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## Prostate Cancer

# Which Type of Exercise During Radiation Therapy Is Optimal to Improve Fatigue and Quality of Life in Men with Prostate Cancer? A Bayesian Network Analysis

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## Article info

## Abstract

*Context:* Physical exercise in men with prostate cancer (CaP) has shown benefits in improving cancer-related fatigue (CRF) and quality of life (QoL) during radiation therapy. However, types of exercises that are more effective are not well understood.

*Evidence acquisition:* We searched PubMed, Web of Science, and ClinicalTrials.gov up to November 2021 to identify potentially relevant studies. Randomized controlled trials (RCTs) testing the effects of exercise training on CRF, QoL, and treatment-related toxicities in patients with CaP undergoing radiation therapy were included. The quality of individual studies was evaluated using the Tool for the assEssment of Study qualiTy and reporting in Exercise (TESTEX) scale. The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation method. A meta-regression analysis was conducted to test the study-level covariates. A random-effect network meta-analysis was conducted based on a Bayesian model.

*Evidence synthesis:* Eight RCTs with 466 participants were included. Exercise achieved significant improvements in CRF (standardized mean difference [SMD] = 1.24, 95% confidence interval or CI [0.43, 2.06], $I^2$ = 93%) and QoL (SMD = 1.40, 95% CI [0.05, 2.75], $I^2$ = 95%). Based on the meta-regression and Bayesian model, combined moderate-intensity continuous training aerobic exercise and resistance exercise (MICT/RES) showed the highest probability of ranking first in terms of CRF and QoL improvement, but the results of QoL were unstable. Exercise training also had a positive effect on urinary toxicities (SMD = –0.53,

95% CI [−0.79, −0.27], $I^2$ = 0%). A subgroup analysis indicated that MICT/RES might be the most promising exercise modality for reducing intestinal toxicities (SMD = −1.76, 95% CI [−2.32, −1.20]).

*Conclusions:* MICT/RES might be superior to any other types of exercise at reducing CRF. MICT/RES was more effective on significantly mitigating urinary and intestinal toxicities.

*Patient summary:* In prostate cancer (CaP) survivors during radiation therapy, exercise training is an effective and safe intervention to reduce cancer-related fatigue (CRF) and improve quality of life (QoL), and should be prescribed as a rehabilitation option for clinical management. As for the types of exercises, moderate-intensity continuous training aerobic exercise and resistance exercise seem to be the most effective interventions to reduce CRF, improve QoL, and mitigate treatment-related symptoms.

## 1. Introduction

For men, prostate cancer (CaP) is the most common cancer newly diagnosed in 2021 in the USA, which accounts for 248 530 estimated new cases and 26% of diagnoses [1]. Radiation therapy (RT) with or without androgen deprivation therapy (ADT) is one of the commonly used and effective treatment modalities for localized and locally advanced CaP [2,3]. Numerous studies indicated that both RT and ADT are significantly associated with adverse effects (AEs) including fatigue and treatment-related toxicities, such as urinary, intestinal, and hormone toxicities [4,5]. Additionally, the symptom of cancer-related fatigue (CRF) can appear in up to 70% of CaP survivors during RT, and CRF may persist in approximately 23% of them 1 yr after their treatment, which may contribute to poor quality of life (QoL), and difficulty in independent living and returning to work [6–8].

Improved prognosis has created growing needs to address the unique health issues facing CaP survivors that result from CaP, its treatment, and related comorbid conditions. Current guidelines recommend that moderate-intensity continuous training (MICT) aerobic exercise, resistance exercise (RES), and MICT plus RES (MICT/RES) performed two to three times per week for at least 12 wk could result in improvements in CRF and QoL of cancer survivors [9]. However, differences among cancer survivors by cancer type, treatment received, and other factors are known to exist, which limit their applications in individual patients. Furthermore, high-intensity interval training (HIIT) aerobic exercise, which has been investigated in CaP survivors in recent years [10], has not been included in the most recent exercise guidelines for cancer survivors [9].

For CaP survivors during RT, the existed randomized controlled trials (RCTs) and pairwise meta-analysis are often designed to compare one or more exercise types with data from usual care (UC) groups. In this context, it is difficult to determine the superiority of the different exercise types. Therefore, the present study aims to perform a network meta-analysis (NMA) utilizing the reconstructed clinical data derived from RCTs to evaluate the efficacy of exercise types in CRF and QoL of CaP survivors during RT, and try to establish a hierarchy of different exercise types.

## 2. Evidence acquisition

### 2.1. Search strategy and selection criteria

We performed a systematic review and NMA following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline and its extension for NMA [11,12]. We searched PubMed, Web of Science, and ClinicalTrials.gov up to November 2021 to identify potentially relevant studies. The following searching terms were used: ("Prostate Cancer") AND ("Exercise" OR "Physical Activity" OR "Resistance Training" OR "Aerobic"). We conducted the study eligibility using the population, intervention, comparator, outcome, and study (PICOS) approach: (P) studies focused on patients with CaP during RT with or without ADT, (I) who received clinic- and/or home-based exercise, (C) in which UC was used as a comparator, (O) reporting one or more of treatment-related AEs (S) in RCTs.

### 2.2. Study selection and data extraction

Two independent investigators screened all titles and abstracts, and assessed full text for eligibility. Figure 1 shows the PRISMA flowchart about the selection process. Two reviewers extracted the following data from included studies: author, year of publication, country, study period, sample size, age, cancer stage, details of RT and exercise intervention, and relative outcomes. Any disagreements were resolved by a third reviewer.

### 2.3. Definition of exercise and outcomes

Each type of exercise was devised using the frequency, intensity, time, and type (FITT) principle of exercise prescription according to the American College of Sports Medicine (ACSM) [9,13]. HIIT was defined as repeated high-intensity interval bouts between 80% and 100% of the theoretical maximal heart rate (THRmax) interspersed with recovery periods or light exercise [14]. MICT was defined as an appropriate intensity of 60–75% of the THRmax [14].

Studies using percentage of peak oxygen consumption to define exercise intensity were included when the values were equivalent to 60–75% or 80–100% of THRmax according to the ACSM [15].

The primary outcomes were CRF and QoL. CRF was measured by the Functional Assessment of Chronic Illness Therapy-Fatigue, the Brief Fatigue Inventory, or the revised Piper Fatigue Scale. QoL was evaluated with the Functional Assessment of Cancer Therapy-General (FACT-G). The secondary outcomes were disease/treatment-related toxicities, including CaP-specific symptoms; urinary, intestinal, sexual, and hormone toxicities; and sleep problems. CaP-specific symptoms were assessed by the Functional Assessment of Cancer Therapy-Prostate. The five types of treatment-related toxicities/problems were evaluated with the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer, the Expanded Prostate Cancer Index Composite and QLQ-C30 version 3.0, the International Index of Erectile Function Questionnaire, the International Prostate Symptom Score Sheet, the Pittsburgh Sleep Quality Index, and a specific module for CaP (QLQ-PR25).

