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ARTICLE

Clinical Research

Effects of high-intensity interval training compared with resistance training in prostate cancer patients undergoing radiotherapy: a randomized controlled trial

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Abstract

Background Exercise training has shown beneficial effects in the management of radiotherapy-related side effects in prostate cancer (PCa) patients undergoing radiation therapy (RT). However, the optimal modality of the exercise programs have not been yet determined. The aim of this randomized controlled trial was to investigate the effects of high-intensity interval training (HIIT) and resistance training (RES) compared to usual care (UC) on cancer-treatment-related fatigue (CTRF) (primary outcome), quality of life, depression, daytime sleepiness, insomnia, sleep quality, functional exercise capacity and executive function in PCa patients during RT.

Methods PCa patients undergoing RT with or without ADT were randomized in HIIT, RES or UC. Both exercise programs included three sessions per week during 5–8 weeks. HIIT consisted of 8–15 × 60 s intervals (≥85% maximal heart rate). RES was performed with 1–3 sets of 8–12 repetitions for each large muscle groups. The primary outcome was changed in CTRF measured with the Functional Assessment of Chronic Illness Therapy–Fatigue.

Results Seventy-two subjects (69.1 ± 8.2 years) completed the study. No exercise-related adverse events occurred. HIIT ($p = 0.012$) and RES ($p = 0.039$) training attenuated increases in CTRF compared to UC. Functional exercise capacity, evaluated by the 6-min walk test, increased after HIIT ($p = 0 = 0.43$) and RES ($p = 0.041$) compared to UC (+0.1%). No other secondary variables were different between groups.

Conclusions Both intervention groups displayed beneficial effects on CTRF and functional exercise capacity in PCa patients undergoing RT. In addition, HIIT and RES are both safe with an excellent attendance rate to the exercise sessions.

Introduction

Radiation therapy (RT) with or without androgen deprivation therapy (ADT) is one of the standard of care for localized and locally advanced prostate cancer (PCa) [1]. RT and ADT are associated with distressing adverse effects in PCa patients such as fatigue that may have a considerable impact on quality of life (QoL) [2, 3]. Cancer-treatment-related fatigue (CTRF) is experienced by ~70% of men with PCa during RT [4, 5] and one-third of patients still reported CTRF one year after treatment completion [6]. In addition, reduced activity, physical functioning worsening, depression, sleep disturbance and cognitive deficits are often associated with CTRF in these patients [7–10].

Previous studies have reported benefits and improvements in CTRF, exercise capacity, body composition and pro-inflammatory cytokines with different exercise program including aerobic, resistance or a combination of both training in men receiving RT for PCa [11–15]. Aerobic training consisted of walking or cycling three to five times a week over a 4- to 24-week period at a moderate intensity [16]. Resistance training consisted of exercises targeting the major muscle groups three to five times a week for 8 and 24 weeks [16]. However,

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Table 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Diagnosis of prostate cancer	Uncontrolled cardiac or pulmonary diseases
Over 18 years	Uncontrolled insulin-dependent diabetes mellitus
At least 25 scheduled radiation sessions with or without androgen deprivation therapy	Neuropsychiatric disorders or orthopedic conditions or any contraindications to exercise
No distant metastases and/or disease progression	Participation in a regular exercise program
Able to read, write, and speak French or English	

clarifications are required on the most beneficial exercise modality. Segal et al. investigated the effects of 24 weeks of resistance training (RES) or moderate-intensity continuous aerobic training (MICT) compared to usual care (UC) and reported that both RES and MICT counteract the increase in CTRF at the midpoint. From baseline to post-intervention, RES yielded improvements in fatigue, QoL, exercise capacity, upper and lower muscle strength while MICT only improved upper muscle strength compared to UC [13]. These results suggest that RES provides more benefits than MICT in PCa patients during RT. However, if aerobic training is performed at high-intensity interval training (HIIT), it could have better benefits than MICT. Indeed, a meta-analysis has reported that HIIT is almost twice as effective as MICT to increase cardiorespiratory fitness in patients with lifestyle-induced chronic diseases [17]. HIIT seems to be an effective alternative to MICT by inducing similar or superior physiological adaptations in maximal oxygen uptake, mitochondrial capacity, cardiac function, oxidative stress or inflammation, and is perceived to be more enjoyable [17, 18]. In addition, considering that lack of time is a frequently reported barrier to physical activity during cancer treatment [19], implementing HIIT concomitantly RT would be time-efficient while providing health-enhancing benefits [20].

