EXERCISE MEDICINE PRIOR TO OPEN RADICAL CYSTECTOMY: FEASIBILITY AND PRELIMINARY EFFICACY

DETAILED BACKGROUND AND RESEARCH PLAN

Background and rationale

Worldwide bladder cancer is the 9th most common cancer with more than 430,000 new cases per year and 165,000 deaths (1). It is more common in men than women with a male to female ratio of ~3 to 1 (1-3), and is an expensive if not the most expensive cancer to manage (4,5). However, it has a poor 5-year survival rate of 53% compared to other common cancers such as prostate at 93% and breast cancer at 90% (3). In Australia, the projected number of new cases of bladder cancer in 2017 is 2,995 with mortality predicted to be 1,172 persons (3). For those with muscle-invasive bladder cancer (MIBC) the primary treatment is radical cystectomy (RC) which involves the surgical removal of the bladder with lymph node dissection and urinary diversion (in men the prostate, seminal vessicles and distal ureters are also removed while in women the uterus and ovaries, adjavent vagina, fallopian tubes and distal ureters are removed), and a hospital stay of 1-2 weeks. However, RC is a complex, technically demanding and high-risk surgical procedure which is associated with significant morbidity, readmission rates, and mortality (6-8). Postoperative complications are common and are related to pre-existing morbidity, age, surgical procedure and type of urinary diversion (2). Further, patients with poor pre-operative cardiopulmonary capacity have a higher risk of complications post-surgery and increased hospital length of stay (9,10). Moreover, given the age of the patients (median age at diagnosis in Australia is 76 years) as well as the fact that smoking is a major risk factor (11), patients may have associated pulmonary and cardiovascular diseases which contribute to poorer overall function and quality of life. As a result, enhancing functional capacity prior to RC may reduce the stress of surgery and attenuate the general deconditioning process in the immediate post-surgical period which may reduce the length of hospital stay, complications, and time to return to usual activities. However, little information is available regarding the feasibility of pre-surgical exercise or the potential beneficial effect that exercise may have prior to surgery in this patient group. Therefore, we propose to undertake a feasibility and preliminary efficacy exercise trial in men and women scheduled to undergo RC and follow them for 3 months post-surgery. The exercise program will be supervised and consist of resistance and aerobic training undertaken two to three times per week.

Aim

Our aim is to improve the functional status of patients prior to radical cystectomy and improve patient outcomes following surgery.

Objectives

To determine:

1. If undertaking a structured exercise program prior to radical cystectomy is feasible;
2. Improves physical function prior to surgery;
3. Reduces length of hospital stay and complications;
4. Potentially reduces the time to return to usual daily or work activities;
5. Improves quality of life (QOL), psychological distress and body image; and
6. Improves body composition (lean mass and fat mass).

Hypotheses

We hypothesise that undertaking a structured and supervised pre-operative exercise program will be feasible, improve physical function prior to surgery, reduce the length of hospital stay and complications, potentially reduce the time required to return to usual or work activities, and enhance QOL, psychological distress, body image, and body composition. Results from this preliminary study will inform larger multi-centre trials and has the potential to substantially improve bladder cancer patient outcomes following radical cystectomy.

Population and setting

Twenty patients scheduled to undergo RC will be recruited by invitation from their attending Urologist (CI-Professor Hayne and CI-Dr La Bianca). Potential patients will be those with muscle-invasive bladder cancer (≥ T2), patients with high-risk non-muscle-invasive bladder cancer (NMIBC) with atypical pathologic features (e.g., nested variant, micropapillary, etc.) or who prefer upfront cystectomy, and those undertaking salvage cystectomy after failed curative intent treatment with external beam radiation therapy (EBRT). Exclusion criteria will include musculoskeletal, cardiovascular or neurological conditions that could inhibit patients from exercising.

