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2 **Vigorous intensity aerobic interval exercise in bladder cancer patients prior to radical cystectomy: a**
3 **randomized controlled feasibility study**
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ABSTRACT

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2 **Purpose:** Strategies to improve pre-operative cardiopulmonary fitness could positively impact recovery after
3 surgery. This study investigated the feasibility of pre-operative vigorous intensity aerobic interval exercise in
4 bladder cancer patients prior to radical cystectomy (RC). **Methods:** A total of 60 patients were randomised (1:1)
5 to an exercise or control group following a cardiopulmonary exercise test (CPET). The exercise group was
6 offered twice-weekly pre-operative supervised vigorous intensity aerobic interval exercise in addition to
7 standard treatment, whilst the controls received standard treatment only. A repeat CPET was undertaken before
8 surgery and post-operative recovery outcomes were recorded. **Results:** Over half of the 112 eligible patients
9 approached in the clinic were recruited to the study (53.5%), with 52 of the 60 recruited patients (87%)
10 attending both pre-operative CPETs and post-operative recovery data being available for 55 of the patients
11 (92%). Patients attended a median of 8 (range: 1-10) exercise sessions over a pre-operative period of 3-6 weeks.
12 Improvements in peak values of oxygen pulse ($P=0.001$), minute ventilation ($P=0.002$) and power output
13 ($P<0.001$) were observed at the follow-up CPET in the exercise group versus controls and there were no adverse
14 events. Although this feasibility study was not powered to detect changes in post-operative recovery outcomes,
15 there were marginal (non-significant) differences in favour of the exercise group in post-operative Clavien-
16 Dindo score and need for High Dependency Unit inotropic support. **Conclusions:** Vigorous intensity aerobic
17 interval exercise could be an effective strategy for improving pre-operative physiological reserve and post-
18 operative recovery outcomes in bladder cancer patients undergoing RC. **Implications for Cancer Survivors:**
19 Bladder cancer patients respond well to pre-surgical interval exercise and the improvements in cardiopulmonary
20 fitness variables could have important implications for post-operative recuperation after RC.
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Key words:

42 Pre-operative care, exercise, urinary bladder neoplasms
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INTRODUCTION

1 Pre-operative cardiopulmonary fitness is increasingly being recognised as an important factor influencing post-
2 operative recovery outcomes. Almost two decades ago, Older *et al.* identified an association between low
3 cardiopulmonary fitness in older people and poor outcome following major surgery [1]. Other studies have since
4 provided further evidence of the utility of pre-operative cardiopulmonary exercise test (CPET) variables for risk
5 stratification of surgical patients, including those undergoing radical cystectomy (RC) [2, 3]. However, the role
6 of pre-operative exercise programs (prehabilitation) for optimising cardiopulmonary fitness prior to surgery has
7 received less attention [4]. Although systematic review evidence suggests that exercise training can improve
8 cardiopulmonary fitness before surgery in older people and can reduce the risk of post-operative complications
9 following major abdominal surgery [5-7], the paucity of high quality clinical trials has been highlighted [5].
10 Furthermore, studies that have investigated the effects of exercise prehabilitation programs on post-operative
11 recovery outcomes cancer patients have yielded equivocal results.
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26 Intensive supervised pre-operative exercise programs resulted in modest improvements in pre-operative
27 cardiopulmonary fitness measures in lung cancer patients, including the six-minute walk test [8] and peak
28 aerobic capacity [8, 9], but with no effect on pre-surgical or longer-term quality of life [10]. In addition, a
29 supervised exercise program involving trunk and limb-strengthening exercise improved chemoradiotherapy
30 completion rate in patients with gastrointestinal cancers, but did not improve post-operative recovery outcomes
31 [11]. In contrast, Sekine *et al.* [12] reported a reduction in post-operative pulmonary complications and hospital
32 length of stay in lung cancer patients with chronic obstructive pulmonary disease after daily hospital-based
33 pulmonary exercises and walking (5000 steps/day) in the two weeks prior to lobectomy. Similarly, in prostate
34 cancer patients undergoing radical prostatectomy, there is evidence that home-based pelvic floor muscle
35 exercise has favourable effects on post-operative urinary continence outcomes up to 12 months of follow-up
36 [13-15]. However, home-based exercise programs involving aerobic and resistance exercise have had minimal
37 impact on post-operative hospital length of stay or severity of complications in colorectal or bladder cancer
38 patients [16-19], although Jensen *et al.* [19] reported improved post-operative mobility in the latter.
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54 Because of the short time-window between decision for surgery and RC, there is a need to optimise the exercise
55 stimulus for cardiopulmonary adaptations and the potential advantages of vigorous intensity interval exercise in
56 this respect, were recently highlighted [20]. Interval training enables patients to undertake aerobic (endurance)
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1 exercise at a higher intensity than would be possible for continuous exercise at the same intensity but the
2 feasibility of this exercise modality in bladder cancer patients awaiting RC is unknown. Hence, the main
3 purpose of this study was to investigate the feasibility of randomizing bladder cancer patients to a short-term
4 program of pre-operative vigorous intensity aerobic interval exercise versus standard care prior to elective RC.
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6 A secondary aim was to collect and report preliminary data on CPET and post-operative recovery outcomes
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8 before and after the exercise prehabilitation program.
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13 **METHODS**