### 2.4. Study quality assessment

Two independent investigators evaluated the quality of individual studies using the Tool for the assEssment of Study qualiTy and reporting in Exercise (TESTEX) scale [16], which is a study quality and reporting assessment tool and designed specifically for use in exercise training studies. Furthermore, TESTEX is a 15-point scale (five points for study quality and ten points for reporting) and addresses previously unmentioned quality assessment criteria specific to exercise training studies [16].

### 2.5. Certainty of evidence (GRADE)

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) process was used to evaluate the quality of evidence for CRF; QoL; CaP-specific symptoms; urinary, intestinal, sexual, and hormone toxicities; and sleep problems [17–19]. GRADE specifies four categories for each outcome: high, moderate, low, and very low. Randomized trials begin as high-quality evidence, and then address five reasons (limitations of study design, inconsistency of results, indirectness of evidence, imprecision, and reporting or publication bias) to possibly rate down the quality of evidence and three reasons (large magnitude of effect, confounding which would reduce the effect, and dose-response gradient) to possibly rate up the quality. Any disagreements were solved by a third reviewer.

### 2.6. Statistical analyses

Standardized mean differences (SMDs) were estimated for all our results because a part of our results was assessed by different questionnaires. As recommended in the Cochrane Handbook for Systematic Reviews of Interventions, for reverse scaled outcomes of CRF and QoL (where lower values indicate a better outcome) and disease/treatment-related toxicities (where higher values indicate a better outcome), the mean values in each group were multiplied by –1 to ensure same direction of measuring effects [20]. The analysis was conducted in two steps:

Firstly, a pairwise meta-analysis was conducted to calculate the SMD of both primary and secondary outcomes between the mean values in the exercise and UC groups. Considering the underlying qualities/differences of the populations of each included study, the Mantel-Haenszel random-effect model was applied. We combined the SMDs of both overall population and subgroups, which were based on the different types of exercise, given the aim of the present NMA and the existing pairwise meta-analysis [21,22]. Heterogeneity across studies was formally tested using chi-square ($p < 0.05$) and the $I^2$ statistic.

Secondly, Bayesian analyses were applied for an NMA with random effects only for our primary outcomes [23]. We reported consistent results between direct and indirect comparisons assessed by node-splitting analyses. Convergence is evaluated by applying the Brooks-Gelman-Rubin method. Within- and between-chain variance was compared by this method to calculate the potential scale reduction factor (PSRF). A PSRF close to 1 suggested that approximate convergence has been reached [24]. There were four chains, initial value scaling was 2.5, tuning iterations were 40 000, simulation iterations were 100 000, and thinning interval was 10. For each iteration, the ranking of different types of exercises and UC was determined using the SMD from that iteration. Surface under the cumulative ranking curve (SUCRA) was assessed from the ranking by summing the cumulative probabilities of all ranks divided by the number of ranks minus 1.

Additionally, to test whether study-level covariates could explain the heterogeneity of treatment effects between trials, univariate meta-regressions were performed for our primary outcomes [25]. The adjusted $R^2$, which was calculated from the between-trial variance $\tau^2$, was applied to explain the variability for each model [26]. Radiation dose, usage of concurrent ADT, length of the intervention, frequency of exercise, dose of exercise, and type of exercise were included in this analysis. Except the type of exercise, all these study-level covariates were fitted as continuous variables.

The significant level was $p < 0.05$ for statistical tests. All statistical analyses were conducted, and forest plots were generated using the "gemtc," "rjags," "meta," and "metafor" packages from R 4.1.2 (R project) and Review Manager v5.4 software.

## 3. Evidence synthesis

### 3.1. Study selection and network geometry

A total of 1358 studies were identified for eligibility. Following a review by title and abstract, 271 unique records progressed to a full-text review. Of these, eight unique studies fulfilled our inclusion criteria. Figure 1 illustrates the detailed process. Additionally, the included eight studies came from seven trials, as one of our included trials reported their outcomes in two studies [27,28].

In total, seven [29–35] and five [29,32–34] trials comparing five interventions (HIIT, MICT, RES, MICT/RES, and UC)
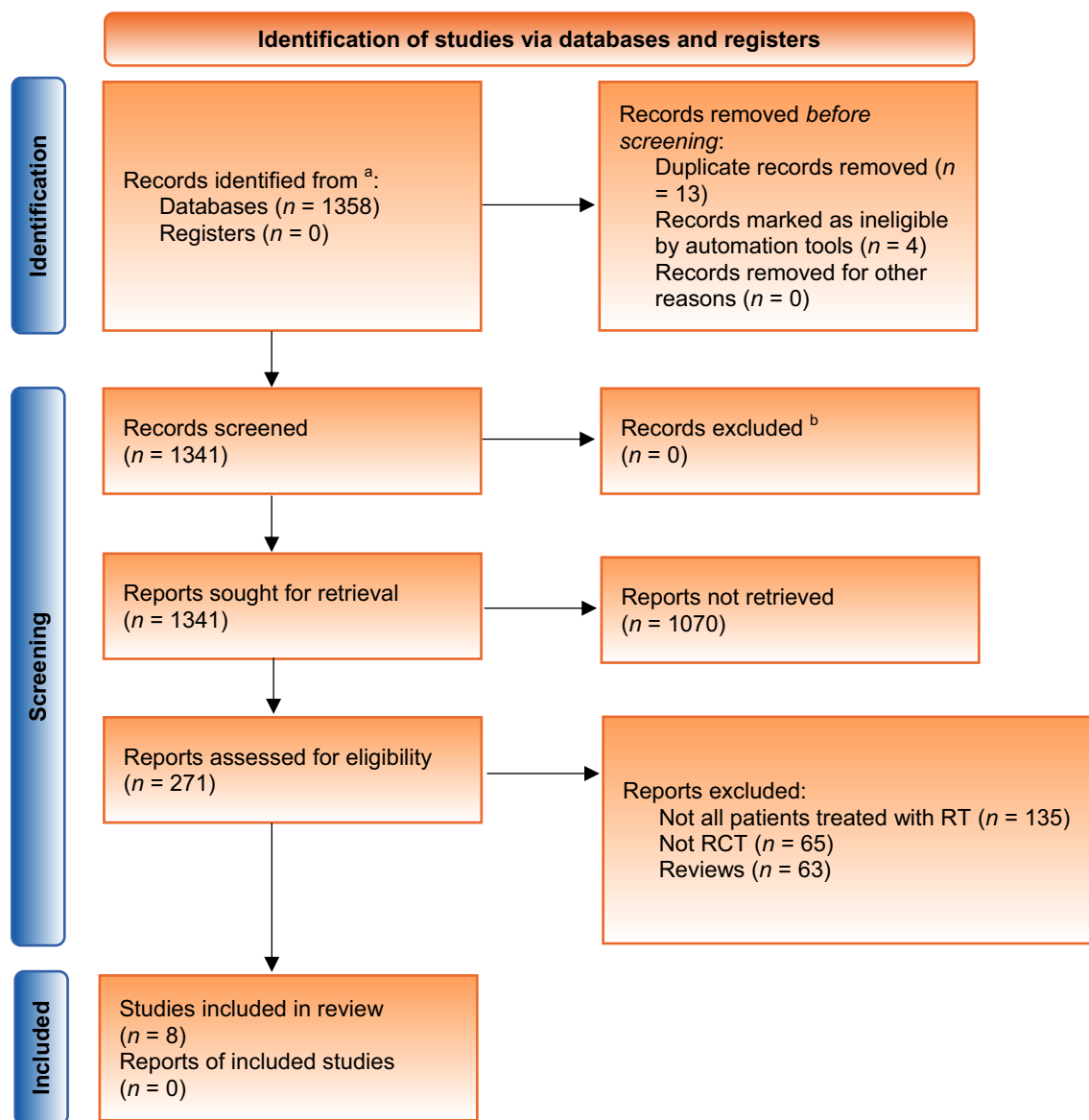
Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram of study selection. RCT = randomized controlled trial; RT = radiation therapy; [a]Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). [b]If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

