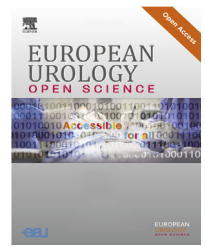


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European Association of Urology



## Review – Prostate Cancer

# Fatigue in Prostate Cancer: A Roundtable Discussion and Thematic Literature Review

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### Abstract

**Context:** Cancer and its treatments cause fatigue in up to 90% of men with advanced prostate cancer. As men with prostate cancer are surviving longer, cancer-related fatigue is becoming increasingly important for clinicians to understand and proactively manage.

**Objective:** The aim of this work is to identify knowledge gaps that may support healthcare professionals to recommend personalised fatigue management strategies. **Evidence acquisition:** This manuscript is based on a roundtable discussion held during the European Association of Urology 2022 Annual Symposium, combined with a review of the literature. Five core themes were generated from the roundtable: (1) meaning of fatigue in prostate cancer patients, (2) impact of fatigue, (3) association between fatigue and treatment selection, (4) benefits of managing fatigue, and (5) barriers to exercise.

**Evidence synthesis:** Cancer-related fatigue has complex underlying aetiology and is a subjective experience that may be under-reported. Some studies have shown that techniques such as education, cognitive behavioural therapy, guided imagery, and progressive muscle relaxation can result in clinically meaningful improvements in fatigue. However, the largest body of evidence, and a theme echoed in the roundtable discussions, was the benefit of exercise on fatigue. Despite the benefits of exercise, for some men, objective barriers to exercise exist and knowledge of benefits does not automatically translate into implementation and adherence.

**Conclusions:** Understanding the specific health needs of individual patients and their desired health outcomes is essential to identify personalised strategies for minimising fatigue. As an outcome of the roundtable meeting, we developed a quick reference guide for healthcare providers. A high-resolution copy can be downloaded from <https://patients.uroweb.org/library/fatigue-in-prostate-cancer-patients-guide/>.

**Patient summary:** This article is based on dialogue between a group of specialists, patients, and caregivers, which took place at a roundtable meeting during the European Association of Urology 2022 Annual Symposium. The group discussed how healthcare providers can best support their patients who experience fatigue.

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The group subsequently developed a guide to help healthcare providers during appointments.

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## 1. Introduction

Prostate cancer remains one of the most common cancers diagnosed in men and the fifth leading cause of death worldwide (Supplementary material [S1,2]) [1]. Increased survival rates for men with metastatic disease have been achieved with intensified treatment [2], which can exacerbate the mental and physical challenges of living with advanced disease. Androgen deprivation therapy (ADT), the mainstay of therapy for metastatic disease, has been shown to significantly increase overall survival (Supplementary material [S3]) [3]; yet, it is also known to cause metabolic complications including cardiovascular disease, obesity, and diabetes (Supplementary material [S4]) [4]. ADT is more likely to cause fatigue than surgery or radiation alone even when used to treat localised prostate cancer (Supplementary material [S5,6]) [5,6].

Cancer-related fatigue is often cited as the most distressing side effect for patients (Supplementary material [S7]) [7,8], affecting up to 90% of patients with advanced prostate cancer [1,8,9]. It is defined as a “distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment, that is unrelated to recent activity and which interferes with usual functioning” [10].

Cancer-related fatigue is a multifactorial phenomenon, with symptoms ranging from physical effects such as reduced energy and motivation levels, to impaired cognitive abilities, worsened emotional state, and adversely affected mental health (Supplementary material [S8,9]) [1,6]. ADT often causes fatigue that is persistent and often intertwined with depression and insomnia [11]. These adversely impact a man’s ability to work and carry out daily activities, thereby negatively affecting his personal relationships and overall quality of life (Supplementary material [S10]) [12]. As men with prostate cancer are surviving longer, side effects of treatment, such as cancer-related fatigue, are becoming increasingly important to understand and manage, as these may disrupt the lives of prostate cancer patients more than the cancer itself (Supplementary material [S10]) [5,12].

To support urologists and oncologists in managing cancer-related fatigue in prostate cancer patients, the European Association of Urology held a roundtable discussion during their annual congress in July 2022, to understand the meaning of cancer-related fatigue and how it impacts their prostate cancer patients. The roundtable included two urologists, two prostate cancer patients, one caregiver, one patient advocate, and one prostate cancer specialist nurse. Coding was used for anonymisation purposes.

This manuscript is based on the discussions that took place, combined with a review of the literature to support

or refute the findings, with the aim of identifying knowledge gaps and how these may be answered, in order to support healthcare professionals in recommending targeted and personalised fatigue management strategies for their prostate cancer patients.

