

## Literature Review

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# From fatigued to fit: an investigation of the impact of physical exercise in the management of radiotherapy-induced fatigue in prostate cancer patients

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## Abstract

**Aim:** The aim of this paper is to investigate the effectiveness of physical exercise in managing fatigue during radiotherapy for prostate cancer patients. It explores the impact of various physical exercise regimes and their role in the prevention and management of fatigue to help inform best practice.

**Method:** A literature search was conducted on OVID Medline database with a follow-up search on google scholar to include relevant references found during the initial search. Relevant systematic reviews and randomised controlled trials (RCTs) arising from this search were reviewed.

**Findings:** There is evidence to support the notion that physical exercise in all its forms is an effective and safe intervention for fatigue management for prostate cancer patients undergoing radiotherapy. Although widely studied, there is limited evidence of fatigue management strategies being clearly implemented into current radiotherapy practice for patients with prostate cancer. This information is essential to enable therapeutic radiographers to educate prostate cancer patients regarding effective exercise strategies and ensure that fatigue is managed optimally.

**Conclusion:** Further research is required into the optimum physical exercise prescription to reduce radiation-induced fatigue, and standardised best practice guidelines should be developed nationally. A future move toward patient education into physical exercise and wellbeing should be a central component of the therapeutic radiographer role with specialist advice offered by review radiographers, empowering patients to become more physically active during treatment. Therapeutic radiographers have a unique opportunity to educate and promote physical exercise through a holistic wellbeing approach that aims to mitigate fatigue and improve quality of life.

## Introduction

Prostate cancer has become the second most common cancer in men and the fifth most common cause of death worldwide.<sup>1</sup> In the United Kingdom alone, there were approximately 48,500 new diagnoses of prostate cancer annually between 2015 and 17.<sup>2</sup> Due to medical and technological advances, the treatment for prostate cancer has become a multi-modality approach. Treatment regimens vary depending on prostate cancer risk factors, including gleason score, staging and prostate specific antigen (PSA) score.<sup>3</sup> Radiotherapy alone, or with androgen deprivation therapy (ADT), is widely used as a primary treatment<sup>4</sup> with more than 30% of all men diagnosed, receiving radiotherapy.<sup>5</sup>

Radiotherapy has been clinically established to significantly improve prostate cancer survival rates.<sup>1</sup> However, despite its known benefits, radiotherapy is associated with various life changing adverse side effects. Fatigue is often reported as the most common radiotherapy-induced side effect, with up to 80% of cancer patients reporting increased fatigue during and after treatment.<sup>6</sup> Fatigue can be defined as a multifaceted, persistent, subjective, psycho-physical level of exhaustion that is not alleviated by rest.<sup>7–9</sup> This review was undertaken in order to investigate the effectiveness of physical exercise in managing fatigue during radiotherapy for prostate cancer.

## Methods

A literature search was conducted on OVID Medline database using the following search terms within the title;

‘Prostate’ AND ‘Radiotherapy OR Radiation Therapy’ AND ‘Exercise OR Fatigue OR Physical Activity OR Lifestyle’.

English language restrictions and date limitations were applied (2000–20), and 46 potential articles were identified. A number of these articles were deemed not relevant due to being murine studies or predominantly exploring areas like cost analysis. Google scholar yielded additional studies identified through the 46 articles. This overview focuses on findings from systematic reviews with/without a meta-analysis and randomised controlled trials (RCTs) as these form the top level in the hierarchy of quality evidence available.<sup>10</sup> The main purpose of this investigation is to explore the impact of exercise on radiotherapy-induced fatigue in patients with prostate cancer.

## Findings

### Fatigue

A literature review into radiotherapy-induced fatigue by Jereczek-Fossa et al.<sup>6</sup> states that fatigue can affect a patient's wellbeing more than any other treatment-related side effects, with many prostate cancer patients ranking fatigue as being more impacting to their quality of life than lower urinary tract symptoms (LUTS). Research by Aghili et al.<sup>11</sup> supports this statement, finding that patients viewed fatigue more adversely impacting than pain, sexual dysfunction and other treatment side effects. Vashistha et al.<sup>12</sup> found that fatigue impacts physically, physiologically and psychologically, and is the major contributor to poor quality of life in cancer patients.