Although the findings of Segal et al. seem to give the advantage of RES to manage RT-related side effects [13], no study has investigated the effects of HIIT and RES compared to UC in PCa patients undergoing RT. Therefore, the aim of this randomized controlled trial (RCT) was to investigate the comparative effectiveness of HIIT and RES compared to UC on CTRF, QoL, depression, daytime sleepiness, insomnia, sleep quality, functional exercise capacity and executive function in PCa patients undergoing RT.

Patients and methods

Study design, participants and randomization

This three-arm RCT was conducted at the Cliniques universitaires Saint-Luc in Brussels from September 2017 to October 2019. Ethics approval was obtained by the regional Ethics Committee of the Cliniques universitaires Saint-Luc and Université catholique de Louvain in Brussels (B403201732718) and each participant provided written informed consent. This study was registered at clinicaltrials.gov (NCT03252821) and follow the CONSORT guidelines [21]. The inclusion and exclusion criteria are presented in Table 1. Included subjects were randomly assigned in a 1:1:1 manner, using computer-generated numbers (JMP Pro 12 software), to either HIIT, RES or UC groups. Subjects attributed to HIIT undergo a cardiac stress test at inclusion to check potential contraindications to high-intensity training. The principal investigator (PI) allocated the subjects.

Radiotherapy regimen

Intensity-modulated radiation therapy or volumetric intensity-modulated arc therapy were used to deliver the treatment. PCa patients received a total dose of 62.0–78.0 Gy to the prostate gland in 26–39 fractions for 5–8 weeks. In addition, irradiation could be provided to the seminal vesicles in 27–28 fractions (2.0 Gy per fraction) to a total dose of 54–56 Gy and/or the pelvic lymph nodes including 46.0–50.4 Gy in 23–28 fractions, each at 1.8–2.0 Gy.

Intervention

Exercise intervention groups

Patients (HIIT and RES) performed three training sessions per week for 5 or 8 weeks, according to their RT treatment time. Exercise sessions started on the same day as RT and ended the penultimate fraction of RT. A physiotherapist provided the exercise program 1-on-1 and reported exercise attendance, achieved intensity and duration, reason of missed sessions or any exercise-related adverse events at each session.

HIIT was conducted on a cycle ergometer during 26–40 min. Continuous heart rate was monitored with a heart rate monitor (Polar, FT7, Electro Oy, Kempele,

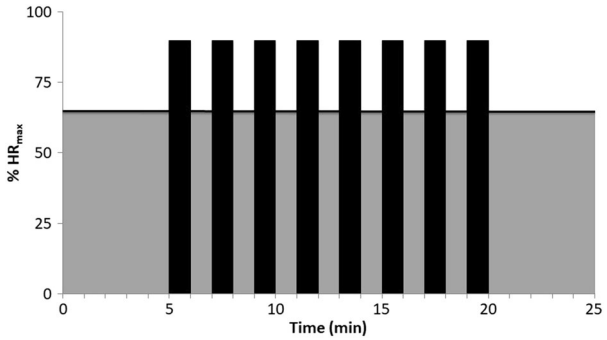

Fig. 1 Overview of HIIT protocol of the first session. The black bars represent the high-intensity intervals of 60 s for which patients were asked to cycle at a speed of 90–100 revolutions per minute and the workload was increased to reach the target heart rate of ≥85% THRmax. The gray area represents the warm-up, the rest period between high-intensity intervals and the cool down. During rest periods, the workload was reduced to its minimum and the pedaling speed was between 50 and 60 revolutions per minute.

Finland). Patients performed 5 min warm-up at an intensity of 65–70% of the theoretical maximal heart rate ($THR_{max} = 220 - age$), followed by 8×60 s sessions at ≥85% THR_{max} interspersed by 60s interval rest at a slow intensity (Fig. 1) and finished with a 5-min cool down. The first session started with eight intervals and increased from week to week until 15 intervals based on target heart rate and effort perception. During high-intensity bouts, patients were asked to cycle at a speed of 90–100 revolutions per minute and the workload was individually increased until patients reached the target heart rate. During rest periods, the workload was reduced to its minimum and the pedaling speed was between 50 and 60 revolutions per minute.

Resistance program consisted of eight exercises targeting the major muscle groups (abdominal, pectoral, deltoid, trapezius, latissimus dorsi, erector spinae, biceps, triceps, quadriceps, hamstrings, gastrocnemius, soleus, and gluteus) with one to three sets of 8–12 repetitions. Exercises were performed using body weight, resistance bands or dumbbells for about 30 min. The perceived exertion was assessed using the modified Borg scale [22] and a score between four and six rating of perceived exertion (RPE) was attended. When subjects did not score perceived exertion between four and six RPE, the intensity of the program was modified for the next session. Participant progression was individualized throughout intervention.