14 *Patient recruitment, randomization and sample size*

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16 Patients were recruited from the Urology Department at the Norfolk and Norwich University Hospitals National
17 Health Service (NHS) Foundation Trust, United Kingdom, between 2012 and 2014, and were randomized to
18 standard treatment or pre-operative exercise training. Medical clearance to participate in the study was given by
19 one of four consultant urologists, who were blind to treatment allocation. Randomization was undertaken using
20 a pre-generated random sequence (nQuery Advisor 6.1; Statistical Solutions) which was held by a research
21 administrator not involved in the day to day running of the study. Upon completion of the baseline assessments,
22 the study urologist (SB) phoned the administrator for details of group allocation (exercise or standard care). As
23 the main purpose was to assess the feasibility of the exercise program, there was no formal sample size
24 calculation but we aimed to recruit 60 patients (30 in each group) in accordance with published
25 recommendations [21, 22]. Written informed consent was obtained prior to study participation and ethical
26 approval was granted by the East of England Regional Ethics Committee.
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42 *Inclusion and exclusion criteria*

43 Bladder cancer patients listed for RC via the multi-disciplinary team were included in the study (eligibility was
44 not limited by choice of surgical technique). Patients undergoing neo-adjuvant chemotherapy before RC were
45 also included but entered the trial at least 2 weeks after completion of treatment. Patients offered urinary
46 diversion for benign disease were excluded from the study.
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54 *Standard treatment*

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

14 Twice-weekly exercise training sessions were supervised by a team of exercise science staff working closely
15 with the study urologist (SB) in an exercise facility at the University of East Anglia, UK, which is close to the
16 treating hospital. Sessions comprised vigorous intensity aerobic interval exercise on a cycle ergometer (Monark
17 824E; Varberg, Sweden) using the Borg Ratings of Perceived Exertion (RPE) Scale to control intensity [23].
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22 The Borg RPE Scale is a psychophysiological scale, ranging from "No exertion" to "Maximal Exertion".
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24 Following a 5-10 min warm-up against light resistance (50 W), the aim was for patients to perform 6 x 5 min
25 intervals at a target perceived exertion of 13-15 ('somewhat hard' to 'hard', equating to 70-85% predicted
26 maximum heart rate based on 220-age), with 2.5 min interpolated active rest intervals against light resistance
27 (50 W). They were instructed to maintain a steady pedalling cadence of 50-60 rev·min⁻¹ during the aerobic
28 intervals and the exercise program was progressed by gradually adding more load to the flywheel to maintain
29 the target perceived exertion (Figure 2). Immediately following the aerobic intervals, patients performed a 'cool-
30 down' against low resistance (50 W).
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42 ***Feasibility outcomes***

