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Review

Effectiveness of Exercise-Based Interventions on Fatigue among Head and Neck Cancer Patients on Radiotherapy: Systematic Review with Meta-Analysis

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A R T I C L E   I N F O

Key Words:
Aerobic exercise
Fatigue
Head and neck cancer
Intensity-modulated radiotherapy
Resistance training
Well-being

A B S T R A C T

Objectives: Fatigue is a significant challenge among head and neck cancer patients undergoing radiotherapy, impacting their well-being and daily functioning. Exercise-based interventions hold promise in alleviating this fatigue burden. This systematic review aims to evaluate the effectiveness of exercise-based interventions on fatigue among patients with head and neck cancer receiving radiotherapy.
Methods: We systematically searched for the studies in Cumulative Index to Nursing and Allied Health Literature, PubMed, Cochrane Library Database, MEDLINE, and Google Scholar in the English language from 2000 to 2023. Two reviewers independently identified the articles using key thesaurus and free text terms based on the inclusion criteria. The review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. Meta-analysis was done by using RevMan 5.3 software.
Results: The systematic review included nine trials encompassing 647 participants, out of which five were randomized control trials and were selected for meta-analysis. Pooled data from randomized control trials showed that exercise-based interventions were effective in reducing few dimensions of fatigue such as general fatigue, physical fatigue, emotional fatigue significantly ($P < .001$) among Head and Neck Cancer patients receiving radiotherapy.
Conclusion: Preliminary evidence from the review suggests that engaging in exercise-based interventions may reduce fatigue among patients with head and neck cancer receiving radiotherapy. However, future research is necessary, as most of the articles in current review were either pilot studies or feasibility trials.
Implications for Nursing Practice: This systematic review and meta-analysis protocol was registered in PROSPERO with the register number CRD42023428284.

Globally, head and neck cancer (HNC) ranks as the seventh most prevalent cancer, with over 660,000 new diagnoses and 325,000 fatalities reported each year.[1,2] The primary approach for treating locally advanced head and neck squamous cell carcinoma typically involves either surgical intervention followed by adjuvant radiation therapy or concurrent chemoradiation (CRT) as the definitive treatment.[3] The intricacy of HNC necessitates a multidisciplinary approach, and radiotherapy plays an important role in the effective management of patients with HNC.[3] Radiotherapy induces damage to the deoxyribonucleic acid within the cancer cells, thereby producing the desired therapeutic outcome.[4]

As with other cancer therapies, radiotherapy can induce side effects that differ based on the cancer type, its location, the radiation dosage, and the patient's overall health. Damage to healthy cells and tissues in close proximity to the treatment areas results in side effects. Innovative and highly precise developments in radiotherapy have significantly decreased the adverse effects of treatment when compared to earlier practices.[5] Normal structures close to the target area are nevertheless vulnerable to various harmful impacts (eg, mucositis, edema, radionecrosis, fistula, sialadenitis), despite these advancements in radiation delivery technology.[6] Early side effects such as mucositis, xerostomia, pain, odynophagia, dysphagia, nausea, vomiting, weight loss, and inadequate nutrition can interfere and delay the treatment.[7]

Fatigue is a subjective experience, which is a complex physiological state characterized by a temporary decrease in the capacity for

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Layperson Summary

What we investigated?

Fatigue is one of the most common and debilitating side effects experienced by patients receiving radiotherapy for head and neck cancers that can impact the daily functioning. This review examines the effect of exercises on relieving fatigue among head and neck cancer patients during radiotherapy.

How we did our research?

We examined the effect of exercises on relieving fatigue among head and neck cancer patients during radiotherapy based on the research studies conducted between 2000 to 2023.

What we have found?

The aggregated findings from nine research studied showed promising findings on reducing the few dimensions of fatigue such as general fatigue, physical fatigue, emotional fatigue significantly among head and neck cancer patients receiving radiotherapy. This review also confirmed that the exercises are generally safe for head and neck cancer patients during radiotherapy.

What it means?

Though the preliminary evidence from the review suggests that engaging in exercises may reduce fatigue among head and neck cancer patients receiving radiotherapy, this domain also requires more studies with larger sample as most of the studies included in this review are pilot or feasibility studies.

physical or mental activity. Early fatigue is observed in up to 80% of cancer patients during the treatment or shortly thereafter.[8] Fatigue is among the most common side effects of radiotherapy among patients with HNC, and radiotherapy has the potential to induce cumulative fatigue,[7] which is progressive and intensified exhaustion due to the cumulative physiological impact of radiotherapy. It impacts between 50% and 90% of patients with HNC who are receiving radiotherapy.[9] Additionally, cancer-related fatigue (CRF), that is, the most distressing, persistent, subjective sense of physical, emotional, and cognitive exhaustion related to cancer or treatment,[10] is a significant issue frequently overlooked in patients with HNC.[8] Over the course of the radiotherapy, the fatigue is intensified,[9,11] and affects global, behavioral affective, and sensory/psychological domains of patients with HNC.[9] At the completion of their treatment, patients experience an exacerbation of fatigue, significantly affecting their general quality of life.[8] In a previous systematic review by Souza et al, reported fatigue to affect 70% of patients with HNC receiving CRT, and to be commonly related to pain, dyspnea, sleep disorders, lack of appetite, depression, and emotional stress.[12] It is also associated with psychoneurological symptoms such as sleeplessness, cognitive dysfunctions, and depression.[13,14] Fatigue is identified as one of the most common predictors for nonadherence to the treatment among HNC receiving radiotherapy.[15] It is significantly worst shortly followed by the treatment,[16] and also commonly identified symptom among patients with HNC.[16,17] Hence, assessing and managing fatigue during radiotherapy is crucial for improving the overall well-being of patients with HNC.[18]

