Efficacy and Feasibility of Presurgical Exercise in Bladder Cancer Patients Scheduled for Open Radical Cystectomy

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ABSTRACT

TAAFFE, D. R., S. P. MCCOMBIE, D. A. GALVÃO, R. U. NEWTON, S. LA BIANCA, S. K. CHAMBERS, N. SPRY, F. SINGH, P. LOPEZ, O. SCHUMACHER, C. HAWKS, and D. HAYNE. Efficacy and Feasibility of Presurgical Exercise in Bladder Cancer Patients Scheduled for Open Radical Cystectomy. *Med. Sci. Sports Exerc.*, Vol. 55, No. 7, pp. 1123–1132, 2023. **Purpose:** This study aimed to examine the feasibility and potential efficacy of presurgical exercise in patients with bladder cancer scheduled for open radical cystectomy with follow-up postsurgery. **Methods:** Prospective single-group design with assessments at baseline, presurgery, and 3 months postsurgery was used in this study. Multimodal supervised resistance and aerobic exercise was undertaken 2–3 d·wk^{-1} at moderate intensity for a median of 3.5 wk (interquartile range [IQR] = 1.3–5.6). 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-min walk test [6MWT], timed up-and-go, 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 yr) and a presurgery 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 presurgery; however, there were improvements ($P < 0.05$) in leg press strength (16%), 6MWT distance (8%), timed up-and-go (12%), chair rise (10%), and multiple QoL domains including mental health. Median LOS was 8.0 d (IQR = 7.0, 15.0). Postsurgery, there were declines in components of QoL and apparent body image dissatisfaction. **Conclusions:** A preradical cystectomy exercise program is feasible, safe, and well tolerated with improvements in physical function and QoL. Supervised multimodal exercise in bladder cancer patients before cystectomy can enhance physical and mental health potentially buffering the effects of surgery. **Key Words:** BLADDER CANCER, EXERCISE, CYSTECTOMY, NEOADJUVANT CHEMOTHERAPY

Radical cystectomy, with or without neoadjuvant chemotherapy (NAC), 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 an orthotopic neobladder fashioned from small intestine. Radical cystectomy is a complex, technically demanding, and high-risk surgical procedure that 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 preexisting morbidity and age (4). Furthermore, patients with poor preoperative cardiopulmonary capacity have a higher risk of complications postsurgery

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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 (QoL), and risk of mortality.

Exercise before 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 the beneficial effects of presurgical exercise in prostate cancer (10) and rectal cancer patients (11), and others have reported improvements in lung cancer (12) as well as in noncancer patients (13). In regards to cystectomy, Jensen and colleagues (14) reported improvements in leg extension muscle power after a 2-wk home-based preoperative exercise program, and Banerjee et al. (15) found improvements in cardiopulmonary fitness variables after 3–6 wk of aerobic interval exercise. Recently, Kaye et al. (16) reported that a presurgical exercise program improved physical health outcomes and patient-reported QoL, and Minnella et al. (17) reported prehabilitation that included home-based exercise enhanced postcystectomy recovery as assessed by the 6-min walk test (6MWT).

Here we report the findings from our recently completed exercise trial in patients scheduled for open radical cystectomy with follow-up 3 months postsurgery. In this report, we extend findings from previous trials by including patients exercising while undergoing NAC 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 LOS, an important clinical/patient/economic outcome, to a historical patient series. We hypothesized that undertaking a structured and supervised preoperative multimodal resistance and aerobic exercise program apart from being feasible in the current setting would improve physical function and QoL before 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 preoperative 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 before surgery with follow-up 3 months postsurgery. Supervised training was undertaken 2–3 times per week for approximately 60 min in duration and comprised resistance and aerobic exercise, with a home program of walking 2 d·wk^{-1} or more that consisted of 20–30 min of activity. For patients undergoing surgery only, supervised training was anticipated to be for ~4 wk duration with a minimum of 2 wk and undertaken 3 times per week. For patients undergoing NAC, which was anticipated to be for ~12 wk, supervised sessions were generally 2 d·wk^{-1}. The supervised sessions were initially one on one with an accredited exercise physiologist and then progressed to small groups of three to five cancer patients undertaken in several exercise clinics. Resistance exercise comprised six to eight 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 wk, then 4 sets could be undertaken). The aerobic exercise component was between 15 and 20 min at an intensity of ~60% to 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 min 60% HR_{max}
Weeks 3–4: resistance exercise, 3 sets of 10 RM; aerobic exercise, 15–20 min 70% HR_{max}
Weeks 5–6: resistance exercise, 3 sets of 8 RM; aerobic exercise, 20 min 70%–80% HR_{max}.

