Resistance Exercise in Prostate Cancer Patients: a Short Review

Andrej Zdravkovic¹ · Timothy Hasenoehrl¹ · Richard Crevenna¹

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Abstract

Purpose of Review The aim of this paper is to provide an overview of recent findings concerning the utilization of resistance exercise (RE) in prostate cancer (PCa), in particular as pertaining to the management of cancer therapy side effects.

Recent Findings As of late, studies investigating the effects of RE in PCa patients have found positive effects on muscle strength, body composition, physical functioning, quality of life, and fatigue. The combination of RE and impact training appears to decrease the loss of bone mineral density. RE seems to be well accepted and tolerated, even by patients with bone metastatic disease, although a modification of the RE prescription is often necessary.

Summary In PCa patients, RE has been well-researched and the data are clear that it is beneficial in multiple ways. Future directions should look at the long-term effects of RE, including mortality and relapse, as well as implementation of exercise programs.

Keywords Resistance training · Exercise oncology · Prostatic neoplasms · Prostate cancer · Androgen antagonists

Introduction

The Impact of Prostate Cancer and Its Therapy

Prostate cancer (PCa) is one of the most common oncologic diseases worldwide [1] with an increasing incidence and prevalence especially in younger males [2]. In recent years, the mortality of PCa has improved in most countries for which data is available [3•]. The therapy for PCa, particularly for hormone-dependent variants, usually includes androgen deprivation therapy (ADT), and its side effects often present as loss of muscle mass, increase in fat mass, insulin resistance, sexual dysfunction and loss of libido, gynecomastia, hot flashes, anemia, fatigue and potentially increases in cardiovascular and metabolic disease risk [4, 5]. Due to the improving survival rates, the potential long-term side effects of ADT are steadily gaining the attention of the scientific community [6]. Recent studies suggest that only a minority of PCa patients

(PCaP) die of the malignant disease, the predominant cause of death being cardiovascular disease, among other comorbidities [7, 8]. Correspondingly, all-cause mortality increases with an increasing number of comorbidities in PCaP, whereas the disease-specific mortality remains relatively constant [8]. Consequently, the mitigation of the side effects of PCa therapy, which can largely be achieved by exercise, notably resistance exercise (RE), is a rapidly growing field of research.

History of Resistance Exercise in Cancer

After many years of recommendations to “rest and recover,” one of the earliest aerobic exercise (AE) interventions was reported in 1989, investigating the effects on body composition [9] and functional capacity [10] in breast cancer patients, paving the path for the emerging field of exercise oncology. Unfortunately, and most probably due to misconceptions of RE and hence the avoidance of the presumed risk of RE, the first studies investigating the effects of RE in cancer patients, regarding the risk of lymphedema in breast cancer patients [11] and the effects of moderate-intensity RE on the quality of life, body composition and muscular fitness in PCaP [12], were not published until 14 years later in 2003. Knowing the effects of RE in healthy subjects, PCaP on ADT seemed at the time to be the perfect target group for RE, meanwhile an assumption supported by ample evidence [13–15]. Indeed,

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✉ Richard Crevenna
richard.crevenna@meduniwien.ac.at

¹ Department of Physical Medicine, Rehabilitation and Occupational Medicine, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

the vast majority of studies investigating the effects of RE were conducted on PCaP receiving ADT. Specifically, RE alone or in combination with endurance exercise has been shown to improve the body composition, muscle strength, cardiovascular capacity, physical functioning and fatigue of PCaP [13–15]. Moreover, the first study on PCaP with bone metastatic disease was published in 2011 [16]. However, trials not excluding patients with bone metastatic disease, as well as those investigating the effects of free weight exercises, are still rare [13–15].

Current Approach to Resistance Exercise in Prostate Cancer Patients

General Resistance Exercise Recommendations

Although the influence of the modality, volume, intensity and frequency of RE has not been extensively studied in PCaP, there is little evidence to suggest that the physiological response to RE, albeit often blunted due to ADT, is fundamentally different to that of healthy older individuals [17]. The exercise guidelines for cancer survivors published in 2019 recommend performing at least two sets of 8 to 12 repetitions at 60–75% of the one repetition maximum two to three times per week [18•]. This recommendation is only slightly more conservative than that for healthy novice trainees [19]. According to recent meta-analyses, training volume seems to be the primary driver of muscle hypertrophy, irrespective of training intensity, provided the sets are performed until failure [20, 21]. However, the local muscular fatigue induced by low intensity contractions to failure might be more pronounced in older individuals [22, 23], conceivably leading to lower training volumes than would be accumulated with moderate- or high-load RE. In addition, high-load RE may be superior in improving functional performance than low-load RE, as measured by 30-second chair stand performance, arm curl and grip strength [24]. Finally, research suggests that PCaP report higher training intensities than objectively measured [25], indicating a need for objective measurement of the administered training intensity, in order to provide effective stimuli.