were assessed for CRF and QoL in our included studies, respectively. Only one study was not included in the present NMA due to missing data on CRF at baseline [35] and after RT, and total data of QoL [31]. The well-connected network structure for both CRF and QoL are displayed in Figure 2. The width of the lines represents the number of trials comparing each pair of treatments. The size of the circle represents the sample size in each arm. More details of the numbers of trials and sample size of each treatment are presented in Figure 2.

### 3.2. Characteristics of included studies

The characteristics of the included studies and exercises are presented in Tables 1 and 2. A total of 466 participants with average age ranging between 62.2 and 71.9 yr were included. All our included patients were treated with RT with or without ADT. A detailed description of RT and disease stage is provided in Table 1. Two of our included studies did not report the details of RT [31,33]. In terms of different types of exercises, 24 participants were included in the HIIT group, 127 in the MICT group, 36 in the MICT/RES group, 85 in the RES group, and 194 in the UC group. A detailed definition of each type of exercise using FITT is provided in Table 2.

The evaluation of study quality and reporting of included studies are described in Table 3. The studies achieved a mean score of 10.6/15 on the TESTEX scale. Three of our included studies demonstrated whether these specified and fulfilled diagnostic test values of CaP for all participants
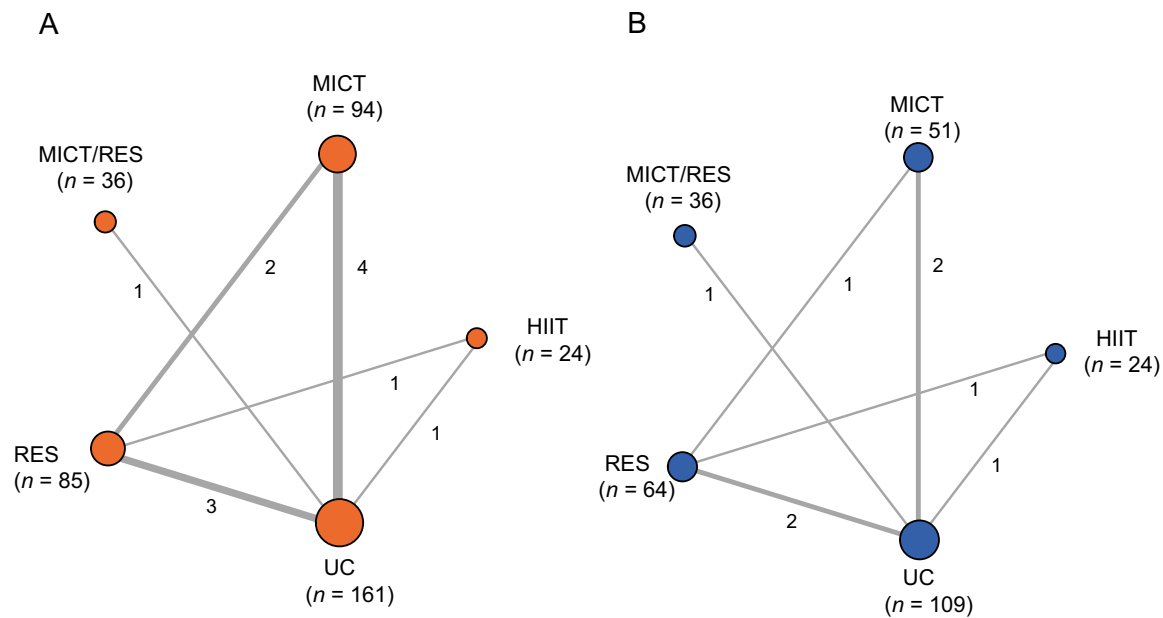
Fig. 2 – Network of the comparisons for the Bayesian network meta-analysis: (A) CRF and (B) QoL. The size of the nodes is proportional to the number of patients (in parentheses) randomized to receive the treatment. The width of the lines is proportional to the number of trials (the numbers between each node) comparing the connected treatments. CRF = cancer-related fatigue; HIIT = high-intensity interval training aerobic exercise; MICT = moderate-intensity continuous training aerobic exercise; QoL = quality of life; RES = resistance exercise; UC = usual care.

[31–33]. Additionally, only one study clearly stated whether the assessors of primary outcome measures were blinded to the intervention allocation of the patients [32].

### 3.3. Acceptability, feasibility, and safety of exercise

Among 1074 patients initially screened for inclusion, 525 (48.9%) were accepted; of them, 450 (85.7%) completed the trials (Table 1). Five of our included studies had the rates of >90% [27,29,32,33,35]. Some of the commonly reported reasons for refusing to take part in or for early dropping out of the study were treatment-related time constraints, lack of motivation, unable to contact, low interest, and physical or medical contraindications.

Four of our included studies mentioned AEs related to exercise during their follow-up [29,31–33]. Totally, six AEs occurred among the four trials (6/313, 1.9%). Additionally, no exercise-related AEs were recorded in two of the four studies [29,31]. Both Hojan et al. [32] and Segal et al. [33] reported three AEs. Hojan et al. [32] reported three overuse injuries to the lower extremities in exercise group. Segal et al [33] reported that one man experienced chest pain in the RES group during exercise, one man had syncope before his treadmill exercise test in the MICT group, and one man suffered acute myocardial infarction in the MICT group.

### 3.4. Results of primary outcomes

#### 3.4.1. Cancer-related fatigue
Seven studies (Table 1) with 466 participants and five interventions contributed to the pairwise meta-analysis assessing CRF. The pooled results of these studies indicated a large-sized and significant amelioration in the CRF of the exercise group compared with UC (SMD = 1.24, 95% confidence interval or CI [0.43, 2.06], $I^2$ = 93%; Table 4). A sensi-

tivity analysis showed consistent results. Comparisons of the changes from before to after intervention between each type of exercise and UC revealed significant differences in CRF, except for RES (HIIT vs UC: SMD = 0.80, 95% CI [0.21, 1.39]; MICT vs UC: SMD = 0.71, 95% CI [0.12, 1.30]; RES vs UC: SMD = 0.41, 95% CI [–0.11, 0.94]; MICT/RES vs UC: SMD = 4.19, 95% CI [3.33, 5.04]; Fig. 3A).