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 min 60% HR_{max}
Weeks 3–4: resistance exercise, 3 sets of 12 RM; aerobic exercise, 15–20 min 70% HR_{max}
Weeks 5–8: resistance exercise, 3 sets of 10 RM; aerobic exercise, 20 min 70%–80% HR_{max}
Weeks 9–12: resistance exercise, 3 sets of 8 RM; aerobic exercise, 20 min 70%–80% HR_{max}
Weeks 13–19: resistance exercise, 4 sets of 8 RM; aerobic exercise, 20 min 70%–80% HR_{max}.

Sessions commenced and concluded with a 5-min warm-up and cooldown consisting of low-level aerobic activities and stretching. Because of COVID-19 restrictions, two 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 using the 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 min at an 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 QoL/distress/body image were undertaken at baseline, presurgery, and 3 months postsurgery. Hospital LOS, complications, and return to usual activities were assessed at 3 months postsurgery. For the two patients undergoing the telehealth program, body composition was not assessed and for physical function only the chair rise test was performed.

Primary Study End Point

Feasibility. Feasibility was assessed by the following: 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 vs 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 to 15 (equivalent to "somewhat hard" to "hard").

Secondary Study End Points

Length of hospital stay and complications. LOS and complications (up to 3 months postsurgery) were obtained from hospital records (including the use of the 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) 1RM strength (21) for chest press and leg press which represents upper- and lower-body muscle strength, respectively; 2) 6MWT as a validated submaximal surrogate measure for $\dot{V}O_{2max}$ (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 before surgery, a familiarization session before 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) before testing. The coefficients of variation (CV) for repeat chest press and leg press 1RM measures in our laboratory are 2.2% and 7.5%, respectively, and 5.6% for the repeated chair rise test, whereas the reported CV for the 6MWT in cancer patients is 3% (25) and 6.5% for the TUG test (26).

QoL, psychological distress, and body image. Health-related QoL 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 two summary health measures (physical component summary and mental component summary). Higher scores on the SF-36 indicate higher health-related QoL. Bladder cancer–specific QoL 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 QoL (28,29). The Brief Symptom Inventory-18 (BSI-18) was used to assess psychological distress across the domains of anxiety, depression, and somatization, 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). 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 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, socializing, traveling, and recreation was 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 behaviors, 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 ($kg \cdot m^{-2}$). Self-reported physical activity was assessed by the Leisure Score Index 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 Anesthesiologists Physical Status Classification System (37), respectively. LOS was obtained from hospital records, and the Clavien–Dindo classification was used for complications postsurgery (38).

