Can exercise delay transition to active therapy in men with low-grade prostate cancer? A multicentre randomised controlled trial

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ABSTRACT

Introduction Active surveillance is a strategy for managing low-risk, localised prostate cancer, where men are observed with serial prostate-specific antigen assessments to identify signs of disease progression. Currently, there are no strategies to support active surveillance compliance nor are there interventions that can prevent or slow disease progression, ultimately delaying transition to active treatment before it is clinically required. Recently, we proposed that exercise may have a therapeutic potential in delaying the need for active treatment in men on active surveillance.

Methods and analysis A single-blinded, two arm, multicentre randomised controlled trial will be undertaken with 168 patients randomly allocated in a ratio of 1:1 to exercise or usual care. Exercise will consist of supervised resistance and aerobic exercise performed three times per week for the first 6 months in an exercise clinical setting, and during months 7–12, a progressive stepped down approach will be used with men transitioning to once a week supervised training. Thereafter, for months 13 to 36, the men will self-manage their exercise programme. The primary endpoint will be the time until the patients begin active therapy. Secondary endpoints include disease progression (prostate specific antigen), body composition and muscle density, quality of life, distress and anxiety and an economic analysis will be performed. Measurements will be undertaken at 6 and 12 months (postintervention) and at 24 and 36 months follow-up. The primary outcome (time to initiation of curative therapy) will be analysed using Cox proportional hazards regression. Outcomes measured repeatedly will be analysed using mixed effects models to examine between-group differences. Data will be analysed using an intention-to-treat approach.

Ethics and dissemination Outcomes from the study will be published in peer-reviewed academic journals and presented in scientific, consumer and clinical meetings.

Trial registration number ACTRN12618000225213.

INTRODUCTION

Prostate cancer (PCa) is a major challenge for our health system and its workforce and for Australian society as a whole. In 2017, more than 200 000 Australian men were living with PCa, 80% of them were long-term survivors.1 2 The widespread prostate-specific antigen (PSA) screening for PCa has led to concerns about the overdiagnosis and overtreatment of this disease with the overdiagnosis estimated to be as high as 67%.3 Overtreatment rates are also high with reports of 80% of men receiving treatments on initial diagnosis.4 Active surveillance (AS) is a strategy for managing low-risk localised PCa, where men are observed with regularly schedule serial PSA assessments to identify signs of disease progression.5 AS reduces overtreatment in clinically insignificant disease,5 reducing PCa burden for the individual, the healthcare system and the society. Problematically, most men will not comply with AS and those who convert to active treatment too...
soon. Currently there are no strategies to (1) support AS compliance applying a lifestyle approach or (2) prevent or slow disease progression, ultimately delaying transition to active treatment before it is clinically required.5–10 These are the two critical unanswered questions in applying AS to men with PCa.

We recently presented a preliminary evidence6 that exercise may have therapeutic potential in delaying the need for active treatment (eg, surgery/radiation) in men on AS. Exercise is implicated in decreasing the number of patients undergoing active treatment,11 reducing PSA,12 as well as modulating the biological processes involved with tumourigenesis.13 It may act through systemic mechanisms, as exercise alters circulating factors that inhibit PCa cell proliferation in vitro.14–16 Further, increased adiposity is associated with increased risk of PCa progression specifically during AS,17 and exercise can be an effective countermeasure to this in the setting of AS (figure 1).5

Exercise as a therapeutic intervention in such men may also have important additional benefits by addressing other adverse consequences. The psychological burden of AS, in terms of cancer-related anxiety, also influences adherence and treatment decisions as much as clinical disease progression.18 Not treating a cancer runs against the norm and the surveillance process is inherently stressful. Exercise presents as a supportive care approach that closely maps onto core male values and has the potential to both combat illness but also help prevent and/or minimise anxiety and uncertainty related to living with a PCa diagnosis. Specifically, by supporting male values around strength, self-reliance and action,19 exercise may

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**Figure 1** Proposed mechanisms of exercise on prostate cancer and disease progression. Reprinted with permission from Galvao et al.6
increase men’s self-efficacy or feelings of control over their health, and thereby support adherence to AS while improving psychological outcomes and physical and mental quality of life (QoL).5 20

To characterise and quantify the benefits of exercise for men on AS, we propose to undertake a multicentre randomised controlled trial (RCT) of 12-month supervised resistance and aerobic exercise versus usual care in men with PCAs on AS, with subsequent follow-up of over 2 years to monitor therapeutic progression and psychological well-being.