Although widely researched, the cause and prevalence of radiotherapy-induced fatigue are not fully understood and commonly underestimated by health care professionals.<sup>6,13–15</sup> Kinney et al.<sup>14</sup> state that fatigue is common, yet it is under-recognised and under-treated, leading to patients becoming isolated, less active and physically deconditioned, contributing to the exacerbation of fatigue levels during treatment. Within current literature, there is limited evidence to support current 'standard care' for fatigue management. Patients experiencing fatigue are frequently advised to rest and avoid strenuous physical activity. However, new research has found this to be counterproductive and potentially detrimental to patients' quality of life.<sup>1,16</sup> Prolonged inactivity in prostate cancer patients due to treatment causes declined physical functioning and reduced fitness, which, in turn, negatively impacts quality of life. Evidence by Monga et al.<sup>17</sup> reports fatigue incidences ranging from 68 to 100% in prostate cancer patients undergoing radiotherapy. Due to the huge impact fatigue has on patients' quality of life, Aghili et al.<sup>11</sup> state that it is imperative to find a non-invasive, non-pharmacological cost-effective solution to fatigue management.

### Exercise

Exercise is renowned for its multitude of physical and physiological health benefits, while reducing feelings of depression and benefiting cognitive function, resulting in improvement to overall wellbeing.<sup>18,19</sup> New knowledge and understanding into the benefits of exercise have unearthed a growing interest in the potential of prescribed exercise therapy, especially in cancer patients. Although most studies focus on breast cancer, some studies have reviewed the potential impact of exercise on radiotherapy-induced fatigue in prostate cancer patients.

A comprehensive systematic review of 13 RCTs involving 1,057 prostate cancer patients across multiple centres was undertaken by Vashistha et al.<sup>12</sup> into the effects of exercise on fatigue. This review reported that 96% of patients involved in these studies experienced

radiotherapy-induced fatigue. Adopting the Cochrane Collaboration tool for risk of bias assessment, the authors highlighted that ten of the 13 eligible trials had a high risk of bias with seven having poor attrition rates. Many of these studies had limited descriptions of the interventions and selective reporting in favour of their primary objective. However, this review concluded, from the combined evidence, that exercise interventions did improve radiation-induced fatigue and quality of life in prostate cancer patients.

Drouin & Beeler's review<sup>18</sup> of exercise and urology cancers also concludes that exercise has the potential to positively impact patients' physical and physiological wellbeing, stating that exercise would provide unique benefits in the management of treatment side effects and may be necessary in the prevention of fatigue. However, research into the most effective exercise programme is still under debate, with trials focusing on various training aspects, such as exercise type, intensity, frequency and duration. Although most studies have focused on Aerobic training and Resistance training, alternative exercise traditions, such as Pilates, Yoga, Tai Chi and Qigong, have recently become more popular in fatigue management exploration.

### Aerobic exercise

The majority of research studies explore the use of aerobic exercise programmes for fatigue management. This is mainly due to the simplistic nature of aerobic exercise, as it is defined as any type of cardiovascular conditioning, such as walking, running, or cycling.<sup>19</sup> Such exercises can be seamlessly implemented into daily routine without major impact. This training depends primarily on the aerobic energy generating process, which involves oxygen, and can be of low to high intensity.<sup>19</sup>

A prospective RCT carried out by Windsor et al.<sup>16</sup> focused on the impact of a 4-week aerobic exercise programme on radiotherapy-induced fatigue in prostate cancer patients. The study included a cohort of 66 men undergoing prostate radiotherapy, 33 being placed in a control group and 33 in an aerobic exercise intervention group. The exercise intervention employed was a 4-week home-based, moderate intensity, continuous 30-minute walking programme, three times per week. Patients in the control group were given standard advice to rest if they became fatigued and continue with daily activities. Windsor et al.<sup>16</sup> conducted a robust study with a definitive result in favour of aerobic exercise in the prevention and management of fatigue. However, this study fails to address its limitations including being a single centre study, which only illustrates the results of a small sample of patients. Furthermore, patients enrolled into this study mainly had a diagnosis of early stage prostate cancer, hence may be in a better physical condition than those with more advanced prostate cancer, and therefore, findings may not be generalizable to all prostate cancer patients.

A review of current literature by Luan et al.<sup>20</sup> into exercise as a prescription for various diseases supports the findings of Windsor et al.<sup>16</sup> One hundred eighty-eight articles reporting on RCTs were included for data analysis with the primary focus of exercise intervention. Luan et al. state that aerobic exercise for prostate cancer patients increases activity levels, improves cardiovascular health and reduces fatigue. They describe a walking programme, by Pernar et al.,<sup>21</sup> which is similar to that of Windsor et al.,<sup>16</sup> which concluded that implementing 10,000 steps per day has an overall positive impact on patient fatigue during treatment. This review also promotes the clinically significant role of exercise therapy as a fatigue management strategy. However, this review does not

solely focus on prostate cancer, and it is not clear how many prostate cancer studies were used in the findings and if counter arguments were addressed.

