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The impact of physical activity on health-related fitness and quality of life for patients with head and neck cancer: a systematic review

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ABSTRACT

Background Patients with head and neck cancer often face a plethora of cancer and treatment-related side effects, negatively impacting their lean body mass, physical functioning, quality of life and fatigue management. Physical activity is a potential mediator of many of these side effects. This is the first systematic review reporting on head and neck cancer and physical activity literature.

Methods A literature search was conducted up to January 2015. Two reviewers independently identified articles using the outlined inclusion criteria, assessing the study methodology, risk of bias and extracting the necessary data from studies evaluating the impact of full-body physical activity on patients with head and neck cancer. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement was used to guide this review.

Results We identified 16 articles published from 2003 to 2014, the majority of which were published within the past 5 years. Physical activity interventions were feasible, safe and beneficial in mediating cancer and treatment-related side effects. Specifically, patients experienced improvements in lean body mass, muscular strength, physical functioning, quality of life and fatigue management. Owing to significant study heterogeneity, data were not pooled. Reflecting the early state of the literature, included studies were found to vary greatly in design, quality and reporting characteristics.

Conclusions There is early evidence that supports the benefit of physical activity interventions for patients with head and neck cancer, both during and following treatment. Future research is necessary to determine the benefits of different physical activity interventions, and their impact on patients with different head and neck cancers.

INTRODUCTION

Each year, over 650 000 people worldwide are diagnosed with head and neck cancer, including cancers of the hypopharynx, larynx, oropharynx, lip, oral cavity, tonsil, salivary glands, nasopharynx, nasal cavity, paranasal sinus and middle ear.[1 2] The sixth most common type of cancer globally, head and neck cancer represents 6% of all newly diagnosed cancer cases, and leads to over 350 000 deaths per year.[1 3] Considering all head and neck cancers together, the average 5-year survival rate has increased to 66% (from 55% in 1992–1996).[2]

Rationale

Many head and neck cancer patients experience a wide range of cancer and treatment-related side effects including weight loss, muscle wasting, fatigue and decreased quality of life.[4–7] With improved survival rates, and an increased awareness of the significant short-term and long-term symptom burden on patients, supportive care services designed to improve overall quality of life and survivorship are warranted.

Physical activity is a viable and effective treatment that may positively impact head and neck cancer patients' body composition, physical functioning and overall quality of life.[8 9] Since 2003, the body of research has grown significantly, with a number of studies and the first narrative literature review published within the past 2 years.[8 10–12] We systematically reviewed the experimental and observational studies of physical activity for patients with head and neck cancer.

Objectives

The objective of this review was to systematically summarise the head and neck cancer and physical activity literature to date, and to report on (1) observed physical activity levels and associated outcomes, (2) the recruitment and retention feasibility of interventions, (3) the safety of these interventions, (4) the effect of physical activity on body mass index, lean body mass, muscular strength and physical functioning, (5) the effect of physical activity on fatigue, and (6) overall quality of life.

METHODS

Protocol

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement guidelines (see online supplementary appendix A).[13]

Eligibility criteria

Types of studies

This review examined quantitative studies comprised of experimental as well as observational study designs. Since this is the first systematic review examining physical activity in head and neck cancer, it was considered valuable to include experimental and observational studies. Only studies examining full-body physical activity were included, and those targeting specific rehabilitation needs (ie, swallowing, shoulder or leg function), or focused on prevention, were excluded. Only studies published in a peer-reviewed journal in English were included, and no publication date restriction was implemented.

Types of participants

Studies involving participants aged 18 years, diagnosed with head and neck cancer at any stage, were included. Head and neck cancers included: carcinomas of the head and neck, hypopharynx, larynx, oropharynx, lip, oral cavity, tonsil, salivary gland, nasopharynx, nasal cavity, paranasal sinus and middle ear. Studies were required to include participants who were either on active treatment (chemoradiation or just radiation), had finished chemotherapy and/or radiation treatment, or who had only undergone surgical treatment.

Types of experimental studies

Only full body physical activity intervention trials were included (aerobic, resistance/strength, progressive resistance or flexibility).

Types of outcomes

Physical activity levels, preferences and barriers were examined. In addition, feasibility related to physical activity interventions, particularly recruitment, retention, adherence and safety, were evaluated. Outcome measures included body mass index, lean body mass, muscular strength, functional capacity/performance, fatigue and quality of life.

Information sources

Prior to the start of this review, a search was conducted to identify if any similar systematic reviews had been published. Relevant articles were identified by two independent reviewers (LCC and KCN) through searching the following databases up to and including 22 January 2015: PubMed, Medline, EMBASE, CINHAL, Cochrane Library Database and Sport Discuss.

Search

Figure 1 describes the search terms used.

Study selection

The study selection process is outlined in figure 1. Two reviewers (LCC and KCN) assessed eligibility of each article independently. Eligibility was based first on the title and abstract of each article; if the reviewers were unable to determine if the article met eligibility, the full text was evaluated. These same reviewers evaluated full text versions of all relevant studies. A consensus was required between both reviewers, and disagreements, if any, were resolved by a third independent reviewer (SNC-R).

Head and neck cancer: "head" or "neck" or "head and neck" or "hypopharynx" or "larynx" or "oropharynx" or "lip" or "oral cavity" or "oral" or "tonsil" or "salivary gland" or "nasopharynx" or "nasal cavity" or "nasal" or "paranasal sinus" or "paranasal" or "middle ear"
AND
Cancer: "cancer" or "carcinoma" or "squamous cell carcinoma" or "neoplasm" or "tumor" or "tumour"
AND
Physical activity: "physical activity" or "exercise" or "aerobic exercise" or "strength training" or "strength exercise" or "resistance training" or "resistance exercise" or "yoga" or "flexibility training" or "flexibility exercise"

Figure 1 Search terms used.

Data collection process

A data collection form was created and used by a reviewer (KCN) to obtain data from individual studies. A second reviewer (LCC) cross-examined the data. Author names, patient treatment, study intervention, sample size and outcome measures were reviewed to ensure studies were not counted twice. All collected data were stored in a Microsoft Office Word document.

Data items

Data items extracted from each individual study are listed in figures 2 and 3.

Risk of bias in individual studies

To determine the quality of the included randomised controlled trials (RCTs), two authors (LCC and MLM) independently evaluated the sufficiency of randomisation and allocation concealment, assessor blinding and completeness of outcome data for all, using the Cochrane Collaboration tool for assessing risk of bias.[14] The same two authors also independently assessed the risk of bias of all non-randomised studies using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS), evaluating the adequacy of participant selection, risk of confounding variables, measurement exposure, blinding of assessors and completeness of outcome data.[15]

Summary measures

We summarised the results of the observational and experimental studies separately. For the experimental studies, timing of the intervention, either during or following radiation or chemoradiation treatment, was recorded. When data were available, differences in mean change and associated variance (SD) were reported, including 95% CIs.

Risk of bias across studies

Given the early stage of evidence, publication bias was not assessed. Selective outcome reporting was assessed using the Cochrane Collaboration tool for assessing risk of bias for included RCTs and the RoBANS was used for all non-randomised studies.[14 15]

RESULTS

Study selection

A search of six electronic databases produced 3486 studies. Once duplicates were removed, 2099 studies were assessed for eligibility from the title, abstract and full text, which revealed 16 eligible studies (see figure 1). Agreement on article eligibility between the two independent reviewers was 100%.

Study characteristics

Methods

Of the studies meeting our eligibility criteria, four were RCTs,[10 12 16 17] one was a retrospective cohort,[18] six were prospective cohorts,[19–25] one was a non-randomised controlled study[11] and four were cross-sectional studies.[25–28] The sample size varied significantly. The experimental studies included between 6 and 90 participants, while the observational studies ranged from 17 to 504 participants.