43 Feasibility was assessed in terms of recruitment and attrition, willingness to be randomized, acceptability of the
44 outcome measures, adherence to the intervention, safety and suitability of the exercise dose and adverse events.
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50 ***Cardiopulmonary exercise test and post-operative recovery outcomes***

51 Cardiopulmonary exercise tests (CPETs) and post-operative recovery outcomes were blindly assessed by an
52 exercise physiologist who was not directly involved in the supervision of exercise sessions and clinical staff at
53 the treating hospital who were unaware of group allocation, respectively.
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1 All patients performed a baseline incremental CPET to maximum exercise tolerance on an electronically-braked
2 cycle ergometer (Excalibur Sport, Lode, Netherlands). Following a 2-min warm-up against no resistance (0 W),
3 work rate was increased using a ramp protocol (10-20 W·min⁻¹) to maximum exercise tolerance. Heart rate was
4 recorded continuously by ECG (Cardioperfect, Cardioperfect, Welch Allyn, USA). Pulmonary gas exchange
5 variables ($\dot{V}O_2$, $\dot{V}CO_2$, minute ventilation [$\dot{V}E$] and other respiratory variables) were measured breath-by-breath
6 with an on-line expired gas analysis system (Ultima, CardioO2; Medical Graphics Corporation). AT was
7 determined from 30 s averaged data by two experienced exercise physiologists (JS and GC) using the V-slope
8 method and confirmed by analysing the ventilatory equivalents [24]. Peak values for all variables were recorded
9 as the highest value over any 30-s averaged period, with peak oxygen pulse calculated as the amount of oxygen
10 consumed per heartbeat.
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22 *Post-operative recovery outcomes*

23 Clavien-Dindo grading was used to score post-surgical complications [25, 26]. Post-operative ileus and chest
24 infection prevalence, time spent in HDU, need for inotropic support and hospital length of stay (LoS) were used
25 as other post-operative recovery outcomes.
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31 *Data analysis*

32 All statistical analyses were undertaken using SPSS (SPSS Inc., Chicago, Illinois, USA). CPET and post-
33 operative recovery outcomes were tested for normality of distribution using Kolmogorov-Smirnov test. BMI
34 and CPET variables were normally distributed and analysed using ANCOVA, with baseline values as the
35 covariate [27], to compare differences between the groups at follow-up (prior to surgery). Post-operative
36 recovery outcomes were not normally distributed and non-parametric statistical tests were used. The Chi -
37 Square test was used to compare categorical data. The Spearman's rank correlation coefficient was used to
38 investigated bivariate associations between CPET variables and post-operative recovery outcomes in pooled
39 baseline data (independent of group assignment). Normally distributed data are presented as mean \pm SD and
40 non-normally distributed data as medians and range (unless otherwise stated). The significance level was set at
41 $P < 0.05$.
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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). 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. Post-operative recovery outcomes were available for 27/30 (90%) patients in the exercise group and 28/30 (93%) patients in the control group (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-age) and 90-92% of the measured peak HR during the

1 CPET (Figure 2), demonstrating the safety and suitability of the exercise dose. Flywheel load (power output)
2 was gradually increased from 111 ± 5.5 W to 122 ± 5.8 W during this time to ensure target HRs for vigorous
3 intensity exercise were maintained as patients adapted to the exercise program (Figure 2). The average number
4 of aerobic intervals achieved in the first week of exercise was 5.5 (range: 3.5-6.0), whereas all patients were
5 achieving 6 intervals per session in the fourth week. There were no adverse events resulting from the supervised
6 exercise sessions.
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11 ***CPET and post-operative recovery outcomes***

