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authors have no conflicts of interest to disclose. The results of this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

ABSTRACT

Purpose: To examine the feasibility and potential efficacy of pre-surgical exercise in patients with bladder cancer scheduled for open radical cystectomy with follow-up post-surgery. **Methods:** Prospective single-group design with assessments at baseline, pre-surgery and 3 months post-surgery. Multimodal supervised resistance and aerobic exercise was undertaken 2-3 days/week at moderate intensity for a median of 3.5 (IQR 1.3-5.6) weeks. Feasibility was assessed by recruitment and completion rates, patient safety, program tolerance, adherence, and compliance. Lean and fat mass were assessed by dual-energy X-ray absorptiometry, physical function by a battery of tests [chest press and leg press strength, 6-minute walk test (6MWT), timed up-and-go (TUG), repeated chair rise], and quality of life (QoL), psychological distress and body image by questionnaire. Hospital length of stay (LOS) and complications were assessed by medical records. **Results:** Thirty-seven patients were referred with 20 recruited (67.3±12.2 years) and a pre-surgery intervention completion rate of 80% (16 of 20). The individual median program adherence was 100.0% (IQR 89.4-100.0) with compliance of 100.0% (IQR 90.5-100.0) for resistance exercise and 81.8% (IQR 55.0-99.5) for aerobic exercise. There were no exercise-related adverse events. Body composition did not change pre-surgery, however, there were improvements ($p<0.05$) in leg press strength (16%), 6MWT distance (8%), TUG (12%), chair rise (10%), and multiple QoL domains including mental health. Median LOS was 8.0 (IQR 7.0, 15.0) days. Post-surgery there were declines in components of QoL and apparent body image dissatisfaction. **Conclusions:** A pre-radical cystectomy exercise program is feasible, safe, and well-tolerated with improvements in physical function and QoL. Supervised multimodal exercise in bladder cancer patients prior to cystectomy can enhance physical and mental health potentially buffering the effects of surgery.

Key Words: BLADDER CANCER, EXERCISE, CYSTECTOMY, NEOADJUVANT CHEMOTHERAPY

INTRODUCTION

Radical cystectomy, with or without neoadjuvant chemotherapy, is widely considered to be the best oncologic treatment option for patients of reasonable performance status with muscle-invasive bladder cancer, and some patients with high-risk non-muscle-invasive bladder cancer. In the male radical cystectomy involves removal of the bladder and prostate and in the female anterior pelvic exenteration (removal of bladder, utereus, Fallopian tubes, ovaries and an anterior cuff of vagina). Pelvic lymphadenectomy is routinely performed and urinary diversion is fashioned, usually with either an ileal conduit or orthotopic neobladder fashioned from small intestine. Radical cystectomy is a complex, technically demanding and high-risk surgical procedure which is associated with long periods of hospital stay, significant morbidity, high readmission rates, and mortality (1-3). Postoperative complications are common and are related to pre-existing morbidity and age (4). Furthermore, patients with poor pre-operative cardiopulmonary capacity have a higher risk of complications post-surgery and increased hospital length of stay (LOS) which increases healthcare costs (5,6). Given that patients are older and smoking is a major risk factor (7), associated pulmonary and cardiovascular diseases may also contribute to increased risk of surgical complications, poorer overall function, quality of life and risk of mortality.

Exercise prior to surgery as a single intervention or as part of prehabilitation or Enhanced Recovery After Surgery (ERAS) programs (8) may improve preoperative patient status and postoperative patient outcomes by enhancing 'fitness for surgery' thereby reducing hospital LOS and complications, reducing healthcare costs and time to return to usual activities (9). We have previously reported beneficial effects of pre-surgical exercise in prostate cancer (10) and rectal cancer patients (11), and others have reported improvements in lung cancer (12) as well as in non-cancer patients (13). In regards to cystectomy, Jensen and

colleagues (14) reported improvements in leg extension muscle power following a 2-week home-based preoperative exercise program and Banerjee et al. (15) found improvements in cardiopulmonary fitness variables following 3-6 weeks of aerobic interval exercise. Recently, Kaye et al. (16) reported that a pre-surgical exercise program improved physical health outcomes and patient-reported quality of life, and Minnella et al. (17) reported prehabilitation that included home-based exercise enhanced post-cystectomy recovery as assessed by the 6-minute walk test.

Here we report the findings from our recently completed exercise trial in patients scheduled for open radical cystectomy with follow-up 3 months post-surgery. In this report we extend findings from previous trials by including patients exercising while undergoing neoadjuvant chemotherapy resulting in a longer training period, including exercise delivery via telehealth, undertaking a comprehensive assessment battery for both objective and patient-reported outcomes, and comparing hospital length of stay, an important clinical/patient/economic outcome, to a historical patient series. We hypothesised that undertaking a structured and supervised pre-operative multimodal resistance and aerobic exercise program apart from being feasible in the current setting would improve physical function and quality of life prior to surgery, potentially reducing hospital LOS and complications.

METHODS

Patients

Twenty patients scheduled to undergo open radical cystectomy were recruited by invitation from their attending Urologist at two hospitals in Perth, Western Australia, between May 2018 and April 2021. Potential patients were those with muscle-invasive bladder cancer

(≥ T2), patients with high-risk non-muscle-invasive bladder cancer with atypical pathologic features (e.g., nested variant, micropapillary, etc.) or who preferred upfront cystectomy, and those undertaking salvage cystectomy after failed curative intent treatment with external beam radiation therapy. Exclusion criteria included musculoskeletal, cardiovascular or neurological conditions that could inhibit patients from exercising as determined by their physician. All patients undergoing cystectomy were managed using an established ERAS pathway without a formal pre-operative exercise component. The study was approved by the Human Research Ethics Committee of Edith Cowan University, the South Metropolitan Health Service, and St John of God Health Care, and all participants provided written informed consent.