Furthermore, protein supplementation should be considered in PCaP not suffering from chronic kidney disease, considering that the protein requirements of older adults may exceed the recommended amounts [26, 27] and given the synergistic effect of RE and protein supplementation across varying supplementation protocols [28•]. Research on healthy adults supports spreading protein intake evenly throughout the day, with possible additional benefits of pre-sleep supplementation of slow-digesting protein, such as casein [29]. Creatine monohydrate supplementation should be considered as well, as it augments the response to RE [30, 31•].

In practice, PCaP are not treated differently than healthy older adults, apart from a targeted approach to mitigating disease-specific needs and the consideration of disease-specific risks. In our clinical experience, PCaP profit from patient empowerment and should be encouraged to perform their preferred mode of RE, provided that the principles of progressive overload are followed [19]. This is typically achieved by incremental increases in training intensity in the early stages of an RE intervention, as motor learning and neural adaptations take place [32, 33]. Once a plateau is reached, the training frequency, and thus the training volume, is increased [20, 34]. After a training frequency of three times per week is established, further progress is accomplished by an increase in the training volume [19, 20], either by the addition of sets or supplementary exercises. This practical approach is summarized in Table 1.

Disease-Specific Goals

Although often confounded by older age, the negative effects of ADT on muscle strength, body composition, metabolic risk, bone health, physical functioning, fatigue and sexual health are well documented in the literature [5]. In addition, other PCa treatment options, such as surgery and radiotherapy, are often undertaken prior to beginning ADT and have been associated with urinary incontinence (UI), decreased sexual health and a reduced quality of life [38, 39].

As many of these treatment side effects are, at least in part, attenuated by RE, a concise overview of disease-specific goals of RE in PCaP is warranted.

Improving Muscle Strength and Body Composition

Significant increases in muscle strength and muscle mass with a concurrent decrease in fat mass have been found in PCaP [15, 40], as well as in patients with sarcopenic obesity [41] undertaking RE. Although the basic principles (progressive overload and exercise specificity) were followed in the majority of studies on PCaP, the optimal training method has yet to be determined [42]. Whether free weight training offers additional benefits for muscle strength and mass is not clear, with a single study finding a greater effect of free weight training on gains in triceps and leg strength in older adults [43•].

Improving Bone Health and Reducing Fall and Fracture Risk

The data on the effects of RE on bone mineral density (BMD) is heterogeneous, possibly due to different training methods used and differing responsiveness of the spine and femur to stimuli [44]. It is also possible, that BMD underestimates the extent of the adaptation of bones to loading [45]. Notwithstanding the above, research seems to indicate that

Table 1 Practical approach to strength training in prostate cancer patients. *PCa* prostate cancer, *RM* maximum resistance that can be used for a given number of repetitions, *PFM* pelvic floor muscle

Exercise testing	Resistance exercise modality	Warm-up	Frequency	Intensity	Training volume	Complementary measures	Additional comment
-Consider testing for common symptoms of PCa and its therapy [18•]	-Full body training, preferably implementing multiple-joint exercises, if feasible [19].	-Start each exercise by performing one or more sets with a lighter resistance prior to beginning work sets.	Begin with two training sessions per week, add one session when progress stagnates	Begin at 60% of the 1RM, increase up to 80% depend-ing on tolerance [19]	Begin with two sets of 15 to 20 repetitions, decreasing to 8 to 12 repetitions with increasing load. After increasing training frequency, add up to two sets before adding complementary exercises	-Consider supplementing protein to reach at least 1.2 g/kg bodyweight [27, 28•]	-For patients with an increased risk of falls, consider balance training [35•].
-Exercise testing for patients with a history of cardiovascular, renal and metabolic symptoms [18•]	-Otherwise, prescribe exercises targeting all major muscle groups.	-Consider non-specific warm-up, e.g., 5–10 min of low-intensity aerobic exercise		-If the 1RM cannot be determined, begin with 20RM, progress to 8RM		-Consider supplementing approximately 5 g of creatine monohydrate per day [30, 31•]	-For patients with urinary incontinence, consider PFM training [36•]
-Obtain medical clearance for patients with cardiopulmonary disease, bone metastatic disease, after abdominal/lung surgery and ostomy, worsening physical condition and severe fatigue or malnutrition, consider referral to specialist treatment left [18•]	-Take pre-existing musculoskeletal issues into account						-For patients with osteoporosis, consider impact training [37•]
	-Prevent loading parts of skeleton affected by metastatic disease, taking co-contraction of muscles in other areas into account (e.g., abdominal wall muscles during leg press)						
	-Ensure proper breathing, avoiding the Valsalva maneuver						