As for the NMA, six studies with 400 participants and five interventions were included. HIIT contributed 6.0% of the data, MICT 23.5%, RES 21.3%, MICT/RES 9.0%, and UC the remaining 40.2% (Fig. 2A). The results of the NMA are shown in Table 5. Indirect evidence could be generated for four comparisons for which direct evidence was not available (HIIT vs MICT, HIIT vs MICT/RES, MICT vs MICR/RES, and RES vs MICT/RES). MICT/RES was significantly more efficacious for improving CRF than the other four interventions (Table 5). Although there were no significant differences, HIIT, MICT, and RES could also show the potential for improving CRF. In addition, there were no significant differences among the efficacy of HIIT, MICT, and RES on CRF (Table 5). Based on Bayesian modeling, MICT/RES showed the highest probability of ranking first; HIIT, MICT, and RES displayed a similar probability of ranking first in terms of improving CRF (Fig. 4A). Last, we ranked the probability of each type of exercise in improving CRF applying the SUCRA, which indicated that the probabilities of HIIT, MICT, RES, MICT/RES, and UC were 39.1%, 57.5%, 45.4%, 99.6%, and 8.3% for ameliorating CRF, respectively. The quality of evidence for CRF was moderate (Table 4).

#### 3.4.2. Quality of life
Four studies, including 284 participants and all five interventions, contributed to both pairwise meta-analysis and NMA. The pooled results of the four studies showed a

**Table 1 – Summary of studies included in network meta-analysis indicating the exercise intervention used and the outcome measures reported for comparison within the analysis**

| Study | Arm | Patients screened | Patients accepting intervention (%) | Patients completing intervention (%) | Sample size | Disease stage | Age, mean (SD) | Treatment details | Outcome measures reported |
|---|---|---|---|---|---|---|---|---|---|
| Piraux (2021) [29] | HIIT | 84 | 78 (92.9) | 72 (92.3) | 24 | Localized and locally advanced prostate cancer | 67.4 (8.9) | 62.0–78.0 Gy in 26–39 fractions for 5–8 wk | CRF, QoL, toxicity: sleep |
| | RES | | | | 24 | | 67.9 (7.1) | | |
| | UC | | | | 24 | | 71.9 (8.1) | | |
| McQuade (2017) [30] | MICT | 210 | 90 (42.9) | 62 (68.9) | 21 | Prostate cancer (stages I–III) | 62.2 (7.4) | 75–76 Gy in 36–42 fractions for 6–8 wk | CRF, toxicity: urinary, intestinal, hormonal, sleep |
| | RES | | | | 21 | | 65.0 (5.9) | | |
| | UC | | | | 24 | | 66.0 (8.4) | | |
| Ben-Josef (2017) [31] | MICT | 213 | 68 (31.9) | 50 (73.5) | 22 | Prostate cancer (stages I–II) | 66.2 (5.3) | NR | CRF, QoL, toxicity: sexual |
| | UC | | | | 28 | | 68.2 (7.3) | | |
| Hojan (2017) [32] | MICT/RES | 100 | 72 (72.0) | 70 (97.2) | 36 | High-risk prostate cancer | 67.4 (8.3) | 76 Gy in 38 fractions for over 8 wk | CRF, QoL, toxicity: urinary, intestinal, hormonal, sexual, sleep |
| | UC | | | | 34 | | 69.9 (7.2) | | |
| Kapur (2010) [27] | MICT | 77 | 66 (85.7) | 65 (98.5) | 33 | Localized prostate cancer | 68.3 (0.9) | 52 Gy in 20 fractions over 4 wk | Toxicity: urinary, intestinal, hormonal |
| | UC | | | | 33 | | 69.3 (1.3) | | |
| Segal (2009) [33] | MICT | 325 | 121 (37.2) | 110 (90.9) | 40 | Prostate cancer | 66.2 (6.8) | NR | CRF, QoL, toxicity: prostate |
| | RES | | | | 40 | | 66.4 (7.6) | | |
| | UC | | | | 41 | | 65.3 (7.6) | | |
| Monga (2007) [34] | MICT | 65 | 30 (46.2) | 21 (70.0) | 11 | Localized prostate cancer | 68.0 (4.2) | 68–70 Gy in 34–38 fractions for 7–8 wk | CRF, QoL, toxicity: prostate |
| | UC | | | | 10 | | 70.6 (5.3) | | |
| Windsor (2004) [35] | MICT | 77 | 66 (85.7) | 65 (98.5) | 33 | Localized prostate cancer | 68.3 (0.9) | 52 Gy in 20 fractions over 4 wk | CRF |
| | UC | | | | 33 | | 69.3 (1.3) | | |

CRF = cancer-related fatigue; HIIT = high-intensity interval training aerobic exercise; MICT = moderate-intensity continuous training aerobic exercise; NR = not reported; QoL = quality of life; RES = resistance exercise; SD = standard deviation; UC = usual care.

**Table 2 – Definition of the exercise training interventions using the FITT principle**

| Study | Type of exercise | Definition | | | |
|---|---|---|---|---|---|
| | | Frequency | Intensity | Time (wk) | Type |
| Piraux (2021) [29] | HIIT | 3 times/wk, each session lasting 26–40 min | ≥85% THRmax | 5 or 8 | Cycle ergometer |
| | RES | 3 times/wk, each session lasting 30 min | Four and six RPE | | Major muscle groups |
| McQuade (2017) [30] | MICT | 3 times/wk, each session lasting 40 min | NR | 6–8 | QGTC |
| | RES | 3 times/wk, each session lasting 40 min | NR | | A combination of 3 levels of resistance tubes |
| Ben-Josef (2017) [31] | MICT | 2 times/wk, each session lasting 75 min | NR | 6–9 | Eischens yoga |
| Hojan (2017) [32] | MICT/RES | 5 d/wk, each session lasting 50–55 min | MICT: 65–70% THRmax; RES: 70–75% 1RM | >8 | MICT: brisk walking, running indoors or on a treadmill, or various cycling activities; RES: two sets of eight repetitions of five different exercises |
| Kapur (2010) [27] | MICT | 3 times/wk, each session lasting 30 min | 60–70% THRmax | >4 | Continuous (aerobic) walking |
| Segal (2009) [33] | MICT | 3 times/wk, each session lasting 45 min | 50–75% VO$_2$peak | 24 | Cycle ergometer, treadmill, or elliptical trainer |
| | RES | 3 times/wk, each session lasting 45 min | 60–70% 1RM | | Major muscle groups |
| Monga (2007) [34] | MICT | 3 times/wk, each session lasting 45 min | <75% THRmax | 8 | NR |
| Windsor (2004) [35] | MICT | 3 times/wk, each session lasting 30 min | 60–70% THRmax | >4 | Continuous (aerobic) walking |

FITT = frequency, intensity, time, and type; HIIT = high-intensity interval training aerobic exercise; MICT = moderate-intensity continuous training aerobic exercise; NR = not reported; QGTC = Qiqong/tai chi; RES = resistance exercise; RM = repetition maximum; RPE = rate of perceived exertion; THRmax = theoretical maximal heart rate; VO$_2$peak = maximal oxygen uptake.