12 CPET variables at baseline and follow-up are presented in Table 2. The time between baseline and follow-up
13 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
14 controls. Improvements in peak values of oxygen pulse ($P=0.001$), $\dot{V}E$ ($P=0.002$) and power output ($P<0.001$)
15 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
16 controls (Table 2). Although this feasibility study was not powered to detect changes in post-operative recovery
17 outcomes, four patients (15%) in the exercise group versus 10 controls (36%) had some deviation from the
18 normal post-operative course of recovery (Clavien-Dindo Grade ≥ 1 ; $P=0.075$), whereas one patient (4%) in the
19 exercise group and four controls (14%) had a Clavien-Dindo Grade ≥ 3 ; ($P=0.172$). The prevalence of post-
20 operative ileus ($P=0.808$) and chest infection ($P=0.609$) were similar between the exercise and control groups (6
21 versus 7 patients and 3 versus 2 patients, respectively). Median time spent in HDU was 1 day in both the
22 exercise and control group (range 1-10 and 1-7 days, respectively; $P=0.938$), although fewer patients in the
23 exercise group needed HDU inotropic support, reaching borderline statistical significance (2 versus 7 patients;
24 $P=0.078$). The median hospital LoS was 7 days in both the exercise and control groups (range 4-78 and 5-107
25 days, respectively; $P=0.865$). When the pre-operative data were pooled and considered independent of group
26 assignment, inverse associations were observed between LoS (HDU and hospital) and pre-operative CPET
27 variables ($P<0.05$; Table 3).
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DISCUSSION

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2 This is the first study to show that vigorous intensity aerobic interval exercise is feasible in bladder cancer
3 patients awaiting RC. Patients adapted to the program quickly and all were able to perform six aerobic intervals
4 per exercise session at the vigorous intensity target HR by the fourth week of exercise. The demographic profile
5 of our patients was representative of bladder cancer patients undergoing RC in terms of age, comorbidities and
6 risk factors, and the recruitment rate of eligible patients was very good (53.5%). The main reason for non-
7 participation amongst eligible patients was distance between the exercise facility and their home. As the hospital
8 serves a large rural community, with some patients living >80 km away, twice-weekly travel to the supervised
9 exercise sessions was considered to be too onerous by some participants. We also observed excellent retention
10 over the course of the study (8.3% attrition), which is likely to be at least in part due to flexible exercise
11 scheduling (i.e. exercise sessions were arranged at suitable times for patients). In addition, most patients (87%)
12 were able to attend both CPET assessments prior to RC and there were no adverse events. The time between
13 baseline and follow-up CPET assessments was in the range of 20-45 days across both groups. This provided an
14 opportunity for all patients in the exercise arm to attend a minimum of six supervised exercise sessions prior to
15 RC.