Usual care control group

Participants received standard medical care as a pamphlet including World Health Organization's recommendations on physical activity and health.

Outcome measures

A demographic questionnaire was self-reported at baseline and medical data were recorded from the patient's medical records. Participants were assessed 10 days before RT treatment start (T0) and after the last fraction of RT (T1). The primary outcome was CTRF evaluated with the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) [23]. Secondary outcomes included the following parameters: cancer-related QoL measured by the Functional Assessment of Cancer Therapy–General (FACT-G) questionnaire [24]; depressive symptoms evaluated using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D) [25]; daytime sleepiness measured using the Epworth Sleepiness Scale (ESS) [26]; the severity of both nocturnal and daytime symptoms of insomnia evaluated with the Insomnia Severity Index (ISI) [27]; sleep quality and disturbances assessed with the Pittsburg sleep quality index (PSQI) [28]; functional exercise capacity evaluated by the total distance walked during a 6-min walk test (6MWT) [29] and cognitive function estimated with the trail-making test following Spreen and Strauss guidelines [30]. All questionnaires were self-reported and objectively measured variables were collected by the PI. Attendance was calculated as the percentage of the number of exercise sessions attended out of the prescribed number of sessions.

Statistical analysis

The estimated sample size was calculated with a power of 80% and a p value of 0.05 to detect a difference in the FACIT-F of 3.5 points (SD = 5.8) [31]. Considering 5% of drop-out, 78 subjects (26 in each group) were required. The normality of distribution was verified by the Shapiro–Wilk test. Baseline comparisons were done using the chi-square test for categorical variables and one-way analysis of variance for continuous and normally distributed variables. Data were analyzed on an intention-to-treat analysis to determine the effectiveness of the interventions in enrolled patients and a sub-group analysis including only PCa patients receiving RT with ADT were also performed. Changes in self-reported questionnaires and percentage changes in objectively measured variables from pre- to post-intervention between groups were compared using a one-way analysis of variance or the Kruskal–Wallis test, depending on the distribution. Tukey post hoc corrections were used to perform adjustment for multiple groupwise comparisons. Data were expressed as mean ± standard deviation and mean (95% CI) or median [interquartile range] and mean (95% CI) according to the distribution. The statistical significance was set at 0.05. Statistical analyses were performed using the IBM SPSS software Version 25.0 (IBM Corp., Armonk, NY, USA).