**Table 3 – Assessment of study quality and reporting of included studies**

| Study | Study quality | | | | | Score (0–5) | Study reporting | | | | | | | | | | Score (0–10) | Total score (0–15) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | | 6a | 6b | 6c | 7 | 8a | 8b | 9 | 10 | 11 | 12 | | |
| Piraux (2021) [29] | 0 | 1 | 1 | 1 | 0 | 3 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 | 12 |
| McQuade (2017) [30] | 0 | 1 | 1 | 1 | 0 | 3 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 6 | 9 |
| Ben-Josef (2017) [31] | 1 | 1 | 1 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 5 | 8 |
| Hojan (2017) [32] | 1 | 1 | 1 | 0 | 1 | 4 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 9 | 13 |
| Kapur (2010) [27] | 0 | 1 | 1 | 1 | 0 | 3 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 8 | 11 |
| Segal (2009) [33] | 1 | 1 | 1 | 1 | 0 | 4 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 10 | 14 |
| Monga (2007) [34] | 0 | 1 | 0 | 1 | 0 | 2 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 6 | 8 |
| Windsor (2004) [35] | 0 | 1 | 1 | 1 | 0 | 3 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 7 | 10 |

1. Eligibility criteria specified.
2. Randomization specified.
3. Allocation concealment.
4. Groups similar at baseline.
5. Blinding of assessor.
6. Outcome measures assessed in 85% of patients; 6a, if adherence >85%; 6b, if adverse events are reported; 6c, if exercise attendance is reported.
7. Intention-to-treat analysis.
8. Between-group statistical comparisons reported; 8a, if between-group statistical comparisons are reported for the primary outcome measure of interest; 8b, if between-group statistical comparisons are reported for at least one secondary outcome measure.
9. Point measures and measures of variability for all reported outcome measures.
10. Activity monitoring in control groups.
11. Relative exercise intensity remained constant.
12. Exercise volume and energy expenditure.

large-sized and significant improvement in QoL of the exercise group compared with that of the UC group (SMD = 1.40, 95% CI [0.05, 2.75], $I^2$ = 95%; Table 4). The sensitivity analysis showed consistent results. The results of a pairwise meta-analysis indicated that only MICT/RES could significantly improve QoL of CaP patients treated with RT (MICT/RES vs UC: SMD = 3.74, 95% CI [2.95, 4.53]; Fig. 3B). As the FACT-G instrument was consisted with four subscales that measured symptoms or problems associated with

malignancies across physical well-being, social well-being, emotional well-being, and functional well-being [28], we further combined the results of the four subscales to determine the effect of exercise on QoL more deeply (Supplementary Table 1). The combined results suggested that there was a large-sized and significant improvement in physical and functional well-being of the exercise group compared with the UC group (Supplementary Table 1). On the contrary, there were no significant changes from before

**Table 4 – GRADE evidence profile: exercise for patients with prostate cancer during radiation therapy**

| Quality assessment | | | | | | | | | Summary of findings | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Design (no. of studies) | Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Large magnitude of effect | Confounding which would reduce the effect | Dose-response gradient | No. of patients | Outcomes SMD 95% CI | Quality |
| CRF (7) | VS (−2) | S (−1) | NS | NS | NS | VL (+2) | N | N | 466 | 1.24 (0.43, 2.06) | Moderate (++ +) |
| QoL (4) | S (−1) | S (−1) | NS | S (−1) | NS | VL (+2) | N | N | 268 | 1.40 (0.05, 2.75) | Moderate (++ +) |
| Urinary toxicities (4) | VS (−2) | S (−1) | NS | S (−1) | NS | N | N | N | 247 | −0.53 (−0.79, −0.27) | Very low (+) |
| Intestinal toxicities (3) | VS (−2) | S (−1) | NS | S (−1) | NS | L (+1) | N | N | 197 | −0.84 (−1.95, 0.27) | Very low (+) |
| Hormone toxicities (2) | VS (−2) | NS | NS | S (−1) | NS | | N | N | 132 | −0.20 (−0.54, 0.15) | Very low (+) |
| Prostate symptoms (2) | S (−1) | NS | NS | S (−1) | NS | N | N | N | 142 | −0.34 (−0.69, 0.01) | Low (++) |
| Sexual toxicities (2) | S (−1) | NS | NS | S (−1) | NS | N | N | N | 120 | −0.30 (−0.66, 0.06) | Low (++) |
| Sleep toxicities (3) | NS | NS | NS | S (−−1) | NS | N | N | N | 204 | −0.11 (−0.40, 0.17) | Moderate (++ +) |

CI = confidence interval; CRF = cancer-related fatigue; GRADE = Grading of Recommendations Assessment, Development and Evaluation; L = large; N = no; NS = not serious; QoL = quality of life; S = serious; SMD = standardized mean difference; VL = very large; VS = very serious.

to after intervention of social and emotional well-being between the exercise and UC groups (Supplementary Table 1).

As for the NMA, HIIT contributed 8.5% of the data, MICT 18.0%, RES 22.5%, MICT/RES 12.7%, and UC the remaining 38.4% (Fig. 2B). Network geometry was similar to CRF. Likewise, MICT/RES was also significantly more efficacious for improving QoL than the other four interventions (Table 5). There was also no significant difference between HIIT, MICT, and RES in terms of the effect on QoL. In the same way, Bayesian modeling indicated that MICT/RES had the highest probability of improving QoL (Fig. 4B). The SUCRA indicated that the contributions of HIIT, MICT, RES, MICT/RES, and UC were 39.3%, 57.4%, 45.4%, 99.7%, and 8.2% towards improving QoL, respectively. For QoL, the quality of the evidence was also moderate (Table 4).

### 3.5. Results of secondary outcomes

Treatment/disease-related toxicities before and after RT in patients with CaP were reported in seven studies (Table 1). Figure 5 presents the results of our pairwise meta-analysis for the efficacy of each type of exercise compared with UC.

As for urinary toxicities, the interventions that were found to significantly ameliorate urinary toxicities with a medium-sized effect compared with UC (exercise vs UC: SMD = −0.53, 95% CI [−0.79, −0.27]; Table 4). Additionally, MICT, RES, and MICT/RES could all significantly improve RT-related urinary toxicities compared with UC in patients with CaP (MICT vs UC: SMD = −0.33, 95% CI [−0.65, 0.02]; RES vs UC: SMD = −0.89, 95% CI [−1.54, −0.24]; MICT/RES: SMD = −0.83, 95% CI [−1.32, −0.34]; Fig. 5A). However, no significant difference was observed between the exercise and UC groups in terms of improving intestinal toxicities (Table 4). Subgroup results indicated that only MICT/RES could reduce the RT-related intestinal toxicity (MICT/RES vs UC: SMD = −1.76, 95% CI [−2.32, −1.20]; Fig. 5B). As for the remaining four types of toxicities, there were no significant differences between the exercise and UC groups in both overall and subgroup levels (Fig. 5C–F, and Table 4). The GRADE process assessed the quality of evidence for urinary, intestinal, and hormone toxicities as very low; prostate-specific symptoms and sexual toxicities as low; and sleep toxicities as moderate (Table 4).