Participants

A total of 1582 patients with head and neck cancer participated in the reviewed studies, with 1360 participating in observational

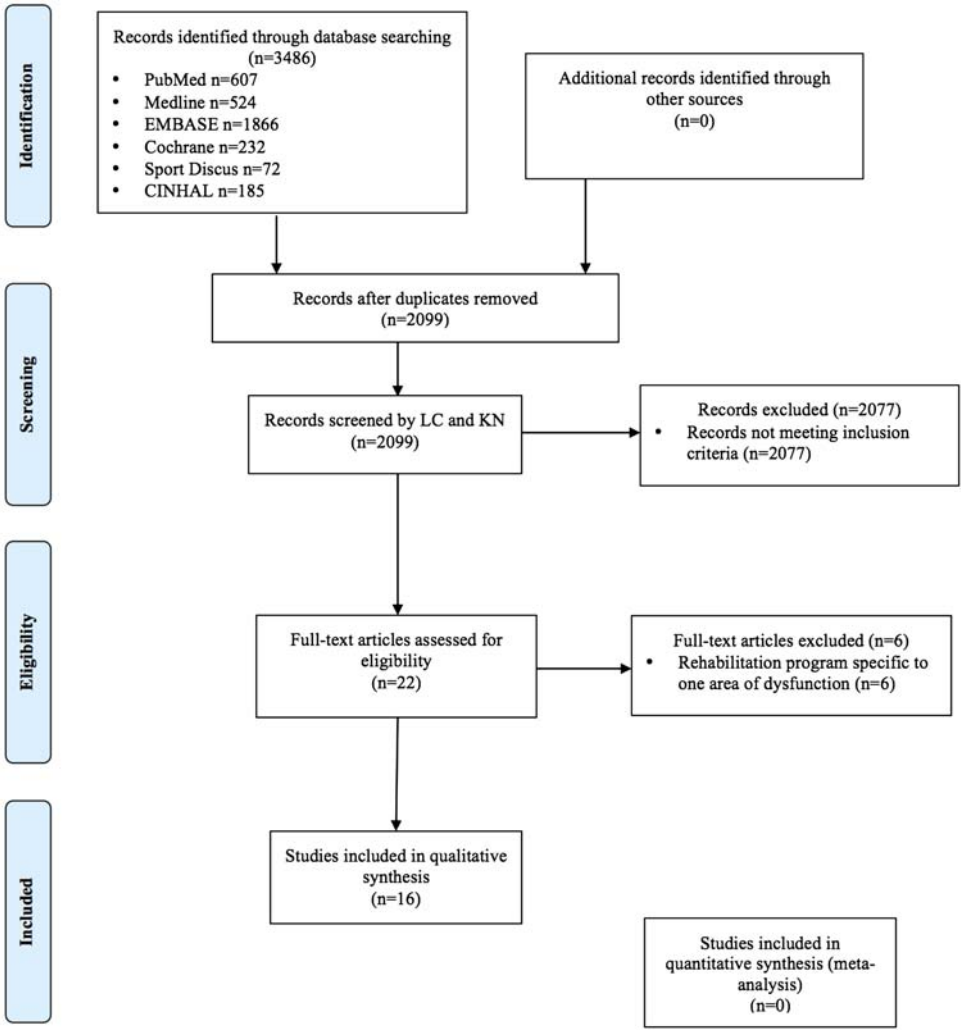

Figure 2 Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) flow diagram of study selection processes.

studies, 190 participating in interventions and 32 receiving usual care. In addition, 24 healthy individuals were used as controls in Lonbro *et al*.[11] Of the studies that reported on characteristics, the mean age of participants was 57.1 years, ranging from 25 to 92 years of age.

Interventions

Intervention details are summarised in table 1. Eight of the nine experimental studies implemented original physical activity interventions,[10 12 16–21] while one study compared previous intervention data from two of these studies[10 12] to healthy controls in an additional, original article.[11] Four interventions examined a resistance-training programme,[10 12 16 21] one an aerobics programme,[19] two had aerobic and resistance combination programmes,[17 18] and one was a hydrotherapy programme.[20] Four of the eight interventions started with participant supervision during physical activity and transitioned to independent physical activity,[10 12 16 19] while two made use of a fully supervised programme[17 20] and two included supervised sessions with an additional unsupervised home-based programme.[18 21] The length of the interventions ranged from 3 to 12 weeks.[10 12 16 19 21]

The FITT principle is used to describe overall physical activity levels, and accounts for frequency (F), intensity (I), time or duration (T) and type of physical activity (T).[29] All interventions reported frequency and type of physical activity, but only 62.5% (5 of 8) reported intensity[10 12 17 21] and 75% (6 of 8) reported time or duration of the activity.[10 12 16 17 21] Progression of physical activity was reported in only five interventions, specific to resistance-training prescriptions.[10 12 16 17 21] Three of the interventions were conducted during active radiation or chemoradiation treatment,[16 17 19] while three were conducted following radiation or chemoradiation treatment,[10 12 18] and one included patients during as well as after treatment.[21] One study did not report on the timing of their intervention with regards to radiation or chemotherapy.[20]

Risk of bias in individual studies

In general, the risk of bias associated with the individual studies was high or unclear. Analysis of the risk of bias for the individual RCTs and non-RCT/cohort studies are presented in tables 2 and 3, respectively. κ Statistics for agreement between the raters for the Cochrane Risk of Bias and the RoBANS item scores were 0.92 and 0.69, respectively. All disagreements were resolved by review and consensus.

Outcomes

Review of observational studies

Seven observational studies reported on physical activity levels, preferences, barriers and associations between physical activity

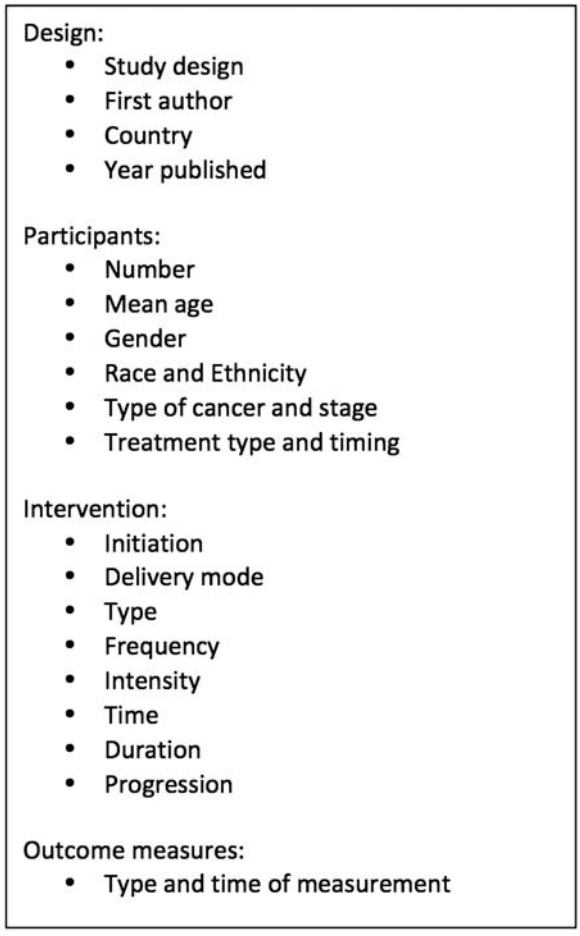

Figure 3 Data extraction items from each article included for systematic review.

levels, and biomarkers and survival (see table 4).[22–28] These studies ranged in size from 17 to 283 participants, and evaluated head and neck cancer patients from diagnosis to 2 years postsurgery, and/or active radiation or chemoradiation treatment. Only one study reported the number of patients with head and neck cancer meeting the American Cancer Society's aerobic physical activity guidelines, finding that only 31% of patients were meeting these guidelines pretreatment, followed by a substantial decrease in activity levels after diagnosis (only 8.5% reported meeting guidelines postdiagnosis).[27 30] Three studies consistently reported decreases in physical activity levels following diagnosis and during radiation or chemoradiation treatment, including decreases in average physical activity levels associated with household activities, sports activities and overall activity.[24 26 27] When compared to physical activity levels among healthy individuals, Lonbro *et al*[11] showed that a lower percentage of patients with head and neck cancer who had completed radiation or chemoradiation treatment 2 months prior were participating in activity.