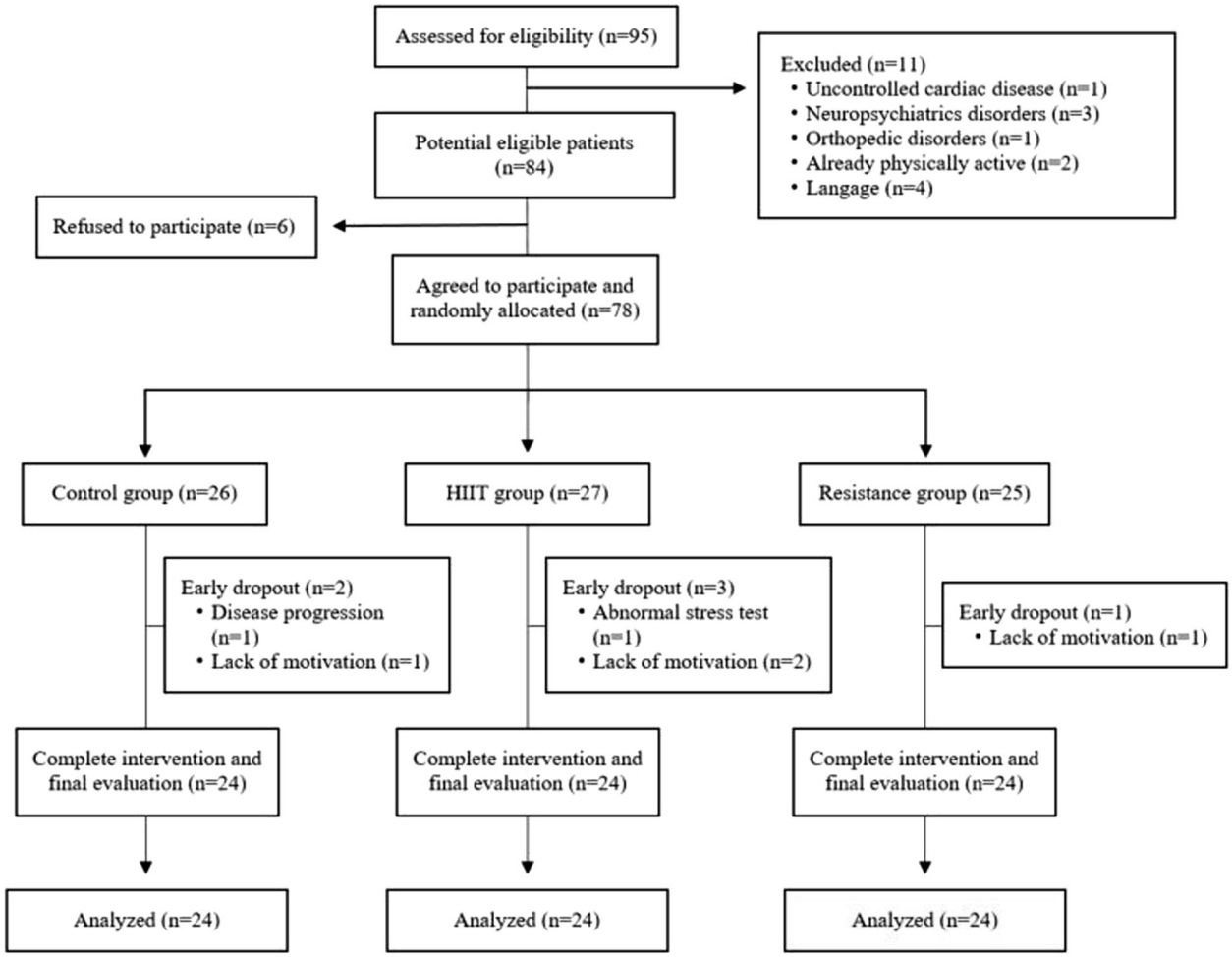

Fig. 2 CONSORT flow diagram. *HIIT* high-intensity interval training.

Results

Patient flow and baseline characteristics

Among the 84 potentially eligible patients, 78 subjects were randomized (Fig. 2). Six of them who never showed up for the baseline testing and intervention were considered as "early dropouts" and were not included in the analyses. Seventy-two PCa patients completed the study. Baseline characteristics of the enrolled patients are presented in Tables 2 and 3. All patients received the RT treatment plan drawn up at baseline and a mean total prostate radiation dose of 72.8 ± 5.4 Gy over 32.8 ± 6.2 fractions. Eighty-one percent of subjects were on androgen deprivation therapy. Sociodemographic, clinical and outcomes measures were comparable between the three groups at baseline.

Primary and secondary outcomes

Changes in primary and secondary outcomes are shown in Table 3. HIIT (+0.2 points; $p = 0.012$) and RES (−0.7 points; $p = 0.039$) training attenuated increases in CTRF compared to UC (−5.3 points). The 6-minute walk distance increased after HIIT (+7.5%; $p = 0.043$) and RES (+6.6%; $p = 0.042$) compared to UC (+0.1%). Changes in executive function, cancer-specific QoL, depressive symptoms, daytime sleepiness, insomnia, sleep quality and disturbance were not different between groups ($p > 0.05$). The subgroup analysis including PCa patients undergoing RT with ADT ($n = 58$) showed similar significant results between the three groups for CTRF and functional exercise capacity and no significant change for other variables (Supplementary Table S1).

Attendance and safety

Attendance to sessions was 93.5% (range: 67–100%) in HIIT and 91.4% (range: 60–100%) in RES from which 12 out of 24 in the HIIT and 11 out of 24 in the RES attended 100% of the prescribed sessions. Two patients out of 24 in the HIIT and 4 out of 24 in the RES had an attendance <80%. The most common reported reasons for missing a

Table 2 Baseline characteristics of participants.