There is consistent evidence that the exercises during cancer treatment in oncology are helpful in mitigating fatigue,[19,20] improving QOL,[19,21] for undergoing various treatments,[19,20] or even among patients with metastatic tumors.[21] Exercise during cancer treatment has proven beneficial in decreasing CRF and enhancing the QOL among patients undergoing cancer treatment.[22] Aerobic exercise programs and multimodal exercises (including resistance, aerobic, and flexibility exercises) have demonstrated effectiveness in improving fatigue symptoms among cancer patients receiving treatment.[23] Currently, the focus is on nonpharmacological and complementary treatments, with exercise during cancer treatment offering a multitude of advantageous results for patients affected by cancer.[24] A combination of exercise therapy and radiotherapy is deemed safe and easily tolerated among cancer patients, showing enhancement in patient-related outcomes and physical function.[25] Among patients with HNC, exercise training during CRT is well tolerated and feasible.[26] Engaging in exercise regimens could potentially avert decreasing muscle strength and increasing fatigue.[26]

Although there are studies on various exercise therapies to reduce fatigue in patients with HNC undergoing radiotherapy,[27–31] these are not yet explored systematically and synthesized. Thus, this underscores the need for conducting this systematic review and meta-analysis to examine the evidence pertaining to the effect of exercise-based interventions on fatigue in patients with HNC undergoing radiotherapy. This review findings would provide new insights into the effectiveness of exercise-based interventions in alleviating fatigue among patients with HNC undergoing radiotherapy.

Methodology

Review Design

The protocol for this systematic review and meta-analysis was officially registered in PROSPERO under the registration number CRD42023428284 and is accessible in the site. This review followed to the guidelines set forth in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement during its conduction.[32]

Eligibility Criteria

A quantitative approach involving a systematic review and meta-analysis was used to evaluate the effectiveness of exercise-based interventions on fatigue of patients with HNC subjected to radiotherapy and examined the quantitative studies composed of experimental study designs. We have included the studies examining the exercise-based interventions used on full body focusing on training of major muscle groups in a single training session during radiotherapy. The studies published only after 2000 and underwent peer review in the English language were considered for inclusion. We excluded the studies that initiated the implementation of exercise-based interventions after the completion of radiotherapy. We have excluded the studies involving patients with HNC including all the types of treatments and if the data related to only-radiotherapy group of patients with HNC was not available. Interventions related to expiratory muscle strength training and measured vocal fatigue as outcome were also excluded.

Search Strategy

Two independent reviewers (SGN and AG) conducted searches across five electronic citation databases: CINAHL, PubMed, Cochrane Library Database, MEDLINE, and Google Scholar. The free-text phrases and thesaurus were combined using appropriate Boolean operators with the filters of title and abstract. The detailed search strategy from each database is described in the Supplementary File. The citations and bibliography within the included studies were additionally examined to explore any further relevant research studies to include in this review. All articles found in the searches were transferred to Rayyan, an online systematic review software,[33] for