Six studies evaluated outcomes correlated with physical activity levels.[11 22–26] Physical activity was most strongly correlated with higher activity enjoyment, alcohol use and task self-efficacy, and lower symptoms index scores, perceived barriers and comorbidity scores.[26] Lower levels of physical activity were associated with lack of spouse, feeding tube dependence at 1 year post-treatment, higher interleukin levels, increased cancer-related comorbidities and age, as well as decreased sleep and survival.[22–25]

Only one study examined physical activity preferences, finding that 75% of patients reported possibly (42%) or definitely (33%) being interested in physical activity counselling, with 66% reporting lack of preference for counselling source and 47% reporting lack of preference for delivery channel.[28]

Two observational studies assessed the relationship between physical activity and quality of life.[27 28] Overall, total physical activity minutes were positively associated with improved general, and head and neck cancer-specific quality of life, as reported using the Functional Assessment of Cancer Therapy-General (FACT-G) and the Functional Assessment of Cancer Therapy-Head and Neck (FACT-HN).[27] Lower functional well-being was associated with interest in a physical activity programme, while a higher functional well-being was associated with preference for exercising alone.[28]

Barriers to physical activity included dry mouth, fatigue, drainage in the mouth or throat, difficulty eating, shortness of breath, muscle weakness, difficulty swallowing and decreased food intake.[26] Over 39% of patients reported additional barriers including lack of interest in activity, as well as lack of enjoyment, self-discipline or prioritisation.[26]

Review of experimental studies

Of the reviewed experimental studies, feasibility indices (recruitment, retention and safety) and outcomes are discussed (see table 5). See table 5 for a summary of all experimental studies

Recruitment and retention

Feasibility was a primary outcome in five studies.[12 16 20 21] When reported, feasibility was determined by study recruitment and retention rates, adherence to the intervention and adverse events. Recruitment rates were reported in five of the eight interventions,[10 12 16 17 21] and ranged from 22% to 92.3%. Retention rates were reported in five of the interventions,[10 12 16 17 21] and ranged from 52.4% to 89.6%. Intervention adherence was reported in five of the studies.[10 12 16 20 21] Supervised physical activity programme adherence rates ranged from 66% to 88%,[16 20 21] mixed supervision physical activity programmes rates ranged from 95% to 97%,[10 12] and the reported home-based unsupervised physical activity programme had a 53% adherence rate.[16]

Review of safety

Overall, issues with safety were minimal or not reported, and adverse events were discussed by five of the seven intervention studies.[10 12 16 17 21] Rogers' was the only article to report adverse events, however, all instances were categorised as unrelated to the physical activity intervention.[16] Lonbro *et al*[12] reported that four participants took a break from the intervention due to overuse symptoms, but no further detail was provided.

Changes in body mass index

On radiation or chemoradiation treatment: To date, two studies have reported on body mass index in patients before treatment initiation,[16 17] with the mean body mass index ranging from 18.8±3.4 to 29.9±8.3 kg/m^2. Rogers *et al*[16] found that, over the course of the 12-week intervention, participants' body mass index decreased by 2.3 kg/m^2, while that in the usual care group decreased by 1.4 kg/m^2 (small to medium effect, d=−0.29). Neither of these changes was reported as statistically significant.

Following radiation or chemoradiation treatment: Three studies reported on baseline body mass index in interventions following treatment, but none reported on changes in body

Table 1 Description of exercise intervention programmes in reviewed studies

Author	Initiation	Delivery mode	Type	Frequency	Intensity	Time	Length	Progression
Capozzi *et al*[21]	Mean time after treatment completion: 9.7±10.0 months	Once-weekly supervised sessions plus home programme	Resistance training	3 days per week, 12 sessions supervised	8–10RM; moderate intensity	2 sets of 8–10 for 10 full body exercises	12 weeks	Progression to meet prescription offered at 4, 6, 9 weeks
Lonbro *et al*[12]	2 months post-treatment completion	Mostly unsupervised (supervised 2–3 sessions first 2 weeks, average 5 sessions over past 10 weeks)	Resistance training	30 sessions	12RM	2 sets of 12 for 7 full body exercises	12 weeks	Work up to 3 sets of 8RM
Lonbro *et al*[10]	2 months post-treatment completion	Mostly unsupervised (supervised 2–3 sessions first 2 weeks, average 5 sessions over past 10 weeks)	Resistance training	30 sessions	12RM	2 sets of 12 for 7 full body exercises	12 weeks	Work up to 3 sets of 8RM
Samuel *et al*[17]	During treatment	Supervised	Brisk walking Active exercises	5 days per week 5 days per week	RPE 3–5/10 RPE 3–5/10	15–20 min 4 exercises; 8–10 reps, 2–3 sets	6 weeks 6 weeks	NR Active to active resisted
Eades *et al*[18]	Mean time after treatment completion: 8.2±11.2 months	Semi-weekly exercise session with physiotherapist and home-based exercise programme	Endurance walking/biking, strength with free weights, flexibility, shoulder and neck exercises	Median of 10 sessions (5–23) over 8 weeks	NR	NR	8 weeks	NR
Rogers *et al*[16]	During treatment	First 6 weeks supervised, second 6 weeks unsupervised	Resistance exercise	2 days per week	Light to heavy bands were used	60–75 min (up to 10 reps of 9 exercises)	12 weeks	Light resistance first 2 weeks, gradually increased every 2 weeks if patient could easily do 12 reps, reps increased for BW exercises
Aghili *et al*[19]	During treatment	First week supervised	Walking	Daily	NR	20 min (2×10 min)	3 weeks	NR
Crevenna *et al*[20]	Mean time after laryngectomy: 30±26 months	Supervised	Hydrotherapy programme	3 days per week	NR	NR	8 weeks	NR

BW, body weight; NR, not reported; RM, repetition maximum; RPE, rated perceived exertion.

Table 2 Risk of bias of included randomised controlled trials

Author/year	Randomisation—sequence generation	Allocation concealment	Assessor blinding	Patients blinded	Incomplete outcome data	Selective outcome reporting
Lonbro *et al*, 2013[10]	Unclear	Unclear	Yes	No	No	Yes
Lonbro *et al*, 2013[12]	Unclear	Unclear	Yes	No	No	Yes
Rogers *et al*, 2013[16]	Yes	Yes	No	No	Yes	Yes
Samuel *et al*, 2013[17]	Unclear	No	No	No	No	Yes

Tool used: the Cochrane Collaboration tool for assessing risk of bias.[14]
No, high risk of bias; Yes, low risk of bias; unclear.

mass index over the course of the physical activity intervention.[10 12 18] Baseline body mass index scores ranged from 22.9±0.4 to 23.6±3.0 kg/m^2,[10 12] with one study only reporting that 14.8% of participants had a body mass index <20 kg/m^2.[18]

Changes in lean body mass

On radiation or chemoradiation treatment: To date, only one study has examined the impact of progressive resistance exercise on changes in lean body mass among patients undergoing treatment.[16] At 6 weeks into this resistance-training programme, patients in the intervention group experienced a loss of 0.18 ±9 kg (0.3% change) of lean body mass, a non-significant change from baseline, while those in the control group lost 2.5 ±3.6 kg (4.0%) of lean body mass, a change trending towards significance ($p<0.1$).[16] At 12 weeks, no statistically significant difference was noted between the groups.

Following radiation or chemoradiation treatment: Three studies evaluated the impact of a post-treatment physical activity intervention on lean body mass changes.[10–12] Two of these studies were RCTs, with one study comparing a resistance-training programme to resistance-training plus creatine supplementation, while the second compared the timing of the progressive resistance-training programme at either 8 or 20 weeks post-treatment. When not undergoing the 12-week progressive resistance-training programme, participants in this second study were allowed to engage in self-chosen activity.[10] The third study combined the results of these first two and compared the findings to age-matched controls from the general population.[11] All three studies included dual X-ray absorptiometry (DXA) scans to evaluate lean body mass.

Overall, creatine and the timing of the intervention did not significantly impact lean body changes, yet significant changes were associated with the 12-week resistance programme itself.[10 12] Lean body mass, on average, increased between 2.8–5.0% (mean change of 2.3–2.6 kg, $p<0.0001$) from baseline measures, and these lean body mass changes were found to be significantly associated with measures of maximal strength ($R^2=0.59–0.67$, $p<0.0001$). When compared to healthy age-matched controls, lean body mass was found to be 10% lower among patients with head and neck cancer following radiation or chemoradiation treatment (−5.6±1.5 kg; $p<0.0001$), with no significant difference noted once patients with head and neck cancer had completed the 12-week progressive resistance-training programme (−2.1±1.5 kg, $p>0.05$).[11] Of note, changes in lean body mass were associated with human papillomavirus (HPV) status in one study, finding that the lean body mass increase in HPV positive patients was 1.8 kg greater than that in HPV negative patients ($p=0.06$; 95% CI −0.04 to 3.7).[12] However, the next study evaluating the impact of timing of progressive resistance exercise found no significant association between lean body mass change and HPV status.[10]

Muscular strength

On radiation or chemoradiation treatment: For patients on treatment, muscular strength was evaluated only by Rogers *et al*[16] in their randomised controlled pilot study comparing the benefit of a 12-week progressive resistance-training programme to usual care. Muscular strength was evaluated using a handgrip dynamometer, with a small to medium effect reported at a 6-week ($d=0.22$) and 12-week ($d=0.34$) follow-ups.[16] Patients on the 12-week progressive resistance-training intervention experienced medium effect size decreases in chair rise time at 6 weeks ($d=−0.63$) and at 12 weeks ($d=−0.60$), with a mean intervention versus usual care group difference of −1.9±3.0 s at 6 weeks and −2.0±3.3 s by 12 weeks.[16]