Exercise Program

This was a single-armed trial with patients undertaking exercise prior to surgery with follow-up 3 months post-surgery. Supervised training was undertaken 2-3 times per week for approximately 60 minutes in duration and comprised resistance and aerobic exercise, with a home program of walking 2 or more days per week that consisted of 20-30 minutes of activity. For patients undergoing surgery only, supervised training was anticipated to be for ~ 4 weeks duration with a minimum of 2 weeks and undertaken 3 times per week. For patients undergoing neoadjuvant chemotherapy, which was anticipated to be for ~ 12 weeks, supervised sessions were generally 2 days/week. The supervised sessions were initially one-on-one with an accredited exercise physiologist and then progressed to small groups of 3-5 cancer patients undertaken in several exercise clinics. Resistance exercise comprised 6-8 exercises that targeted the major upper and lower body muscle groups, and included chest press, seated row, leg press, leg extension, leg curl, calf raise, biceps curl and triceps extension. Intensity was set at 8-12 repetition maximum (RM, the maximal weight that can be

lifted 8 to 12 times) for 2-3 sets per exercise (if training extended beyond 12 weeks then 4 sets could be undertaken). The aerobic exercise component was between 15 and 20 minutes at an intensity of ~60-80% of estimated maximum heart rate, using a variety of modes such as walking or jogging on a treadmill, cycling or rowing on a stationary ergometer. For patients undergoing surgery only and hence training 3 times per week the resistance and aerobic training progression was as follows:

Weeks 1-2: resistance exercise, 2 sets of 12 RM; aerobic exercise, 15-20 mins 60% HR max
Weeks 3-4: resistance exercise, 3 sets of 10 RM; aerobic exercise, 15-20 mins 70% HR max
Weeks 5-6: resistance exercise, 3 sets of 8 RM; aerobic exercise, 20 min 70-80% HRmax.

For patients undergoing neoadjuvant therapy and training 2 times per week the progression was as follows:

Weeks 1-2: resistance exercise, 2 sets of 12 RM; aerobic exercise, 15-20 mins 60% HR max
Weeks 3-4: resistance exercise, 3 sets of 12 RM; aerobic exercise, 15-20 mins 70% HR max
Weeks 5-8: resistance exercise, 3 sets of 10 RM; aerobic exercise, 20 min 70-80% HRmax
Weeks 9-12: resistance exercise, 3 sets of 8 RM; aerobic exercise, 20 min 70-80% HRmax
Weeks 13-19: resistance exercise, 4 sets of 8 RM; aerobic exercise, 20 min 70-80% HRmax.

Sessions commenced and concluded with a 5-minute warm-up and cool-down consisting of low-level aerobic activities and stretching. Due to Covid-19 restrictions, 2 patients underwent telehealth sessions supervised by an accredited exercise physiologist instead of in-clinic sessions. The exercise sessions incorporated similar exercises/movements to the in-clinic program utilising resistance equipment provided to them (set of dumbbells) or

bodyweight. Exercises were chest press, bent over row, biceps curl, lateral raise, sit-to-stand, squat, calf raise and gluteal bridge at 8-12 RM for 2-3 sets per exercise. The aerobic component was walking outside for 15-20 minutes at a perceived exertion (RPE) of 12-15 (somewhat hard to hard) using the Borg 6-20 scale (18).

Outcomes and Measures

Measurements of physical function, body composition, and quality of life/distress/body image were undertaken at baseline, pre-surgery, and 3 months post-surgery. Hospital LOS, complications and return to usual activities were assessed at 3 months post-surgery. For the 2 patients undergoing the telehealth program, body composition wasn't assessed and for physical function only the chair rise test was performed.

Primary Study Endpoint

Feasibility. Feasibility was assessed by: 1) recruitment and completion rates (number referred, number eligible, number enrolled, number of withdrawals, trial recruitment rate, trial completion rate), 2) patient safety (number and severity of adverse events), 3) program tolerance [sessional RPE using the Borg 6-20 scale (18) after every exercise session], 4) program adherence (number of completed sessions, number of missed sessions), and 5) program compliance (prescribed versus actual exercise completed, % of total volume completed). The trial was considered feasible in the absence of severe or life-threatening adverse events (19) and achieved three or more of: recruitment rate ≥50% (19), completion rate ≥80% (20), program adherence ≥80% (19,20), program compliance ≥75% (20), and program tolerance from 12-15 (equivalent to 'somewhat hard' to 'hard').

Secondary Study Endpoints

Length of hospital stay and complications. LOS and complications (up to 3 months post-surgery) were obtained from hospital records (including use of Clavien-Dindo Classification of surgical complications) with comparison to a prospectively collected radical cystectomy patient series at a single institution from investigator DH.

Physical function. Physical function was assessed by a battery of standard tests that included: 1) one-repetition maximum (1RM) strength (21) for chest press and leg press which represents upper- and lower-body muscle strength, respectively, 2) 6-minute walk test (6MWT) as a validated sub-maximal surrogate measure for VO2 max (aerobic capacity or aerobic fitness) (22), 3) repeated chair rise (time to rise from a chair 5 times as a measure of lower body muscle function) (23), and 4) the timed up-and-go (TUG) test to assess agility and dynamic balance (24). Given the potential limited time for training prior to surgery, a familiarization session prior to the physical function testing session was not undertaken; however, instructions and a demonstration were provided, and patients performed a practice trial (except for the 6MWT) prior to testing. The coefficient of variation (CV) for repeat chest press and leg press 1RM measures in our laboratory are 2.2% and 7.5%, respectively, and for the repeated chair rise test 5.6%, while the reported CV for the 6MWT in cancer patients is 3% (25) and for the TUG test the reported CV is 6.5% (26).

