Med (Lond)* 5:2.
22. Lancaster GA, Dodd S, Williamson PR (2004) Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract* 10:307-312.
23. Browne RH (1995) On the use of a pilot sample for sample size determination. *Stat Med* 14:1933-1940.
24. UK Department of Health, Physical Activity, Health Improvement and Protection (2011). *Start Active, Stay Active: A report on physical activity for health from the four home countries' Chief Medical Officers.*
25. Borg GA (1970) Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 14:377-381.
26. Wasserman K, Hansen JE, Sue DY, Stringer WW, Sietsema KE et al (2012) *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications (Fifth Edition).* Baltimore, USA: Lippincott, Williams & Wilkins.
27. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D et al (2009) The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 250:187-196.
28. Yoon PD, Chalasani V, Woo HH (2013) Use of Clavien-Dindo classification in reporting and grading complications after urological surgical procedures: analysis of 2010 to 2012. *J Urol* 190:1271-1274.

29. Vickers AJ, Altman DG (2001) Statistics notes: Analysing controlled trials with baseline and follow up measurements. *BMJ* 323:1123-1124.
30. US Department of Health and Human Services (1996). Physical Activity and Health: A Report of the Surgeon General. In. Atlanta: Centers for Disease Control and Prevention, National Centre for Chronic Disease Prevention and Health Promotion; 1996: 33.
31. Huang G, Wang R, Chen P, Huang SC, Donnelly JE et al (2016) Dose-response relationship of cardiorespiratory fitness adaptation to controlled endurance training in sedentary older adults. *Eur J Prev Cardiol* 23:518-529.
32. Bassett DR Jr, Howley ET (2000) Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Med Sci Sports Exerc* 32:70-84.
33. West MAL, Lythgoe D, Barben CP, Adams VL, Bimson WE et al (2014) The Effect of Neoadjuvant Chemoradiotherapy on Whole-Body Physical Fitness and Skeletal Muscle Mitochondrial Oxidative Phosphorylation In Vivo in Locally Advanced Rectal Cancer Patients – An Observational Pilot Study. *PLoS ONE* 9:e111526.
34. Hojman PF, Zerahn B, Christensen JF, Dethlefsen C, Lonkvist CK et al (2014) Voluntary Exercise Prevents Cisplatin-Induced Muscle Wasting during Chemotherapy in Mice. *PLoS ONE* 9:e109030.
35. West MAL, Lythgoe D, Barben CP, Sripatham R, Kemp GJ et al (2015) Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. *Brit J Anaesth* 114:244-251.
36. Valkenet K, van de Port IG, Dronkers JJ, de Vries WR, Lindeman E et al (2011) The effects of preoperative exercise therapy on postoperative outcome: a systematic review. *Clin Rehabil* 25:99-111.
37. Lemanu DP, Singh PP, MacCormick AD, Arroll B, Hill AG (2013) Effect of preoperative exercise on cardiorespiratory function and recovery after surgery: a systematic review. *World J Surg* 37:711-720.
38. Tolchard S, Angell J, Pyke M, Lewis S, Dodds N et al (2015) Cardiopulmonary reserve as determined by cardiopulmonary exercise testing correlates with length of stay and predicts complications after radical cystectomy. *BJU Int* 115:554-561.
39. Wilson RJ, Davies S, Yates D, Redman J, Stone M (2010) Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. *Br J Anaesth* 105:297-303.

FIGURE LEGENDS

Figure 1. Participant flow through the trial.

Figure 2. Average weekly heart rate (HR; top figure) and power output (bottom figure) over four pre-operative weeks of supervised aerobic interval exercise. Average heart rate data are presented as percentage of the peak heart rate measured during the pre-operative CPET and predicted maximum heart rate based on $220 - \text{age}$.