Following radiation or chemoradiation treatment: For patients who had completed treatment, strength was examined in three studies that utilised a 12-week progressive resistance-training program.[10–12] Lonbro *et al*[12] found that both groups (12 weeks progressive resistance vs 12 weeks progressive resistance plus

Table 3 Risk of bias of included non-randomised studies

Author/year	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting
Capozzi *et al*, 2014[21]	Low risk	High risk	Low risk	High risk	High risk	High risk
Lonbro *et al*, 2013[11]	High risk	Unclear	Low risk	Unclear	Low risk	Low risk
Eades *et al*, 2013[18]	High risk	High risk	Low risk	High risk	Low risk	Low risk
Aghili *et al*, 2007[19]	Unclear	Unclear	High risk	Unclear	Low risk	Unclear
Crevenna *et al*, 2003[20]	Unclear	High risk	Low risk	High risk	Low risk	Low risk
Duffy *et al*, 2009[23]	Low risk	Low risk	High risk	Unclear	Low risk	Low risk
Duffy *et al*, 2008[22]	Low risk	Low risk	High risk	Unclear	Low risk	Low risk
Silver *et al*, 2007[24]	Low risk	Unclear	Low risk	High risk	Low risk	Low risk

Tool used: The Risk of Bias Assessment tool for Non-randomized Studies (RoBANS).[15]

Table 4 Observational studies of exercise levels, preferences, barriers and associations, with biomarkers and survival in patients with head and neck cancer

Author, year, location (type)	Participants	Measurement outcomes	Results
Duffy *et al*, 2013[25] USA (cross-sectional)	N=407 Age: 58.8±10.7 years Gender ratio: 87F, 320M Race: 363 white, 33 African American, 11 African, Indian/ other Cancer type: HNSCC (larynx, pharynx, oral cavity, sinus or unknown primary) Cancer stage: 0–II: 83, III–IV: 324 Treatment: NR	Smoking status Alcohol problem (AUDIT) body mass index Physical activity (PASE) Sleep (MOS) Interleukin 6 levels Survey was given once in otolaryngology clinic waiting room	(Only reporting on physical activity outcomes) ▶ Lower levels of physical activity associated with higher interleukin levels versus those with higher physical activity levels ($p<0.001$), but not significant after multivariate analysis ▶ Mean score for physical activity was 113
Duffy *et al*, 2009[23] USA (prospective cohort)	N=504 Age: 58.8±10.8 years Gender ratio: 110F, 394M Race: 448 white, 56 non-white/Hispanic Cancer type: HNSCC (larynx, pharynx, oral cavity, sinus or unknown primary) Cancer stage: 0–II: 104, III–IV: 400 Treatment: radiation, chemotherapy, surgery or combination	Smoking status Alcohol problem (AUDIT) Diet/fruit intake (Willett food frequency questionnaire) Body mass index Physical activity (PASE) Sleep (MOS) Survival Survey was given once in otolaryngology clinic waiting room, with resurvey every 3 months for 2 years and annually each year thereafter	(Only reporting on physical activity outcomes) ▶ Univariate analysis showed physical activity significantly associated with survival and was approaching significant in multivariate analysis (HR=0.98; 95% CI 0.95 to 1.00) ▶ Mean score for physical activity was 115
Rogers *et al*, 2009[28] USA (cross-sectional)	N=90 Age: N=58 (65%) <65 years Gender ratio: 20F, 70M Race or ethnicity: 84 white, 2 African-American, 2 Native American Indian Cancer type: head and neck cancer (oropharynx, larynx, hypopharynx, oral, nasopharynx, nasal cavity/sinuses, salivary gland) Cancer stage: I–II: 17, III–IV: 70 Treatment: surgery, radiation, chemotherapy or combination	Exercise counselling and programme preferences Quality of life (FACT-HN and FACT-G) Symptom severity (FACT-HN) Depression (CED-D) Rural residence Survey was given once while 13 participants were on treatment and 77 were off treatment	▶ Daily physical activity minutes, including mild+moderate+vigorous leisure physical activity, was 184±293 min ▶ Exercise counselling and programme preferences: 75% reported interest in exercise programme (33% reported definitely interested; 42% reported possibly interested) and 51% definitely able to participate ▶ 66% reported lack of preference for counselling source and 17% preferred exercise specialist. 47% reported lack of preference for delivery channel and 40% preferred face to face. 49% preferred exercise outside, while 35% preferred at home, and 50% preferred exercise alone. 55% preferred unsupervised exercise and 66% preferred flexible scheduling. 47% preferred morning exercise. 50% preferred moderate intensity and 52% had no preference to exercise variability. 47% preferred walking in the summer and 44% in the winter. 25% preferred a general activity programme with physical therapy and 56% preferred without physical therapy ▶ No association with rural residence and counselling or programme preference. No association between exercise preference and quality of life, symptom index or depression and perceived ability, counselling delivery channel, location, supervision, structure, exercise intensity or variability
Duffy *et al*, 2008[22] USA (prospective cohort)	N=283 Age: 59.4±11.1 years Gender ratio: 63F, 220M Race: 241 white, 42 non-white/Hispanic Cancer type: head and neck cancer (larynx, pharynx, oral cavity, sinus or unknown primary) Cancer stage: 0–II: 59, III–IV: 224 Treatment: chemotherapy, radiation, surgery, combination or none	Smoking status Alcohol problem (AUDIT) Nutrition status/fruit intake (Willett food frequency questionnaire) body mass index Physical activity (PASE) Sleep (MOS) Survey was given at baseline and 1 year after diagnosis	▶ Lower physical activity associated with lower SLEEP scores, older age, not married, moderate to severe comorbidities and oral cavity cancer both at baseline and 1 year post ▶ Lower physical activity associated with stage II and IV at baseline ▶ Lower physical activity associated with having a feeding tube at 1 year