Quality of life, psychological distress, and body image. Health-related quality of life was assessed using the Medical Outcomes Short Form 36 (SF-36) (27), which is used to assess patient-rated physical and mental health outcomes across the domains of physical function, role function (physical, emotional), bodily pain, general health, vitality (encompassing energy level and fatigue), social functioning and mental health, with 2 summary health measures

(physical component summary and mental component summary). Higher scores on the SF-36 indicate higher health-related quality of life. Bladder cancer-specific quality of life was assessed using the Functional Assessment of Cancer Therapy – Bladder (FACT-Bl) which includes additional questions covering urinary and bowel function, sexual symptoms and body image with higher scores indicating better quality of life (28,29). The Brief Symptom Inventory-18 (BSI-18) was utilised to assess psychological distress across the domains of anxiety, depression, and somatisation, as well as a global severity index where higher scores indicate higher distress (30). Body image was specifically assessed using the 10-item Body Image Scale (BIS) where higher scores indicate increasing dissatisfaction/distress (31).

Body composition. Whole body lean mass and fat mass, percent body fat, and appendicular skeletal muscle (ASM) were derived by dual-energy x-ray absorptiometry (DXA, Hologic Discovery A, Waltham, MA, USA). ASM was calculated as the sum of upper-limb and lower-limb bone-free lean mass (32).

Return to usual activities. Return to usual activities was assessed using the Resumption of Activities of Daily Living (RADL) Scale (33), modified for time since surgery. The extent to which the patient resumed their normal activities in the areas of self-care, sexual activity, household chores, shopping, socialising, travelling, and recreation were assessed with scores averaged over the 11 items with 0 for “not at all”, 50 for “moderate resumption” and 100 for “complete resumption”.

Other Measures

Demographics, lifestyle behaviours, and health history were obtained by questionnaire and medical records. Height and weight were assessed using a stadiometer and

electronic scales, respectively, with body mass index (BMI) calculated from weight divided by height squared (kg/m^2). Self-reported physical activity was assessed by the Leisure Score Index (LSI) from the Godin Leisure-Time Exercise Questionnaire (34) and nutritional status by the Mini Nutritional Assessment (35). Preoperative comorbid status and risk were assessed using the Charlson Comorbidity Index (36) and the American Society of Anaesthesiologists Physical Status Classification System (37), respectively. LOS was obtained from hospital records and the Clavien-Dindo classification was used for complications post-surgery (38).

Statistical Analyses

Data were analysed using IBM SPSS Version 28 (IBM Corp., Armonk, NY, USA). Our recruitment target was 20 patients to determine feasibility and potential efficacy. With 20 patients we would have 80% power (alpha = 0.05, two-tailed test) to detect a moderate effect size of 0.67 in a number of our secondary outcome measures such as physical function which we would consider to be clinically meaningful. For the primary outcome, rates for recruitment, completion, adherence, and compliance, as well as adverse events were calculated. For the secondary outcomes, normality of the distribution was assessed using the Shapiro-Wilk test. Analyses included standard descriptive statistics and for baseline and pre-surgery analyses Student's t-tests or the Wilcoxon signed-rank test, as appropriate. For three timepoints, given the reduced number of participants and that not all variables were normally distributed, Friedman's ANOVA was used to enable consistency in reporting, and where appropriate a Bonferroni corrected Wilcoxon signed-rank test to locate the source of significant differences. Tests were two-tailed with significance set at an alpha level of 0.05. Estimates of effect size were calculated using Cohen's d where a small effect is 0.2, medium effect is 0.5, and large effect is 0.8, and for the Freidman's test Kendall's W was calculated

(across all time points) with a small effect 0.1, moderate effect 0.3, and large effect 0.5. Values are reported as the mean ± SD, median and interquartile range (IQR), or n (%).

RESULTS

Patient flow through the study is shown in Figure 1. Thirty-seven patients were referred for screening with 20 consenting and undertaking baseline assessments. The main reason for exclusion was distance from or access to the exercise clinics for training (n = 9) as well as commencing chemotherapy and did not wish to exercise (n = 2). Sixteen patients completed pre-surgery measures with 4 ceasing exercise due to rescheduling of cystectomy which was brought forward (n = 2), a cardiac event post their first dose of chemotherapy (n = 1), and family commitments (n = 1). Of these 16 patients, 1 patient had undergone immunochemotherapy and did not require cystectomy but completed the post-exercise assessment at the end of immunochemotherapy treatment, 2 patients had neoadjuvant chemotherapy (NAC) while undertaking exercise and 1 patient had NAC prior to exercise. Follow-up was undertaken at 3 months post-surgery with clinical data on all 15 patients and questionnaires for 14 patients, with varying patient numbers for the other outcome measures.

Characteristics of the patients are shown in Table 1. The patients were aged 32-83 years with a mean age of 67.3 ± 12.2 and a BMI of 29.0 ± 4.5, predominantly married and no longer employed, and with a Godin LSI indicating insufficiently active. The median weeks of exercise training was 3.5 (IQR 1.3 – 5.6) and ranged from 1-19 weeks. The median number of sessions completed was 9.5 (IQR 4.0 – 13.0) and ranged from 1-36 sessions, with the median number of missed sessions being 0.0 (IQR 0.0 – 1.0) and ranged from 0-12. Of the 16 patients with pre-surgery measures, 9 had complete home-based exercise logs with a median of 15 sessions (IQR 7.5 – 19.5) with a range of 6-42 sessions.