Statistical Analyses

Data were analyzed using IBM SPSS Version 28 (IBM Corp., Armonk, NY). 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, the normality of the distribution was assessed using the Shapiro–Wilk test. Analyses included standard descriptive statistics, and for baseline and presurgery analyses Student's *t*-tests or the Wilcoxon signed-rank test, as appropriate. For three time points, 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 was used 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, a medium effect is 0.5, and a 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, a moderate effect 0.3, and a large effect 0.5. Values are reported as the mean ± SD, median and 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 presurgery measures, with 4 patients 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 postexercise assessment at the end of immunochemotherapy treatment, 2 patients had NAC while undertaking exercise, and 1 patient had NAC before exercise. Follow-up was undertaken at 3 months postsurgery 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 32–83 yr old with a mean ± SD age of 67.3 ± 12.2 and a BMI of 29.0 ± 4.5, predominantly married and no longer employed, and with a Godin Leisure Score Index indicating insufficiently active. The median weeks of exercise training was 3.5 (IQR = 1.3–5.6) and ranged from 1 to 19 wk. The median number of sessions completed was 9.5 (IQR = 4.0–13.0) and ranged from 1 to 36 sessions, with the median number of missed sessions being 0.0 (IQR = 0.0–1.0) and ranged from 0 to 12. Of the 16 patients with presurgery 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 two serious adverse events, although these were not directly related to the exercise sessions: one patient had a cardiac event after his first chemotherapy treatment and withdrew from the trial, and one patient developed a blood clot during chemotherapy treatment (forearm at site of cannula) and ceased exercise (the patient initially underwent exercise for 6 wk then ceased for the following 6 wk before assessments and surgery). There were 241 exercise sessions scheduled with 212 attended with the

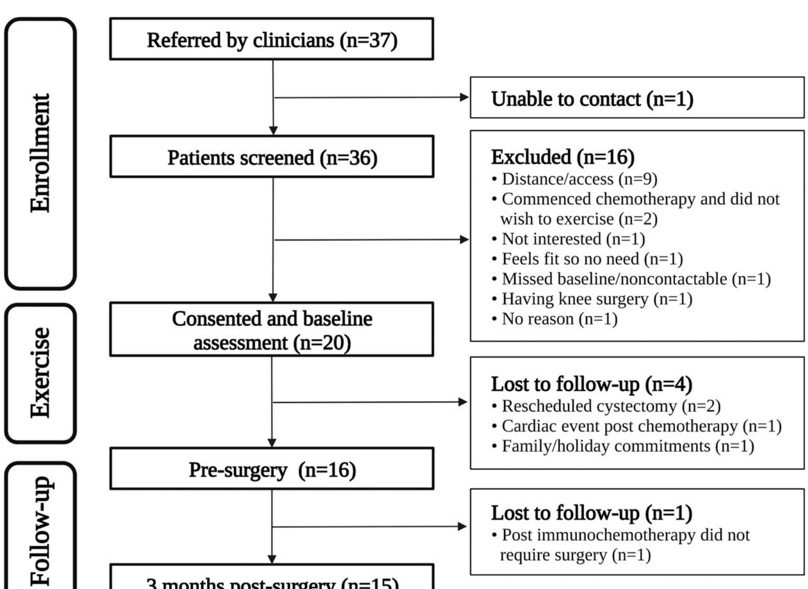

FIGURE 1—Consolidated Standards of Reporting Trials (CONSORT) diagram.

TABLE 1. Patient characteristics (n = 20).

Variable	Value	Range
Age (yr)	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)	
Postsecondary education, n (%)	5 (25)	
Employed, n (%)	3 (15)	
Ever smoked, n (%)	13 (68)	
Drinks per week	9.2 ± 8.9	0–24
MNA[a]	25.3 ± 2.7	19.5–28
Godin LSI[b]	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)	
Hypercholesterolemia, n (%)	10 (50)	
Diabetes, n (%)	2 (10)	

Values are presented as mean ± SD unless otherwise indicated.
[a]Malnourished <17, undernourished 17–23.5, well-nourished >23.5.
[b]Moderate-to-strenuous LSI ≥ 24 classed as active and ≤23 classed as insufficiently active.
MNA, Mini Nutritional Assessment; LSI, Leisure Score Index; CVD, cardiovascular disease; ASA, American Society of Anesthesiologists physical status.

average median individual program adherence of 100.0% (IQR = 89.4, 100.0). Program compliance (actual exercise completed vs 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 to 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 postintervention before 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 subgroup of patients who underwent follow-up assessments at 3 months postsurgery are shown in Table 3. The patient numbers for the tests vary compared with presurgery because of 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, presurgery, and postsurgery measures for lean mass (P = 0.012), ASM (P = 0.018), and chest press strength (P = 0.022), the source of the differences was not located with follow-up testing. However, for the chair rise test (P = 0.005), performance significantly declined postsurgery.