### 3.6. Meta-regression

The effect of a 1-unit change of each study-level continuous variable and the type of exercise on the change in SMD, and the proportion of between-trial variability explained by univariate models for each variable are displayed in Table 6. For CRF, exercise more times a week and MICT/RES were significantly associated with a higher SMD in favor of exercise, especially MICT/RES (adjusted $R^2$ values were 37.54% and 75.06%, respectively; Table 6). However, as for QoL, our meta-regression analysis indicated that five of our tested variables, except the length of invention, were significantly associated with a higher SMD in favor of exercise (Table 6).
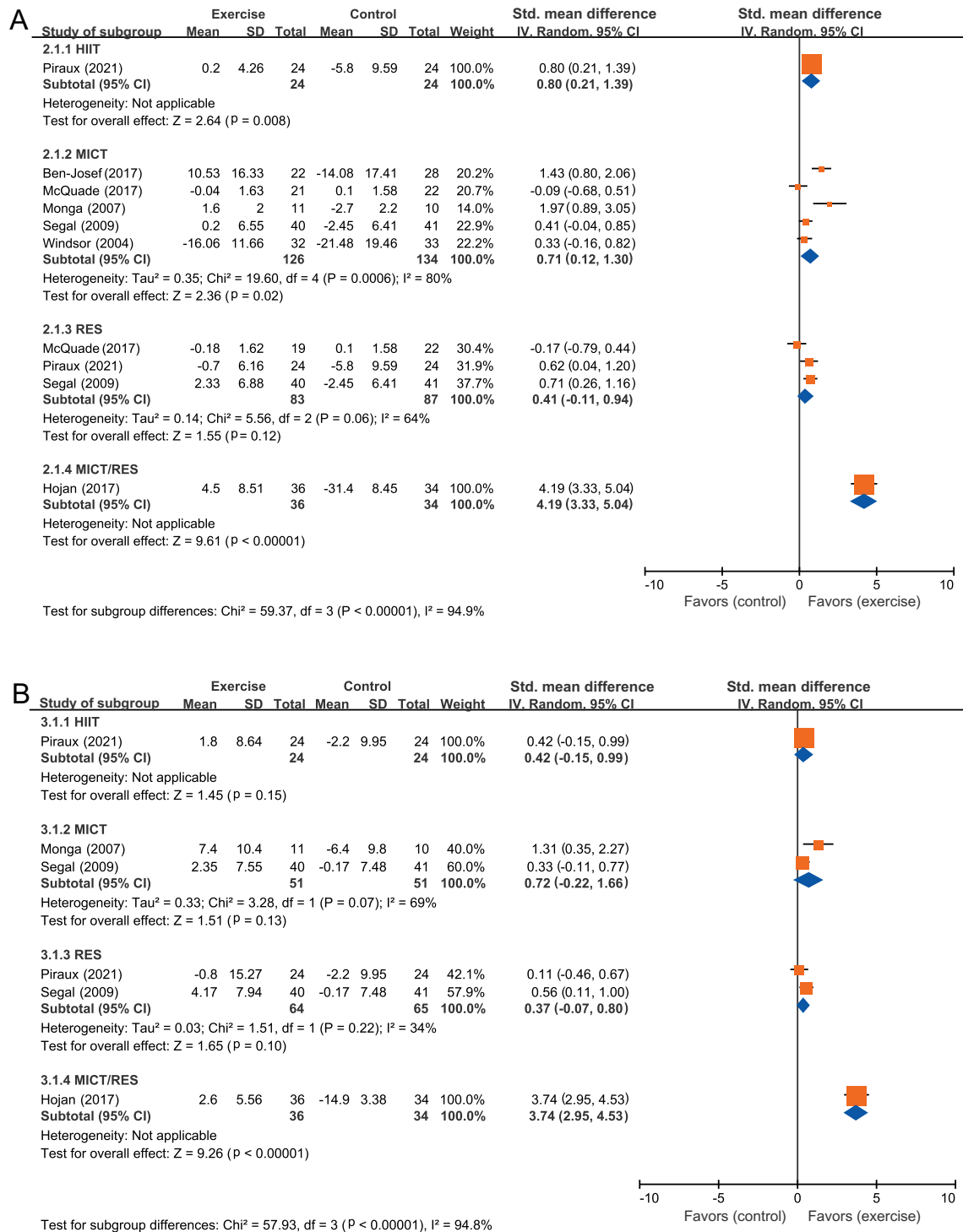
Fig. 3 – Pairwise meta-analysis for (A) CRF and (B) QoL among included studies. CI = confidence interval; CRF = cancer-related fatigue; df = degree of freedom; HIIT = high-intensity interval training aerobic exercise; IV = inverse variance; MICT = moderate-intensity continuous training aerobic exercise; QoL = quality of life; RES = resistance exercise; SD = standard deviation; Std. = standard.

### 3.7. Discussion

Based on evidence of moderate quality, the present results showed that exercise could significantly improve CRF and QoL for CaP patients during RT with or without ADT. More importantly, considering the results of the Bayesian modeling and meta-regression analysis, MICT/RES might have the highest probability of improving CRF and QoL among the five interventions; however, the results of QoL were unstable based on the present data. As for treatment-related tox-

**Table 5 – Network meta-analysis for RR of CRF (below diagonal) and QoL (above diagonal)**

| | | | | |
|---|---|---|---|---|
| HIIT | −0.01 (−3.29, 3.17) | **−4.97 (−9.09, −0.65)** | 0.10 (−2.60, 2.90) | 0.36 (−2.49, 3.27) |
| −0.33 (−2.53, 1.62) | MICT | **−4.96 (−8.47, −1.04)** | 0.12 (−2.43, 2.65) | 0.40 (−1.67, 2.40) |
| **−4.34 (−7.29, −1.47)** | **−4.00 (−6.46, −1.55)** | MICT/RES | **5.05 (1.31, 8.75)** | **5.35 (2.22, 8.29)** |
| −0.06 (−2.07, 1.78) | 0.27 (−0.98, 1.68) | **4.27 (1.88, 6.79)** | RES | 0.28 (−1.87, 2.38) |
| 0.46 (−1.52, 2.30) | 0.80 (−0.14, 1.93) | **4.80 (2.67, 7.04)** | 0.53 (−0.67, 1.75) | UC |