## 2. Evidence acquisition

During the roundtable discussion, five themes stood out:

1. Meaning of fatigue to prostate cancer patients.
2. Impact of fatigue on prostate cancer patients.
3. Association between fatigue and treatment selection.
4. Benefit of exercise on fatigue and overall quality of life.
5. Barriers to exercise in prostate cancer patients.

Based on the core themes, a “search string” was developed to enable a structured search of the literature (Supplementary material and Supplementary Fig. 1). Medline was used to search for relevant original research or review articles published between 2012 and 2022. The reference lists of included articles were also searched. Only articles written in English and full texts were included in the review.

The intention of the literature review was to corroborate or refute the themes raised at the roundtable. Articles were excluded on the basis that they were not within the scope of the core themes.

## 3. Evidence synthesis

### 3.1. *Meaning of fatigue to prostate cancer patients*

Fatigue can be viewed as multifaceted with physical, mental, and emotional consequences. During the roundtable discussion, panel members described how cancer-related fatigue impacted patients’ lives in all three domains. Symptoms of physical fatigue such as spending more time resting or sleeping, or changes in quality of sleep were presented. Symptoms of mental fatigue included increased difficulty in concentrating, thinking clearly, or making decisions and impaired visual spatial processing (such as difficulty locating one’s car in a vast car parking area). Lastly, feeling depressed, a lack of motivation in daily life, and feeling overwhelmed by their cancer diagnosis and treatment were identified as being symptoms of emotional fatigue. Being worn out by the emotional burden, stress, and disruption in their lives from having cancer had an impact on patients’ social well-being.

Indeed, fatigue is well documented to significantly affect the lives of prostate cancer patients and their ability to cope with everyday activities (Supplementary material [S11,12]) [13]. In previous studies investigating the prevalence of

cancer-related fatigue for prostate cancer patients, rates have varied between 13% and 82% ([Supplementary material \[S13\]](#)) [13–15]. A more recent meta-analysis, however, suggests prevalence in the region of 40% [13]. This still represents a sizeable proportion of men with prostate cancer who experience debilitating fatigue. Certain treatment types cause more fatigue than others ([Supplementary material \[S14-16\]](#)) [16–19]. When patients undergo more than one type of treatment concurrently, such as ADT and radiotherapy, this effect is magnified ([Supplementary material \[S17\]](#)).

It is important that healthcare practitioners (HCPs) are aware of and understand the meaning and impact that fatigue has on individual patients and their overall quality of life. This resonated among the panellists.

“[Fatigue] means lots of things for different people... what are they talking about when they say fatigue? And most importantly, what’s the impact of it?” (C2)

Furthermore, the clinician panellists emphasised the importance of working together with patients to identify personalised strategies for mitigating physical, mental, and emotional fatigue.

“Probably one of the most important things that I’ve learned over the years is the skill of listening... Because if you don’t listen, you don’t know, and assumptions are never good... I also quite like to know what [the patient has] tried, because there’s no point in me waxing lyrical about all my great ideas if [they’ve] already tried [them].” (C2)

### 3.2. *Impact of fatigue on prostate cancer patients*

From the roundtable discussions, it was apparent that cancer-related fatigue has the capacity to disrupt a person’s life almost in its entirety, which can cause sleep disturbance, reduced ability to care for oneself, changes in relationship dynamics, diminished ability to do activities, inability to work, cognitive difficulties, and the resulting emotional fatigue that can occur.

Fatigue is a common problem for prostate cancer patients and can be provoked by treatments ([Supplementary material \[S16-18\]](#)) [17]. Furthermore, it is often part of a cluster of symptoms that includes insomnia and depression [20]. For example, anxiety about whether cancer treatments will be successful can disrupt sleep, leading to poor sleep quality and subsequent daytime fatigue. Fatigue itself can lead to depression, and while antidepressant medications may help manage the symptoms of depression and insomnia, some of these can exacerbate fatigue [20].

One patient panellist described how his physical fatigue was so significant that he needed to re-evaluate his career as he no longer had the physical energy to perform his role effectively.

“In the midst of a two-day training workshop that I was giving, my legs just gave away. They turned to jelly. That was embarrassing enough, [then I had] to cope to continue through the planned session... I had to change my way of earning a living because I just could not cope at that point with the fatigue of doing training courses.” (P3)

Another panellist who was on ADT treatment described visual motor spatial processing difficulties. Although evidence in this area is limited, ADT has been shown to be associated with impaired cognitive function [21,22].