Feasibility

The trial recruitment rate was 54% (20 recruited from 37 patients referred) with a completion rate of 80% (16 of the 20 enrolled). Throughout the study, there were 2 serious adverse events although these were not directly related to the exercise sessions: 1 patient had a cardiac event following his first chemotherapy treatment and withdrew from the trial and 1 patient developed a blood clot during chemotherapy treatment (forearm at site of canula) and ceased exercise (the patient initially underwent exercise for 6 weeks then ceased for the following 6 weeks prior to assessments and surgery). There were 241 exercise sessions scheduled with 212 attended with the average median individual program adherence of 100.0% (IQR 89.4, 100.0). Program compliance (actual exercise completed versus prescribed) was a median of 100.0% (IQR 90.5, 100.0) for resistance exercise and 81.8% (IQR 55.0, 99.5) for aerobic exercise. Program tolerance based on session RPE ranged from 8-17 with a median of 13.5 (IQR 12.9 to 13.8) equivalent to “somewhat hard”.

Body composition and physical function

There were no significant changes in lean mass, fat mass, percent body fat or ASM from baseline to post-intervention prior to surgery (Table 2). However, leg press strength improved (16%) as did 6MWT distance (8%), as well as the time to undertake the TUG test (12%) and repeated chair rise test (10%) (p=0.003-0.008). Results for a sub-group of patients who underwent follow-up assessments at 3 months post-surgery are shown in Table 3. The patient numbers for the tests vary compared to pre-surgery due to an unwillingness during Covid-19 outbreaks to return for in-person testing as well as concerns in undertaking some of the physical function tests. Although there was a significant difference across baseline, pre-surgery and post-surgery measures for lean mass (p=0.012), ASM (p=0.018), and chest press

strength (p=0.022), the source of the differences wasn't located with follow-up testing. However, for the chair rise test (p=0.005), performance significantly declined post-surgery.

Quality of life, psychological distress, and body image

Following the intervention, several domains for health-related quality of life improved ($p<0.05$) including physical functioning, vitality, mental health as well as the physical component summary of the SF-36 (Table 4). Similarly, there was an improvement ($p<0.05$) in emotional well-being, the bladder cancer subscale as well as the total score for the FACT-Bl. Results for patients who had complete measures at all time points are shown in Table 5. At 3 months post-surgery there was a decline ($p<0.05$) in patient-reported physical functioning as well as role-physical compared to pre-surgery. There was also a significant change across time for body image (p=0.010), with an apparent increase in dissatisfaction post-surgery.

Length of hospital stay, complications, and resumption of usual activities

For the 15 patients that underwent exercise and cystectomy, LOS ranged from 4-30 days with a median of 8.0 (7.0, 15.0) days (Table 6). In comparison, for a patient series of 100 patients undergoing open radical cystectomy by a study urologist (DH) from the one participating hospital, LOS ranged from 4-27 days with a median of 9.0 (IQR 7.0, 13.0) days. Of the 15 exercised patients, rates of 90-day Clavien-Dindo complications of severity grade I-II and III-IV were 11/15 (73%) and 2/15 (13%) in comparison to 69/100 (69%) and 16/100 (16%) for the study urologist series.

Five patients from the current trial visited the emergency department for a total of 7 visits with wound infection/leak and pain being the most common reasons. The 30-day readmission rate was 33.3% (5 patients) and was due to urosepsis (n=2), abdominal pain/diarrhea, intra-abdominal collection (abscess), and pyelonephritis. Between 30- and 90-days post-surgery, 1 of these patients was readmitted a further 3 times for intra-abdominal collection, vasovagal syncope, and intra-abdominal collection and drain insertion. For resumption of usual activities (n=13), scores ranged from 41.8 to 93.6 out of 100 with a mean of 73.2 ± 17.7 with no one completely resuming all activities and with scores for return to sexual activity ranging from 0-40 and for recreational activities ranging from 0-90.

DISCUSSION

This is the first Australian study to examine the feasibility and potential efficacy of pre-surgical multimodal exercise in the setting of open radical cystectomy. There were three important findings: (i) combined resistance and aerobic exercise was feasible to undertake, safe, and well-tolerated; (ii) improvements in several components of physical function that included muscle strength, aerobic capacity, agility/balance, and lower-body function, as well as multiple QoL domains including mental health were observed; and (iii) declines in the repeated chair rise test and components of QoL occurred 3 months post-surgery along with an apparent increase in body dissatisfaction and no patient completely resuming all usual activities.

Our trial indicates that it is feasible and safe to undertake combined resistance and aerobic exercise in patients prior to cystectomy with a recruitment rate of 54% and a completion rate of 80%. For the 4 patients who withdrew from the study, surgery was brought forward for 2 patients resulting in only 1 and 2 sessions being undertaken, a third

patient had a cardiac event post-chemotherapy, and the fourth patient withdrew after 4 sessions due to family commitments. The recruitment rate is comparable to that of Banerjee et al. (15) who recruited 53.5% of eligible patients to their aerobic interval training trial in the UK. Feasibility to recruit this patient group is also supported by recruitment rates of 81.6% by Jensen and colleagues (39) for their 2-week preoperative home-based program in Denmark and Minnella et al. (17) of 77.8% for their ~4-week multimodal prehabilitation program undertaken in Canada. In addition, adherence and compliance to exercise was high in our trial and well-tolerated based on session RPE values. Importantly no patient withdrew due to the exercise program itself and there were no exercise-related adverse events.