Continued

Table 4 Continued

Author, year, location (type)	Participants	Measurement outcomes	Results
Rogers *et al*, 2008[26] USA (cross-sectional)	N=59 Age: 58±12.8 years Gender ratio: 10F, 49M Race: 54 Caucasian, 3 African American, 2 other Cancer type: head and neck cancer (oropharynx, larynx, hypopharynx, oral cavity, nasopharynx, nasal cavity/sinuses, salivary gland and other) Cancer stage: I–II: 16, III–IV: 43 Treatment: surgery, radiation, chemotherapy or combo	Physical activity (Godin leisure-time exercise questionnaire) Social cognitive theory constructs Perceived physical activity barriers Physical activity enjoyment Social support Role model Depression (CES-D) Symptom index (FACT/NCCN) Survey was given once, at a mean of 18.6±50.9 months since diagnosis. 51 participants not on treatment at time of survey	▶ Participants were inactive (110.2±164.8 weekly minutes) which was a decrease from 383.7 weekly minutes prediagnosis ▶ Strongest correlations to physical activity were enjoyment (r=0.41, p=0.002), symptoms index (r=−0.36, p=0.006), alcohol use (r=0.36, p=0.007), task self-efficacy (r=0.33, p=0.013), perceived barriers (r=−0.27, p=0.047) and comorbidity score (r=−0.27, p=0.042). Regression showed enjoyment (0.38, p=0.002) and symptom index (−0.33, p=0.006; R^2=0.28) independently associated with physical activity ▶ Barriers significantly associated with physical activity were dry mouth/throat (r=−0.32, p=0.016), fatigue (r=−0.27, p=0.043), drainage in mouth or throat (r=−0.41, p=0.002), difficulty eating(r=−0.32, p=0.015), shortness of breath (r=−0.30, p=0.024), muscle weakness (r=−0.29, p=0.033), difficulty swallowing (r=−0.28, p=0.039) and decreased food intake (r=−0.28, p=0.039) ▶ ≥39% reported lack of interest, enjoyment or self-discipline, not a priority, not in routine and procrastination as barriers, but these were not significantly associated with activity. Fear of injury was the only non-physical barrier (r=−0.27, p=0.042) ▶ Strong correlations between symptoms index prevalence with total exercise minutes were fatigue (r=−0.33 p=0.012), pain in mouth/throat/neck (r=−0.33, p=0.012) and discontent with current quality of life (r=−0.28, p=0.038) ▶ Difficulty communicating was significantly associated with activity (only reported by 9%, r=−0.28, p=0.036)
Silver *et al*, 2007[24] USA (prospective cohort)	N=17 Age: 58.9±5.4 years Gender ratio: 2F, 15M Race: 14 White, 2 Black, 1 Asian Cancer type: HNSCC (pharynx, larynx, oral cavity) Cancer stage: all(17) III–IVa Treatment: concurrent chemoradiation	Dietary intake Body composition (DXA) Energy balance (BreezeSuite software V.6.1B) Physical function (PAL) Biomarkers (Inflammatory markers) Survey was given at baseline and 1 month post treatment	▶ Average physical activity level decreased from baseline to final assessment (household activities, sport activities and overall) p=0.003 ▶ Increased serum interleukin 6 levels associated with decrease independence of ADLS (r=−0.56; p=0.04) and of IADL (r=−0.60; p=0.02) ▶ Significant association between anti-inflammatory cytokine IL-10 and reduced physical activity level (r=−0.63; p=0.01)
Rogers *et al*, 2006[27] USA (cross-sectional study)	N=59 Age: 58±12.8years Gender ratio: 10F, 49M Race: 54 Caucasian, 3 African American, 2 Other Cancer type: head and neck cancer (oropharynx, larynx, hypopharynx, oral cavity, nasopharynx, nasal cavity/sinuses, salivary gland and other) Cancer stage: I–II: 16, III–IV: 43 Treatment: surgery, radiation, chemotherapy or combo	Physical activity (Godin leisure-time exercise questionnaire) Quality of life (FACT-HN) Fatigue (PWB scale) Depression (CES-D) Survey was given once, at a mean of 18.6±50.9 months since diagnosis. 51 participants not on treatment at time of survey	▶ Reported activity participation before a cancer diagnosis: 17% moderate, 34% vigorous activity, and 30.5% meeting physical activity guidelines. Reported activity participation after diagnosis: 12% moderate, 5% vigorous activity and 8.5% meeting guidelines. Those meeting guidelines were off treatment. Decrease 268.3±870.2 weekly active minutes post diagnosis. 71% reported no change, but sedentary both times ▶ FWB and AC were slightly higher than midrange, other quality of life components above possible midrange. Mean fatigue 2.2/4, depression 18.7 ▶ Weekly active minutes associated with younger age (r=−0.24, p=0.080), absence of medical comorbidity (r=−0.29, p=0.031) and alcohol use (r=0.36, p=0.007) ▶ No association with physical activity and gender, race, education, income, body mass index, cancer stage, on/off treatment, months since diagnosis or smoking ▶ Younger age associated with higher depression (r=−0.26, p=0.051), but not quality of life or fatigue. Higher quality of life, not depression or fatigue, associated with absence of comorbidity(r=−0.25, p=0.059) and alcohol use (r=−0.35, p=0.008) ▶ Higher quality of life associated with higher weekly active minutes: small to medium effect size with PWB (r=0.20), SWB (r=0.15), EWB (r=0.21) and AC (r=0.26), medium effect size with FWB (r=0.38), fact G (r=0.33) and FACT HN (=0.33). Adjusted for age, one comorbidity and alcohol use, FWB (r=0.30, p=0.027)

AC, additional concerns; ADL, activities of daily living; AUDIT, alcohol use disorders identification test; CES-D, Center for Epidemiological Studies Depression scale; DXA, dual-energy X-ray absorptiometry; EWB, emotional well-being; F, female; FACT/NCCN, Functional Assessment of Cancer Therapy/National Comprehensive Cancer network; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-HN, Functional Assessment of Cancer Therapy-Head and Neck; FWB, functional well-being; HNSCC, head and neck squamous cell carcinoma; IADLs, instrumental activities of daily living; M, male; MOS, medical outcomes study questionnaire; N, number of participants; NR, not reported; PAL, modified Baecke questionnaire for older adults physical activity level; PASE, physical activity scale for the elderly; PWB, physical well-being; SWB, social well-being.

Table 5 Experimental trials with patients with head and neck cancer, and full body exercise interventions

Author, year, location (type)	Participants	Measurement outcomes	Results
Capozzi *et al*, 2014[21] Canada (prospective cohort)	N=21 Mean age: 52.9±9.4 years Gender ratio: 3F:18M Race: NR Cancer type: HNSCC (oral, oropharynx, nasopharynx, hypopharynx, larynx, nasal cavity/sinuses, salivary gland) Cancer stage: I: 0, II: 6, III: 1, IV: 12, Unknown: 2. Treatment: 15 completed treatment (radiation or chemoradiation), 6 on active treatment	Feasibility (recruitment rate, retention, adherence and adverse events) Symptom Severity (ESAS) Anthropometrics (height, weight, and circumference measurements) Muscle strength (hand grip dynamometer) Functional performance (30 s sit-to-stand) Functional aerobic capacity (6MWT)	▶ Recruitment rate to assessment 71.9% (23 of 32); Recruitment rate for intervention 65.6% (21 of 32); Programme retention rate 52.4%; adherence rate 65.7%; no adverse events ▶ Participants performed an additional 5.4±4.9 stands in 30 s sit to stand (p=0.004) and 49.6±65.4 m in the 6MW test (p=0.059) ▶ No statistically significant change was noted in body weight, grip strength or circumference measurements ▶ Over one exercise class: participants experienced acute improvements in symptom management for tiredness (p=0.003), depression (p=0.027), anxiety (p=0.012), drowsiness (p=0.019) and overall well-being (p=0.009). Clinically meaningful differences noted in decreased tiredness and improved well-being. ▶ Over the 12-week programme: statistically significant and clinically meaningful decreases in tiredness (p=0.038) and drowsiness (p=0.035). Clinically meaningful reductions in pain, tiredness, depression, anxiousness, drowsiness, issues with appetite, issues with well-being and shortness of breath
Lonbro *et al*, 2013[11] Denmark (non-randomised controlled study)	N=90 (66 HNSCC; 24 healthy) Mean age: 56±8 years HNSCC; 59±9 years healthy Gender ratio: 12F:54M HNSCC; 7F:17M healthy Race: NR Cancer type: HNSCC Cancer stage: NR Treatment: Radiation or chemoradiation	Lean body mass (DXA) Muscle strength (isokinetic dynamometry) Functional performance (10 m walk, sit to stand 30 s, stair climb, 30 s max arm curl) Level of leisure time physical activity (Saltin and Grimby Questionnaire)	▶ Baseline lean body mass 10% lower in HNSCC compared to healthy (5.6±1.5 kg); p<0.0001; 95% CI −8.6 to 2.7); at 12 weeks significant difference is absent ▶ Baseline muscle strength 15% lower in HNSCC and significant difference in isometric muscle strength (p<0.0001); at 12 weeks significant difference is absent ▶ Baseline functional performance was 18% lower in HNSCC; at 12 weeks significant difference is absent ▶ 83% of HNSCC participated in at least light physical activity for a minimum of 4 h/week ▶ 95% of healthy individuals participated in at least light physical activity for a minimum of 4 h/week Other: ▶ Significant association between lean body mass and all measures of maximal strength R^2=0.59–0.67 (p<0.0001); KE strength 4.8–5.5 nm/kg lean body mass, KF strength 2.0–2.2 nm/kg lean body mass ▶ Significant association between total body weight and muscle strength R^2=0.50–0.57 (p<0.0001) ▶ Association between maximal isometric KE strength and 30 s arm curl R^2=0.44 (p<0.0001), 10 m max gait speed R^2=0.31 (p<0.0001), 30 s chair rise R^2=0.34 (p<0.0001), not significant with stair climb R^2=0.21 (p=0.007) ▶ No association between functional performance tests and physical function of EORTC QLQ-C30
Lonbro *et al*, 2013[12] Denmark (RCT)	N=30 (16 PROCR; 14 PLA) Median age: 56 y PROCR; 59y PLA Gender ratio: 7F:23M Race: NR Cancer type: HNSCC (pharynx, larynx, pharynx and larynx, nasopharynx, oral cavity, unknown primary) Cancer stage: I-II: 1, III-IV: 29 Treatment: radiation or chemoradiation	Feasibility (Recruitment rate, retention, adherence and adverse events) Body Composition/Lean body mass (DXA) Muscle strength (isokinetic dynamometry) Functional performance (10 m walk, sit to stand 30 s, stair climb, 30 s max arm curl)	▶ Recruitment rate 28% (30 of 109); retention rate 70% (21 of 30); Adherence to PRT 97% (29 out of 30 sessions over mean of 13 weeks); No adverse events ▶ lean body mass increased significantly by 5.0±3.8% (50.5±9.3 to 53.1±10.8 kg) in PROCR group (p<0.0001) and 2.8±2.5% (50.4±8.4 to 51.7±8.3 kg) in PLA group (p=0.07); lean body mass increase in HPV positive patients was 1.8 kg larger than HPV negative (p=0.06; 95% CI −0.04 to 3.7) ▶ Both groups increased muscle strength significantly pre to post exercise programme but no difference between groups ▶ Both groups increased functional performance significantly pre to post exercise programme but no difference between groups Other: ▶ No difference between group in BW, lean body mass or BM ▶ BW increase non-significant in PROCR and unchanged in PLA ▶ FM decreased non-significant in PROCR and PLA
Lonbro *et al*, 2013[10] Denmark (RCT)	N=41 (20 EE 21 DE) Mean age: 55±7 years EE; 58±7 years DE Gender ratio: 7F:23M Race: NR Cancer type: HNSCC (pharynx, larynx, oral cavity, unknown primary) Cancer stage: I–II: 8, III–IV: 33 Treatment: Radiation or chemoradiation	Lean body mass (DXA) Muscle strength (isokinetic dynamometry) Functional performance (10 m walk, sit to stand 30 s, stair climb, 30 s max arm curl) Quality of life (EORTC QLQ-C30)	▶ EE increased lean body mass by 4.3% (2.3 kg; p<0.001; 95% CI 0.5 to 2.5) DE increased lean body mass by 4.2% (2.4 kg; p<0.001; 95% CI 1.1) after PRT ▶ EE Isometric KE increased by 20% (33 nm; p<0.001; 95% CI 16 to 50) DE increased 21% (34 nm; p<0.001; 95% CI 17 to 50) after PRT. Similar results observed for isokinetic KF; larger increase in isometric KF and isokinetic KE in DE ▶ DE improved functional tests: arm curl and chair raise ▶ EE improved overall quality of life and 'cognitive function' after PRT than DE self chosen activity; DE improved 'physical function' more after PRT than EE self chosen activity Other: ▶ Recruitment 22%; retention rate 83%; adherence to PRT 95% for both groups; no adverse events reported ▶ Stratification factors (HPV/p16 positive, presence of feeding tube, treatment induced weight loss) not significantly related to lean body mass increase

