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REVIEW

The effects of physical exercise in the palliative care phase for people with advanced cancer: a systematic review with meta-analysis

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Abstract

Purpose The purpose of this systematic review with meta-analysis was to evaluate the safety, feasibility and effectiveness of exercise in the palliative care phase for people with advanced cancer.

Methods Electronic databases were searched for exercise randomised controlled trials involving individuals with incurable cancer that were published prior to April 14, 2021. Meta-analyses were performed to evaluate the effects of exercise on health outcomes. Subgroup effects for exercise mode, supervision, intervention duration and cancer diagnosis were assessed.

Results Twenty-two trials involving interventions ranging between 2 weeks and 6 months were included. Interventions comprised of aerobic ($n=3$), resistance ($n=4$), mixed-mode ($n=14$) and other exercise ($n=1$) modalities. Cancer types consisted of lung ($n=6$), breast ($n=3$), prostate ($n=2$), multiple myeloma ($n=1$) and mixed cancer types ($n=10$). Meta-analysis of 20 RCTs involving 1840 participants showed no difference in the risk of a grade 2–4 adverse event between exercise and usual care ($n=110$ adverse events (exercise: $n=66$ events; usual care: $n=44$ events), RD = −0.01 (91% CI = −0.01, 0.02); $p=0.24$). Overall median recruitment, retention and adherence rates were 56%, 80% and 69%, respectively. Meta-analysis of health outcomes showed effects in favour of exercise for quality of life, fatigue, aerobic fitness and lower-body strength (SMD range = 0.27–0.48, all $p<0.05$).

Conclusions Participants who engaged in exercise experienced an increase in quality of life, fitness and strength and a decrease in fatigue.

Implications for Cancer Survivors Physical activity programs were found to be safe and feasible for people with advanced cancer in the palliative care phase.

Keywords Palliative · Advanced · Cancer · Neoplasm · Aerobic exercise · Resistance exercise · Exercise oncology

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Introduction

It is well recognised that both patients with an advanced, life-limiting illness and their family and carers face multiple challenges [1, 2]. These include not only physical symptoms, such as pain and nausea, but multiple psychosocial issues including a decline in function, complex advanced care decisions and emotional distress [1, 2]. One of the fundamental aims of palliative care is to address these issues through patient-centred care to optimise quality of life (QOL). Historically, medical care has focussed on managing physical symptoms to achieve this, but it is increasingly recognised that a multi-disciplinary, multimodal approach is needed to adequately manage both a patient's physical and psychosocial issues [3]. Exercise for the purpose of this review includes physical activity (PA) and structured rehabilitation programs. Multiple studies support the safety and effectiveness of exercise during and following treatment for cancer [4–6], and while these studies focused on individuals undergoing treatment for cancer regardless of cancer stage, there is now increasing evidence to also support its use specifically in the palliative phase. It has been shown that exercise if implemented alongside usual medical care provides multiple benefits, such as improved QOL, physical function and independence, emotional well-being and symptom control (such as cancer-related fatigue and pain) [7, 8]. Even those with advanced disease can derive meaningful benefits from increased levels of exercise, particularly when the program is supervised and tailored to the individual [9]. It has also been shown to be a safe, low-cost, feasible and an accepted option for people in recent studies [10, 11].

Despite this, exercise is not always straightforward in the palliative phase as many barriers prevent people diagnosed with cancer from participating. These include significant negative physical symptoms and comorbidities, poor patient motivation, lack of patient knowledge and inadequate access to facilities/resources and time [12–14]. It is not yet fully understood whether similar barriers to exercise impacts people receiving palliative care; however, it could be assumed that having advanced cancer would increase such obstacles. A recent qualitative study by Frickel et al. [15] investigated barriers to PA in advanced cancer patients with moderate to severe fatigue. It was found that the patients' physical symptoms were the greatest barrier, particularly fatigue or weakness, but this could be overcome if they had adequate motivation for PA (interest in an exercise program), knowledge about the positive impact of exercise on QOL and increased levels before their cancer diagnosis [16, 17].