“I found myself spatially challenged, losing my car in a large parking lot and having trouble finding papers or doing simple computer spatial puzzles which now became impossible to solve.” (P1)

From a carer panellist’s perspective, fatigue had impacted almost every aspect of joint social health, including the couple’s ability to enjoy former hobbies. She described the impact of physical and mental fatigue on their daily lives and how chemotherapy resulted in her husband developing lymphoedema, which further impacted his fatigue and ability to exercise.

“For me as a carer, the difficulty was getting that balance between being a nagging wife [and] cajoling him into doing more exercise when he really wasn’t feeling like doing... But we did, and I’m sure that that made a very big difference to his lymphoedema.” (P2)

Studies assessing the physical and cognitive aspects of fatigue found that many prostate cancer patients experience poor sleep ([Supplementary material \[S19,20\]](#)) [11,23], increased cognitive interference, and decreased physical endurance ([Supplementary material \[S21,22\]](#)) [24,25]. These findings support the mental and physical nature of cancer-related fatigue, as described by the roundtable panellists.

Unlike other cancer side effects such as pain, nausea, or anxiety, which are more easily recognised and, in many cases, treatable with medication, cancer-related fatigue has a complex underlying aetiology [26,27]. Indeed, the need for HCPs to be aware of and to acknowledge the impact of fatigue on quality of life has been reported previously [6,27–29].

During the roundtable discussions, the clinician’s perspective revealed that consultations tended to focus on oncological treatment options, rather than on fatigue per se. Furthermore, it was suggested that there was a belief among some healthcare professionals that fatigue may not be a priority for patients as they may not believe it to be a “treatable” symptom.

“A lot of my colleagues will not ask [about fatigue] because you cannot do anything about it... I have to convince my colleagues to talk more about fatigue.” (C1)

“As health professionals we want to go in and we want to fix things—it’s what we’re here for.” (C2)

From a patient’s perspective, it would appear that fatigue has the potential to affect cognitive processing, which may prevent patient-clinician discussions beyond treatment side effects and possible complications. In turn, this may suggest that prostate cancer patients need more time during consultations to account for cognitive processing. Furthermore, it is essential that clinicians ask patients about the impact of fatigue on their lives to find ways of managing fatigue as well as informing them about treatment options.

“Before deciding [on a treatment], I will ask them about brain fog and if they have it or not. Or I ask their loved

ones if the patient already has brain fog, because it is important when choosing [treatments].” (C1)

### 3.3. Association between fatigue and treatment selection

The clinician panellists recognised that nearly all prostate cancer treatments were likely to induce fatigue, so treatment options in this regard were limited.

“Switching from one treatment to another certainly in terms of ADT isn’t going to make much difference, and in terms of chemotherapy, radiotherapy, etc., you don’t have an alternative. So, there isn’t a lot of choice... If somebody’s already fatigued, you might be more prone to give them something with a steroid, which is going to increase their energy, rather than [something] which is going to make it worse.” (C1)

The lowest rates of cancer-related fatigue (14–22%) are seen in men who have undergone a radical prostatectomy (Supplementary material [S15]) [30]. However, radical prostatectomies tend to be performed on men who are younger [31]. Older men are more likely to be offered radiotherapy and ADT, although ADT treatment may be avoided when medical comorbidities contraindicate its use [30]. The prevalence of cancer-related fatigue after radiotherapy is estimated to be in the region of 33–56% (Supplementary material [S14]) [19,30], suggesting that the presence of fatigue after prostate cancer treatment may be influenced by age, as well as the type of treatment. Fatigue is also likely to be increased if one or more types of treatment, which cause fatigue, such as radiotherapy and ADT, are used concurrently (Table 1).

In a qualitative study of 21 clinicians and 71 patients regarding the impact of cancer medicines on health-related quality of life, there was discordance between clinicians’ beliefs of what mattered the most to patients versus patients’ own beliefs [32]. For example, while clinicians were mindful of the impact of mood and emotion on quality of life and rated patient needs as high in this regard, patients ranked symptoms and side effects of treatment,

the ability to ask questions during consultations, and health information more highly [32].

HCPs are aware of the psychological effects of cancer on patients, but the full impact of fatigue may be overlooked, highlighting the importance of awareness of the dimensions of fatigue and the debilitating effect it can have on patients’ lives, when making treatment recommendations.

### 3.4. Benefit of exercise on fatigue and overall quality of life

Studies have shown that psychosocial methods, such as education and cognitive behavioural therapy, can be beneficial in reducing cancer-related fatigue [33]. Other techniques include guided imagery and progressive muscle relaxation, which have been shown to produce clinically meaningful improvements in fatigue in advanced prostate cancer patients undergoing chemotherapy [34].