Continued

Table 5 Continued

Author, year, location (type)	Participants	Measurement outcomes	Results
Samuel *et al*, 2013[17] India (RCT)	N=48 (24 Ex, 24 UC) Mean age: 52.5±8.27 years ex; 51.7±10 years UC Gender ratio: 6F:42M Race: NR Cancer type: head and neck cancer Cancer stage: NR Treatment: concurrent chemoradiation	Functional capacity (6MWT) Quality of life (SF36)	▶ 6MW test increased 42 m in exercise group and decreased 96 m in UC (p<0.05); statistically significant different 6MWD from baseline with and between groups with moderate effect size (d=0.46) for between group ▶ Physical component score decreased to 32.7(18%) in UC while exercise group stayed the same ▶ Mental component score increased to 40.9 (11.73%) in exercise group, while decreased to 23 (75.21%) in UC Other: ▶ Adherence was not monitored ▶ No adverse events
Eades *et al*, 2013[18] Canada (Retrospective cohort)	N=31 enrolled, data on 27 reported Mean age: 54.9±9.2 Gender ratio: 5F:22M Race: NR Cancer type: head and neck cancer (nasal cavity, oral cavity, pharynx, larynx) Cancer stage: I–II: 6, III–IV: 21 Treatment: surgery, radiation, chemotherapy or combo	Functional status (6MWT) Quality of life (ESAS) Nutritional (BW and presence of PEG) Symptoms severity (ESAS) Interference with function (MD Anderson symptom inventory) Distress level (thermometer)	▶ Improved 6MWD 59 m (95% CI 27 to 91) after programme (effect size, d=0.8) ▶ Improved quality of life change mean 1.8 (effect size, d=0.8) ▶ 11 gained >1 kg, 10 maintained, 6 lost >1 kg BW ▶ Baseline most severe symptoms: weakness, anorexia, pain and depression. End of programme strong decrease in pain and weakness (effect size: d=0.8–0.9), moderate decrease in shortness of breath, anorexia, insomnia and depression (effect size: 0.6–0.7) and non-significant decrease in nausea, vomiting, constipation and sleepiness (effect size d=0.1–0.4) ▶ No clinically meaningful reduction in symptom interference (d=0.2–0.4) ▶ Patients reported moderate decrease in distress (d=0.7). Percentage exceeding clinical important distress fell from 73% to 42% (p=0.008)
Rogers *et al*, 2013[16] USA (RCT)	N=15 (7 Ex; 8 UC) Mean age: 60.5±12.5 years Gender ratio: 3F:12M Race: 15 white Cancer type: head and neck cancer (nasopharyngeal, salivary gland, scalp, oral cavity, tongue, oropharyngeal, larynx, unknown primary) Cancer stage: I–II: 7, III–IV: 8 Treatment: radiation or chemoradiation	Feasibility (recruitment, completion, adverse events, adherence) paid $25 for completed assessment Lean body mass (BIA) Muscle strength (leg and hand dynamometer) Physical functioning (tandem balance, 8 foot walk time, 5 rise and sit) quality of life (FACT-H&N, FACT G) Fatigue (FACT-fatigue subscale)	▶ Recruitment rate 45% (15 of 33); Retention rate 100% at 6 weeks and 87% at 12 weeks; Adherence 83% (70 of 84) first 6 weeks, 53% (32 of 60) at home; 3 unrelated adverse events ▶ Small to medium effect size increase in 6 week lean body mass (d=0.35) ▶ Small to medium effect size increase for hand grip at 6 (d=0.22) and 12 weeks (d=0.34). Small decreases in back/leg extensor strength at 6 (−0.21) and 12 weeks (d=−0.19) ▶ Small to medium effect size increase in chair rise 6 (d=−0.63) and 12 weeks (d=−0.60); minimal increases in physical functioning (d=0.15–0.19) ▶ Medium and small effect size increase for overall quality of life 6 (d=0.52) and 12 weeks (d=0.39), physical well-being 6 (d=0.44) and 12 weeks (d=0.36), emotional well-being 12 weeks (d=0.45), functional well-being 6 (d=0.41) and 12 weeks (d=0.33) ▶ Small to medium effect size, significant increase in fatigue control in 6 week (d=−0.64) ▶ Small decrease in head and neck cancer specific symptoms at 6 weeks (d=−0.23) and 12 weeks (d=−0.25). Little increase in social well-being
Aghili *et al*, 2007[19] Iran (Prospective non-randomised parallel group design)	N=30 Mean age: NR Gender ratio: NR Race: NR Cancer type: Breast and head and neck cancer Cancer stage: NR Treatment: radiation	Fatigue (BFI)	▶ Baseline moderate fatigue 56% (exercise) and 43% (UC) (no significant difference, p=0.632) ▶ 4th week exercise 44% mild fatigue UC 57% severe fatigue (significant difference reported, p=0.011) ▶ 2–4th week median severity unchanged in exercise group, increased in UC (p=0.039) ▶ Median fatigue for 24 h period first week—exercise 56% and UC 43% had equal moderate fatigue (p=0.647) ▶ Median fatigue 24 h period at 4 week exercise 38% mild and UC 57% severe (p=0.001) ▶ 2–4th week median 24 h period severity unchanged in exercise group increase in UC (p=0.013)
Crevenna *et al*, 2003[20] Austria (Prospective cohort)	N=6 laryngectomy patients Mean age: 57±10 Gender ratio: All male	Feasibility (acceptance, compliance, safety in a group, impact on goals of therapy) Endurance capacity (cycle ergometer and 6MWT) Quality of Life (SF36) Postural control (SMART Equitest system)	▶ Adherence rate 88% (127 of 144) ▶ Improved endurance capacity (p<0.028); longer 6MWD (p<0.028) ▶ Improved quality of life sub scales: 'physical functioning' (p<0.027), 'vitality' (p<0.027) 'role-physical' (p<0.027) and social functioning (p<0.043) other subscales improved not significantly ▶ Improved postural stability ▶ Decreased perception of fatigue (p<0.028) ▶ Expectoration improved (p<0.043) ▶ Improved perceived neck and shoulder mobility (p<0.027) ▶ Improved perception of flexibility (p<0.027) ▶ Improved perception of postural control (p<0.028)