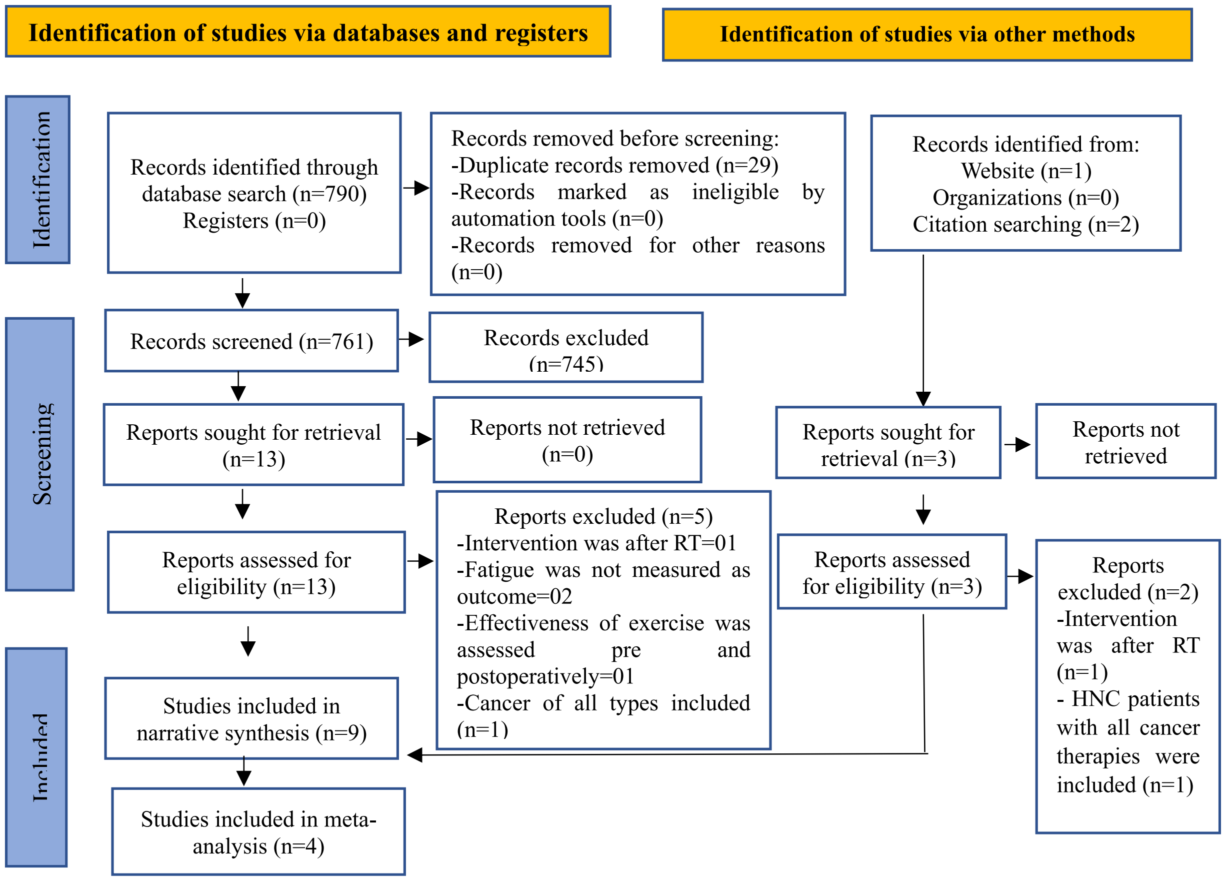

FIG 1. PRISMA Flow diagram of the study selection

eliminating duplicates and the title and abstract screening. Titles, abstracts, and full texts were independently evaluated by 2 reviewers in order to examine the studies for inclusion according to predefined eligibility criteria. Any discrepancies in the reviewers' assessments regarding the eligibility of studies were resolved through the discussion involving a third reviewer (KS).

Data Extraction and Analysis

A data extraction template was formulated and used by the reviewer (SGN) to collect data from individual studies. The data were collected independently by a single reviewer (SGN), and the second reviewer (AG) verified the data. Authors' details, country, year of publication, sample size, study design, description of exercise-based intervention, treatment details of control group, fatigue measurement tools and outcomes, and other outcomes measured were the elements in the data extraction template. A pilot test of the data extraction template was conducted ahead of the review, and it was decided to include pre- and post-intervention fatigue in the meta-analysis.

The search yielded 793 titles, and 29 duplicate records were removed. The remaining 764 articles were assessed for titles and abstracts, leading to the removal of 748 articles as they did not meet the review's inclusion criteria. The complete texts of the remaining 16 articles were examined, and 7 of them were excluded as they did not align with the review's inclusion criteria. Finally, 9 articles remained for both quantitative analysis and descriptive summary, while 5 trials[27,28,30,31,34] were specifically included in the meta-analysis. Fig. 1 illustrates the visual representation outlining the process of study selection.

The Cochrane risk of bias tool-2 (RoB-2)[35] was used for evaluating the quality of the included Randomized Controlled Trials (RCTs) (Table 1), while the ROBINS-1 tool[36] was used to assess the quality of quasi-experimental studies. Two reviewers (SGN and KS) independently assessed the studies for risk of bias. A meta-analysis was conducted to pool the findings from the randomized controlled trials (RCTs) and the findings from other selected studies are presented

TABLE 1
Cochrane Risk of Bias Tool-2 (RoB-2) of Included Randomized Controlled Trials

Author/ year	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result
Grote et al, 2018[34]	No	No	No	No	no
Hu et al, 2020[31]	No	No	Probably yes/no Some concerns	No	no
Zhou et al, 2018[28]	No	No	No	No	no
Samuel et al, 2019[30]	No	No	Probably yes/no Some concerns	No	no
Rogers et al, 2012[27]	No	No	No	No	no

descriptively in tables. The impact of the exercise-based intervention was assessed by using a random-effects model to calculate weighted mean differences and standardized mean differences between the control and intervention groups. The calculation of the standardized mean difference involved adjustments for standard deviation. The heterogeneity among the studies was assessed using the I^2 test. The heterogeneity levels were categorized based on the I^2 values: less than 25% as low, between 25% and 75% as moderate, and greater than 75% as high heterogeneity. The software RevMan v5.3 was used to analyze and pool the data. To ensure the quality of evidence, we adopted the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach and guidelines.