The purpose of this systematic review with meta-analysis was to evaluate the safety, feasibility and effectiveness of exercise for people with advanced cancer in the palliative care phase. Specifically, this review will evaluate (1) the number, type and severity of adverse events (safety), and (2) trial recruitment, retention and program adherence rates (feasibility). Secondary outcomes of this work included the evaluation of the effect of exercise on health-related outcomes including QOL, aerobic fitness, fatigue, upper-body strength, lower-body strength, anxiety, depression, pain and sleep.

Methods

Search strategy and selection criteria

The protocol for this systematic review and meta-analysis was registered on PROSPERO (CRD42021255388). An electronic database search using combinations of MeSH and free-text words for "palliative", "cancer", "physical activity" and "exercise" was undertaken using the following databases: Cochrane Library, EMBASE, SPORTDiscus (via EBSCOhost), ProQuest Health and Medical Complete, ProQuest Nursing and Allied Health Source, Science Direct, Web of Science, CINAHL, Scopus and PubMed (full search details are shown in Supplementary content 1). Database searches were restricted to English (language) articles published in peer-reviewed journals prior to 14/4/2021. Searches were conducted between 1/04/2021 and 14/04/2021 with a final search on 26/10/2021 (no additional eligible studies were identified). The Participant, Intervention, Comparator, and Outcome (PICO) framework [18] was used to define the inclusion criteria.

Participants

Trials involving female or male adult participants, diagnosed with any type of incurable cancer currently in the stable palliative care phase (as classified by The Australian Institute of Health and Welfare), were eligible [19]. Studies were excluded if the sample included curative cancer cases or where incurable cancer was not the reason for palliation.

Intervention

Randomised controlled trials (RCTs) designed to evaluate the effects of exercise interventions were eligible. Non-RCTs and single-group pre-post studies were ineligible. An RCT assessing an exercise intervention was defined as a comparative trial designed to evaluate the safety, feasibility or effectiveness of exercise with random allocation of participants to exercise and usual care groups. The following definition of the exercise was used: "any form of planned, structured, and repetitive bodily movements performed to improve or

maintain fitness, performance or health" [20]. Eligible studies were categorised into subgroups based on the mode of exercise (aerobic based, resistance based, mixed mode or other). "Other" exercise was any type of exercise that was not specified as aerobic based or resistance based (e.g. yoga). Quasi-experimental studies and studies that involved another intervention in addition to exercise were ineligible unless the effects of exercise could be isolated. Studies were eligible regardless of the type and amount of intervention supervision, intervention length or exercise dose (e.g. exercise duration or intensity).

Comparators

Studies that compared exercise to either no exercise, a different mode of exercise, including exercise performed at a different amount or intensity or other intervention were included if there was a non-exercise usual care group.

Outcomes

Studies that evaluated the safety, feasibility and/or the effectiveness of exercise on health-related outcomes (e.g. QOL) were eligible. Health-related outcomes included QOL, aerobic fitness, fatigue, upper-body strength, lower-body strength, anxiety, depression, pain and sleep.

Outcomes of interest

Safety and feasibility

Safety was assessed by evaluating the frequency and severity of adverse events. Adverse events were considered as any undesirable health or medical event that occurred during the study and categorised as either exercise-related adverse events (events which occurred during or as a direct result of participating in exercise) or non-exercise adverse events (occurred during the study but reported as being unrelated to exercise). Adverse events severity was categorised by one author (BS) using the Common Terminology Criteria for Adverse Events (Version 6.0) as either grade 1 (asymptomatic or mild symptoms, clinical or diagnostic observations only and/or intervention not indicated); grade 2 (moderate, minimal, local or non-invasive intervention required and/or limiting age-appropriate activities of daily living); grade 3 (severe or medically significant but not immediately life-threatening; hospitalisation and/or prolongation of hospitalisation indicated; disabling and limiting self-care activities of daily living); grade 4 (life-threatening consequences and urgent intervention indicated) or grade 5 (death). An event was considered "serious" (i.e. grade 3+) if it resulted in hospitalisation, disability, was life-threatening or death [21]. To reduce adverse event underreporting, we considered any withdrawal from a study that occurred due to a medical, health or disease-related reason (e.g. illness) as an adverse event [22]. If the severity of an adverse event was not specified, then the event was categorised as grade 3 if it caused withdrawal from a study [22]. If a study did not comment on adverse events and there were no health-related withdrawals, then it was considered that no adverse events had occurred [22].