QoL, psychological distress, and body image. After the intervention, several domains for health-related QoL improved (P < 0.05), including physical functioning, vitality, and 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, and 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 postsurgery, there was a decline (P < 0.05) in patient-reported physical functioning as well as role–physical compared with presurgery. There was also a significant change across time for body image (P = 0.010), with an apparent increase in dissatisfaction postsurgery.

Length of hospital stay, complications, and resumption of usual activities. For the 15 patients that underwent exercise and cystectomy, LOS ranged from 4 to 30 d with a median of 8.0 d (7.0, 15.0) (Table 6). In comparison, for a patient series of 100 patients undergoing open radical cystectomy by a study urologist (D.H.) from the one participating hospital, LOS ranged from 4 to 27 d with a median of 9.0 d (IQR = 7.0, 13.0). Of the 15 exercised patients, rates of the 90-d Clavien–Dindo complications of severity grades I–II and III–IV were 11/15 (73%) and 2/15 (13%) in comparison with 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 seven visits with wound infection/leak and pain being the most common reasons. The 30-d readmission rate was 33.3% (five patients) and was due to urosepsis (n = 2),

TABLE 2. Body composition and physical function at baseline and presurgery.

	Baseline	Presurgery	Mean Change (95% CI)	Effect Size[a]	P
Body composition (n = 13)					
Lean mass (kg)	55.3 ± 11.7	54.7 ± 11.4	−0.5 (−1.8 to 0.7)	−0.27	0.354
Fat mass (kg)	28.1 ± 9.5	27.8 ± 9.0	−0.2 (−1.5 to 1.0)	−0.11	0.710
Body fat (%)	32.2 ± 6.7	32.3 ± 6.6	0.1 (−1.0 to 1.1)	0.04	0.891
ASM (kg)	23.5 ± 5.2	23.2 ± 4.9	−0.3 (−0.8 to 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 to 4.2)	0.37	0.140[b]
Leg press (kg), n = 13	85.4 ± 35.2	99.0 ± 39.1	13.6 (5.2 to 22.0)	0.98	**0.004**
6MWT (m), n = 14	504.4 ± 105.2	543.1 ± 81.8	38.7 (14.7 to 62.8)	0.93	**0.004**
TUG (s), n = 14	7.7 ± 1.6	6.8 ± 1.2	−0.8 (−1.4 to −0.3)	−0.84	**0.008**
Chair rise (s), n = 16	13.0 ± 2.6	11.7 ± 1.8	−1.3 (−2.1 to −0.5)	−0.88	**0.003**

Values are presented as mean ± SD.
Bold P values indicate statistical significance.
[a]Cohen's d.
[b]Wilcoxon signed-rank test.
TUG, timed up and go test.

TABLE 3. Body composition and physical function at baseline, presurgery, and postsurgery.

	Baseline	Presurgery	Postsurgery	Effect Size[a]	*P*
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**[b]
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**[b]
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**[b]
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**[c]

Values are presented as median (IQR).
Bold *P* values indicate statistical significance.
[a]Kendall's *W* (across all time points).
[b]Differences not located in *post hoc* analysis.
[c]*Post hoc* analysis: baseline, postsurgery > presurgery.
TUG, timed up and go test.

abdominal pain/diarrhea, intra-abdominal collection (abscess), and pyelonephritis. Between 30- and 90-d postsurgery, one of these patients was readmitted a further three 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 to 40 and for recreational activities ranging from 0 to 90.

DISCUSSION

This is the first Australian study to examine the feasibility and potential efficacy of presurgical 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 postsurgery 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 before cystectomy with a recruitment rate of 54% and a completion rate of 80%. For the four patients who withdrew from the study, surgery was brought forward for two patients, resulting in only one and two sessions being undertaken, a third patient had a cardiac event after chemotherapy, and the fourth patient

TABLE 4. Patient-reported outcomes at baseline and presurgery.