Results

The systematic review encompassed 674 participants across 9 experimental studies, with study population ranging between 15 and 148 in individual studies. Among these, 350 were assigned to the intervention group, while 324 subjects were allocated to the control group.

Intervention details are summarized in Tables 2 and 3. Eight of 9 studies had only exercise-based interventions, while 1 had head and neck rehabilitation exercises combined with nutritional counseling.[37] Three of the 9 experimental studies examined resistance exercises,[27,31,34] while another 2 had aerobic and active resistance exercise.[30,38] One each included combined endurance and resistance training,[39] Tai Chi exercise,[28] rehabilitation exercises of the head and neck,[37] and daily walking.[29] The FITT principle serves as a framework to characterize general physical activity levels. This encompasses frequency (F), intensity (I), time (T), and the specific type of physical activity (T) (Table 3).[40] The exercise-based interventions implemented were reported to be safe and feasible for patients with HNC who were receiving RT in 5 experimental studies.[27,28,30,34,39] Three of the 5 experimental studies had low risk of bias,[27,28,34] while another 2 had moderate risk of bias (Table 1).[30,31]

Multiple tools were used to measure fatigue in the research studies included in this review: Multidimensional Fatigue Inventory (MFI).[34,38,39] Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF),[28,31] National Comprehensive Cancer Network (NCCN) Scale,[30] Functional Assessment of Cancer Therapy-Fatigue (FACT-F) subscale,[27] chronic disease self-management questionnaires,[37] and Brief Fatigue Inventory (BFI)[29] (Table 2). The MFI assessed various aspects of fatigue, such as general fatigue and physical fatigue, emotional fatigue, cognitive fatigue, and mental fatigue. The scores obtained from these multifaceted questionnaires directly correlated with the level of fatigue, where higher scores indicated heightened fatigue.[41,42] Although fatigue was the primary outcome, we used forest plots along with the summarization for evaluating the effectiveness of the exercise-based interventions based on these aspects of fatigue. In 3 interventions, fatigue was measured at baseline,[29,38,39] while another 3 compared the fatigue at baseline to that at the end of radiotherapy.[28,30,34] Three studies measured fatigue at mid-intervention: 2-4 weeks,[29] 3rd week,[30] and 5th week.[39] Seven studies had a follow-up even after radiotherapy: 8 weeks,[34] 11 weeks,[30] and 12 weeks after the end of radiotherapy.[27,31,37–39] Only 1 study reported outcomes at 12 months[37] (Table 2).

We conducted a meta-analysis of only RCTs, which included 5 studies comprising 443 participants, that included 221 and another 222 in the intervention and control groups, respectively. We used forest plots containing summaries to evaluate the effectiveness of exercise-based interventions in reducing the fatigue and its domains among patients with HNC. The impact of exercise-based interventions was measured postintervention (Figs. 2 and 3). The summary of the forest plot showed that exercise-based interventions were not statistically effective in reducing overall fatigue (MD: −5.9; 95% CI: −13.6, 1.65; $P = .12$; $I^2 = 96\%$) (Fig. 2). The exercise interventions were varied from resistance training,[27] progressive resistance training,[31] and aerobic and active resistance exercises[30] to Tai Chi exercises.[28] The duration of the exercise intervention varied from 7 weeks to 12 weeks. In 2 trials,[28,31] the exercise intervention was supervised, whereas Samuel et al performed it as supervised and monitored for home-based exercises,[30] and the trial by Rogers et al used a combination of supervised and unsupervised.[27] Of 4 studies included in the meta-analysis, 2 had a low risk of bias[27,28] and the remaining 2 were with moderate risk of bias.[30,31]

Exercise-based interventions were proved to be effective in reducing specific dimensions of fatigue, such as general fatigue (MD: −2.4; 95% CI: −3.3, −1.6; $P < .001$; $I^2 = 22\%$), physical fatigue (MD: −2.3; 95% CI: −3.4, −1.1; $P < .001$; $I^2 = 51\%$), emotional fatigue (MD: −2.4; 95% CI: −2.9, −1.8; $P < .001$; $I^2 = 0\%$), and vigor (MD: 2.4; 95% CI: 1.7, 3.2; $P < .001$; $I^2 = 19\%$) (Fig. 3). In all trials included in the meta-analysis of physical and general fatigue, the exercise-based interventions were supervised. One trial did not report the duration of intervention,[34] whereas another 2 had it for 7[28] and 12 weeks.[31] However, the sample size ranged from 20[34] to 146.[31] The trials included in the analysis of emotional fatigue and vigor reported that the exercise-based interventions were for the durations of 7[28] and 12 weeks[31] and were with adequate sample size. Two of 3 studies included in the meta-analysis of general and physical fatigue had low risk of bias,[28,34] whereas 1 contributed a moderate risk of bias.[31] Only 2 studies were included in the meta-analysis of emotional fatigue and vigor, with a low risk of bias[28] and a moderate risk of bias.[31] Very low (0%) to substantially high (96%) heterogeneity among the study results might be contributed to by the varying sample size. Differences in sample sizes among studies can influence the precision and reliability of effect estimates. Studies with smaller sample sizes may produce more variable effect sizes due to limited statistical power, potentially contributing to heterogeneity. No sensitivity analysis was performed as there was no subgroup analysis. All studies included in systematic reviews were found to be moderate or high certainty evidence as assessed by GRADE approach.