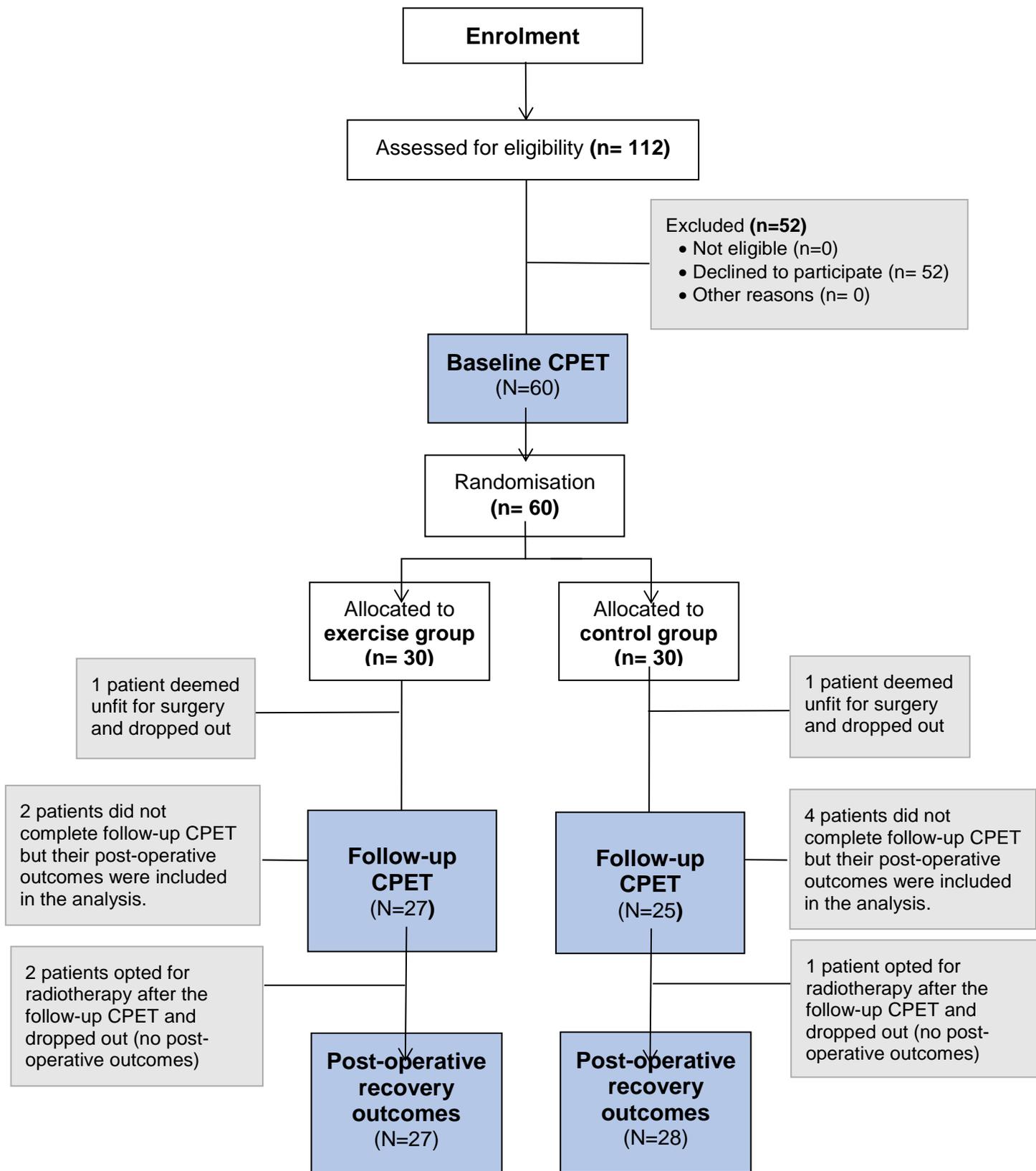


Figure 1. Participant flow through the trial

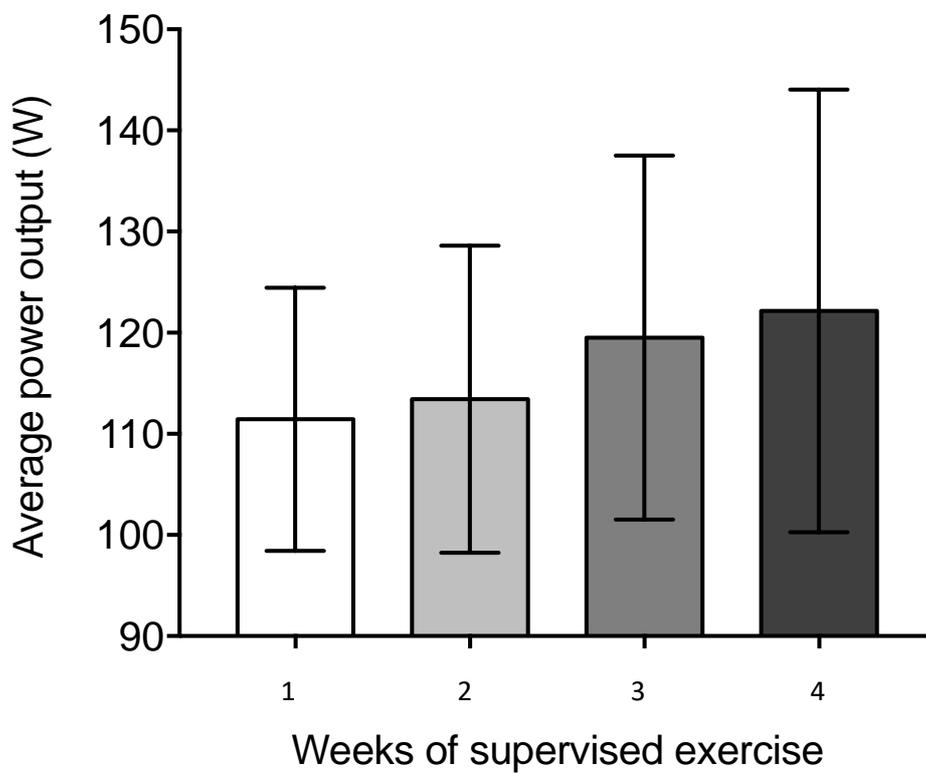
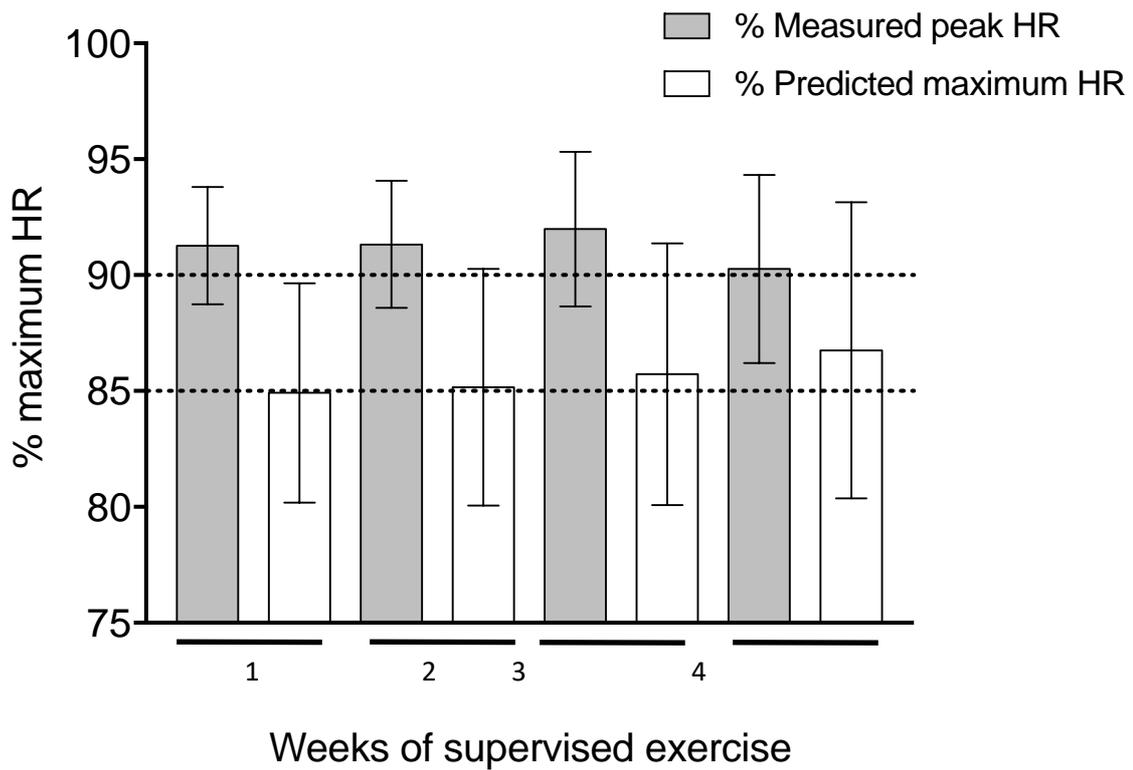


Table 1. Baseline characteristics of participants allocated to exercise plus standard care or standard care only. Data are presented as mean \pm SD or numbers (percentages).