Characteristics	UC ($n = 24$)	HIIT ($n = 24$)	RES ($n = 24$)	P value
Age (years)	71.9 ± 8.1	67.4 ± 8.9	67.9 ± 7.1	0.115[b]
Height (cm)	177.7 ± 5.8	176.5 ± 6.1	177.4 ± 5.9	0.771[b]
Body mass (kg)	81.9 ± 15.2	82.8 ± 13.4	82.2 ± 9.8	0.969[b]
BMI (kg/m²)	25.8 ± 4.4	26.5 ± 3.9	26.1 ± 2.9	0.812[b]
Ethnicity				0.558[a]
Caucasian	23 (95.8)	23 (95.8)	23 (95.8)	
African/American	1 (4.2)	0 (0.0)	1 (4.2)	
Hispanic	0 (0.0)	1 (4.2)	0 (0.0)	
Marital status				0.366[a]
Married/cohabitant	17 (70.8)	20 (83.3)	15 (62.5)	
Divorced/separated	2 (8.3)	3 (12.5)	4 (16.7)	
Widowed/single	5 (20.8)	1 (4.2)	5 (20.8)	
Highest education level				0.591[a]
Elementary school or less	1 (4.2)	0 (0.0)	0 (0.0)	
Secondary school	7 (29.2)	5 (20.8)	5 (20.8)	
Higher education	16 (66.7)	19 (79.2)	19 (79.2)	
Employment status				0.326[a]
Working	3 (12.5)	8 (33.3)	5 (20.8)	
Unemployed	2 (8.3)	0 (0.0)	1 (4.2)	
Retired	19 (79.2)	16 (66.7)	18 (75.0)	
Smoking status				0.910[a]
Non-smoker	12 (50.0)	13 (54.2)	15 (62.5)	
Occasional smoker	1 (4.2)	1 (4.2)	2 (8.3)	
Current smoker	2 (8.3)	1 (4.2)	1 (4.2)	
Ex-smoker	9 (37.5)	9 (37.5)	6 (25.0)	
Cancer risk group				0.845[a]
Intermediate	11 (45.8)	12 (50.0)	10 (41.7)	
High	13 (54.2)	12 (50.0)	14 (58.3)	
Gleason score				0.652[a]
7	11 (45.8)	12 (50.0)	11 (45.8)	
8	4 (16.7)	7 (29.2)	6 (25.0)	
9	9 (37.5)	5 (20.8)	6 (25.0)	
10	0 (0.0)	0 (0.0)	1 (4.2)	
RT treatment plan				0.705[a]
Prostate only	2 (8.3)	2 (8.3)	5 (20.8)	
Prostate – SV	9 (37.5)	7 (29.2)	6 (25.0)	
Prostate – SV and LN	13 (54.2)	15 (62.5)	13 (54.2)	
Total prostate dose (Gy)	72.7 ± 5.0	72.5 ± 5.1	73.3 ± 6.0	0.872[b]
RT fraction (no.)	32.6 ± 5.9	32.3 ± 5.9	34.0 ± 6.1	0.564[b]
Comorbidities (no.)	1.5 ± 1.0	1.0 ± 1.0	1.3 ± 0.9	0.228[b]
Previous prostatectomy	3 (12.5)	4 (16.7)	7 (29.2)	0.316[a]
On androgen deprivation therapy	17 (70.8)	21 (87.5)	20 (83.3)	0.316[a]
Days between the start of ADT and the start of RT (no.)	116 [86.5; 135]	104 [74.0; 127.0]	98 [64.5; 132.5]	0.688[c]

Values are presented as mean ± SD or median [Q1–Q3] for continuous variables and number (%) for categorical data.

BMI body mass index, *RT* radiotherapy, *SV* seminal vesicles, *LN* lymph nodes, *ADT* androgen deprivation therapy, *UC* usual care, *HIIT* high-intensity interval training, *RES* resistance training.

[a]Analyzed by χ^2 test.

[b]Analyzed by one-way analysis of variance.

[c]Analyzed by Kruskall–Wallis test.

session were diarrhea or intense fatigue. In terms of safety, no exercise-related adverse events were recorded.

Discussion

Our findings showed that HIIT and RES counteract the increase in CTRF and enhanced functional exercise capacity compared to UC in PCa patients undergoing RT.

Growing strong evidence reported exercise during cancer treatment as an effective intervention to manage treatment-related side effects [32]. Nevertheless, research on exercise training during RT in PCa is still limited and optimal modality has to be determined. To our knowledge, this study is the first to examine the effectiveness of HIIT and RES in PCa patients undergoing RT. Both HIIT and RES showed benefits on CTRF and functional exercise capacity compared to UC but no difference were observed between these exercise programs in managing RT-related side effects. Hence, HIIT or RES should be considered as a concurrent treatment alongside RT in PCa patients undergoing RT.