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32 Because of the short time-window between decision for surgery and RC, there is a need for pre-surgical exercise
33 programs to be effective and time efficient and the potential advantages of vigorous interval exercise were
34 recently highlighted [20]. Our exercise program involved aerobic interval exercise training at “somewhat hard”
35 to “hard” intensity (Borg RPE 13-15), equating to ~70-85% predicted maximum heart rate [28], which is
36 reported to be optimal for inducing improvements in cardiopulmonary fitness in previously sedentary older
37 people [29]. Improvements in peak values of oxygen pulse, $\dot{V}E$ and power output in the exercise group suggests
38 that the exercise program could be an effective stimulus for inducing cardiopulmonary adaptations in the short
39 time available before surgery. Both the improvement in peak oxygen pulse and progressive increase in flywheel
40 load (power output) needed to maintain the vigorous intensity target HR (Figure 2) are indicative of adaptations
41 in cardiac stroke volume, which commonly result from endurance training [30]. These improvements were
42 accompanied by a marginal (non-significant) increase in peak $\dot{V}O_2$, which in conjunction with enhanced
43 mechanical efficiency following exercise training, probably account for the increase in peak power output
44 observed in the exercise group. In contrast, AT was unchanged at the CPET follow-up, suggesting metabolic
45 adaptations influencing oxygen utilisation within the active skeletal muscles were negligible. In the exercise
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1 group, the ability of skeletal muscle to utilise any additional oxygen resulting from enhanced delivery may have
2 been compromised to a greater degree because a higher proportion of participants had undergone neoadjuvant
3 chemotherapy prior to the study (33% versus 17% in the control group). Neoadjuvant chemotherapy was shown
4 to adversely affect skeletal muscle mitochondrial oxidative phosphorylation in patients with locally advanced
5 rectal cancer, probably influencing the reported decline in cardiopulmonary fitness (AT and peak $\dot{V}O_2$) prior to
6 surgery [31]. Furthermore, cisplatin (commonly used in the neoadjuvant chemotherapeutic treatment of bladder
7 cancer patients) causes skeletal muscle atrophy and alterations in a range of metabolic signalling pathways that
8 were shown to be only partially reversed by exercise training in healthy mice [32]. As improvements in AT
9 following endurance training are strongly influenced by adaptations in metabolic pathways that enhance fat
10 utilization and oxidative ATP production [30], a higher volume of pre-operative aerobic interval exercise and/or
11 longer period of recovery may be needed to overcome the adverse effects of neoadjuvant chemotherapy on
12 skeletal muscle mitochondria and signalling pathways prior to RC. In this respect, a 6-week program of thrice-
13 weekly cycle ergometer interval training was needed to restore AT to pre-neoadjuvant chemotherapy levels in
14 patients with locally advanced rectal cancer [33]. Given the feasibility of twice-weekly vigorous aerobic interval
15 exercise in this patient group, programs which offer additional weekly sessions could be tested and might
16 enhance the stimulus for metabolic adaptations, particularly in patients who have recently undergone
17 neoadjuvant chemotherapy.
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36 Systematic reviews have reported encouraging evidence supporting the positive impact of pre-operative exercise
37 on post-operative recovery outcomes in patients undergoing cardiac and abdominal surgery but there has been
38 significant heterogeneity in study design and a paucity of high quality evidence [34, 35]. Our results for post-
39 operative recovery outcomes are to be considered with caution as adequately powered clinical trials are needed
40 to establish whether improvements in pre-operative cardiopulmonary fitness are associated with enhanced
41 recovery following RC. Nevertheless, these preliminary data show marginal (non-significant) differences in
42 favour of the exercise group in post-operative Clavien-Dindo score (≥ 1) and need for HDU inotropic support. It
43 has been proposed that pre-operative exercise has the potential to improve physiological reserve, thereby
44 helping to counter the physical challenges of surgery and enhancing post-operative recuperation [4]. However,
45 the magnitude of change in pre-operative cardiopulmonary fitness required to positively influence surgical
46 outcomes is unclear. Previous research suggests that improvements of 2-3 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in pre-operative peak
47 $\dot{V}O_2$ following supervised aerobic exercise programs [8, 9] might not translate into quality of life enhancements
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2 in lung cancer patients before or after surgery [10]. Other exercise prehabilitation studies in lung, colorectal and