Physical function improved following exercise which would improve the patient's reserve capacity and provide a buffer or a greater safety margin to the effects of surgery and reduced activity in the post-operative period. These changes were relatively substantial ranging from 8-16% over a median of 3.5 weeks of exercise training. Similarly, Jensen et al. (14) reported an 18% increase in leg muscle power following a 2-week program of daily exercise in patients scheduled for cystectomy while Banerjee et al. (15) noted an improvement in peak power output of ~13% when performing a cardiopulmonary exercise test although there was no significant improvement in VO_2 peak compared to non-exercisers following twice weekly training for 3-6 weeks. Recently, Kaye et al. (16) reported an improvement in 6MWT (5.1%), submaximal VO_2 (10.2%), gait speed (7.5%) and the TUG test (5.5%) following thrice weekly exercise for 4 weeks prior to cystectomy. However, at 3 months post-surgery, chair rise performance substantially declined in our patients and there were indications that other components of function such as 6MWT and chest press strength also declined. These declines following surgery, even at 3 months post, indicate the importance of enhancing the patient's reserve capacity prior to surgery, especially for those

older and close to thresholds for maintaining activities of daily living, in order to preserve independence.

Improvement in physical function was accompanied by improvements in several components in QoL including vitality, mental health, and the physical component summary of the SF-36 as well as emotional well-being, the bladder score, and total score of the FACT-Bl. Similarly, Kaye et al. (16) reported improvements in the physical health component summary with a mean change of 4.2 points and mental health component summary of 3.4 points in the SF-36 following pre-surgical exercise in patients scheduled for cystectomy. Improvement in mental health is important given that lower preoperative mental health has been associated with high grade complications following radical cystectomy (40). The accompanying improvement in mental health was noted by the patients who commented in feedback of the program with "on a physical level I found an increase in my overall fitness and more importantly my mental state" and "felt good during and after each session…improved physical and mental state." However, for those completing questionnaires at 3 months post-surgery, there was a general decline in the components of the SF-36, which was significant for physical functioning and role physical, with scores for the FACT-Bl also reverting to be similar to pre-exercise levels. Anxiety and depression did not change following the exercise intervention or at 3 months post-surgery, however, there was an apparent increase in body image dissatisfaction following surgery. Change in body image is an important concern post-cystectomy with associated effects on sexual and social functioning (41).

We found no changes in lean mass or fat mass over the pre-operative period, although for most patients this was a relatively short duration and detecting changes would be unlikely. Similarly, Kaye et al. (16) reported no change in lean mass following 4 weeks of resistance and aerobic exercise prior to cystectomy. However, sarcopenia has been implicated as a predictor of major complications (42) and for cancer-specific and overall survival following radical cystectomy (43). Consequently, screening for sarcopenia and implementing strategies such as resistance training and protein/dietary supplementation to counteract sarcopenia prior to cystectomy may be one strategy to target patients at risk for complications and post-operative mortality.

Hospital LOS was a median of 8 days for our patients which was similar to that of the historical controls of 9 days. Similarly, Jensen et al. (39) reported a median LOS of 8 days with no difference between intervention or standard treatment patients in their trial, while the median LOS was 7 days for both exercise and control groups in the study by Banerjee et al. (15) in which over 90% of patients had laparoscopic radical cystectomy. Minnella et al. (17) also reported no significant difference between their prehabilitation group and controls for LOS following radical cystectomy with 9 and 10 days, respectively. In contrast, Kaye et al. (16) reported a mean LOS of 6.5 ± 2.5 days, although 58% underwent robot-assisted compared to open radical cystectomy which may have contributed to the shorter stay (44). Our patients and those of the historical series underwent open radical cystectomy followed by a similar ERAS protocol, and it may be this group of patients who benefit more from pre-operative exercise than those undergoing robot-assisted radical cystectomy. Our 30-day readmission rate is similar to that of Jensen et al. (39) of 30% in exercisers and Kaye et al. (16) of 23%, with 90-day readmission similar to that reported by others following radical cystectomy (2). However, both Jensen et al. (39) and Minnella et al. (17) reported no

difference in complications or readmission between those who exercised and controls in their studies.

There are a number of strengths of this study which extend previous findings from trials in this area. First, we undertook a comprehensive series of objective and patient-reported assessments that included DXA for body composition and a battery of tests that captured different components of physical function, as well as the FACT-BI, BSI-18, Body Image Scale, and Resumption of Activities of Daily Living Scale in addition to the SF-36. Second, supervised exercise was delivered not only in the exercise clinic but also via telehealth increasing the potential reach and uptake by patients. Third, we included patients undergoing NAC which resulted in a longer training period than past studies involving patients undergoing radical cystectomy. Given that more patients may receive NAC in the future (4), this is of importance as it shows that exercise can be undertaken during this time without any adverse effects and may potentially improve NAC tolerability (45). Fourth, all patients underwent open radical cystectomy, a patient group that may benefit most from pre-surgical exercise, and lastly, we were able to compare to a historical patient series for LOS.

However, there are also limitations worthy of comment. This was a single-group trial with a recruitment target of 20 and limited to those in the metropolitan area who would have access to the supervised exercise training sites. However, due to Covid-19 and the need to pivot to telehealth delivery, we have shown that the program can also be delivered via the Internet and smart phones, which enhances access for this patient group and would be especially applicable to those living in regional and rural areas. A familiarization session for the physical function tests was not undertaken in this trial, however, the change in all physical function outcomes exceeded the CV for that measure. Nevertheless, although we

can't discount that there was a contribution of a learning effect for the outcome measures, it is likely that exercise training also contributed to the changes observed. In this respect, given the lack of change in body composition as assessed by DXA, changes in physical function were likely mediated by other factors such as neural adaptations (46). Lastly, given the number of comparisons/analyses undertaken we cannot discount that a few of the significant findings may be due to chance.