Exercise has been reported to be an effective intervention to counteract fatigue during treatment in contrast to pharmacological intervention [33]. Our results confirmed that and showed that HIIT and RES prevented a worsening in CTRF compared to UC in PCa patients undergoing RT. This decrease of 5.3 point between pre- and post-intervention in the UC outstrips the minimal clinically important difference of 3.0 reported for the FACIT-F [31]. These findings are consistent with previous studies performing aerobic, resistance or a combination of both training in men receiving RT for PCa [11–15]. Similarly, others short-term (12 weeks) and long-term (1 year) interventions of aerobic and/or resistance training reduced or prevented the worsening of fatigue in PCa patients undergoing ADT [34–36].

One of the potential mechanisms by which exercise may counteract the increase in fatigue is the improvement of functional capacity [37]. In our study, significant improvements in functional walking capacity were observed in both HIIT and RES compared to UC. Previous studies demonstrated the same results after aerobic training or a combined aerobic and resistance training during RT in men with PCa [11, 15]. However, our results are somewhat different from the study of Segal et al. that compared MICT and RES to UC in PCa patients undergoing RT. The authors showed significant benefits for cardiovascular fitness after RES compared to UC but no significant difference between MICT and UC [13]. This discrepancy with our results can be explained by the difference in intensity between the aerobic programs. Indeed, previous studies have reported that HIIT is more effective than MICT to increase cardiorespiratory fitness in cardiometabolic diseases and cancer population [17, 38]. Therefore, an increase in functional exercise capacity was an expected result after HIIT because of its ability to increase oxygen consumption. On the other hand, the increase in functional exercise capacity in the RES is a surprising result that can be explained by neuromuscular adaptations in the lower limbs induced by the resistance training.

This increase in physical fitness could help to improve QoL [39]. In this study, despite an improvement in functional walking capacity in both exercise groups, changes in cancer-specific QoL were not different between groups. These findings are line with a previous systematic review that reported a non-significant improvement in QoL (SMD, −1.01; 95% CI, −2.19 to +0.18) in PCa patients undergoing RT [40].

Sleep disturbance is a significant problem in PCa patients who undergo RT [41]. Indeed, PCa patients' sleep was disturbed by an increase in nocturia due to radiation-induced inflammation of the prostatic urethra [42]. A previous study investigated if aerobic training had any effect on acute bladder toxicity but no impact was found [43]. In addition, 81% of the included participants received ADT for which hot flashes are a common symptom and increase sleep disturbance [44]. Therefore, treatment-related symptoms including urinary disorders and hot flashes may have played a role in the non-significant effect of exercise on sleep disturbance.

The findings of our study showed that any exercise modalities (HIIT or RES) has benefits on CTRF and functional exercise capacity in PCa patients undergoing RT. Similarly, Taaffe et al. showed that three different exercise modalities (RES and impact loading, MICT and RES or MICT only) had a beneficial effect on fatigue in PCa patients undergoing ADT [34]. In Segal et al. in which they examined the effects of 24 weeks of RES or MICT compared to UC in PCa patients during RT, additional benefits were observed for the RES [13]. Indeed, RES yielded improvements in fatigue, QoL, exercise capacity, upper and lower muscle strength after 24 weeks of intervention while MICT only improved upper muscle strength compared to UC. Another study investigated the effects of RES, MICT and UC in breast cancer patients receiving adjuvant chemotherapy [45]. Neither MICT nor RES significantly improved fatigue, QoL, anxiety and depression but MICT was superior to UC for improving self-esteem, aerobic fitness and percent body fat while RES was superior to UC for improving self-esteem, muscular strength and lean body mass. Attendance to sessions was excellent in both exercise groups, similar or better to rates reported in previous studies in PCa patients during RT [11–15]. No adverse events related to HIIT or RES occurred. To our knowledge, only one study that investigated the effects of exercise in PCa patients receiving RT reported

Table 3 Differences between groups at baseline and (%) change differences from pre- to post-intervention between groups for the measured outcomes in prostate cancer receiving radiotherapy.