3 bladder cancer patients have not reported changes in cardiopulmonary fitness following exercise prehabilitation
4 programs that resulted in improvements [12] or no improvements [16-19] in post-operative recovery outcomes.
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6 Observational studies suggest that an AT of less than 11-12 ml·kg⁻¹·min⁻¹ is associated with major post-
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8 operative complications (Clavien Class ≥3) and poorer recovery outcomes (including hospital length of stay) in
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10 bladder cancer patients undergoing RC [2, 36] and this is consistent with evidence from a large-scale study of
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12 patients (N=843) undergoing intra-abdominal surgery [37]. AT was >11 ml·kg⁻¹·min⁻¹ in >50% of our
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14 participants prior to surgery and when our data were pooled and considered independent of group assignment,
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16 higher scores for pre-operative peak $\dot{V}O_2$, peak $\dot{V}E$, peak power output and AT were associated with improved
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18 recovery outcomes (Table 3). This observational evidence, in conjunction with the lack of intervention studies
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20 linking changes in pre-operative cardiopulmonary fitness to post-operative recovery outcomes, raises the
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22 question of whether cardiopulmonary fitness gains that fail to reach a given AT or peak $\dot{V}O_2$ threshold could
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24 positively influence post-operative recovery outcomes in this patient group. In addition, the relative importance
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26 of cardiopulmonary fitness versus other factors in optimising post-operative recovery, e.g. adequate nutrition,
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28 mental preparation, etc. [4], is an important avenue for future research.
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32 This study had some limitations. Firstly, the sample size was insufficient to draw definitive conclusions about
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34 the effects of improved pre-operative cardiopulmonary fitness on post-operative recovery. Although we showed
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36 that the exercise program has the potential to improve indices of cardiopulmonary fitness, a larger-scale
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38 randomized controlled trial with a sufficient number of patients to detect changes in key recovery outcomes and
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40 longer-term quality of life, is needed to address this important question. Secondly, as patients were recruited
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42 from a single centre serving a large rural community, the recruitment rate and reasons for non-participation may
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44 be less representative of patients living closer to treating hospitals. Travel distance to the exercise facility was
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46 cited as the main reason for non-participation in the study but this is likely to be less of an issue in patients
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48 living in closer proximity. Nevertheless, other reasons (including physical limitations or a lack of confidence to
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50 engage in the exercise program) prevented >26% of eligible patients from taking part. This suggests that a
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52 program of hospital supervised vigorous intensity aerobic interval exercise is unlikely to be feasible for all
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54 bladder cancer patients. For this reason, other forms of pre-operative exercise, particularly exercise that can be
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56 undertaken in the home or community environment, should be evaluated in future research.
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In conclusion, the results of this study show that vigorous intensity aerobic interval exercise in the short time-window between decision to operate and RC was feasible in a significant proportion (54%) of bladder cancer patients being treated in a large Urology Department. In addition, we present preliminary evidence of improvements in some cardiopulmonary fitness variables that could potentially impact on post-operative recovery outcomes. Because of the small sample size, it is not possible to make definitive conclusions about the impact of pre-operative improvements in cardiopulmonary fitness on post-operative recovery outcomes. Nevertheless, these encouraging preliminary data provide a strong foundation for an adequately powered randomized controlled trial.