Discussions at the roundtable provided further insight into how different types of exercises can alleviate fatigue in prostate cancer patients (Supplementary material [S23]). One panellist recounted that being part of a prostate cancer dragon boat racing team with regular practice sessions not only increased his stamina and reduced his physical fatigue symptoms, but the social bonds that were formed inspired team mates to continue to exercise together, in a reciprocal fashion.

“The exercising gives a rationale for socialising and the socialising builds a commitment to one’s fellow team members to show up for the next practice. I believe we need to encourage more such team activities for prostate cancer patients.” (P1)

Another panellist described how a group activity in the form of a hill walking club helped him increase the stamina he had lost following prostate cancer treatment.

Exercise in the form of, for example, walking, aerobic training, or weightlifting, or in the form of a sport such as a team or individual activity, for instance, football or golf, is equally valid when it comes to benefitting fatigue symptoms.

There is a wealth of literature on the benefits of exercise as one approach to reducing fatigue in prostate cancer patients (Supplementary material [S24,25]) [5,33,35–38]. In meta-analyses of radiotherapy treatment, moderate exercise, such as resistance training, has been demonstrated to be an effective approach to alleviating fatigue (Supplementary material [S26]) [36]. Resistance training or high-intensity interval training has also shown greater efficacy at reducing fatigue and increasing quality of life than aerobic exercise for some men [39–42]. In a more recent systematic review of 18 clinical trials comprising 1112 men, the effects of exercise on cancer-related fatigue in prostate cancer patients receiving ADT revealed that low-volume resistance-based exercise of medium to high intensity reduced fatigue significantly [43]. Studies on the benefits of nutrition in combination with exercise have yielded similar results [39,40]. However, the panel commented that many patients are poorly motivated to attend gym-based sessions as an individual endeavour, whereas peer-driven team or group exercises may have greater impact in encouraging adherence to incorporating exercise into lifestyle.

**Table 1 – Overview of fatigue rates: recent and large prostate cancer clinical trials**

Trial and treatment	Incidence of fatigue (%)	
	Any grade	Grade $\geq 3$
EMBARK (biochemical recurrence) [47]		
Leuprolide	32.8	1.4
Enzalutamide	46.6	4
Leuprolide and Enza	42.8	3.5
STAMPEDE (high risk, nonmetastatic) [48]		
ADT alone	56	1.6
ADT plus abiraterone	66	2
STAMPEDE (metastatic disease) [49]		
ADT alone	58	2
ADT plus abiraterone	68	2
ARCHES (metastatic disease) [50]		
ADT alone	19.5	1.6
ADT plus enzalutamide	24.1	1.7
ARESENS (mHSPC) [51]		
ADT plus docetaxel	32.9	NA
ADT plus docetaxel plus darolutamide	33.1	NA

ADT = androgen deprivation therapy; Enza = enzalutamide; mHSPC = metastatic hormone-sensitive prostate cancer; NA = not available.

The importance of patients being well educated about the benefits of exercise, in reducing treatment-related adverse effects such as fatigue, was evident from both the roundtable discussions and the corresponding literature. However, understanding preferences and potential barriers to exercise is equally important for clinicians to recognise, as these may vary greatly among their patients.

### 3.5. Barriers to exercise in prostate cancer patients

The roundtable discussion on barriers to exercise and methods of overcoming them centred on motivation, moral support, physical exhaustion, and accessibility. Patient panellists described how attempts at exercising individually had not been successful and, it was evident that the collegiality and comradeship offered by group activities helped generate a commitment to exercise.

“I found that you can’t do it on your own. So, I joined a hill walking club, and my stamina levels improved no end. It [was] much better than walking solo.” (P3)

“When we meet... for the walking group, there is a lot of camaraderie for both the patients and for the carers.” (P2)

This mutual support and camaraderie with peers are echoed in the literature [44]. However, for some men, treatment side effects, physical limitations, pain, poor mental health, general lack of motivation, or financial implications present barriers to exercise, despite the knowledge that it can decrease fatigue (Supplementary material [S24,25,27–29]) [44]. The panel discussed the importance of self-efficacy in this regard, that is, the belief in one’s ability to complete a task or achieve a goal [45].

“That’s what we need to work on. Because we can give people all the advice in the world. But if they don’t have that perceived, what we call self-efficacy, then it’s not going to translate into action.” (C2)

However, for healthcare professionals to encourage self-efficacy, it is important to understand the potential barriers and how these may be overcome.