Discussion

This is an initial systematic review exploring the impact of exercise-based interventions during radiotherapy on fatigue in patients with HNC. The findings of our meta-analysis reveal that performing exercises during radiotherapy for patients with HNC is beneficial in reducing multidimensions of fatigue such as general fatigue, emotional fatigue, physical fatigue, and vigor at a statistically significant level, although the reduction in overall fatigue was not statistically significant. Fatigue stands out as a significant problem noted by cancer patients, particularly those undergoing radiotherapy, and early screening and rehabilitation are essential for alleviating symptoms.[24] Exercise-based interventions are practicable, safe, and advantageous for patients with HNC during radiotherapy or CRT[43] and have shown promising results in amelioration of fatigue in the HNC continuum.[44] They were found safe, feasible, and acceptable in research and clinical work during radiotherapy among patients with HNC.[27,28,30,34,39] Exercising is a safe, cost-effective, nonpharmacological therapy that can give numerous health advantages to cancer patients and survivors, including a reduction in treatment side effects and cancer symptoms.[45] However, commitment to physical activity can be of concern in this population and tends to decline following therapy.[43] Several reasons for withdrawal from exercise-based interventions were reported in the included studies, such as treatment intolerance (myelosuppression, oral shin reaction),[28] mucositis,[28,34] pain,[34] and treatment toxicity.[39] The negative effects of physical activity on cancer patients receiving systemic treatment remain unclear, and presently there are insufficient data on adverse outcomes.[46] Overall adherence to the supervised sessions was 54%, and only 44% attended at least

TABLE 2
Characteristics of the Studies in the Review

Author/ year	Country	Study design	Sample size	Control	Fatigue measurement scale	Fatigue measurement points	Other outcomes	Outcome measure (fatigue)
Grote et al, 2018[34]	Germany	Pilot RCT	T = 20 I = 10 C = 10	Usual care	Multidimensional Fatigue Inventory	At baseline before radiotherapy, after 7 wk of starting radiotherapy and 8 wk after the end of radiotherapy.	QOL, bioelectrical impedance analysis	Decrease in general and physical fatigue (P = .393), mental fatigue (P = .436), reduced activity (P = .912), and reduced motivation (P = .853)
Hu et al, 2020[31]	China	RCT	T = 146 I = 73 C = 73	Perform relaxation control	Multidimensional Fatigue Symptom Inventory-Short Form	At discharge and at 12 wk postdischarge	Quality of life, complications of chemoradiotherapy	No statistically significant difference at discharge. AT 12 wk postdischarge, significantly lower scores favoring intervention group in general fatigue (P = .035), physical fatigue (P = .027), emotional fatigue (P = .044) and mental fatigue (P = .013), and higher vigor (P = .014).
Zhou et al, 2018[28]	China	RCT	T = 114 I = 57 C = 57	Usual care	Multidimensional fatigue symptom inventory-short form (MFSI-SF)	Before chemoradiotherapy and after chemoradiotherapy	Heart rate variability parameters	Findings favoring the experimental group with lower total, general, physical, and emotional fatigue score and higher vigor score (P < .01 for all)
Samuel et al, 2019[30]	India	RCT	T = 148 I = 74 C = 74	Three 10-min walks during the day for 5 days a week and encouraged to stay active and to follow the standard hospital care	10-point NCCN scale	At baseline and 3rd, 7th, and 11th wk of CRT	Quality of life Functional capacity Hemoglobin Platelets	Significant prevention of worsening of fatigue (P < .001) in the exercise group.
Rogers et al, 2012[27]	Southern Illinois	Pilot RCT	T = 15 I = 7 C = 8	No specific recommendations regarding engaging or not engaging in aerobic or resistance exercise was provided	13-item Functional Assessment of Cancer Therapy-Fatigue subscale	At baseline (preintervention), week 6 and week 12	Muscle strength, lean body mass, Physical functioning, Quality of life	Small to ES improvements (intervention compared with control) were noted for fatigue at 6 weeks (i.e., d = -.64). The negative ES for fatigue resulted from a significant increase in fatigue in the control group (ie, baseline to 6 weeks = 15.4; paired t test P < .05), whereas the intervention group reported an increase of only 7.4 points (P value not significant).