An RCT carried out by Monga et al.<sup>17</sup> reviewed the impact of an 8-week supervised cardiovascular conditioning programme on fatigue prevention and quality of life improvement in men with localised prostate cancer undergoing radiotherapy. This two-armed, single centre study included 21 men, enrolled in either a prevention group or 'standard care' group. In comparison with Windsor et al.'s<sup>16</sup> self-directed home-based programme, Monga et al.'s intervention group participated in a structured programme led by a kinesiologist and supervised by a physician. Pre- and post-radiotherapy main outcome measures were recorded including fatigue, cardiac fitness, depression, physical functioning and social wellbeing. It was noted that no significant difference between groups was recorded prior to radiotherapy. However, clinically significant improvements were documented in the exercise intervention group post-assessment. Monga et al. concluded that the implementation of a cardiovascular exercise programme can prevent fatigue and improve quality of life; however, due to their small cohort of patients, the results of their study were limited and cannot be generalised.

Overall, more research is required to establish the extent of the benefits of aerobic exercise for patients with prostate cancer, especially those with more advanced disease.

### Resistance exercise

Resistance exercise, defined as exercise that focuses on improving muscular strength and endurance,<sup>22</sup> has also received some investigation. This exercise can take many forms, including traditional weightlifting, bodyweight exercises or resistance band exercises.<sup>22</sup>

Segal et al.<sup>23</sup> carried out an RCT of usual care versus resistance versus aerobic exercise in men undergoing radiotherapy for prostate cancer. This three-armed, single-centre study was carried out over a 3-year period and incorporated 121 men. The primary endpoint was the comparison of fatigue between groups. The 'Functional Assessment of Cancer Therapy–Fatigue scale' assessed fatigue levels at baseline, 12 and 24 weeks. Data from this study showed that both training regimes mitigated acute fatigue, but resistance training also produced long-term improvements in patients' fatigue and quality of life. Segal et al. state that the strengths of this trial include a large sample size, a well-defined population, supervised exercise regimes and a comprehensive assessment of endpoints, highlighting that supervised exercise regimes have the added benefit of high levels of patient compliance, providing rigor and reliability. However, despite being of high methodology quality, this study has weaknesses that have not been addressed. The sample size, although quoted as large, is relatively small on a global scale, with a heterogeneous group of patients. Though primary endpoints were regularly assessed, a self-assessment tool was used, which is open to subjectivity. Overall, this study does find correlations between exercise and reduced fatigue, and authors do support the use of structured exercise regimes for prostate patients undergoing radiotherapy as a mechanism for fatigue prevention. This study also highlights the superior, favourable long-term effects of resistance training that previous studies fail to address.

A systematic review of 17 RCTs by Menichetti et al.,<sup>24</sup> looking at various lifestyle interventions to improve quality of life in men with prostate cancer, supports results by Segal et al.,<sup>23</sup> in the use of resistance training. Although this review looked at various lifestyle

interventions, it was noted that exercise was the most frequently implemented non-medical intervention and showed the most positive results compared to diet and combined interventions. Menichetti et al. found that in most studies, resistance training yielded the most positive effects, significantly improving fatigue, physical functioning and wellbeing when compared to aerobic exercise. However, the main limitation of this study was the variation in the quality of trials included; therefore, primary endpoints, although in favour of resistance exercise, are restricted.

Three hundred ninety-two participants were explored in a systematic review by Horgan et al.,<sup>1</sup> into exercise during radiotherapy for prostate cancer patients. Horgan et al. found exercise to be effective in preventing fatigue but concluded that the impact of exercise on quality of life was not significant. Due to limited evidence, it was not feasible for Horgan et al. to analyse effects of resistance training in depth. However, like Segal et al.,<sup>23</sup> this review does conclude that post-treatment results showed resistance training to be more advantageous in fatigue management when compared to control groups and aerobic exercise. This study also addresses the benefits of supervised programmes, alluding to better patient compliance. Although a large sample size was used for this study, inter-study samples were relatively small and focused on single exercise interventions and regimes. This limits results of comparison exercise interventions, and therefore, as with previous studies, a clear superior exercise programme cannot be definitively concluded.

### Alternative exercise

In recent years, there has been a surge of interest in alternative exercise traditions as methods of rehabilitation and symptom management for cancer patients. Movement-based mind-body practices, such as Yoga, Tai Chi and Qigong, could improve treatment side effects and enhance physical functioning and overall quality of life.<sup>18</sup>

Ruddy et al.<sup>25</sup> state that yoga is the most popular and scientifically studied alternative exercise regime. Again, studies in research mainly concentrate on breast cancer with research data supporting the use of yoga to benefit prostate cancer patients, being limited. A review of current RCTs in the use of alternative exercise methods by Ruddy et al.<sup>25</sup> did conclude significant benefit of yoga for fatigue and quality of life in cancer patients. This study characterises yoga as a versatile, non-strenuous alternative to traditional physical activities previously discussed, which is individually adaptable to each patient's ability, regardless of physical status and can aid in symptom management such as fatigue. This type of exercise does show benefit; however, more research is required at different cancer sites before implementation.