interventions lasting at least 6–8 months and utilizing training intensities of at least 80% of the one repetition maximum are necessary to improve, or at least mitigate the loss of, BMD, with the spine being more responsive than the femoral neck [44, 46•]. Furthermore, free weight training might be superior to machine training in improving the BMD in the thoracic spine [47]. In PCaP on ADT, RE has been shown to positively affect BMD only in combination with impact training [13, 46•]. This finding is in line with research on postmenopausal bone loss [48].

The reduction of fall and thereby fracture risk by RE is even less straightforward, nonetheless is RE an integral part of the exercise prescription for reducing fall and fracture risk, alongside balance and impact training [37•]. Indeed, the American Society of Clinical Oncology recommends RE for cancer survivors, especially those at greater risk of falling [49•]. The main driver of the reduction of fall risk may be balance training; however, such programs are usually combined with RE [35•].

Improving Physical Functioning and Reducing Fatigue

Physical functioning, assessed by functional tests, is improved by RE in PCaP [15]. This is in line with data on older adults,

which indicates improvements in physical ability, getting out of a chair and gait speed, with a significant reduction of pain in osteoarthritis patients [50]. Although the optimal method has yet to be determined, free weight training specifically might provide certain benefits for the elderly, as related to the performance of certain functional tests (chair stand, pan carry) [51].

The underlying mechanism in the development of cancer-related fatigue is most likely multifactorial, with inflammation playing a significant role [52, 53]. Research suggests that the positive effects of exercise are induced, at least in part, by the changes in levels of muscle-derived interleukin-6 and down-regulation of tumor necrosis factor alpha and interleukin-1 beta [54, 55]. Patients suffering from cancer-related fatigue seem to benefit most from a combination of RE and AE, alongside other non-pharmacological interventions [56, 57]. In isolation, RE seems to be more effective than AE [58].

Improving Cardiovascular Risk Factors

Exercise interventions in general tend to improve cardiovascular risk factors in PCaP [59•]. The effects of RE in particular are inconclusive in this patient population, which might be a result of the negative effects of ADT or of an insufficient duration of RE interventions [42]. In healthy adults,

medium- and long-term RE interventions have produced positive effects on blood pressure, fasting insulin levels and insulin resistance [60], with the latter two most probably owing predominantly to the improvement in body composition.

Decreasing Incontinence

Due to high efficacy, pelvic floor muscle (PFM) training is the primary form of therapy for UI in PCaP after radical prostatectomy [36]. Although general exercise may have a positive effect on the strength of PFM [61], the high prevalence of UI in female powerlifters [62] suggests that RE in isolation might not be sufficient to prevent UI. Although female athletes profit more from PFM training than non-athletic women [63], the question, whether RE and PFM training have a synergistic effect, especially in relation to PCaP, remains to be answered.

Improving the Quality of Life

In PCaP, positive effects on the quality of life have mostly been found in studies implementing a combination of RE and AE [64], corresponding to findings in breast cancer patients [65]. However, the quality of life has been described as the parameter least responsive to exercise interventions in the latter population [66]. In the studies investigating the effects of RE in PCaP, the quality of life was usually measured as a secondary outcome, implementing a number of questionnaires, such as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires Core-30 and Prostate-25, Medical Outcomes Study Questionnaire Short Form36, Functional Assessment of Cancer Therapy-General and -Prostate, and the Patient Oriented Prostate Utility Scale-Psychometric. In view of the heterogeneity of intervention parameters and a potentially small effect size, it is difficult to ascertain the optimal method for this purpose.

As an important component of the quality of life, sexual health has received little attention in PCaP [13]. Although some aspects of sexual health have been reported to improve by the implementation of RE, further appropriately designed studies are necessary to ascertain the effects of RE on sexual health [13].

Disease-Specific Risks

The current consensus states that RE is generally safe for cancer survivors, even though adverse events might be under-reported in the literature [18]. This is similar to the findings in healthy older adults [50]. In a recent study on cancer patients undergoing cancer treatment, the combination of RE and AE was well tolerated, with the vast majority of adverse events consisting of minor musculoskeletal complaints [67]. However, it is worth noting that pain associated

with knee osteoarthritis, a condition typically exacerbated by exercise, is mitigated by RE [68].