METHODS AND ANALYSIS

This is a single-blinded (investigators blinded to group allocation), two-arm, multicentre RCT that will examine the efficacy of combined resistance and aerobic exercise during AS on disease progression in men with low-risk PCAs. An ‘exercise’ group will complete a 6-month supervised exercise intervention followed by a stepped down programme for 6 months and a subsequent self-managed maintenance programme for 2 years (figure 2). A ‘usual care’ group will maintain usual medical care and receive standard information on current physical activity guidelines for cancer survivors, which will include an unsupervised walking programme.

Patients and methods

One hundred and sixty-eight men (84 patients per arm) within 1 year of diagnosis of PCa and undergoing AS will be recruited by invitation of their attending specialist from two Australian cities (Perth and Melbourne). Patients suitable for AS will be selected from the Multi-Disciplinary Uro-Oncology meeting at the recruiting site. Inclusion criteria are: (1) histologically proven adenocarcinoma of the prostate, (2) no prior therapy for PCa, (3) fit for curative intent therapy, (4) willing to attend follow-up, (5) clinical stage ≤T2, (6) <10% Gleason pattern 4 disease on biopsy and (7) PSA ≤10ng/mL. Exclusion criteria are: (1) already performing regular exercise defined as undertaking structured resistance and aerobic training two or more times per week within the past 3 months, (2) acute illness or any musculoskeletal, cardiovascular or neurological disorder that could inhibit exercise performance or put participants at risk from exercising, (3) variant histopathology (small cell, intraductal, sarcomatoid), presence of extraprostatic extension or lymphovascular invasion, (4) patient no longer considered a candidate for curative intent treatment and (5) intention to move place of residence away from the two study sites. Eligible patients will undertake baseline measurements prior to randomisation. All patients must provide written informed consent prior to participation in addition to a physician consent form. The study coordinator will obtain the consent forms from patients and physicians. All data relevant to the study will be kept on password-encrypted computers accessible only by study investigators situated in the Exercise Medicine Research Institute (Perth, WA, Australia).

Patient and public involvement

We work closely with the Prostate Cancer Foundation of Australia (PCFA), their support groups and state offices. PCFA and support groups have been involved in the development of this proposal and will maintain a very important role on this project in patient recruitment and support as well as translation and dissemination of the research findings. We have used this feedback to inform this project and ensure that it engages participants in a respectful, ethical and impactful way. As the project evolves, PCFA will assist in the dissemination of findings to cancer support groups and the general public, while study participants will receive their individual results as well as overall study findings.

Randomisation

Patients will be randomly allocated in a ratio of 1:1 to the two study arms, and will be stratified according to: (1) age (<60 years≥), (2) PSA (<5 & ≥5) and (3) time on AS (<6months≥). Within each stratum, randomisation will occur in blocks of either 8 or 10, with block size randomly selected in a 1:1 ratio. Patients will be randomised via a central web-based service (Griffith University) to ensure allocation concealment until study entry. Randomisation will occur immediately after each patient completes their baseline questionnaire (figure 3). The study coordinator will assign participants to groups.

Measurements

All measurement study endpoints will take place at baseline, 6 months, postintervention (12 months) and 1 and 2-year follow-up (months 24 and 36). All assessment tools/procedures have established validity and reliability and are used widely in clinical research including by our team.

Primary study endpoint

Patients undergoing active therapy

The number of patients undergoing active therapy (radical prostatectomy, radiotherapy or androgen deprivation) and the time they began active therapy will be extracted directly from the urologist clinical investigators.
as part of their routine clinical practice; therefore, all patients will be captured. Data will be extracted for the 3 years following randomisation, and the reasons for progression to active therapy will be recorded.

**Secondary study endpoints**

**Disease progression (PSA)**

For all patients, PSA will be measured commercially by an Australian National Association of Testing Authorities accredited laboratory.\(^{21}\)

**Body composition and muscle density**

Regional and whole-body lean mass and fat mass will be derived from the whole-body dual-energy X-ray absorptioniometry scans. Trunk adiposity, visceral fat and adipose indices will be assessed using standard procedures.\(^{21-23}\) Peripheral quantitative CT will be used to measure muscle density (an indicator of fat infiltration within the muscle) and muscle cross-sectional areas of the lower limbs.\(^{21}\)

**QoL, prostate cancer-specific distress, overall psychological distress and PSA anxiety**

Health-related QoL will be assessed using the Medical Outcomes Short Form 36 (SF-36v2).\(^{25}\) A three-item cancer standardised anxiety scale developed by Latini et al\(^{18}\) will assess men’s fears about cancer recurrence. This scale has

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Figure 3  CONSORT diagram. CONSORT, Consolidated Standards of Reporting Trials.
previously been found to predict receipt of active treatment independent of PSA velocity in a sample of men on active surveillance. Overall cancer-specific distress will be assessed by the Impact of Events Scale revised which has been used extensively by our team and is valid and reliable in patients with prostate cancer. The Brief Symptom Inventory-18 will be used to assess psychological distress across the following domains: anxiety, depression, somatisation and global distress severity. Antidepressant use will be recorded. The Memorial Anxiety Scale for Prostate Cancer will be used to assess anxiety specifically focused on PSA testing (the PSA Anxiety Subscale).