CRF = cancer-related fatigue; HIIT = high-intensity interval training aerobic exercise; MICT = moderate-intensity continuous training aerobic exercise; QoL = quality of life; RES = resistance exercise; UC = usual care.
Bold values indicate statistically significant.
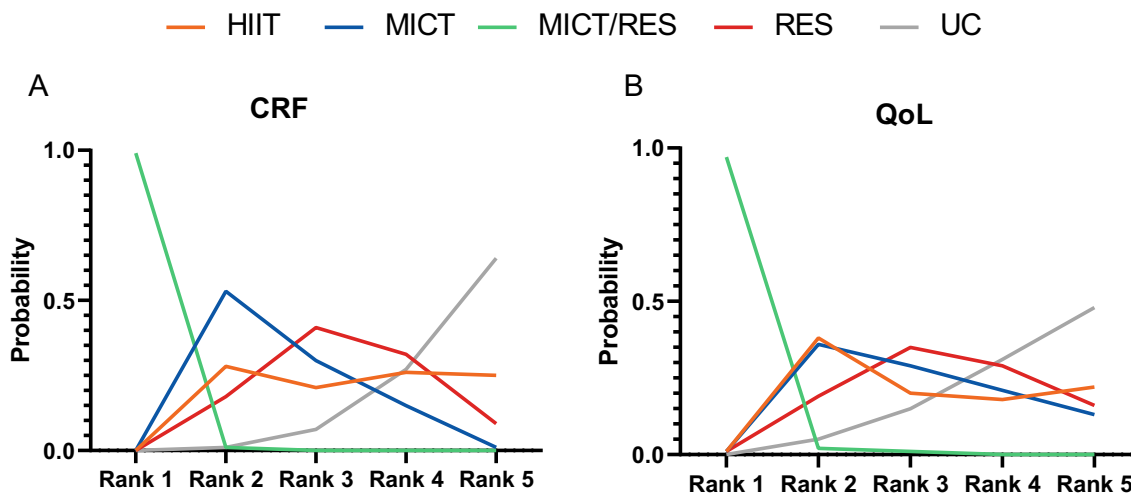


Fig. 4 – Ranking of treatments in terms of (A) CRF and (B) QoL. CRF = cancer-related fatigue; HIIT = high-intensity interval training aerobic exercise; MICT = moderate-intensity continuous training aerobic exercise; QoL = quality of life; RES = resistance exercise; UC = usual care.

icities, our results suggested that any type of exercise could improve all urinary symptoms with a medium-sized effect, and only MICT/RES could significantly ameliorate intestinal toxicities with a large-sized effect. However, the quality of evidence for both was assessed to be very low.

Our results that exercise could significantly ameliorate CRF were corroborated by a previous meta-analysis. In the meta-analysis performed by Horgan and O'Donovan [21], the authors found that exercise could significantly improve CRF compared with UC in patients with CaP during RT (SMD = −1.03, 95% CI [−1.82, −0.24]). However, by complementing the latest data, we provide initial evidence of large variability in the exercise training effects on CRF in clinical practice and future clinical trials. A pairwise meta-analysis showed that, out of the five interventions investigated, only RES did not show a significant benefit in terms of improving CRF, and the NMA revealed that MICT/RES was superior to all the remaining interventions.

Although there were no studies directly or indirectly comparing the efficacy of different types of exercises in CaP patients during RT, the highest probability of MICT/RES to improve CRF was in accordance with the findings in breast cancer and noncancer patients [36–38]. Regarding breast cancer patients receiving RT, Lipsett et al. [36] pooled nine RCTs with 802 participants and showed that only combined aerobic exercise and RES could achieve significant benefits for fatigue (SMD = −0.37, 95% CI [−0.63, −0.11]).

Likewise, during adjuvant chemotherapy and RT for breast cancer, Medeiros et al. [37] revealed that combined resistance and aerobic training achieved the largest-sized effect on improvement among all the interventions that were included in the analysis (SMD = −1.13, 95% CI [−2.09, −0.17]). According to the ACSM, components of physical fitness (eg, aerobic capacity and muscular strength/endurance) could be used to evaluate the adaptability and responsiveness of patients to specific types of exercise [9]. Unsurprisingly, an NMA combining direct and indirect evidence from 45 RCTs including over 3566 adults demonstrated that a combined exercise including aerobic and resistance training is most promising for improving lean body mass and increasing cardiorespiratory fitness [38].

Given the impact of CRF on QoL of cancer patients [39], it is not surprising that MICT/RES was superior to any other exercise modality in improving QoL in CaP patients during RT. There was growing evidence that physical exercise could improve CRF and attenuate systemic inflammation, and thereby improve functional QoL [39,40]. Consistently, our results also showed that exercise training could significantly improve physical and functional well-being, and not social and emotional well-being. However, the meta-analysis performed by Horgan and O'Donovan [21] showed a nonsignificant improvement in QoL in CaP patients during RT (SMD = −1.01, 95% CI [−2.19, 0.18]). In our opinion, two major factors were responsible for diversity. Firstly, the lim-
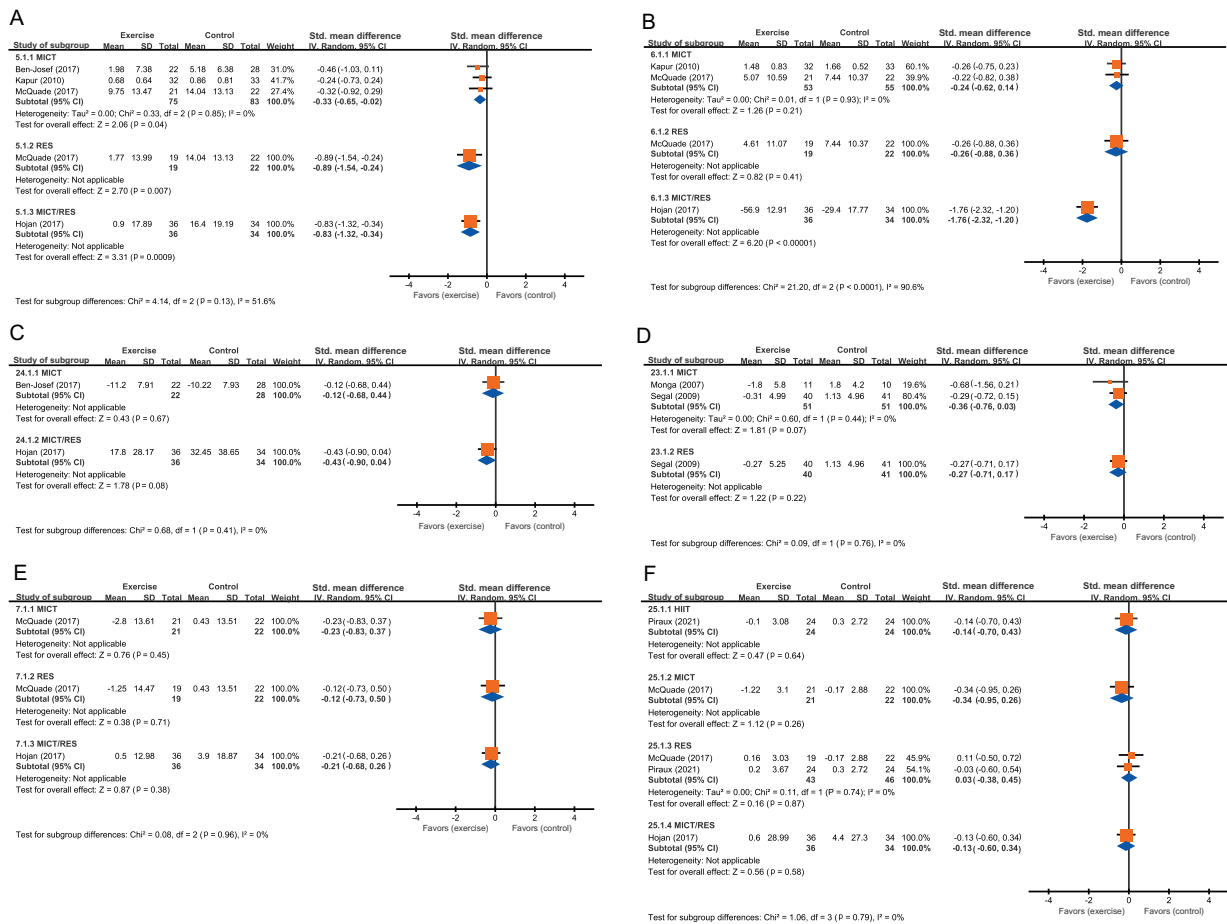
**Fig. 5 – Pairwise meta-analysis for our secondary results among included studies: (A) urinary toxicities, (B) intestinal toxicities, (C) sexual toxicities, (D) prostate-specific symptoms, and (E) sleep problems.** CI = confidence interval; df = degree of freedom; HIIT = high-intensity interval training aerobic exercise; IV = inverse variance; MICT = moderate-intensity continuous training aerobic exercise; RES = resistance exercise; SD = standard deviation; Std. = standard.