(*continued on next page*)

TABLE 2 (*Continued*)

Author/ year	Country	Study design	Sample size	Control	Fatigue measurement scale	Fatigue measurement points	Other outcomes	Outcome measure (fatigue)
Kok et al, 2022[39]	Netherlands	Non-RCT (one group pre-post test design)	34	No control	Multidimensional Fatigue Inventory	At baseline, 5 wk after baseline (mid-intervention), and 12 wk after baseline (postintervention)	Feasibility of the exercise intervention, physical performance, muscle strength, body composition, HR-QoL	At week 5: General fatigue ($P < .01$), physical fatigue ($P = .20$), reduced activity ($P = .05$), reduced motivation ($P < .01$), and mental fatigue ($P = .94$). At week 12: General fatigue ($P < .01$), physical fatigue ($P < .01$), reduced activity ($P = .08$), reduced motivation ($P < .01$), and mental fatigue ($P = .46$).
Su et al, 2020[37]	China	Non-RCT (prospective study)	T = 141 I = 68 C = 73	Received leaflets concerning nutrition and health and were provided with regular assistance	Chronic disease self-management questionnaires	Before, immediately after, and 3, 6, and 12 mo after receiving IMRT	Global health, daily effects of illness, shortness of breath, pain, cognitive symptom management, exercise (min/wk), communication with the physician and self-efficacy	Findings demonstrating significant improvement in fatigue in the intervention group at posttreatment ($P = .002$), at 3 mo ($P = .025$), at 6 mo ($P = .627$), and at 12 mo ($P = .969$).
Aghili et al, 2007[29]	Iran	Prospective nonrandomized parallel-groups design	T = 30 I = 15 C = 15	Did not engage in any exercise program	Brief Fatigue Inventory	At the first week of assessment (before initiation of exercise), 2nd-4th weeks		At 1st week, IG = 56%; CG = 43% had moderate fatigue (U = 100.5, $P = .632$). At 4th week, IG = 44% mild fatigue, CG = 57% severe fatigue (U = 41, $P = .011$). The median severity of current fatigue during the 1st week and 2nd-4th weeks was unchanged in the IG, there was a marked increase in the severity of fatigue in the CG (median score = 8) ($z = -1{:}91$, $P = .039$).
Xiao et al 2020[38]	United States	Nonrandomized controlled trial	T = 26 I = 12 C = 14	Standard care	Multidimensional Fatigue Inventory-20	Baseline and at 3 mo	Physical function, inflammatory markers, and DNA methylation	At the end of the intervention, the exercise group had a marginal decrease in fatigue compared with the control (−5.0 vs 4.9; $P = .10$).

Abbreviations: T, total; I, intervention; C, control; ES, effect size, IG, intervention group, CG, comparison group.

TABLE 3
Description of the Exercise-Based Intervention Program from the Reviewed Studies

Author/ year	Delivery Mode	Type	Frequency	Intensity	Time	Length
Grote et al, 2018[34]	Supervised	Progressive resistance training	3 times weekly	For upper limbs, exercise a progression of 2.5-kg weight loading, and for the lower limbs, exercise a progression of 5.0-kg weight loading	3 sets and 8-12 repetitions for 30 min	NR
Hu and Zhao, 2020[31]	Supervised	Progressive resistance exercises	Twice a week	Exercise therapist adjusts the requested training loads regularly according to the exercise prescription guidelines	60 min, 8 sets of for major upper and lower muscle groups	12 wk
Zhou et al, 2018[28]	Under the direction of the experienced team members and/or instructional video	Tai Chi exercise	5 sessions/wk	-10 minutes of warm-up and review of Tai Chi actions, 30 minutes; 30 minutes of Tai Chi exercise (low- to moderate-intensity); 10 minutes of breathing meditation techniques; 10 minutes of relaxation	1-h session	During chemoradiotherapy (7 wk)
Samuel et al, 2019[30]	Supervised and monitored (home-based exercise program)	Aerobic (brisk walking) Active resistance exercise	5 d/wk	3-5/10 RPE	15-20 min 2 sets (1 set = 8-15 repetitions)	11 wk
Rogers et al, 2012[27]	First 6 wk supervised, second 6 wk unsupervised	Resistance exercise	2 d/wk	Light to heavy bands were used	60-75 min (up to 10 repetitions of 9 exercises)	12 wks
Kok et al, 2022[39]	Supervised and home based	Endurance training Resistance training	6 d/wk 3 times/wk	Moderate-intensity physical activity; brisk walking physical activity-aiming RPE between 12 and 15 6 exercises targeting major muscle groups. Exercise type and resistance adjusted to the participants' capacity based on pragmatic 15-RM testing	30 min; 15 min; 15 min -RPE range 12-15	10 wk
Su et al, 2020[37]	NR	Relaxation massage Slow rhythmic movement of the temporomandibular joint Fast rhythmic movement of the temporomandibular joint Functional training for the neck and shoulder Shoulder exercises	NR	5 s of small, medium, and large mouth opening, each at an interval of 10 s 1 s of small, medium, and large mouth opening, each at an interval of 10 s Look at the abdomen by lowering the head. Look up and enjoy the moon, look to the left and right, shake from left to right	- 15 minutes per time, 3–5 times. -10 times for 1 set, and a total of 5 sets -10 times for 1 set, and a total of 5 sets -Each action repeated 8 times, 3 times per day; (each for 10 seconds) Repeat 10 times	NR
Aghili et al, 2007[29]	First week supervised	Walking	Daily	NR	20 min (2 × 10)	3 wk
Xiao et al, 2020[38]	Home based Instructed to perform	Aerobic exercise Progressive resistance training	5 times/wk 2 times/wk (but not on consecutive days)	Walk at moderate intensity Targeted major upper and lower body muscle groups using color bands with resistance increased from light (5-10 lb) to low moderate (15-20 lb)	Minimum of 30 min/d 2 sets at current band level, 20-30 min initially and increased to 45-60 min	12 wk