Health-related outcomes

Meta-analyses of the effects of exercise compared to usual care on health outcomes were performed for outcomes that were reported in at least two studies [23]. These were quality of life, aerobic fitness, fatigue, upper-body strength, lower-body strength, anxiety, depression, pain and sleep.

Data extraction

Search results that were identified during the electronic database search were transferred to the data management software, Covidence (Version 2579, Melbourne, Australia) and duplicate titles were removed. Title and abstract screening were undertaken by three authors (K.T., A.R. and D.M.), and conflicts were resolved by discussion. Screening of the reference lists of relevant articles (original studies and reviews) was also undertaken to identify potentially eligible studies. Articles that were considered potentially eligible based on the title or abstract were obtained in full text and screened for eligibility. Two investigators (K.T. and B.S.) extracted the following data from each trial into table format: trial and participant characteristics, intervention details, adverse events and feasibility information. Risk of bias assessment of each trial was undertaken using the Physiotherapy Evidence PEDro scale by two investigators (K.T. and B.S.) and uncertainties in ratings were discussed with a third author (M.C.). The PEDro scale is a valid and reliable tool for assessing the risk of bias in RCTs [24, 25]. Each study was evaluated in 11 domains (eligibility criteria, random assignment, concealment, between-group differences at baseline, participant blinding, staff blinding, assessor blinding, attrition, intention-to-treat analysis, between-group analyses and outcome reporting). Studies with a score lower than six were graded as low quality (out of 10; with item one not contributing to the total score), and scores of six or higher were graded as high quality [25].

Statistical analyses

Meta-analysis of adverse events

A Mantel–Haenszel random-effects model was used to assess the total amount of adverse events that occurred in

the intervention and usual care groups. Adverse events were analysed as a count variable and the risk difference (RD) and 95% confidence intervals were calculated as the effect measure. RD was used to ensure that trials with zero adverse events were not excluded from the analysis [26]. A negative value for RD indicated a lower risk of an adverse event in the intervention groups compared with usual care groups. Low-grade adverse events (i.e., grade 1) were likely to have not been comprehensively reported or monitored for usual care participants due to reduced contact with study staff (compared with the interventions groups). Furthermore, grade 1 events would also likely include normal responses to exercise (e.g. mild muscle soreness), rather than undesirable or potentially avoidable adverse events for the participants in the exercise intervention groups [27]. Grade 5 events (death) were also unlikely to occur either during or as a direct result of exercise. Therefore, only grade 2–4 adverse events were included in the meta-analysis. All adverse events (grades $1-5$) were also evaluated descriptively.

Feasibility

Feasibility was assessed by computing overall recruitment, retention and exercise adherence rates (as a percentage) and reported as median (range) due to non-normally distributed data. Recruitment rates were calculated as the percentage of participants who were eligible and consented to participate. Retention rates were calculated as the percentage of enrolled participants who finished the study. Adherence rates were calculated as the percentage of prescribed exercise sessions that were completed by participants. Feasibility was evaluated using the following cutoff values which were considered clinically relevant based on previous research as follows: recruitment rate: $\geq 25\%$ [28]; retention rate: $\geq 75\%$ [29] and adherence rate: $\geq 75\%$ [29].

Meta-analysis of health outcomes

Health-related outcomes were assessed as continuous outcomes by comparing means and standard deviations (SDs) using post-intervention data for the exercise intervention and usual care groups. The standardised mean differences (SMDs) were used as the effect measures, which were calculated using RevMan software (version 5.3), to allow comparisons of data from different scales. Forest plots for each meta-analysis were created using R statistical software (version 3.6.2). If means and/or SDs were not reported in an article, then the authors were contacted or recommended formulas were used to compute the means and/or SDs based on reported data (e.g. using medians, ranges and sample sizes) [30]. If an article reported multiple methods for assessing an outcome, the method with demonstrated validity or reliability or the method defined as being the gold standard was used.