	Baseline	Presurgery	Mean Change (95% CI)	Effect Size[a]	*P*
SF-36 (n = 14)					
Physical functioning	46.4 ± 11.1	50.9 ± 5.6	4.5 (−2.1 to 11.2)	0.39	0.128[b]
Role–physical	41.3 ± 10.1	45.1 ± 8.2	3.8 (0.7 to 7.0)	0.70	**0.021**
Bodily pain	45.7 ± 11.1	50.6 ± 10.7	5.0 (0.4 to 9.6)	0.63	**0.036**
General health	39.2 ± 9.6	40.2 ± 9.5	1.0 (−2.4 to 4.4)	0.17	0.542
Vitality	47.9 ± 8.3	51.2 ± 8.0	3.3 (0.2 to 6.5)	0.62	**0.037**
Social functioning	39.6 ± 9.4	43.0 ± 11.0	3.4 (−0.8 to 7.5)	0.49	0.104
Role–emotional	43.9 ± 15.2	43.4 ± 10.1	−0.6 (−6.5 to 5.4)	−0.05	0.844
Mental health	43.8 ± 11.3	50.0 ± 11.0	6.2 (3.5 to 9.0)	1.32	**0.001**[b]
Physical component summary[c]	42.8 ± 7.4	47.3 ± 7.3	4.4 (2.6 to 6.3)	1.43	**<0.001**
Mental component summary[c]	43.0 ± 12.5	45.4 ± 10.2	2.4 (−1.6 to 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 to 2.6)	0.39	0.166
Social well-being	20.9 ± 3.7	21.5 ± 3.3	0.6 (−1.0 to 2.2)	0.22	0.419
Emotional well-being	14.8 ± 5.0	18.1 ± 3.9	3.4 (1.2 to 5.5)	0.94	**0.003**[b]
Functional well-being	19.4 ± 4.4	20.2 ± 5.7	0.8 (−1.4 to 3.0)	0.21	0.449
Bladder cancer subscale[c]	30.6 ± 6.2	32.8 ± 7.5	2.3 (0.0 to 4.6)	0.61	**0.049**
FACT-BI total score[c]	109.3 ± 12.8	117.5 ± 16.2	8.2 (2.9 to 13.4)	0.94	**0.006**
BSI-18 (n = 14)					
Somatization	2.0 ± 1.9	2.1 ± 2.4	0.1 (−0.8 to 1.0)	0.05	0.777[b]
Depression	3.2 ± 3.7	3.0 ± 4.4	−0.2 (−1.5 to 1.1)	−0.10	0.720
Anxiety	2.0 ± 1.8	1.6 ± 2.1	−0.4 (−1.6 to 0.7)	−0.21	0.443
Global severity index	7.2 ± 5.8	6.6 ± 8.1	−0.6 (−3.0 to 1.9)	−0.13	0.150[b]
BIS (n = 14)					
BIS score	5.1 ± 4.7	4.5 ± 4.3	−0.6 (−1.2 to 0.7)	−0.28	0.316

Values are presented as mean ± SD.
Bold *P* values indicate statistical significance.
[a]Cohen's *d*.
[b]Wilcoxon signed-rank test.
[c]n = 13.

TABLE 5. Patient-reported outcomes at baseline, presurgery, and postsurgery.

	Baseline (1)	Presurgery (2)	Postsurgery (3)	Effect Size[a]	*P*	Comparison
SF-36 (*n* = 12)						
Physical functioning[b]	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[b]	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[c]	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[c]	38.0 (32.5–58.6)	47.2 (35.4–57.2)	42.7 (35.6–55.1)	0.16	0.202	
FACT-Bl (*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[b]	30.0 (25.2–33.6)	33.6 (26.4–38.4)	30.0 (27.6–37.0)	0.13	0.234	
FACT-Bl total score[b]	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	
BIS (*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**	

Values are presented as median (IQR).
Bold *P* values indicate statistical significance.
[a]Kendall's *W* (across all time points).
[b]*n* = 11.
[c]*n* = 10.
PCS, physical component summary; MCS, mental component summary.

withdrew after four sessions due to family commitments. The recruitment rate is comparable with 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-wk preoperative home-based program in Denmark and Minnella et al. (17) of 77.8% for their ~4-wk 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 because of the exercise program itself, and there were no exercise-related adverse events.