6MW, 6 min walk; 6MWT, 6 min walk test; BIA, bioelectrical impedance analysis; BM, body mass; BW, body weight; DXA, dual-energy X-ray absorptiometry; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; ESAS, Edmonton Symptom Assessment System; F, female; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-HN, Functional Assessment of Cancer Therapy-Head and Neck; FM, fat mass; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; KE, knee extension; KF, knee flexion; M, male; N, number of participants; NR, not reported; PEG, percutaneous endoscopic gastrostomy feeding tube; PROCR, creatine PLA, placebo; RT, radiotherapy; SF-36, Medical Outcomes Study Short Form-36.

creatine supplementation) increased muscular strength significantly, evaluated by isometric and isokinetic dynamometry, with no differences noted between groups. Lonbro *et al*[10] found significant increases in isometric knee extension and isokinetic knee flexion, and non-significant changes in isometric knee flexion and isokinetic knee extension, in the intervention group starting the 12-week programme 8 weeks following treatment. The group starting the 12-week intervention 20 weeks post-treatment showed significant changes in all four domains.[10] Together, average increases in isometric knee extension ranged from 32.7±22.7 nm to 53.1±39.0 nm.[10 12] When these results were pooled and compared to age matched controls, Lonbro *et al*[11] found significant differences in isometric knee extension and knee flexion at baseline between these two groups, which became non-detectable following the 12-week resistance-training intervention.

Both on and following radiation or chemoradiation treatment: In a mixed sample with 65.2% of patients having completed treatment and the others receiving treatment, changes in total handgrip strength were found to be non-significant over the 12-week programme ($p<0.309$).[21]

Physical function

On radiation or chemoradiation treatment: Physical function was reported to increase after physical activity in two studies of participants who were on radiation or chemoradiation treatment.[16 17] Samuel *et al*[17] assessed physical functioning using the 6 min walk test (6MWT), while Rogers *et al*[16] used a physical performance battery. After a combined aerobic and resistance-training programme over 6 weeks, there was a 42 m increase in 6MWT scores, while the usual care group experienced a 96 m decrease over the course of treatment ($p<0.05$).[17] A moderate effect size ($d=0.46$) was reported between groups over the course of the intervention.[17] In the Rogers study, minimal improvements in physical functioning were reported over the course of the intervention, and no significant differences were noted between the intervention and usual care groups.[16]

Following radiation or chemoradiation treatment: Functioning following treatment was reported in four studies.[10–12 18] In the three studies conducted by Lonbro *et al*,[10–12] physical functioning was evaluated using 10 m maximal gait speed, 30 s maximal chair rise, maximal stair climb and 30 s maximal arm curls. In their first study, no differences were noted in functional performance between the two groups (physical activity alone vs physical activity plus creatine supplementation).[12] By the end of the 12-week intervention, significant improvements in all functional assessment scores were noted in both groups, except for the mean change in stair climb time in the physical activity only group.[12] In their second study, Lonbro *et al*[10] found no difference in functional improvements between the progressive resistance-training group and the self-chosen activity group, but when the groups crossed over, the delayed progressive resistance-training group improved significantly more in chair rise and arm curl performance scores in comparison to the early progressive resistance-training group. When then comparing the pooled results from these interventions to healthy controls, patients with head and neck cancer had 18% lower functional performance scores 2 months following treatment; yet following a 12-week progressive resistance-training programme, no significant differences in functional performance were reported.[11] Finally, Eades *et al*[18] also found improved physical functioning following a physical activity programme, finding that patients walked on average an additional 59 m (95% CI 27 to 91) in the 6MWT by the end of the programme (effect size, $d=0.8$).

Both on and following radiation or chemoradiation treatment: Physical functioning improved in a mixed-sample of patients including those currently receiving as well as those having completed treatment. Sit to stand scores improved by 5.4±4.9 stands in 30s ($t=3.658$, $p=0.004$), and 6 min walk test scores improved by 49.6±65.4 m ($t=2.515$, $p=0.031$).[21]

One study, which did not report on the radiation and chemoradiation treatment status of the patients involved, but did manage patients postsurgery, described physical functioning changes using the 6MWT.[20] Following their eight-week hydrotherapy physical activity programme, Crevenna *et al*[20] reported improved 6MWT in the intervention group ($p<0.028$).

Fatigue

On radiation or chemoradiation treatment: Two studies reported improved fatigue management with the use of a physical activity intervention while patients were undergoing treatment.[16 19] One study evaluated a 12-week resistance-training programme on fatigue before and after the intervention, finding a medium effect size ($d=-0.64$) for decreased fatigue using the FACT-fatigue subscale.[16] The control group in this study reported significant increases in fatigue, whereas the intervention group reported no statistically significant changes.[16] Aghili *et al*[19] measured the impact of a 4-week aerobic physical activity programme on fatigue, noting a buffering effect in the intervention group compared to the control group, who reported increased fatigue symptoms on the BFI fatigue scale.

Both on and following radiation or chemoradiation treatment: Tiredness and drowsiness were measured using the ESAS in one study, which included patients who were on treatment as well as those who had completed treatment, and clinical and statistically significant improvements were noted in tiredness after one exercise session (mean difference=−0.5±0.6, $p=0.003$), and over the 12-week intervention (mean difference=−0.9±1.7, $p=0.195$).[21] Statistically significant improvements were found in reported drowsiness following one exercise session (mean difference=−1.6±1.8), with statistically and clinically significant improvements found in drowsiness levels over the 12-week exercise programme (mean difference=−1.6±1.8, $p=0.035$).[21]

Quality of life

On radiation or chemoradiation treatment: Two studies reported on changes in quality of life in patients over the course of treatment, finding that physical activity helped to manage quality of life, particularly in the physical functioning domains.[16 17] Following a 6-week walking and resistance-training programme, differences in quality of life, as measured using the Medical Outcomes Study Short Form-36 (SF-36), were noted between the usual care and intervention groups.[17] The physical component score of the SF-36 decreased from 38.6 to 32.7 (18%) in the usual care group, while the physical activity group experienced no decrease (43.2–43).[17] The mental component score decreased from 40.3 to 23 (75.21%) in the usual care group, while the physical activity group experienced an 11.73% increase over the course of the intervention (36.1–40.9).[17]

Rogers *et al*[16] also measured the impact of their intervention on quality of life using the FACT-HN. They reported an overall medium programme effect size over 6 weeks ($d=0.52$) and a small effect size over 12 weeks ($d=0.39$) between the intervention and usual care group on quality of life.[16] When considering the physical, social, emotional and functional well-being components of quality of life at 6 weeks, the largest effect sizes were reported in the physical (6 weeks: $d=0.44$; 12 weeks: $d=0.36$) and functional (6 weeks: $d=0.41$; 12 weeks: $d=0.33$) well-being

domains at 6 weeks and 12 weeks, respectively. A positive effect size was also reported in patient emotional well-being at 12 weeks (d=0.45).[16] Notably, patients in the intervention group, when compared to those in the control group, reported improvements that exceeded the minimally important difference for physical, emotional and functional well-being, as well as overall quality of life.[16]

Following radiation or chemoradiation treatment: Two studies found improvements in quality of life, particularly functional performance.[10 18] Lonbro *et al*[10] used the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). After 12 weeks of progressive resistance-training, all components of functional performance improved when compared to those involved in self-chosen physical activity. Additionally, the group given the 12-week progressive resistance-training intervention at 8 weeks post-treatment experienced significantly more improvement in quality of life than the group that started at 20 weeks post-treatment.[10] Eades *et al*[18] assessed symptom management over the course of an 8-week aerobic and resistance-training intervention, and found clinically meaningful improvements in quality of life (strong effect size, d=0.8), as measured using the Modified Edmonton Symptom Assessment System.

Quality of life was assessed by the SF-36 in the Crevenna *et al*[20] hydrotherapy intervention, however, there is no description of any adjuvant chemoradiation therapy. Postlaryngectomy patients reported improved physical functioning ($p<0.027$), vitality ($p<0.027$), role functioning ($p<0.027$) and social functioning ($p<0.043$).[20]

Both on and following radiation or chemoradiation treatment: Well-being was assessed using the ESAS in a sample of patients on and following treatment, and clinically and statistically significant improvements were noted after a single class session (mean difference -0.6 ± 0.8, $p=0.009$).[21] After the 12-week exercise intervention, clinically meaningful improvements in well-being were noted, but were non-significant (mean difference -1.4 ± 2.4, $p=0.156$).[21]

Synthesis of results

Pooled effect sizes were not calculated due to the significant heterogeneity between the included studies in physical activity protocols, study outcomes and outcome assessment methods.