For each meta-analysis, data were combined at the study level. Funnel plots were created for each meta-analysis to evaluate publication bias by plotting RDs and SMDs against standard errors and assessing for asymmetries or missing sections in the plot [31]. The following cutoffs were used to quantify effect size: <0.20 representing a small effect; 0.20–0.50 representing a medium effect and >0.50 representing a large effect [32]. A p-value of less than 0.05 was considered statistically significant. The Cochran's Q test was used to evaluate statistical heterogeneity and the proportion of the overall outcome attributed to variability was evaluated using the I^2 statistic as follows: $I^2 = <29\%$ represents no heterogeneity; $I^2 = 30$–49% represents moderate heterogeneity; $I^2 = 50$–74% represents substantial heterogeneity and $I^2 = \geq 75\%$ represents considerable heterogeneity [23]. Subgroup analyses were undertaken to assess the effects of (1) exercise mode (aerobic based, resistance based, mixed mode and other exercises); (2) intervention supervision (supervised: defined as over half of the exercise sessions involving face-to-face supervision versus unsupervised: less than half of the exercise sessions involving face-to-face supervision); (3) intervention duration (<12 weeks or ≥ 12 weeks) and (4) cancer type (breast, colorectal, prostate, lung, leukaemia, multiple myeloma or mixed (studies involving a mix of participants with different diagnoses)) on health outcomes.

Results

Literature search

A total of 778 articles were identified after a search of databases (Fig. 1). Following the removal of duplicates, titles and abstracts were screened and 92 full-text publications were retrieved and screened. Seventy ($n=70$) were ineligible (reasons for exclusion are described in Supplementary content 2), and 22 trials were included. Based on PEDro scores, 13 (59%) trials were low quality and $n=9$ (41%) were high quality (Supplementary content 2).

Study and intervention characteristics

An overview of all study and intervention characteristics is shown in Table 3. Median sample size was 60 (minimum = 12; maximum = 269), and mean age of participants across all trials was 61 years (SD = 6.9). Six trials involved participants with lung cancer ($n=6$, 27%; [33–38]), three trials involved breast cancer ($n=3$, 14%; [39–41]); two trials involved prostate cancer ($n=2$, 9%; [42, 43]), one trial involved multiple myeloma ($n=1$, 5%; [44]) and ten trials involved samples with mixed cancer types ($n=10$, 45%;