Economic analysis
An alongside trial economic evaluation will be undertaken to assess the health benefits and additional costs compared with usual care. This will inform the relative value for money of exercise compared with other healthcare interventions in this group of men with PCa. Hospital resource use and associated costs will be obtained to assess costs for secondary healthcare for the exercise and usual care groups. All hospital events, including emergency department attendances, outpatient visits and procedures and inpatient admission for all causes will be sought. These data are important to identify potential PCa-related events as well as identifying total healthcare resource use. In addition, the costs for providing the exercise intervention will be identified through the study. Data on health benefits and costs will be adjusted for covariates such as age, key comorbidities (eg, diabetes), body mass index and so forth. Health benefits will be measured as quality of life via the SF-36v2 and converted to a health utility scale using the Australian SF-6D scoring algorithm. Costs associated with health resource use and the costs of the intervention will be standardised to a common year (eg, 2018). Incremental costs and benefits will then be estimated and reported as the incremental cost utility ratio (ICUR). The ICUR will be bootstrapped to identify the 95% CIs, probability the intervention is good value for money and the risk of anyone in the intervention group not being better off. Deterministic sensitivity analysis will be undertaken to identify the main drivers of the costs, outcomes and value for money.

Effect mediators
The Masculinity in Chronic Disease Scale will assess the extent to which men identify with six masculine values: strength; sexual importance/priority; family responsibilities; emotional self-reliance; optimistic capacity and action approach. This scale was developed for Australian men with prostate cancer; has strong evidence of validity in this target group and has been found to predict men’s help seeking. The General Self-Efficacy Scale will assess men’s perceptions that they can cope with stressful life events. This scale has been used widely internationally as a predictor of adaptation to adversity including cancer treatment effects.

Other measurements: physical function and physical activity levels
A battery of standard tests will be used to assess physical function: (1) 400m walk (aerobic capacity), (2) one repetition maximum for the leg press and chest press (muscular strength) and (3) repeated chair rise (lower body muscle function). Physical activity levels will be assessed objectively over a 7-day period using a validated, reliable triaxial accelerometer activity monitor (ActiGraph GT3X+). Self-reported physical activity will be assessed by the leisure score index from the Godin Leisure-Time Exercise Questionnaire.

Safety and monitoring
Patients will be monitored for any adverse events during training and testing by the exercise physiologists with study clinicians overseeing all aspects of patient management where required.

Exercise intervention
The exercise intervention will consist of supervised resistance and aerobic exercise performed over three sessions per week for 6 months in an exercise clinic setting. During months 7–12, the exercise intervention group will transition to once a week supervised exercise in a clinic for months 7–8, once every 2 weeks supervised exercise in months 9–10 and once per month supervised exercise in months 11–12. This step-down approach will include a self-managed exercise programme consisting of a booklet and training log with detailed information about the exercise prescription and how to implement in a variety of settings. Participants will be encouraged and supported to continue their aerobic and resistance exercise programme in their local fitness centre or other exercise facilities where they can maintain a high-quality exercise programme under their self-management. The self-managed exercise programme is designed to replicate the exercises performed in the supervised sessions and includes resistance, aerobic and flexibility exercises. Finally, from month 13 to 36, the exercise programme will exclusively consist of a self-managed programme and has been implemented by our group previously in a multicentre year-long trial in men with PCa on active therapy. The initial programme will be supervised by exercise physiologists in Perth and Melbourne.