The frequency and intensity of exercise have been shown to present barriers to patients continuing engaging with exercise programmes, which in turn impacts adherence rates adversely [43]. It is, therefore, important for healthcare professionals and patients to be mindful of the impact of fatigue on both physical and mental abilities, and to set realistic exercise goals. One panel member suggested that this can start with as little as 5 min of walking.

The panellists briefly discussed the impact of COVID-19 on the ability to exercise, which required adaptations, such as online exercise classes, to continue to adhere to exercise regimes.

“There is an advanced prostate cancer club which runs many different classes [and] before COVID they were in person, [then] they all went online.” (P2)

“I found COVID great because everything went online. So, exercise classes, which I wouldn’t have turned up to a gym for, were online... [and] you don’t feel as intimidated online as you do in a gym.” (P4)

Although the literature suggests digital technology represents a barrier to exercise for some men [46], our panellists found the convenience of modern technology to be helpful and online sessions to be motivating. Furthermore, in a qualitative study by Evans et al (Supplementary material, Additional references), participants were positive towards the notion of a web-based exercise tool and expressed the need for individualised, professional-embedded information. For patients who are deterred by exercise due to urinary or faecal incontinence (Supplementary material [S27] [44], online exercise classes may present a practical and less intimidating method of exercise [46].

Insight into known barriers and facilitators of exercise can help clinicians work in partnership with patients who are struggling with cancer-related fatigue to promote self-efficacy and find exercise classes or workout sessions that will provide the most benefit.

### 3.6. Discussion

Prostate cancer is a complex disease that requires consideration of both the general health status of the individual and the likelihood of disease progression when making decisions about treatment. Fatigue is a common and often debilitating side effect of all cancer treatments, with the prevalence ranging from 14% to 68%, depending on the treatment received. Fatigue is well documented to have a significant effect on the lives of prostate cancer survivors and their ability to cope with everyday activities. Understanding which treatments have the highest prevalence of fatigue may be useful and important for clinicians when discussing treatment options and how to manage post-treatment fatigue with their patients. Furthermore, understanding the specific health needs of individual patients and their desired health outcomes are the driving force behind all healthcare decisions. Therefore, listening to patients, as well as directly asking them if fatigue is an issue, and working together to identify personalised strategies for minimising fatigue, particularly as it changes over time, should not be under-rated.

Clinicians who arm themselves with the knowledge of a range of interventions aimed at reducing cancer-related fatigue could benefit their patients greatly. Several studies have shown exercise to be critical in reducing fatigue in patients with prostate cancer. It is therefore recommended that the importance of physical exercise and its benefits are keenly conveyed to all patients. However, clinicians should be mindful that equipping patients with knowledge does not automatically translate to adherence. Understanding barriers to exercise can help clinicians work in partnership with patients who are struggling with cancer-related fatigue to find interventions that will provide the most benefit.

It is worth noting that men with the highest levels of fatigue and lowest levels of vitality are the ones who may struggle the most with compliance, and yet they stand to benefit the most from incorporating exercise into their daily routine. In this situation, nonexercise interventions, such as self-efficacy techniques or cognitive behavioural therapy, can be beneficial in encouraging men to exercise to the best of their ability. These interventions can work together to

promote physical activity and build the mental capacity of patients to take on the physical challenge that exercise may pose.

Patient-centred care involves an active collaboration and shared decision-making between patients, their families, and clinicians to develop individualised care plans. The panel agreed that prostate cancer patients may need more time during consultations to account for cognitive processing as well as to be directly asked about the impact of fatigue on their lives.

#### 4. Conclusions

Cancer- and treatment-related fatigue can have a profound effect on quality of life. Its multifactorial effects are difficult to comprehend if these have not been experienced first-hand. The roundtable discussion presented viewpoints from a range of individual perspectives on how fatigue affects prostate cancer patients.

By anticipating fatigue in prostate cancer patients and understanding the importance of an individual approach to fatigue management, as well as the techniques that can help manage fatigue symptoms, clinicians can provide vital support in alleviating the burden that fatigue can have on their prostate cancer patients' lives.

Asking the right questions can help, so HCPs can understand how fatigue manifests for each patient and identify personalised approaches to help their patients manage it.

We hope the quick reference guide provided in [Supplementary Figure 2](#) may prove useful for healthcare professionals during consultations with their patients.

**Author contributions:** Rogers had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Cornford, Rogers.

*Acquisition of data:* Cornford, Rogers.

*Analysis and interpretation of data:* Cornford, Rogers, Wassersug, Fleure.

*Drafting of the manuscript:* Cornford, Rogers, Wassersug, Fleure.

*Critical revision of the manuscript for important intellectual content:* Cornford, Rogers, Wassersug, Fleure.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euros.2024.03.003>.

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