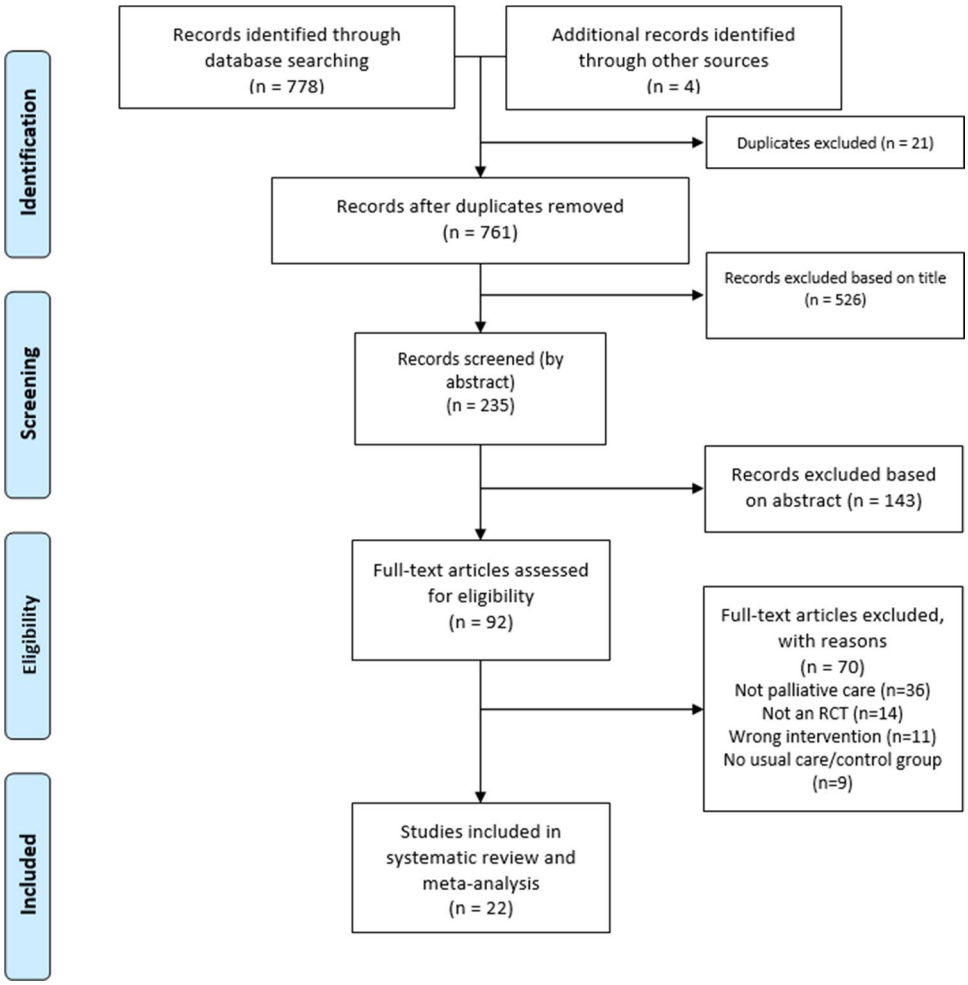

Fig. 1 PRISMA flow diagram

[45–54]). Time since cancer diagnosis was reported in seven trials [36, 40, 42, 43, 49, 53, 55] and ranged between 0.2 and 9.8 years (median 2.8 years). Median intervention duration was 12 weeks (minimum = 2 weeks; maximum = 6 months). Most interventions involved combined exercise (aerobic and resistance exercise) ($n = 14$, 64%; [33–35, 38, 43, 44, 46–49, 51–53, 55]). Four trials involved resistance exercise ($n = 4$, 18%; [42, 45, 50, 54]), three trials involved aerobic exercise ($n = 3$, 14%; [36, 37, 40]) and one trial involved other exercise ($n = 1$, 5%; [41]). Most interventions were supervised ($n = 16$, 76%; [33, 35–38, 40–43, 49–55]), with five trials involving unsupervised interventions ($n = 5$, 24%; [34, 44–47]) and one trial involved one supervised arm and one unsupervised arm ($n = 1$, 5%; [48]). Therefore, there was a total of 23 intervention arms across the 22 included studies. Details of all exercise interventions are shown in Table 1.

Safety—overview of adverse events

Two trials specifically reported that no adverse events had occurred [52, 55] and one trial made no comments around whether adverse events occurred or not [37]. Furthermore, two trials reported brief details about the occurrence of adverse events, which included fatigue, body discomfort, falls and hospitalisation due to pericardial effusion and death [36, 44]; however, the specific number of adverse events [36] and the group in which the events occurred [44] was not reported. Therefore, these two studies [36][36] were excluded from the meta-analysis. Overall, a total of 189 adverse events (including withdrawals due to health-related reasons) occurred in 17 trials [33–35, 38, 40–43, 45–51, 53, 54] (Table 2).

Adverse events among exercise participants

One hundred fifteen adverse events occurred among participants allocated to exercise (grade 1: $n = 9$ events; grade 2: $n = 12$ events; grade 3: $n = 36$ events; grade 4: $n = 18$ events; grade 5: $n = 40$ events, Table 2). The most common adverse events among exercise participants were death ($n = 40$ events, grade 5), disease progression ($n = 16$ events, grade 4) and illness/too unwell ($n = 8$ events, grade 3). Of the 115 events, 111 events (97%) were considered unrelated to exercise and 4 events (3%) were reported as exercise related.