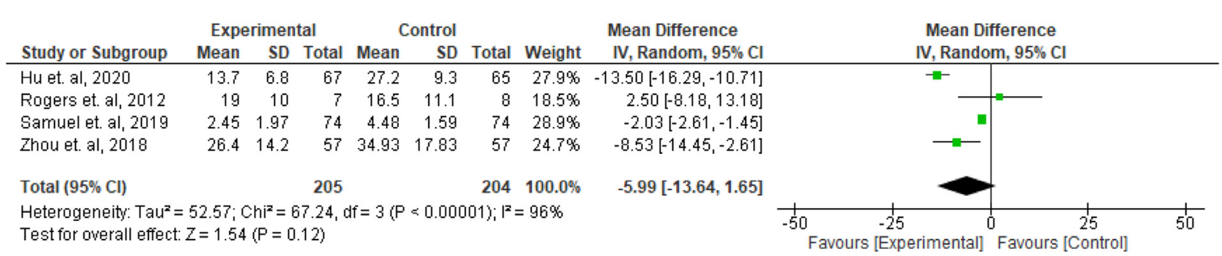

FIG 2. Meta-analysis on the effectiveness of exercise-based interventions for fatigue.

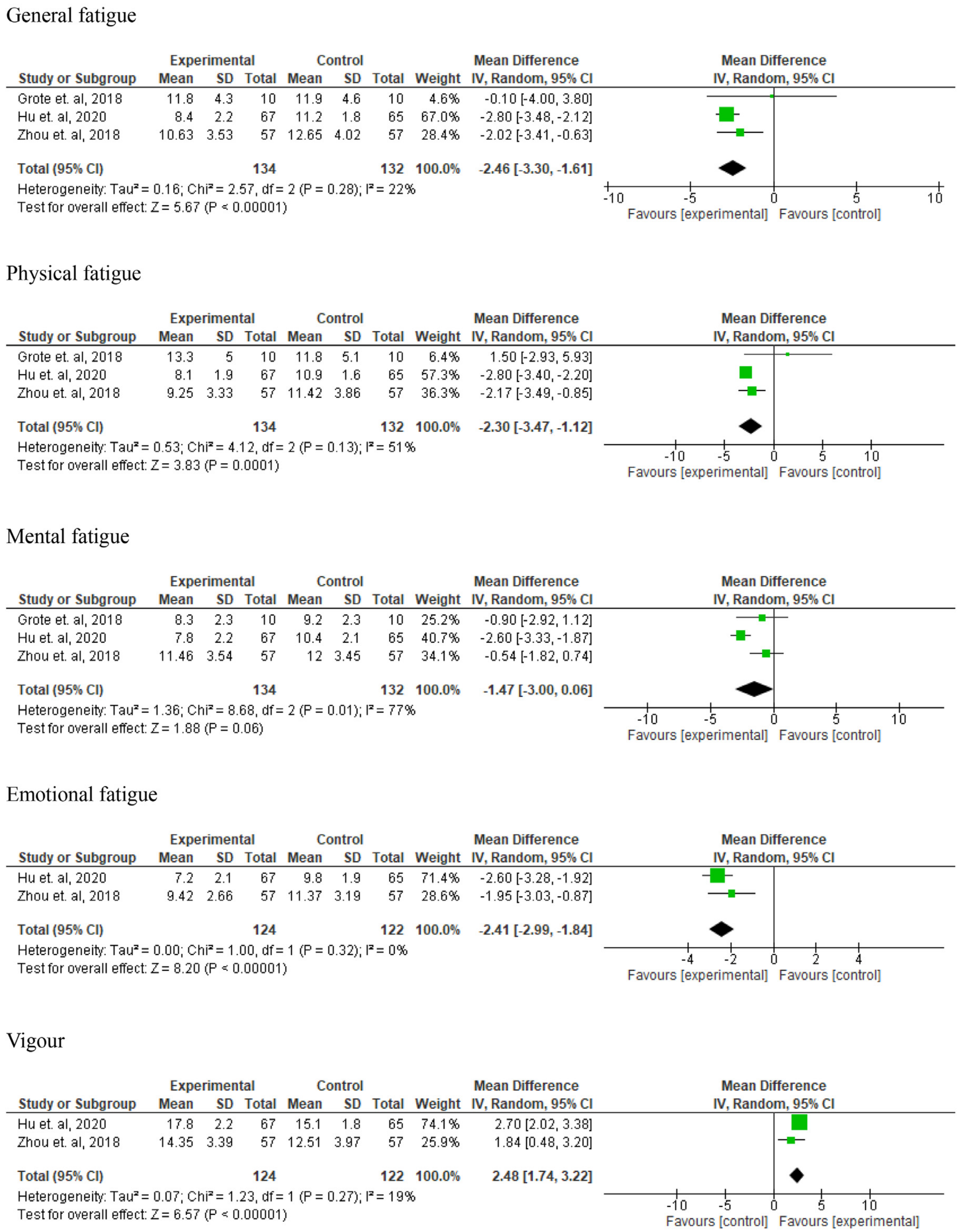

FIG 3. Meta-analysis on the effectiveness of exercise-based interventions for the dimensions of fatigue.

60% of the sessions. However, 65% successfully finished the 10-week intervention period, while the remaining 35% dropped out during this time, and treatment-related toxicity was the most important reason (67%).[39] Abdominal tension causing latissimus pulldown due to a recent percutaneous endoscopic gastrostomy and change from inpatient to outpatient status during radiotherapy were also reported to affect compliance to intervention.[34] Intense feelings of emotions and symptoms, the realization of shortened lifespan, perception of restricted choices in goals of care discussions, and living with the cancer are a few of the identified factors withdrawing cancer patients from participating in clinical trials.[47]

Engaging in physical activity also shows correlation with enhancements in lean body mass both during and after the treatment period.[43] In one of the interventions included in this review, implementing exercises in patients with HNC experiencing cachexia during radiotherapy appeared to be safe and achievable, potentially leading to positive effects on overall fatigue and QOL, despite dealing with advanced tumor stages and demanding treatments.[34] Effects of exercises across the continuum of HNC showed increase in muscle strength in 50% of the investigations.[44] Given the high prevalence of muscle loss in this particular group, it is crucial to establish effective methods to counteract this deterioration. There was also wide variation in the type and duration of exercise interventions among the experiments involved in this review. Despite these differences, most studies reported outcomes favoring the experimental group[27,29,34,37,38] and 3 experiments[28,30,39] had statistically significant differences, indicating the effectiveness of exercise-based intervention in reducing fatigue among patients with HNC on radiotherapy.

Four[27,29,34,38] of 9 studies included in the review were pilot studies. In another 2 experiments,[34,39] exercise interventions were conducted to assess the feasibility. The sample size was 35 or less in 5 studies.[27,29,34,38,39] The studies included in the review were varied in their levels of rigor and had diverse demographics, HNC subsites, stages, exercise-based intervention methods, and duration of follow-up, which might be a limitation of this review. Hence, in particular, future research inquiries should initially focus on determining precise exercise guidelines tailored for patients with HNC, exploring the required dose of physical activity that maximizes its advantages. More experiments with specific intervention designs with adequate sample sizes monitoring the adherence to the exercises are required.