Tai Chi and Qigong are low-impact meditative mind-body exercise interventions that improve holistic wellbeing.<sup>4</sup> McQuade et al.<sup>4</sup> conducted an RCT where 76 patients with localised or advanced prostate cancer were split into three groups; a control group, a light resistance exercise group and a Qigong/Tai Chi group. Outcome measures included sleep duration and fatigue for a period of 3 months post-radiotherapy. This study concluded that the Qigong/Tai Chi intervention increased sleep duration temporarily but did not have a significant impact on fatigue levels. Strengths of this study include high adherence to activities throughout the study period, but a limitation was that it excluded those with physical walking disabilities, and therefore, the findings may not apply to all patients with prostate cancer. This study was also relatively small in terms of population size. Campo et al.'s<sup>26</sup> small RCT with 40 prostate cancer patients

randomised patients into either 12 weeks of Qigong or stretching exercises. In contrast to McQuade et al.'s results, they found that the Qigong group had significantly improved fatigue levels compared to the stretching exercise group. The difference between these two studies findings may be attributable to the differences in baseline fatigue with McQuade et al.<sup>4</sup> describing their participants as having generally mild fatigue at baseline, while Campo et al.'s study only included patients who had a minimum threshold level of fatigue. A ceiling effect may have occurred with McQuade et al.'s results where differences in outcomes were harder to detect due to their favourable baseline score.

Kinney et al.,<sup>14</sup> the team involved in Camp et al.'s previous study, are currently conducting an ongoing large, multi-centre, three-armed clinical trial reviewing the biobehavioural effects of Tai Chi in men with prostate cancer compared with body training and usual care. Although this is an ongoing area of study and the results to date are not conclusive, Kinney et al. hypothesize that the use of alternative exercises may be valuable for treatment of fatigue in prostate cancer patients due to its low intensity and suitability for all age groups regardless of prior activity level. Considering this aspect, Tai chi or Qigong could bridge the gap as an exercise programme that is potentially suitable for all prostate patients irrespective of stage, age or physical ability.

## Discussion

Therapeutic radiographers undertaking the on-treatment review of prostate cancer patients routinely experience the requirement for an increasing focus and discussion regarding holistic patient wellbeing and fatigue management. Radiotherapy-induced fatigue is discussed on a regular basis, yet there remains less clarity into the specific management strategies that might be adopted. Patients may find walking or gym exercises of benefit when managing fatigue but are cautious when undertaking physical activity as no clear guidance is being strongly promoted, and some doubt may remain into what is and what is not considered as safe exercise practice. The guidance provided by therapeutic radiographers, to prostate cancer patients receiving radiotherapy, is often relatively simplistic and non-specific.

Prostate Cancer, UK, along with numerous high quality radiotherapy centres, advises patients to only add light exercise during radiotherapy in the form of short walks<sup>27,28</sup> and to rest when needed,<sup>27-30</sup> though some departments may also provide a booklet demonstrating simple exercise programmes.<sup>30</sup> However, an abundance of evidence from the literature demonstrates that physical exercise in its many forms is considered beneficial to the holistic wellbeing of the patient, including both low and high impact options. There is a growing body of evidence to suggest that resistance exercise is more beneficial than aerobic exercise alone, though the impact of alternative exercises on fatigue is yet to be fully established.

Therapeutic radiographers are well positioned to guide patients' holistic care plan and should be key healthcare professionals in the development and provision of information regarding optimal exercise initiatives during radiotherapy.<sup>31</sup> A national strategy is required in order to change the current standard of care for fatigue management in prostate patients receiving radiotherapy in the United Kingdom. This would involve the production of national guidelines alongside the development of both undergraduate and postgraduate education in order to provide the knowledge and skills necessary to aid this transition in care. Individual patient assessments and plans could then be developed

in order to minimise the effects of radiotherapy on fatigue and ultimately improve quality of life. Patient education and exercise promotion during radiographer led reviews and treatment information sessions could empower patients to become more proactive in self-managing fatigue.

## Conclusion

Exercise therapy undeniably has an important role to play in preventing radiotherapy-induced fatigue in prostate cancer patients, with all studies favouring exercise over current standard care. However, more extensive research on a global multi-centre scale is required into which exercise regime is best in alleviating radiotherapy-induced fatigue in prostate patients, specifically exploring parameters, such as frequency, intensity and duration.<sup>32</sup> Future studies should also consider acute and long-term adaptations from exercise prescriptions in prostate patients treated with radiotherapy.<sup>32</sup>

An approach incorporating physical activity within the radiotherapy department, as part of patient treatment preparation, should become standard care. Therapeutic radiographers have an opportunity to promote exercise as a safe, effective, non-pharmaceutical approach to fatigue management in prostate cancer patients undergoing radiotherapy.<sup>33</sup>

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