In conclusion, we found pre-surgical multimodal exercise in patients scheduled for open radical cystectomy to be safe, feasible and well-tolerated with beneficial effects on physical function and quality of life, including patients undergoing neoadjuvant chemotherapy. These findings, collectively with the positive findings from other trials in this patient group (14-17), indicate that exercise medicine should be prescribed prior to radical cystectomy (and delivered either under supervision in an exercise clinic or via telehealth, or home-based) in order to enhance the patient's reserve capacity and 'fitness for surgery' both physically and mentally, potentially enhancing their post-operative recovery. This may prove to be especially beneficial in patients who are close to thresholds for functional limitations and should be encouraged where possible.

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Clinical Trial Registry

Exercise medicine prior to open radical cystectomy in adults with bladder cancer: feasibility and preliminary efficacy. ACTRN12621000777897.

Conflict of Interest

The authors have no conflicts of interest to disclose. The results of this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

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FIGURE LEGEND

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram.

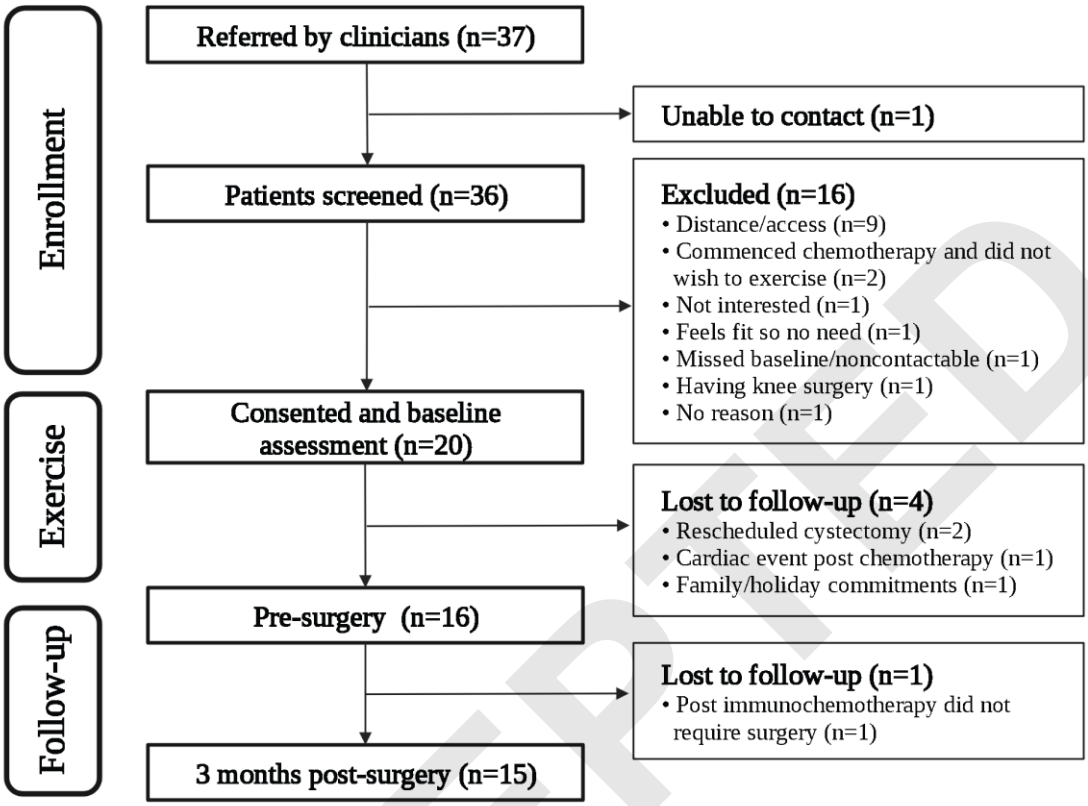

Table 1. Patient characteristics (n = 20)

Variable	Value	Range
Age (y)	67.3 ± 12.2	32 – 83
Sex, male/female	18 / 2	
Height (cm)	173.2 ± 7.9	160 – 193
Weight (kg)	87.0 ± 15.0	63.0 – 125.3
BMI (kg/m^2)	29.0 ± 4.5	22.2 – 36.2
Married, n (%)	13 (65)	
Post-secondary education, n (%)	5 (25)	
Employed, n (%)	3 (15)	
Ever smoked, n (%)	13 (68)	
Drinks/week	9.2 ± 8.9	0 – 24
MNA*	25.3 ± 2.7	19.5 – 28
Godin LSI†	17.2 ± 19.7	0 – 70
Medications (number)	3.6 ± 2.4	0 – 8
Clinical Stage, n (%)		
Tis	2 (10)	
T1	9 (45)	
T2	8 (40)	
Urethral adenocarcinoma	1 (5)	
Charlson Comorbidity Index, n (%)		
0	1 (5)	
1-2 Low	6 (30)	
3-4 Moderate	8 (40)	
≥ 5 Severe	5 (25)	
ASA score, n (%)		
2	10 (50)	
3	9 (45)	
Missing	1 (5)	
Chronic conditions		
Hypertension, n (%)	10 (50)	
CVD, n (%)	4 (20)	
Hypercholesteremia, n (%)	10 (50)	
Diabetes, n (%)	2 (10)	

Values are the mean ± SD unless otherwise indicated.
BMI = body mass index; MNA = mini-nutritional assessment; LSI = Leisure Score index; CVD = cardiovascular disease; ASA = American Society of Anaesthesiologists physical status. * Malnourished < 17, undernourished 17-23.5, well-nourished >23.5. † Moderate-to-strenuous LSI ≥ 24 classed as active and ≤ 23 classed as insufficiently active.