Intervention

For those undergoing cystectomy only, up to a 4-week supervised exercise program (based on scheduling for surgery) will be implemented. For those undergoing chemotherapy prior to surgery, the exercise program will be for the duration of chemotherapy which is usually 12 weeks. Exercise will consist of moderate- to high-intensity resistance- and aerobic-based training. Supervised training will be undertaken 2-3 times per week for approximately 1 hour each session with a home program of walking 2 or more days per week that consists of 20-30 minutes of activity. The sessions will be predominantly one-on-one with an accredited exercise physiologist (AEP) given that time to surgery and patient availability will determine timing of the training sessions. The exercise program is designed to provide optimal stimulus to the cardiorespiratory and neuromuscular systems while maximising safety, compliance and retention. Resistance exercise will involve 6-8 exercises that target the major upper and lower body muscle groups, such as the chest press, seated row, shoulder press, leg press, leg extension, leg curl, biceps curl and tricep extension. Intensity will be manipulated from 6-12 repetition maximum (RM; i.e. the maximal weight that can be lifted 6 to 12 times which is equivalent to ~60-85% of 1RM) using 1-3 sets per exercise. The aerobic exercise component will include ~20 minutes (~60-85% 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. Sessions will commence and conclude with a 5-minute warm-up and cool-down consisting of low level aerobic activities and stretching. The training sessions will take place at the Vario Exercise Clinic in the Exercise Medicine Research Institute (EMRI) at Edith Cowan University in Joondalup (north of Perth CBD) and at our new EMRI exercise clinic at Fiona Stanley Hospital (South of Perth CBD).

Study Design

Single-armed trial with patients undertaking exercise prior to surgery with follow-up at 3 months post-surgery. Three months post-surgery permits 30-day and 90-day assessments of complications and calculation of rates, and sufficient time to assess return to usual or work activities. A single-arm design has been chosen given that this is a feasbility and preliminary efficacy trial, and to aid in determining an appropriate sample size for a larger scale randomised controlled trial if shown to be feasible with potentially beneficial patient outcomes.

Outcomes and measures

Measurements

Hospital length of stay (LOS) will be recorded as will complications over the 3-month follow-up period to provide 30- and 90-day complication rates. Assessments of physical function, quality of life, distress, body image, and body composition will take place at pre-exercise (baseline), pre-surgery, and 3 months post-surgery. Return to usual/work activities will be assessed at 3 months post-surgery.

Primary Study Endpoint:

Feasibility. Feasibility will be 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 rating of perceived exertion (RPE) by the patient using the Borg 0-10 scale 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). Reasons for refusal and barriers to participate, withdrawal, missed sessions and non-compliance will be investigated, as will the patient's views on changes/improvements to the exercise regimen and session format.

Secondary Study Endpoints:

Length of hospital stay and complications. Length of hospital stay and complications (up to 3 months post-surgery) will be obtained from hospital records with comparison (including use of Clavien Classification of surgical complications) to a prospectively collected radical cystectomy patient series at a single institution from CI-Professor Hayne.

Physical function. Physical function will be assessed prior to exercise, pre-surgery and 3 months post-surgery via a battery of standard tests we have used extensively (13-15) that include: 1) one-repetition maximum (1RM) strength for the 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), 3) repeated chair rise (time to rise from a chair 5 times as a measure of lower body muscle function), and 4) the get-up-and-go test to assess agility and dynamic balance.

Quality of life, psychological distress, and body image. Health-related quality of life will be assessed using the Medical Outcomes Short Form 36 (SF-36) (16), which assesses 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. Bladder cancer specific quality of life will be 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 (17). The Brief Symptom Inventory-18 (BSI-18) will be utilised to assess psychological distress across the domains of anxiety, depression, somatisation, and global distress severity (18). Body image will be specifically assessed using the 10-item Body Image Scale (BIS) (19).

Body composition. Whole body and regional lean mass and fat mass will be derived from a whole body dual-energy X-ray absorptiometry (DXA) scan.

Return to work or usual activities. Return to work and usual activities will be assessed using the Resumption of Activities of Daily Living (RADL) Scale (20), modified for time since surgery. The extent to which the patient has resumed their normal activities (scale from 0% to 100%) in the areas of self-care, household chores, shopping, socialising, recreation, and paid employment (if applicable) will be assessed at 3 months post-surgery.