The review's findings should be evaluated considering both strengths and limitations. This review is unique in that it focuses on the effectiveness of exercise-based interventions on fatigue only during the course of radiotherapy for patients with HNC when the fatigue is high. However, 4 studies included in this review were the pilot/feasibility studies and could limit the generalizability of findings. Further, age- and sex-specific fatigue-related data were not separately extracted and analyzed, which could restrict the generalizability as age and sex interact to influence exercise capacity, recovery, and health outcomes with regular physical activity.

Conclusion

This systematic review emphasizes the promising role of exercise interventions in alleviating fatigue among patients with HNC receiving radiotherapy. The synthesis of available evidence demonstrates a positive association between various exercise modalities and reduced fatigue levels in this patient population. However, a well-designed study with patient-centered and -tailored exercise interventions with long-term, longitudinal follow-ups is warranted to effectively manage fatigue in patients with HNC.

These findings emphasize the potential of exercise as a supportive care strategy to mitigate fatigue and improve the overall well-being of patients undergoing radiotherapy for HNC.

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Availability of Data, Code, and Other Materials

The data for this systematic review were derived from the publicly available sources including the academic databases and are appropriately cited in the reference.

Declaration of competing interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: Dr Anice George reports was provided by Manipal College of Nursing. Dr Anice George reports a relationship with Manipal College of Nursing that includes: employment. Dr Shalini Ganesh Nayak reports a relationship with Manipal College of Nursing that includes: employment. Dr Krishna Sharan reports a relationship with K S Hegde Medical Academy that includes: employment. Dr Ravishankar N reports a relationship with Vallabhbhai Patel Chest Institute that includes: employment. Not applicable has patent not applicable pending to not applicable. The authors have no relevant financial or non-financial interests to disclose. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Shalini Ganesh Nayak: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Krishna Sharan:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Data curation, Conceptualization. **Ravishankar Nagaraja:** Writing – review & editing, Validation, Supervision, Software, Formal analysis, Conceptualization. **Anice George:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Data curation, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.soncn.2024.151755.

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