Table 2. Body composition and physical function at baseline and pre-surgery

	Baseline	Pre-surgery	Mean change (95% CI)	Effect Size*	P-value
Body Composition (n=13)					
Lean mass (kg)	55.3 ± 11.7	54.7 ± 11.4	-0.5 (-1.8, 0.7)	-0.27	0.354
Fat mass (kg)	28.1 ± 9.5	27.8 ± 9.0	-0.2 (-1.5, 1.0)	-0.11	0.710
Body fat (%)	32.2 ± 6.7	32.3 ± 6.6	0.1 (-1.0, 1.1)	0.04	0.891
ASM (kg)	23.5 ± 5.2	23.2 ± 4.9	-0.3 (-0.8, 0.3)	-0.29	0.316
Physical Function					
Chest press (kg), n=12	40.1 ± 14.1	41.7 ± 13.0	1.6 (-1.1, 4.2)	0.37	0.140†
Leg press (kg), n=13	85.4 ± 35.2	99.0 ± 39.1	13.6 (5.2, 22.0)	0.98	**0.004**
6MWT (m), n=14	504.4 ± 105.2	543.1 ± 81.8	38.7 (14.7, 62.8)	0.93	**0.004**
TUG (s), n=14	7.7 ± 1.6	6.8 ± 1.2	-0.8 (-1.4, -0.3)	-0.84	**0.008**
Chair rise (s), n=16	13.0 ± 2.6	11.7 ± 1.8	-1.3 (-2.1, -0.5)	-0.88	**0.003**

ASM = appendicular skeletal muscle, 6MWT = 6-minute walk test, TUG = timed up and go test. Values are the mean ± SD, * Cohen's d, † Wilcoxon signed-rank test.

Table 3. Body Composition and physical function at baseline, pre-surgery, and post-surgery

	Baseline	Pre-surgery	Post-surgery	Effect Size*	P-value
Body Composition (n=7)					
Lean mass (kg)	48.1 (45.1, 63.8)	48.9 (47.0, 65.9)	47.8 (45.0, 56.5)	0.63	**0.012**†
Fat mass (kg)	25.4 (20.3, 29.2)	25.4 (19.2, 27.6)	23.6 (19.4, 25.2)	0.33	0.102
Body fat (%)	30.5 (28.9, 33.4)	29.0 (27.5, 33.9)	29.6 (28.7, 32.9)	0.18	0.276
ASM (kg)	20.5 (18.6, 27.8)	21.1 (19.1, 28.4)	20.6 (18.4, 23.6)	0.57	**0.018**†
Physical Function					
Chest press (kg), n=4	43.9 (33.2, 52.9)	45.0 (37.1, 56.3)	31.5 (28.1, 38.3)	0.95	**0.022**†
Leg press (kg), n=3	49.5 (49.5, 105.8)	76.5 (58.5, 128.3)	76.5 (40.5, 76.5)	0.58	0.178
6MWT (m), n=6	567.0 (433.3, 615.5)	593.1 (479.3, 643.9)	482.4 (435.4, 539.0)	0.46	0.065
TUG (s), n=6	7.6 (5.9, 9.0)	6.7 (5.6, 7.8)	7.7 (6.7, 9.9)	0.19	0.311
Chair rise (s), n=8	11.5 (11.1, 15.3)	10.9 (11.8, 17.4)	15.4 (11.8, 17.4)	0.67	**0.005**#

ASM = appendicular skeletal muscle, 6MWT = 6-minute walk test, TUG = timed up and go test. Values are the median (IQR). * Kendall's W (across all time points), † differences not located in post-hoc analysis, # Post-hoc analysis: Baseline, Post-surgery > Pre-surgery.

Table 4. Patient-reported outcomes at baseline and pre-surgery

	Baseline	Pre-surgery	Mean change (95% CI)	Effect Size*	P-value
SF-36 (n=14)					
Physical functioning	46.4 ± 11.1	50.9 ± 5.6	4.5 (-2.1, 11.2)	0.39	0.128†
Role-Physical	41.3 ± 10.1	45.1 ± 8.2	3.8 (0.7, 7.0)	0.70	**0.021**
Bodily pain	45.7 ± 11.1	50.6 ± 10.7	5.0 (0.4, 9.6)	0.63	**0.036**
General health	39.2 ± 9.6	40.2 ± 9.5	1.0 (-2.4, 4.4)	0.17	0.542
Vitality	47.9 ± 8.3	51.2 ± 8.0	3.3 (0.2, 6.5)	0.62	**0.037**
Social functioning	39.6 ± 9.4	43.0 ± 11.0	3.4 (-0.8, 7.5)	0.49	0.104
Role-Emotional	43.9 ± 15.2	43.4 ± 10.1	-0.6 (-6.5, 5.4)	-0.05	0.844
Mental health	43.8 ± 11.3	50.0 ± 11.0	6.2 (3.5, 9.0)	1.32	**0.001**†
Physical component summary#	42.8 ± 7.4	47.3 ± 7.3	4.4 (2.6, 6.3)	1.43	**<0.001**
Mental component summary#	43.0 ± 12.5	45.4 ± 10.2	2.4 (-1.6, 6.4)	0.36	0.216
FACT-BI (n = 14)					
Physical well-being	22.5 ± 3.5	23.6 ± 3.8	1.1 (-0.1, 2.6)	0.39	0.166