Other Measures:

Demographics, lifestyle behaviours, and health history will be obtained by questionnaire and medical records. Height and weight will be measured using a stadiometer and electronic scales, respectively. Self-reported physical activity will be assessed at pre-exercise, pre-surgery and 3 months post-surgery by the Leisure Score Index from the Godin Leisure-Time Exercise Questionnaire (21) as will nutritional status by the Mini Nutritional Assessment (22).

Study procedures

Pre-operative participant recruitment (rolling recruitment), baseline assessment, implementation and undertaking of exercise, pre-surgical assessment, follow-up at 3 months post-surgery, reporting and dissemination of findings. Measurements of physical function, body composition, and quality of life/distress/body image at pre-exercise, pre-surgery and 3-month post-surgery, hospital LOS and complications derived from hospital records, and return to work/usual activities assessed at 3 months post-surgery.

Statistical considerations

Calculation of Sample Size

With a caseload of up to 35 RC patients between CI-Professor Hayne and CI-Dr La Bianca over a 12-month period, we expect that we will be able to recruit at least 20 patients to participate in the study. Nevertheless, although the aim of the study is to determine feasibility and preliminary efficacy, and to use the results to appropriately determine the sample size for a larger trial, with 20 subjects we would have 80% power (alpha = 0.05, two-tailed test) to detect a moderate effect size of 0.67 in our outcome measures such as physical function which we would consider to be clinically meaningful.

Data Analysis

For the primary outcome, rates for recruitment (numbers consent /eligible), completion (undertake baseline and follow-up tests), adherence (participant completed sessions/number of sessions), compliance (volume completed/prescribed volume), and adverse events (number and number per participant hour) will be calculated. Analyses will also include standard descriptive statistics, Student's t-tests, and repeated measures analysis of variance (ANOVA) or non-parametric equivalents as appropriate for continuous data (such as physical function, etc.), and Pearson's chi-square. Where appropriate, the Bonferroni post-hoc test (or Bonferroni corrected Wilcoxon signed-rank test following a significant Friedman's ANOVA) will be used to locate the source of significant differences. Normality of the data will be determined using the Shapiro-Wilk test. Tests will be two-tailed with an alpha level of 0.05 applied as the criterion for statistical significance. In addition, effect sizes will be calculated in accordance with the following criteria: d = 0.2 small; d = 0.5 moderate; d = 0.8 large.

Feasibility

The most significant hurdle for a study such as this would be obtaining sufficient patient recruitment. Our objective is to recruit 20 patients scheduled for a radical cystectomy. Prospective patients will be those of CI-Hayne and CI-La Bianca and the surgical procedures will be carried out by CI-Hayne who is a Urological Surgeon and Head of Urology at the Fiona Stanley Hospital, a major metropolitan hospital in Perth, and CI-La Bianca who is a Urological Surgeon at Perth Urology Clinic, St John of God Murdoch Hospital, which is adjacent to Fiona Stanley Hospital. CI-Hayne has a case load of approximately 15 cystectomy patients per year and CI-La Bianca approximately 20 patients per year for a total case load between them of up to 35 patients per year. Moreover, our team has many years of experience recruiting for short-term and long-term exercise trials in people with cancer, as well as the conduct of exercise interventions for people with cancer. Regarding the access to appropriate training facilities, we have well-established exercise training and testing infrastructure in the Exercise Medicine Research Institute at Edith Cowan University in Joondalup as well as the use of the EMRI exercise clinic at Fiona Stanley Hospital, thereby covering both the north and south regions of the Perth metropolitan area. Although an outcome of this trial if the results are positive is to determine the appropriate sample size for a phase III trial of pre-surgical exercise in cystectomy patients, our team has an established track record of translating research findings into national and international guidelines and the development of patient programs.