Although medical clearance is not recommended for all PCaP beginning gradually progressive RE, as it would pose an unnecessary barrier to exercise, evaluation by a physician is indicated in patients suffering from comorbidities including (but not limited to) cardiopulmonary disease, bone metastatic disease, worsening physical condition and severe fatigue or malnutrition [18]. In order to remove the barriers to RE, the most dreaded potential complications of RE in PCaP are elaborated on below.

Risk of Pathologic Fractures

Approximately 70% of advanced PCaP develop bone metastatic disease, in the form of either osteoblastic, osteolytic, or mixed lesions [69]. Although the overall appearance of osteoblastic lesions suggests areas of increased density, the newly formed, radio-dense tissue consist mostly of immature bone and is prone to mechanical failure [69, 70]. These findings are especially troubling considering the reduced BMD in PCaP on ADT [71]. The prevalence of skeletal-related events is high in patients with metastatic castration resistant PCa and the risk thereof is increased by high baseline prostate-specific antigen, a high number of metastatic lesions, rapidly increasing prostate-specific antigen and progression of PCa [72].

Conversely, RE interventions have been successfully administered in PCaP with bone metastatic disease [16, 73, 74]. Bone metastatic disease should therefore not be seen as an insurmountable obstacle to clinically supervised RE, provided the avoidance of direct loading of affected bones [75]. Concurrent contraction of antagonistic, often stabilizing, muscles should also be taken into account, as the resulting forces on the bone may be considerably increased [76, 77].

A number of scores have been developed in hope of quantifying the fracture risk in bone metastatic disease, such as Mirels' score for long bones [78] and the Spinal Instability Neoplastic Score for the spine [79]. However, the reliability of these scores remains a matter of considerable debate [80] and the referral of afflicted patients to trained personnel is recommended [18•].

Risk of Cardiovascular Events and Hypoglycemia

During RE, the systolic and, to a lesser extent, diastolic arterial blood pressure increases significantly, this response being magnified by the Valsalva maneuver [81]. The magnitude of the increase, however, seems to correlate more with the relative load lifted, rather than the absolute load, with bilateral exercises being more potent than unilateral exercises [82]. Interestingly, in people with hypertension, the systolic blood pressure may increase significantly more when performing a set to failure with 40% of the one repetition maximum, than

with 80% [83]. The Valsalva maneuver, consisting of (attempted) forceful expiration against a closed glottis, seems to increase muscle activation and thus strength, yet possibly not to a greater extent than forceful expiration [84].

Training experience also seems to play a role in the cardiovascular response to RE, with experienced trainees displaying a blunted increase in the systolic blood pressure, compared to novices [85]. Correspondingly, the American Heart Association does not recommend exercise testing prior to initiating RE for people with stable medical conditions, provided the participants begin with a low to moderate intensity of RE [86]. Nevertheless, most recommendations concerning testing prior to initiating exercise seem to be based on findings in AE [87].

In people with hypertension, RE appears to be safe, with pre-exercise testing recommended for people with known disease [88]. However, in a recent systematic review and meta-analysis on the effects of RE in people with coronary heart disease, although presumably under-reported, 63 of 64 cardiovascular adverse events were associated with complementary AE and exercise testing, not RE [89]. Furthermore, in patients with heart failure, RE appears safe, as it does not result in reduced cardiac function, while effectively improving oxygen uptake [90]. In cancer survivors, even high intensity AE and RE were associated with a low risk of adverse events [91•].

The risk of hypoglycemia has not been investigated thoroughly in PCaP. It should be noted, however, that it does not seem to be excessive in patients with type 2 diabetes, although studies investigating this topic are rare [92]. In individuals with impaired fasting glucose, RE appears to exert an acute, volume- and intensity-dependent lowering effect on fasting blood glucose [93]. Concerning longer interventions in patients with type 2 diabetes, AE and RE seem to bear a similar risk of hypoglycemia [92].

Risk of Worsening Lymphedema

Lower extremity lymphedema is a rare complication of the surgical treatment of PCa, occurring in approximately 4% of PCaP after extended pelvic lymph node dissection [94]. Whether lymphedema can be exacerbated by RE has as of date not been investigated in PCaP. In breast cancer patients, RE does not seem to exacerbate upper extremity edema, potentially even decreasing it [95•]. The exercise recommendation regarding lower extremity lymphedema includes light AE and strengthening the calf muscles [96]. In addition, general recommendations for the therapy of secondary lymphedema in cancer patients include RE [97].

Conclusions

In PCa patients, RE has been well-researched and the data are clear that it is beneficial in multiple ways. Future directions

should look at the long-term effects of RE, including mortality and relapse, as well as implementation of exercise programs.

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Declarations

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- Of major importance

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