Social well-being	20.9 ± 3.7	21.5 ± 3.3	0.6 (-1.0, 2.2)	0.22	0.419
Emotional well-being	14.8 ± 5.0	18.1 ± 3.9	3.4 (1.2, 5.5)	0.94	**0.003**†
Functional well-being	19.4 ± 4.4	20.2 ± 5.7	0.8 (-1.4, 3.0)	0.21	0.449
Bladder cancer subscale#	30.6 ± 6.2	32.8 ± 7.5	2.3 (0.0, 4.6)	0.61	**0.049**
FACT-BI total score#	109.3 ± 12.8	117.5 ± 16.2	8.2 (2.9, 13.4)	0.94	**0.006**
BSI-18 (n=14)					
Somatization	2.0 ± 1.9	2.1 ± 2.4	0.1 (-0.8, 1.0)	0.05	0.777†
Depression	3.2 ± 3.7	3.0 ± 4.4	-0.2 (-1.5, 1.1)	-0.10	0.720
Anxiety	2.0 ± 1.8	1.6 ± 2.1	-0.4 (-1.6, 0.7)	-0.21	0.443
Global severity index	7.2 ± 5.8	6.6 ± 8.1	-0.6 (-3.0, 1.9)	-0.13	0.150†
Body Image Scale (n=14)					
BIS score	5.1 ± 4.7	4.5 ± 4.3	-0.6 (-1.2, 0.7)	-0.28	0.316

Values are the mean ± SD, * Cohen's d, † Wilcoxon signed-rank test, # n =13.

Table 5. Patient-reported outcomes at baseline, pre-surgery, and post-surgery

	Baseline (1)	Pre-surgery (2)	Post-surgery (3)	Effect Size*	P-value	Comparison
SF-36 (n=12)						
Physical functioning†	48.6 (46.5, 54.9)	52.8 (46.5, 54.9)	44.4 (36.0, 48.6)	0.51	**0.004**	**3<1,2**
Role-Physical	39.7 (31.1, 48.9)	42.2 (37.9, 56.9)	37.3 (25.6, 48.3)	0.55	**0.001**	**3<2**
Bodily pain	46.5 (37.2, 53.0)	53.2 (42.6, 62.1)	49.0 (42.6, 60.4)	0.20	0.091	
General health	40.1 (32.6, 45.2)	42.9 (35.5, 48.2)	40.5 (33.7, 45.5)	0.17	0.129	
Vitality	47.4 (39.6, 57.6)	52.1 (45.9, 57.6)	44.3 (37.3, 55.2)	0.31	**0.025**	
Social functioning†	40.5 (29.6, 51.4)	45.9 (29.6, 56.9)	35.0 (18.7, 45.9)	0.22	0.092	
Role-Emotional	52.0 (24.8, 55.9)	44.2 (34.5, 55.9)	42.3 (32.6, 55.9)	0.09	0.358	
Mental health	43.0 (35.9, 55.6)	54.2 (38.7, 58.5)	50.0 (27.5, 58.5)	0.40	**0.008**	**1<2**
PCS#	43.9 (40.2, 49.0)	47.3 (42.3, 53.1)	41.9 (35.8, 49.9)	0.37	**0.025**	**1<2**
MCS#	38.0 (32.5, 58.6)	47.2 (35.4, 57.2)	42.7 (35.6, 55.1)	0.16	0.202	
FACT-BI (n = 12)						
Physical well-being	22.0 (20.3, 25.5)	25.5 (20.8, 26.0)	24.0 (20.3, 26.0)	0.15	0.171	

Social well-being	22.5 (19.9, 23.8)	22.5 (19.9, 23.8)	20.0 (18.3, 23.8)	0.06	0.494	
Emotional well-being	16.0 (9.5, 18.5)	19.5 (15.3, 22.0)	19.0 (13.0, 21.8)	0.41	**0.007**	**1<2**
Functional well-being	19.0 (15.5, 22.8)	21.5 (14.3, 24.8)	19.5 (10.8, 23.3)	0.10	0.303	
Bladder cancer subscale†	30.0 (25.2, 33.6)	33.6 (26.4, 38.4)	30.0 (27.6, 37.0)	0.13	0.234	
FACT-BI total score†	112.4 (96.2, 122.3)	121.6 (103.4, 132.0)	114.0 (109.5, 118.2)	0.17	0.148	
BSI-18 (n=12)						
Somatization	2.0 (0.0, 3.0)	1.0 (0.0, 1.8)	2.0 (1.0, 3.0)	0.24	0.055	
Depression	1.5 (0.0, 5.5)	1.5 (0.0, 3.5)	1.0 (0.0, 5.0)	0.05	0.519	
Anxiety	1.5 (0.0, 2.8)	1.0 (0.0, 4.3)	0.0 (0.0, 1.0)	0.11	0.276	
Global severity index	6.5 (2.0, 8.5)	3.5 (0.3, 8.8)	4.0 (1.3, 8.8)	0.18	0.109	
Body Image Scale (n=12)						
BIS score	3.0 (1.3, 7.5)	3.0 (1.3, 6.8)	5.5 (3.0, 13.8)	0.38	**0.010**	

PCS = physical component summary, MCS = mental component summary. Values are the median (IQR), * Kendall's W (across all time points), † n=11, # n = 10.

Table 6. Surgical and postoperative clinical outcomes (n=15)

Duration of surgery (min)	428 (392, 521)
Blood loss (ml)	500 (480, 850)
Urinary diversion, n (%)	
Ileal conduit	12 (80.0)
Neobladder	3 (20.0)
Length of hospital stay (d)	8.0 (7.0, 15.0)
Clavien Classification of complications†, n (%)	
Grade 0	2 (13.3)
Grade I	4 (26.7)
Grade II	7 (46.7)
Grade IIIa	1 (6.7)
Grade IV	1 (6.7)
ED visits	
Patients, n (%)	5 (33.3)
Total visits	7
30-day readmission, n (%)	5 (33.3)
Length of stay (d)	4.0 (2.5, 18.0)
90-day readmission, n (%)	5* (33.3)
Length of stay (d)	4 (2.25, 9.5)

Values are the median (IQR) or n (%) as indicated. ED = emergency department, †surgical or other complications, *1 patient was readmitted 4 times (once within 30 days and 3 times between 30 and 90 days).