The exercise programme is designed to provide optimal stimulus to the cardiorespiratory and neuromuscular systems while maximising safety, compliance and retention. The exercise sessions will be conducted in small groups of up to 10–12 participants exercising in pairs under direct supervision to ensure correct technique and minimise the risk for injury. Resistance exercise will involve 6–8 exercises that target the major upper and lower body muscle groups. Intensity will be manipulated from 6 to 12 repetition maximum (RM; ie, the maximal weight that can be lifted 6 to 12 times which is equivalent to ~60%–85% of 1RM) using one to four sets per exercise. The aerobic exercise component will include 20 to 30min of moderate to vigorous intensity cardiovascular...
exercise (~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. Participants will be encouraged to undertake additional aerobic exercise outside the clinic sessions with the goal of achieving a total of at least 150 min of moderate to vigorous intensity aerobic exercise each week. Exercise prescription will be progressive and modified according to individual response. Both moderate intensity continuous and high-intensity interval training will be implemented to provide greater variety and training stimulus. To reduce the possibility of boredom and over-reaching, the exercise programme will be periodised by cycling emphasis on intensity and volume. We have used this exercise prescription effectively in previous trials involving men with PCa and have reported significant improvements in quality of life, lean muscle mass, fatigue, aerobic capacity and physical function. The step-down approach to self-management is intended to maximise the translation of this intervention to best practice management of this patient population.

Usual care
The usual care group will receive an unsupervised walking programme and an educational booklet outlining the current national physical activity recommendation for cancer survivors along with a logbook to record their physical activity. During the study, both groups will be encouraged to maintain customary dietary patterns and the Mini Nutritional Assessment will be used to monitor nutritional status.

Calculation of sample size
The target sample size of 168 patients is based on having 80% power to be able to detect a HR of undergoing curative therapy in the exercise intervention group, compared with the usual care group, of 0.35 or smaller (alpha=0.05). This is equivalent to a difference between 25% of the usual care group undergoing curative therapy within 3 years postrandomisation versus <10% in the group undertaking the exercise intervention. A difference of this magnitude has been recommended by our practice clinicians to be clinically important. This sample size accounts for a possible 5% dropout due to clinical records not being available at study completion. This sample size will give us sufficient power to examine our secondary outcomes of interest. For example, for muscle mass we will have >80% power to detect differences between groups of 0.8 kg or greater at 6 months post-intervention, assuming an SD for change of ~1.5 kg and 30% loss to follow-up (due to the need for participants to represent to the study team for this outcome to be measured).

Statistical analysis
The primary outcome, initiation of curative therapy, will be analysed using Cox proportional hazards regression, with treatment group (exercise intervention/usual care) entered as the main effect. If data do not meet the proportional hazards assumption, the log-rank test will be used. Outcomes measured repeatedly will be analysed using mixed-effects models to examine differences between groups over time, with treatment group and time included as main effects, as well as an intervention-by-time interaction term. The patient will be included as a random effect to account for the non-independence of observations from the same participant. Continuous outcomes will be analysed using linear models, binary outcomes with logistic models and count outcomes with Poisson models. Depending on the balance between groups post-randomisation, clinically relevant covariates will be included in the models where appropriate. Data will be analysed using an intention-to-treat approach. Tests will be two tailed and an alpha level of 0.05 will be applied as the criterion for statistical significance.

ETHICS AND DISSEMINATION
Outcomes from the study will be published in peer-reviewed academic journals and presented in scientific, consumer and clinical meetings. The study investigators and trial coordinator will have access to the data.

DISCUSSION
PCa is a financial burden to men and their families and our health system. In 2008 and 2009, this was the top male cancer cost to the health system in Australia, totalling $A347 million or 14% of total male cancer expenditure.38 As PCa prevalence increases, the health system will find it increasingly difficult to prioritise care in the absence of clearly developed economic models. There is a deepening realisation by clinicians and patients that many prostate cancers do not require active treatment, and in fact, such interventions may result in devastating adverse effects. Already, a considerably large number of patients are referred for AS.7 51–53 Studies (including our previous work) examining the role of exercise in PCa provide strong evidence that beneficial effects are derived during or following definitive therapy and exercise has recently been included in the 2015 PCa Care Guideline: American Society of Clinical Oncology Clinical Practice Guideline.7 There is, however, no information on and evidence base for the efficacy of exercise medicine interventions during AS in slowing disease progression, reducing anxiety and distress and improving QoL. The study proposed here would be the first to determine the efficacy of a comprehensive exercise programme during AS in substantially delaying or preventing patient morbidity associated with PCa primary therapy. Savings to the health and medical system could be extensive with any delay in prostatectomy, radiation therapy or androgen deprivation therapy reducing costs of current overtreatment substantially. If proven efficacious in this stage of PCa management, exercise medicine could be immediately implemented as an important component of clinical best practice, at minimal
cost and with no side effects. This will dramatically reduce overtreatment, saving the patient considerable suffering, physical pain and possibly extending survival.

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