	UC ($n = 24$)	HIIT ($n = 24$)	RES ($n = 24$)	*P* value, baseline, between-groups	*P* value, change, between groups
FACIT-F				0.622[b]	0.009[b]
T0	41.1 ± 9.0	43.1 ± 6.9	41.2 ± 7.7		
T1	35.3 ± 12.1	42.1 ± 10.3	40.5 ± 9.8		
Change from T0 to T1	−5.8 (−9.9; −1.8)[(HIIT, RES)]	0.2 (−1.6; 2.0)[(UC)]	−0.7 (−3.3; 1.9)[(UC)]		
FACT-G				0.125[a]	0.246[a]
T0	79.3 [73.3; 83,3]	86.0 [78.2; 91.0]	83.5 [75.5; 91.8]		
T1	77.9 [67.5; 85.4]	89.0 [78.5; 92.5]	82.5 [72.3; 93.9]		
Change from T0 to T1	−2.2 (−6.4; 2.0)	1.8 (−1.8; 5.5)	−0.8 (−7.3; 5.6)		
Physical well-being				0.207[a]	0.414[a]
T0	25.6 [23.0; 27.0]	26.5 [24.3; 28.0]	26.0 [23.1; 27.0]		
T1	23.0 [17.5; 26.0]	26.0 [22.3; 27.8]	25.0 [20.3; 26.0]		
Change from T0 to T1	−3.1 (−5.0; −1.2)	−1.1 (−2.5; 0.3)	−1.8 (3.9; 0.3)		
Social/family well-being				0.239[a]	0.414[a]
T0	20.0 [14.4; 21.9]	22.0 [18.3; 23.4]	21.0 [18.0; 24.8]		
T1	21.0 [17.0; 23.3]	21.0 [19.0; 24.9]	21.0 [18.0; 24.4]		
Change from T0 to T1	2.1 (0.1; 4.1)	1.0 (−0.8; 2.8)	0.0 (−2.0; 2.0)		
Emotional well-being				0.719[b]	0.886[b]
T0	17.9 ± 3.7	18.7 ± 3.4	17.8 ± 5.1		
T1	19.0 ± 2.8	20.0 ± 3.3	19.3 ± 4.0		
Change from T0 to T1	1.1 (−0.2; 2.4)	1.3 (0.3; 2.3)	1.5 (−0.1; 3.2)		
Functional well-being				0.108[a]	0.067[a]
T0	17.0 [16.0; 19.8]	19.0 [17.0; 24.0]	20.0 [15.0; 22.0]		
T1	14.5 [13.0; 16.0]	20.0 [17.0; 24.5]	19.5 [14.3; 22.8]		
Change from T0 to T1	−2.3 (−4.2; 0.4)	0.6 (−1.9; 3.0)	−0.6 (−3.1; 1.9)		
CES-D				0.327[b]	0.618[b]
T0	13.1 ± 8.8	9.3 ± 6.7	11.5 ± 10.4		
T1	13.9 ± 9.6	10.5 ± 8.3	10.8 ± 7.7		
Change from T0 to T1	0.8 (−1.8; 3.3)	1.2 (−0.8; 3.1)	−0.7 (−4.6; 3.2)		
ESS				0.538[a]	0.323[a]
T0	4.0 [2.0; 6.0]	5.0 [3.0; 7.0]	5.0 [3.3; 7.0]		
T1	5.0 [2.0; 7.0]	4.0 [2.0; 7.8]	5.0 [3.0; 10.8]		
Change from T0 to T1	0.6 (−0.3; 1.6)	0.0 (−1.3; 1.3)	1.2 (−0.4; 2.7)		
ISI				0.440[a]	0.450[a]
T0	8.0 [4.5; 10.8]	7.5 [4.3; 10.0]	5.5 [2.8; 8.5]		
T1	8.0 [2.0; 11.8]	6.0 [2.3; 10.8]	6.0 [3.3; 9.5]		
Change from T0 to T1	−0.7 (−2.6; 1.3)	−0.5 (−2.1; 1.2)	0.5 (−1.7; 2.7)		
PSQI				0.887[a]	0.979[a]
T0	6.5 [2.5; 7.8]	5.0 [4.0; 11.0]	4.0 [3.0; 7.5]		
T1	5.5 [3.0; 8.8]	5.0 [3.0; 9.8]	4.5 [3.0; 8.5]		
Change from T0 to T1	0.3 (−0.8; 1.5)	−0.1 (−1.4; 1.2)	0.2 (−1.4; 1.7)		
6MWT (m)				0.223[b]	0.022[b]
T0	499.2 ± 74.1	530.6 ± 80.6	533.1 ± 64.9		
T1	502.4 ± 68.7	561.0 ± 77.4	568.9 ± 75.7		
% change from T0 to T1	−0.3 (−4.7; 4.1)[(HIIT, RES)]	7.3 (3.7; 10.8)[(UC)]	7.3 (1.9; 12.7)[(UC)]		
TMT-A (s)				0.082[b]	0.900[b]
T0	47.3 ± 17.1	41.8 ± 17.6	37.4 ± 9.4		
T1	37.8 ± 13.1	37.6 ± 17.3	35.4 ± 11.8		
% change from T0 to T1	−8.4 (−21.7; 4.9)	−4.8 (−17.0; 7.3)	−5.7 (−14.6; 3.3)		
TMT-B (s)				0.606[b]	0.591[b]
T0	106.0 ± 47.4	97.3 ± 53.4	93.1 ± 32.5		
T1	83.7 ± 27.0	82.3 ± 45.9	77.6 ± 29.3		
% change from T0 to T1	−9.9 (−19.9; 0.1)	−13.6 (−20.8; −6.3)	−15.7 (−23.3; −8.2)		
TMT B-A (s)				0.902[b]	0.075[b]
T0	59.8 ± 36.7	56.2 ± 39.2	55.7 ± 25.5		
T1	46.0 ± 21.3	44.7 ± 32.0	41.2 ± 23.1		
% change from T0 to T1	6.8 (−22.6; 36.2)	−16.4 (−32.8; 0.0)	−24.0 (−37.8; −10.3)		