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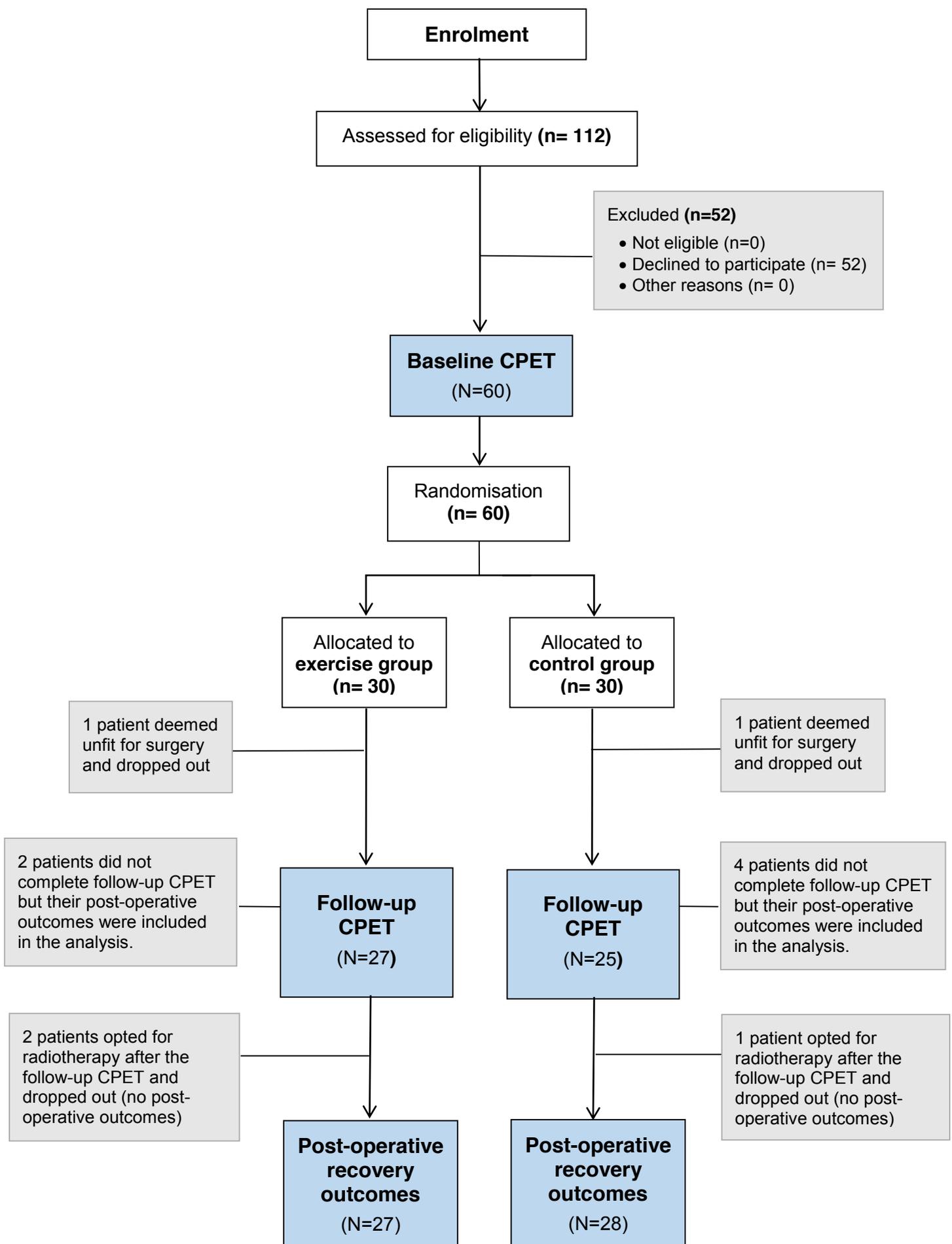