Physical function improved after 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 postoperative period. These changes were relatively substantial ranging from 8% to 16% over a median of 3.5 wk of exercise training. Similarly, Jensen et al. (14) reported an 18% increase in leg muscle power after a 2-wk program of daily exercise in patients scheduled for cystectomy, whereas 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 $\dot{V}O_2$ peak compared with nonexercisers after twice weekly training for 3–6 wk. Recently, Kaye et al. (16) reported an improvement in 6MWT (5.1%), submaximal $\dot{V}O_2$ (10.2%), gait speed (7.5%), and the TUG test (5.5%) after thrice weekly exercise for 4 wk before cystectomy. However, at 3 months postsurgery, 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 after surgery, even at 3 months post, indicate the importance of enhancing the patient's reserve capacity before surgery, especially for those older and close to thresholds for maintaining activities of daily living, 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, bladder score, and total score of the FACT-Bl. Similarly, Kaye et al. (16) reported improvements in the physical health component summary with

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* (%)[a]	
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-d readmission, *n* (%)	5 (33.3)
Length of stay (d)	4.0 (2.5–18.0)
90-d readmission, *n* (%)	5[b] (33.3)
Length of stay (d)	4 (2.25–9.5)

Values are presented as median (IQR) or *n* (%) as indicated.
[a]Surgical or other complications.
[b]One patient was readmitted four times (once within 30 d and three times between 30 and 90 d).
ED, emergency department.

a mean change of 4.2 points and mental health component summary of 3.4 points in the SF-36 after presurgical 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 after 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 postsurgery, 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 preexercise levels. Anxiety and depression did not change after the exercise intervention or at 3 months postsurgery; however, there was an apparent increase in body image dissatisfaction after surgery. Change in body image is an important concern after cystectomy with associated effects on sexual and social functioning (41).

We found no changes in lean mass or fat mass over the preoperative 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 after 4 wk of resistance and aerobic exercise before cystectomy. However, sarcopenia has been implicated as a predictor of major complications (3) and for cancer-specific and overall survival after radical cystectomy (42). Consequently, screening for sarcopenia and implementing strategies such as resistance training and protein/dietary supplementation to counteract sarcopenia before cystectomy may be one strategy to target patients at risk for complications and postoperative mortality.

Hospital LOS was a median of 8 d for our patients, which was similar to that of the historical controls of 9 d. Similarly, Jensen et al. (39) reported a median LOS of 8 d with no difference between intervention or standard treatment patients in their trial, whereas the median LOS was 7 d 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 after radical cystectomy with 9 and 10 d, respectively. By contrast, Kaye et al. (16) reported a mean LOS of 6.5 ± 2.5 d, although 58% underwent robot-assisted compared with open radical cystectomy, which may have contributed to the shorter stay (43). 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 preoperative exercise than those undergoing robot-assisted radical cystectomy. Our 30-d readmission rate is similar to that of Jensen et al. (39) of 30% in exercisers and Kaye et al. (16) of 23%, with 90-d readmission similar to that reported by others after 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 that 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-Bl, BSI-18, BIS, 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 (44). Fourth, all patients underwent open radical cystectomy, a patient group that may benefit most from presurgical exercise, and lastly, we were able to compare with 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, because of 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 cannot 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 (45). Lastly, given the number of comparisons/analyses undertaken, we cannot discount that a few of the significant findings may be due to chance.

CONCLUSIONS

In conclusion, we found presurgical multimodal exercise in patients scheduled for open radical cystectomy to be safe, feasible, and well tolerated with beneficial effects on physical function and QoL, including patients undergoing NAC. These findings, collectively with the positive findings from other trials in this patient group (14–17), indicate that exercise medicine should be prescribed before radical cystectomy (and delivered either under supervision in an exercise clinic or via telehealth, or home-based) to enhance the patient's reserve capacity and "fitness for surgery" both physically and mentally, potentially enhancing their postoperative 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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