Characteristics	Exercise group (N=30)	Control group (N=30)
Age (range)	71.60 \pm 6.80	72.5 \pm 8.40
Female	3 (10)	4 (13)
White	30 (100)	30 (100)
Anthropometric variables and blood pressure		
Height (m)	1.73 \pm 6.85	1.68 \pm 8.05
Body mass (Kg)	81.17 \pm 13.38	76.20 \pm 11.60
BMI (kg·m ⁻²)	27.09 \pm 4.20	26.91 \pm 4.45
Comorbid conditions		
Hypertension	17 (57)	17 (57)
Ischemic heart disease	3 (10)	8 (27)
Type 2 diabetes	3 (10)	4 (13)
Bladder cancer treatment		
Neoadjuvant chemotherapy	10 (33)	5 (17)
Surgical treatment		
<i>Laparoscopic</i>	27 (90)	28 (93)
<i>Open</i>	1 (3)	1 (3)
<i>Neo bladder formation</i>	2 (7)	1 (3)
Smoking status		
<i>Current smoker</i>	4 (13)	4 (13)
<i>Ex-smoker</i>	20 (66)	13 (43)
<i>Never smoker</i>	6 (20)	13 (43)

Table 2. Cardiopulmonary variables at baseline and follow-up (prior to radical cystectomy). Data are presented as mean \pm SD, with 95% confidence intervals in parentheses.

CPET variables	Control group		Exercise group		Adjusted mean difference at follow-up CPET	<i>P</i>
	Baseline	Pre-surgery	Baseline	Pre-surgery		
Peak $\dot{V}O_2$ (ml.kg ⁻¹ .min ⁻¹)	20.38 \pm 5.59 (18.07-22.68)	20.84 \pm 5.43 (18.60-23.08)	19.22 \pm 4.80 (17.32-21.12)	21.07 \pm 5.60 (18.85-23.29)	1.33 (-0.04-2.70)	0.057
PPO (W)	131 \pm 36 (116-145)	129 \pm 44 (111-147)	131 \pm 39 (116-146)	148 \pm 41 (132-165)	19 (10-27)	0.000
Peak HR (beats.min ⁻¹)	143 \pm 24 (134-153)	143 \pm 23 (134-152)	139 \pm 25 (129-149)	137 \pm 26 (127-148)	-2 (-9-6)	0.650
Peak RER	1.38 \pm 0.13 (1.32-1.43)	1.35 \pm 0.12 (1.30-1.40)	1.36 \pm 0.11 (1.32-1.40)	1.35 \pm 0.12 (1.30-1.40)	0.01 (-0.05-0.07)	0.736
Peak $\dot{V}E$: (L.min ⁻¹)	67.04 \pm 19.50 (58.99-75.09)	68.07 \pm 19.30 (60.10-76.03)	70.33 \pm 22.54 (61.41-79.25)	78.63 \pm 23.12 (69.48-87.78)	7.49 (2.86-12.12)	0.002
Peak OP (ml.beat ⁻¹)	10.72 \pm 2.24 (9.79-11.64)	10.83 \pm 2.33 (9.87-11.79)	11.31 \pm 2.74 (10.23-12.40)	12.74 \pm 2.88 (11.60-13.88)	1.36 (0.63-2.10)	0.001
AT (ml.kg ⁻¹ .min ⁻¹)	11.38 \pm 2.57 (10.27-12.49)	12.21 \pm 2.63 (11.07- 13.35)	11.49 \pm 2.08 (10.61-12.37)	12.00 \pm 2.97 (10.74-13.25)	-0.30 (-1.57-0.97)	0.637
OP at AT (ml.beat ⁻¹)	8.33 \pm 2.05 (7.45-9.22)	8.56 \pm 1.99 (7.70-9.42)	8.90 \pm 2.06 (8.03-9.77)	9.76 \pm 2.63 (8.65-10.87)	0.69 (-0.18-1.57)	0.118
$\dot{V}E/\dot{V}CO_2$ at AT	31.00 \pm 5.09 (28.80-33.20)	31.17 \pm 4.95 (29.03-33.31)	31.50 \pm 4.11 (29.77-33.23)	31.17 \pm 3.27 (29.79-32.55)	-0.36 (-1.93-1.21)	0.778

$\dot{V}O_2$: oxygen consumption per minute; PPO: peak power output; HR: heart rate; RER: respiratory exchange ratio; $\dot{V}E$: minute ventilation; OP: oxygen pulse; AT: anaerobic threshold; *P* values are shown for between groups comparisons (ANCOVA).

Table 3. Relationship between CPET variables and post-operative recovery outcomes.

	Peak $\dot{V}O_2$	Peak-OP	Peak $\dot{V}E$	PPO	AT
HDU length of stay	-0.562**	-0.372**	-0.421**	-0.514**	-0.454**
Hospital length of stay	-0.560**	-0.465**	-0.298*	-0.457**	-0.360*

Peak $\dot{V}O_2$: peak rate of oxygen consumption; Peak-OP: peak oxygen pulse; Peak $\dot{V}E$: peak ventilatory volume; PPO: peak power output; *P* values are shown for Spearman's Rank Correlation Coefficient:

* *P* < 0.05; ** *P* < 0.001