Significance

Radical cystecytomy is associated with high complication and hospital re-admission rates, substantial morbidity, and mortality. Moreover, bladder cancer has a poor 5-year survival rate at 53% compared to other cancers, and the surgery can have a significant effect on the patient's QOL. Exercise prior to surgery or prehabilitation 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. Indeed, enhancing perioperative care and potentially reducing hospital LOS as well as perioperative morbidity can reduce the high economic burden associated with RC (4). Moreover, pre-surgical exercise may positively enhance QOL and body image, and provide survivors with a sense of control through the undertaking of exercise. This will be the first Australian study to establish the feasibility and preliminary efficacy of pre-surgical exercise in the setting of RC with opportunities to then proceed to a larger multi-centre Phase III trial. In all, it may be ultimately shown that exercise plays a significant role in pre-operative medical optimisation and optimisation of surgical outcomes, and forms an integral part of enhanced recovery programs to improve postoperative recovery in RC patients. This would result in a change in clinical practice guidelines, enhancing surgical and patient outcomes.

Risks

1. Insufficient recruitment. Extension of study duration up to 3 months to achieve required participant numbers.

2. Patients discontinuing exercise and drop-out from trial. Close monitoring and supervision, and individualising the program as required. Use of an experienced Accredited Exercise Physiologist (AEP) for exercise supervision and patient contact.

3. Exercise-related adverse events. Baseline assessments for appropriate exercise loads, close monitoring and supervision by an AEP. Emergency procedures in place, trained staff to deal with emergencies. Adjustment of program where needed such as with soft tissue injury.

Financial support

The project has been funded for $50,000 by the ANZUP Cancer Trials Group Limited Below the Belt Research Fund.

Timeline

Commencement of funding period and following ethics approval – patient recruitment to begin followed immediately by pre-surgical exercise and 3-month follow-up.

6 months – up to 15 patients enrolled depending on patient presentation to study urologists.

12 months – data collected, data analysis and interpretation, and draft of manuscript. Grant preparation for national schemes (such as NHMRC 2018/19).

References

References:

1. Antoni S, Ferlay J, Soerjomataram I, et al. Eur Urol. 2017;71(1):96-108.
2. Witjes JA, Compérat E, Cowan NC, et al. European Association of Urology 2015:1-72.
3. Cancer in Australia 2017. Cancer series no.101. Cat. no. CAN 100. Canberra: AIHW.
4. Svatek RS, Hollenbeck BK, Holmang S, et al. Eur Urol. 2014;66(2):253-262.
5. Mossanen M, Gore JL. Curr Opin Urol. 2014;24(5):487-491.
6. Goodney PP, Stukel TA, Lucas FL, et al. Ann Surg. 2003;238(2):161-167.
7. Stimson CJ, Chang SS, Barocas DA, et al. J Urol. 2010;184(4):1296-1300.
8. Smith AB, Deal AM, Yu H, et al. J Urol. 2014;191(6):1714-1720.
9. Prentis JM, Trenell MI, Vasdev N, et al. BJU Int. 2013;112(2):E13-19.
10. Tolchard S, Angell J, Pyke M, et al. BJU Int. 2015;115(4):554-561.
11. Freedman ND, Silverman DT, Hollenbeck AR,et al. JAMA. 2011;306(7):737-745.
12. Galvao DA, Taaffe DR, Spry N, et al. J Clin Oncol. 2010;28(2):340-347.
13. Galvao DA, Spry N, Denham J, et al. Eur Urol. 2014;65(5):856-864.
14. Taaffe DR, Newton RU, Spry N, et al. Eur Urol. 2017. http://dx.doi.org/10.1016/j.eururo.2017.02.019.
15. Ware JE, Jr., Sherbourne CD. Med Care. 1992;30(6):473-483.
16. Cella DF, Tulsky DS, Gray G, et al. J Clin Oncol. 1993;11(3):570-579.
17. Zabora J, BrintzenhofeSzoc K, Jacobsen P, et al. Psychosomatics. 2001;42(3):241-246.
18. Hopwood P, Fletcher I, Lee A, et al. Eur J Cancer. 2001;37(2):189-197.
19. Williams RM, Myers AM. Phys Ther. 1998;78(6):613-623.
20. Godin G, Shephard RJ. Can J Appl Sport Sci. 1985;10(3):141-146.

21. Vellas B, Guigoz Y, Garry PJ, et al. Nutrition. 1999;15(2):116-122.