Figure 1. Participant flow through the trial

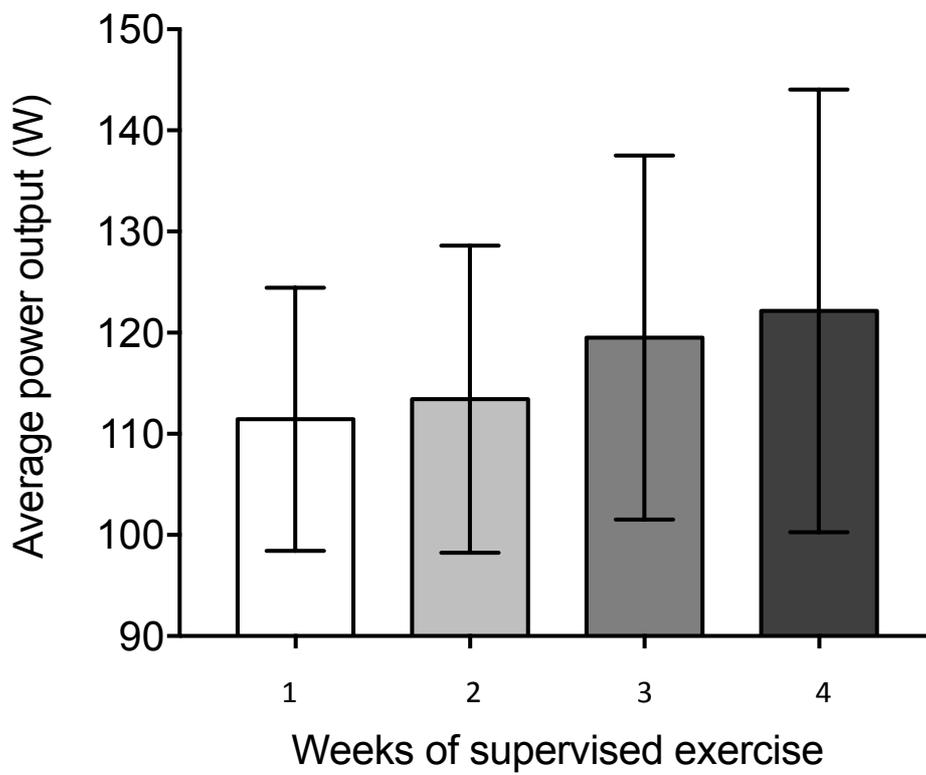
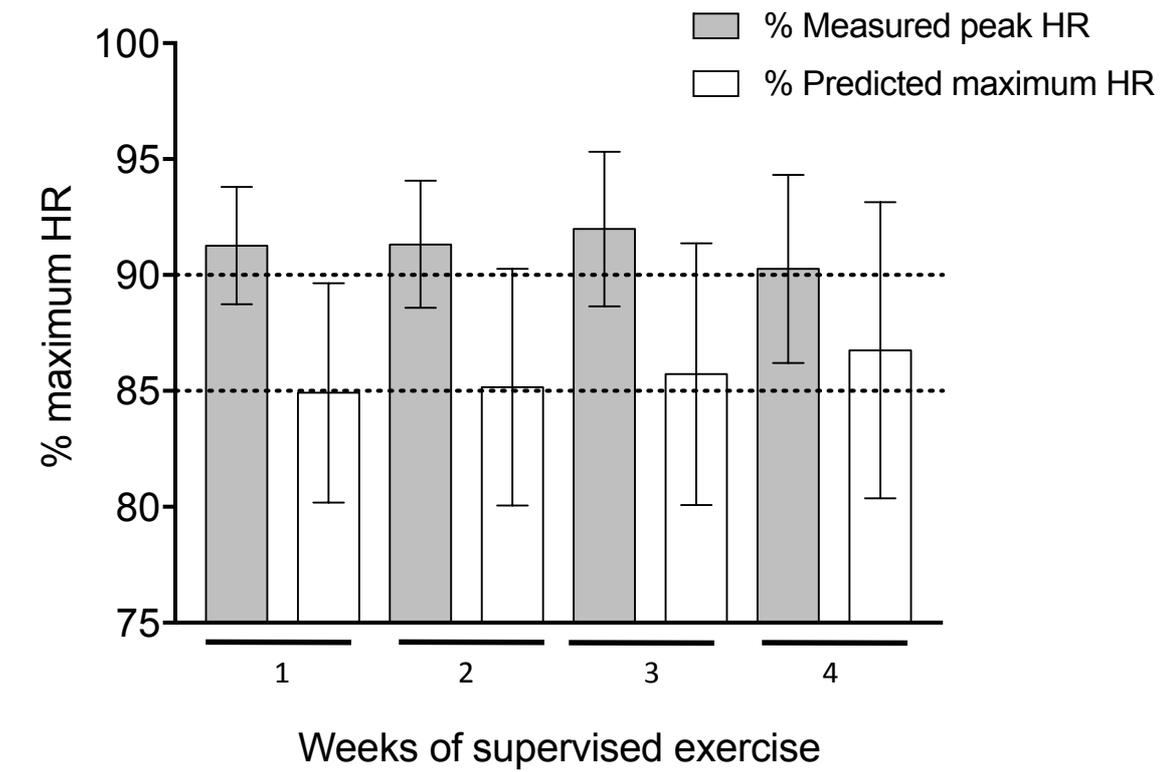


Table 1. Baseline characteristics of participants allocated to exercise plus standard care or standard care only. Data are presented as mean \pm SD or numbers (percentages).

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

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 $220 - \text{age}$.