**Table 6 – The impact of trial-level characteristics on the effects of exercise on CRF and QoL in patients with prostate cancer during radiation therapy**

| Values | CRF | | | QoL | | |
|---|---|---|---|---|---|---|
| | Change in SMD (95% CI) | $p$ value | Adjusted $R^2$ (%) | Change in SMD (95% CI) | $p$ value | Adjusted $R^2$ (%) |
| Radiation dose | 0.0478 (−0.0997, 0.1935) | 0.5252 | 0.00 | 0.4428 (0.0656, 0.8200) | 0.0214* | 62.75 |
| Use of concurrent ADT | 0.0315 (−0.0095, 0.0725) | 0.1321 | 13.35 | 0.0689 (0.0000, 0.1377) | 0.0499* | 42.35 |
| Length of the intervention | −0.0193 (−0.1334, 0.0949) | 0.7407 | 0.00 | −0.0517 (−0.1975, 0.0941) | 0.4872 | 0.00 |
| Frequency of exercise | 1.1088 (0.2058, 2.0117) | 0.0161* | 37.54 | 1.6471 (1.2342, 2.0600) | <0.0001* | 100.00 |
| Dose of exercise | 0.0498 (−0.0038, 0.1035) | 0.0688 | 22.75 | 0.1169 (0.0071, 0.2267) | 0.0369* | 41.97 |
| Type of exercise | | | 75.06 | | | 81.26 |
| MICT | 0.3418 (−1.0785, 1.7622) | 0.6371 | | 0.4360 (−1.1441, 2.0161) | 0.5886 | |
| RES | 0.0013 (−1.4856, 1.4883) | 0.9986 | | −0.0875 (−1.6243, 1.4493) | 0.9111 | |
| MICT/RES | 3.7154 (1.7843, 5.6465) | 0.00002* | | 3.3140 (1.4450, 5.1830) | 0.0005* | |

ADT = androgen deprivation therapy; CI = confidence interval; CRF = cancer-related fatigue; MICT = moderate-intensity continuous training aerobic exercise; QoL = quality of life; RES = resistance exercise; SMD = standardized mean difference.
* $p < 0.05$.

ited data available in that analysis might not be enough to reach statistical significance. Secondly, one of the included RCTs conducted by Segal et al. [33] was designed as a three-arm study; however, the control group was pooled twice in that meta-analysis, which might have led to confusing results.

Our results indicated that exercise training could mitigate urinary toxicities. Additionally, only MICT/RES was

promising for improving intestinal symptoms. As mentioned, MICT/RES was superior to other interventions in improving lean body mass and increasing cardiorespiratory fitness [38]; therefore, it is indicated that this exercise modality is most promising for improving or at least maintaining the current aerobic capacity and muscular strength of pelvic muscle. Additionally, RT is considered a double-edged sword, as RT could improve survival and reduce

cancer-related symptoms, but it might also increase systemic inflammation [41,42], thereby negatively affecting urinary and intestinal functions during pelvic RT. Our results indicated that exercise training could play a positive effect on urinary and intestinal symptoms, especially MICT/RES. Mechanisms that may be hypothesized include the following: (1) exercise has been evidenced to ameliorate inflammation [41], and (2) the effect of exercise on intermediate measures such as insulin-related growth factors or other factors may in turn mediate acute radiation reactions [27]. However, the improvement of symptoms might also be due to a reduction in prostate volume following RT and ADT. Another systematic review performed by Schumacher et al. [22] also showed that exercise training could significantly reduce urinary toxicities in CaP patients during RT (SMD = –0.71, 95% CI [–1.25, –0.18]). On the contrary, there was no evidence of an effect of exercise on other side effects commonly associated with RT in CaP patients both in the present analysis and in the previous review [22], which included hormone toxicities, prostate-specific symptoms, sexual dysfunction, and sleep problems. This may be due to the limited clinical data available in the present analysis.

Nonetheless, the main findings of the present analysis need to be considered in the context of some key limitations. Firstly, a small number of studies with a small sample size were included. Secondly, although we applied a random-effect model for result generation and performed a subgroup analysis, the heterogeneity of our included RCTs might still reduce the robustness of the finding. Thirdly, two of our included studies investigated the efficacy of Qiqong/tai chi and yoga on CRF and QoL [30,31]. As the definitions of exercise training according to FITT were not available, we classified these as MICT according to the training modality that was introduced in these papers. Fourthly, as for CRF, our meta-regression analysis indicated that a higher frequency of exercise also significantly contributed to a higher SMD in favor of exercise, which could account for 37.54% of heterogeneity. Although the effect of the type of exercise in between-study heterogeneity was nearly double the effect of frequency of exercise, further high-quality RCTs should be designed to balance this variable between different exercise groups to generate a more confident conclusion. Regarding QoL, the results of our meta-regression analysis suggested that our subgroup analysis and NMA categories such as type of exercise were unstable. The different roles of exercise modality in QoL during RT should be investigated further. Fifthly, the median age of our included participants ranged between 62 and 72 yr. Therefore, the results of the present analysis might not be suitable for young or old men with CaP. Finally, no RCTs in the current analysis evaluated the impact of exercise training on survival. This might partially be due to excellent survival outcomes of CaP patients. However, it is also an important issue that needs further investigation.

## 4. Conclusions

In CaP survivors during RT, exercise training is an effective and safe intervention to reduce CRF and improve QoL, and should be prescribed as a rehabilitation option to the clinical management. As for the types of exercises, MICT/RES might be the most effective intervention to reduce CRF and mitigate treatment-related symptoms.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.07.008.

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