Risk of bias across studies

Investigation of selective reporting of outcomes within studies is reported in table 2 (for RCTs) and table 3 (non-randomised studies). In general, risk of bias was high among studies included in this review. Risk of bias across studies was not completed due to the limited number of studies.

DISCUSSION

This is the first systematic review investigating the impact of physical activity on body composition, functioning and quality of life outcomes in patients with head and neck cancer, both during and following treatment. Physical activity interventions for patients with head and neck cancer, both during and following radiation or chemoradiation treatment, are feasible, safe and beneficial. Current levels of physical activity participation are low in this population, and tend to decline during treatment without any reported post-treatment rebound.[24 26 27] Despite this low level of current physical activity, the large majority of patients reported being interested in additional information or counselling regarding physical activity.[28]

Patients with head and neck cancer experience significant declines in lean body mass, muscular strength, physical functioning, fatigue management and overall quality of life during and following radiation and chemoradiation treatment.[4–7] Physical activity is a safe, feasible solution to mediate many of the negative treatment side effects patients with head and neck cancer face. Those who do achieve higher levels of physical activity report improvements in both general, and head and neck cancer-specific quality of life, as well as improved fatigue management.[27] Overall, intervention adherence is high when reported, with notably higher adherence experienced during mixed supervised interventions[10 12] versus home based.[16]

To date, nine experimental studies have examined the impact of physical activity on outcomes related to head and neck cancer. The main outcomes from these experimental studies included lean body mass, muscular strength, physical functioning, fatigue management and quality of life. Studies used a number of different assessment tools in the reporting of these outcomes, making it challenging to synthesise the current results. Despite this heterogeneity in tools, findings across studies indicate potential benefits from exercise interventions, both during and following treatment.

Physical activity was associated with improvements in lean body mass during and following treatment.[10–12 16] For example, progressive resistance-training post-treatment revealed a 2.8–5% increase in lean body mass, increasing head and neck cancer patients' lean body mass to match healthy controls post-intervention.[11] Since muscle wasting is exceedingly prevalent in this population, effective approaches to offset this wasting are necessary.[4 31] The current results indicate that progressive resistance-training holds significant promise as a tool to offset the usual declines that occur. Linked to lean body mass improvements, muscular strength is also found to increase with physical activity interventions, both during and following treatment.[10–12 16] Importantly, the lean body mass and strength changes are both further linked to physical functioning, which was found to improve in most interventions during and following treatment.[10–12 17 18] Finally, despite differences in intervention timing, results clearly indicate significant benefits related to symptom management and physical, emotional, social, role and functional well-being, with the greatest gains in physical and functional well-being.[10 11 16 17] Improvements in tiredness, drowsiness and overall well-being immediately following an exercise session were noted, indicating the value of a single exercise session.[21]

An important symptom-buffering effect appears to exist among those patients involved in a physical activity intervention during treatment. One study reported a trend towards improvements in lean body mass preservation in the resistance-training group versus the usual care group at 6 weeks into treatment,[16] while one of the two studies evaluating physical functioning during treatment noted functioning improvements in the physical activity intervention group, while the usual care group experienced significant declines in functioning ($p<0.05$).[17] The two interventions that examined changes in fatigue during treatment found that physical activity alleviated the usual increase in fatigue, helping patients better manage their fatigue during chemotherapy and radiation.[16 19] This was again found in the studies reporting on quality of life.[16 17] This research supports the importance of physical activity in the management and treatment of patients with head and neck cancer during treatment.

Limitations of current research

The field of physical activity for head and neck cancer is new and rapidly evolving. Still, in the early stages, we see a limited

number of studies, generally small samples sizes, a high risk of bias within the included studies, and a variety of study tools and outcomes. It was challenging to examine outcome effect sizes, in particular due to the inconsistency among assessment tools. Additionally, studies in this review are lacking long-term follow-up. Reporting on the long-term implications of physical activity is necessary to confirm the benefits of physical activity over time for this unique patient population.

Future research

Physical activity appears to be beneficial for patients with head and neck cancer both during and following radiation or chemoradiation treatment, however, a number of research questions still exist. Ongoing investigation is required to increase our understanding of the value of physical activity for patients with head and neck cancer, and to determine the benefits of different physical activity prescriptions and their impact on those with different head and neck cancer types. In addition, more work is necessary to decipher the appropriate timing of intervention initiation and the level of supervision required during those interventions. Finally, factors associated with the implementation of physical activity into usual head and neck cancer patient care should be investigated.

More specifically, future research questions should first address the specific physical activity recommendations for patients with head and neck cancer, and the dose–response relationship necessary to optimise the benefits of physical activity. Current guidelines, reported by Rock *et al*,[30] and based on the ACSM Cancer and Exercise Roundtable discussions in 2010, are general, and largely based on research that has been carried out in breast, colon and prostate cancer tumour groups.[32] Patients from these tumour groups experience very different symptoms and side effects in comparison to patients with head and neck cancer.[4 24] Additionally, comparison studies examining the differing benefits of aerobic versus progressive resistance-training have yet to be conducted, as well as those examining the impact of physical activity on different head and neck cancers, stages and treatment modalities. To determine differences between physical activity prescriptions, researchers must be diligent when reporting on intervention protocols.[29] Specifically, further examination must include reporting the type, frequency, duration and intensity (FITT principle) of physical activity, and the implications of physical activity intervention timing (ie, on or following treatment; time since treatment completion) on specific outcomes. Reporting on the FITT principles of physical activity will help researchers and health professionals to better understand and compare study protocols, as well as to translate successful protocols to real world settings.

The goal of an intervention may vary depending on whether patients are undergoing or have completed chemoradiation, since patients may experience different barriers and side effects at these different time points. As highlighted above, the goals of physical activity during treatment are to alleviate the usual decline and maintain functioning (ie, symptom-buffering), versus making gains in outcome variables. Logistical implications are linked to questions of timing as well (ie, patients' readiness to adopt new physical activity habits, and physical activity specialists available to work with patients on treatment vs those having completed treatment). Currently, our group is examining the impact of intervention timing (during or following treatment).[33]

Third, the specifics of intervention design also need to be further examined. Many of the studies reviewed made use of a supervised programme, which then transitioned to an unsupervised community- or home-based programme. Adherence rates were lower with the independent or home-based groups, which may suggest the value of longer duration supervised programmes. Strategies to target commonly reported barriers to physical activity participation are necessary, since patients will only garner the benefit of physical activity if they are able to adopt and adhere to active lifestyles. These should include teaching participants self-regulatory skills to become habitual exercisers, such as goal setting, tracking and coping skills to plan for barriers.[34] A trial comparing the delivery of physical activity interventions would address this issue. Also, studies that include outcomes such as biomarkers will be an important future addition. This is an important future direction as it might help elucidate the mechanisms by which physical activity works, and thus should be considered as an outcome measure in future studies.[35] Finally, studies that examine factors associated with external validity are important for future implementation of these programmes in standard care.[36] This may include evaluating practical clinical trials that address issues related to implementation and dissemination of physical activity programming as a part of standard care.[36]

Limitations of this review

Our review was limited by only reporting on studies published in English, and, due to study and evaluation heterogeneity, we were unable to synthesise results and calculate combined effect sizes and clinical significance. Moreover, studies generally have a high or unclear risk of bias. Future randomised trials are needed with a focus on the design and reporting of factors related to bias such as method of randomisation, allocation concealment and blinding.

What are the new findings?

- Physical activity interventions are feasible, safe and beneficial in mediating head and neck cancer, and treatment-related side effects.
- Physical activity programmes can facilitate improvements in lean body mass, muscular strength, physical functioning, quality of life and fatigue management, for patients with head and neck cancer.
- Studies vary greatly in design, quality and reporting characteristics.
- Additional research is required to determine the best intervention design, initiation time point and exercise prescription, to generate the most beneficial outcomes for patients following a head and neck cancer diagnosis.

How might it impact on clinical practice in the near future?

- This review suggests the value of physical activity as an essential part of head and neck cancer care.
- Referral to a cancer *exercise specialist* may benefit patients with head and neck cancer, and enhance recovery and rehabilitation following treatment.
- Understanding the benefits of physical activity for these patients may help clinicians when considering appropriate symptom management and rehabilitation programmes for patients.

In summary, this systematic review highlights the benefits of physical activity for patients with head and neck cancer, suggesting the value of physical activity as an essential part of head and neck cancer care.

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The impact of physical activity on health-related fitness and quality of life for patients with head and neck cancer: a systematic review

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