Values are presented as mean ± SD and mean (95% CI) for normally distributed data and median [Q1–Q3] and mean (95% CI) for non-normally distributed data.

FACIT-F Functional Assessment of Chronic Illness Therapy-Fatigue, *FACT-G* Functional Assessment of Cancer Therapy-General, *CES-D* Center for Epidemiological Studies Depression Scale, *ESS* Epworth Sleepiness Scale, *ISI* Insomnia Severity Index, *PSQI* Pittsburg Sleep Quality Index, *6MWT* 6-min walk test, *TMT* trail-making-test, *UC* usual care, *HIIT* high-intensity interval training, *RES* resistance training.

[a]Analyzed by Kruskall–Wallis test.

[b]Analyzed by one-way analysis of variance.

one serious exercise-related adverse cardiovascular event during aerobic training [13]. We probably reduced the risk of cardiovascular event by achieving a cardiac stress test before starting HIIT. Indeed, one patient was excluded from the present study because his cardiac stress test was positive. A scientific roundtable has proposed a new evidence-informed model for exercise preparticipation health screening based on three factors: the individual's current level of physical activity, presence of signs or symptoms and/or known cardiovascular, metabolic, or renal disease, and desired exercise intensity [46]. For example, a medical clearance is not necessary prior beginning an exercise program at light- to moderate-intensity for a physically inactive person without presence of signs or symptoms and/or known cardiovascular, metabolic, or renal disease [46]. However, if this person wants to begin vigorous-intensity exercise, a medical clearance is recommended. Therefore, moderate-intensity RES could be more accessible than HIIT because a medical clearance prior to beginning an exercise program may be a barrier to exercise participation.

Despite growing evidence of the benefits of exercise during cancer treatment, patients still reduce their physical activity level once the RT started [47]. Providing an exercise program to patients from the start of RT can help to prevent the deconditioning, which can lead to long-term disabilities. Regarding the completion rate, patients seem interested in practicing physical activity during RT. Some reasons may explain this excellent completion rate including the supervision 1-on-1 by an experienced physiotherapist, the proximity between the radiotherapy and the rehabilitation departments and the direct sequence of the training session after the RT session. Completion rates described by other studies on PCa patients during RT was also good to excellent [11–15] that confirmed previous findings that PCa patients report a high receptivity for health programs [48].

This study has some strengths to highlight including the comparison of different intervention training, the RCT design, the larger sample size, the intention-to-treat analysis and the limit loss to follow-up. Nevertheless, this study has some limitations. Firstly, there was no blind assessor to evaluate outcomes. Secondly, we aimed to observe the effects of two different training modalities on CTRF during RT. However, as CTRF may be still present 1-year after treatment completion, it would have been interesting to carry out a longer follow-up. Because HIIT and RES counteract the increase in CTRF compared to UC during RT, we can hypothesize that the level of fatigue will be lower for patients in both intervention groups than UC in a long-term follow-up. Therefore, further research is required in this field with a longer follow-up.

In conclusion, both HIIT and RES displayed beneficial effects on CTRF and functional exercise capacity in PCa patients undergoing RT. However, none intervention had an effect on cognitive function, cancer-specific QoL, depressive symptoms, daytime sleepiness, insomnia, sleep quality and disturbance. In addition, HIIT and RES are both safe with an excellent attendance to the exercise sessions. In view of our findings, a structured HIIT or RES should be incorporated as a concurrent treatment alongside RT to alleviate CTRF and to improve functional exercise capacity in PCa patients undergoing RT.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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