Table 1 Overview of exercise interventions in the included studies

Parameter	Intervention details
Exercise mode	Aerobic exercise interventions: Walking, treadmill, cycling ergometer or Nordic walking
	Resistance exercise interventions: 4–10 resistance exercise of all major upper and lower-body muscle groups using TheraBands, free weights, bodyweight and/or resistance machines
	Mixed-mode interventions: •Aerobic: stationary cycling, walking, treadmill, cycling, rowing ergometer and/or stair walking •Resistance: 4–10 resistance exercise of all major upper and lower-body muscle groups using TheraBands, free weights, bodyweight or resistance machines (including circuit resistance training)
	Other exercise interventions: yoga
Frequency	3–7 days/week for 2 weeks to 6 months (2–4 days per week of resistance exercise and daily walking)
Intensity	Aerobic exercise interventions: 15–17 Borg RPE; 70–80% VO2peak; overall intervention goals of 150 min of moderate-intensity exercise each week
	Resistance exercise interventions: 2–4 sets per exercise at 8–12 RM
	Mixed-mode interventions: •Overall intervention goal of 150 min of moderate-intensity aerobic exercise each week or 40–45 MET hours per week •Aerobic exercise: 11–15 Borg RPE; 70–250 W; 55–95% HRmax; 30 to 80% of peak work rate or 3.75 MET hours per training session •Resistance exercise: 11–15 Borg RPE; 6–7 out of 10 on the Adult OMNI Perceived Exertion Scale; 40–85% of 1RM; 1–4 sets of 5–20 repetitions per exercise
	Other exercise interventions: not specified
Duration	20–120 min per session (including 5–15-min warm-up and cool-down)

Exercise-related adverse events were back or musculoskeletal pain/soreness ($n=4$ events, grade 1) [34]. Furthermore, one study [56] reported that during pre-screening prior to each supervised exercise session, five participants were excluded from 1–2 exercise sessions due to fever, dizziness, pain and bodily discomfort. These were not considered as exercise-related adverse events; however, they resulted in missed exercise sessions.

Adverse events among usual care participants

There were 74 adverse events among participants allocated to usual care (grade 1: $n=0$ events; grade 2: $n=7$ events; grade 3: $n=22$ events; grade 4: $n=15$ events; grade 5: $n=30$ events, Table 2). The most common adverse events were death ($n=30$ events, grade 5), disease progression ($n=15$ events, grade 4) and illness/too unwell ($n=5$ events, grade 3).

Meta-analysis of adverse events.

Meta-analysis of 20 RCTs involving 1840 participants (exercise: $n=933$; usual care: $n=907$) showed no difference in the risk of a grade 2–4 adverse event between exercise and usual care ($n=110$ adverse events (exercise: $n=66$ events; usual care: $n=44$ events), RD = −0.01 (95% CI = −0.01, 0.02); $p=0.24$; $I^2=0\%$, Fig. 2). Subgroup analyses showed that adverse event risk was similar irrespective of exercise mode (aerobic, resistance, combined and other exercise; $\chi^2=0.15$, $p=0.98$), intervention supervision (supervised and unsupervised; $\chi^2=0.01$, $p=0.94$), intervention duration (< 12 weeks versus ≥ 12 weeks; $\chi^2=0.25$, $p=0.62$) and cancer type (breast, prostate, lung or mixed; $\chi^2=1.87$, $p=0.60$).

Feasibility outcomes

An overview of feasibility results is shown in Supplementary content 4.

Recruitment rates: Overall recruitment rate met the pre-defined criterion of ≥ 25%, with a median rate of 56% (range: 12–91%; reported in $n=19$ trials).

Retention: Median retention rate for the exercise groups was 80% (range: 41–100%), therefore meeting the pre-defined criteria of ≥ 75%. Of note, the median retention rate for the usual care groups was 83% (range: 58–100%). There was a total of 208 withdrawals from the exercise groups ($n=93$, 45% due to health-related reasons; $n=155$, 55% due to non-health-related reasons) and 163 withdrawals from usual care groups ($n=67$, 41% due to health-related reasons; $n=96$, 59% due to non-health-related reasons; Supplementary content 6). Participants being uncontactable or lost to follow-up (with no specified reason) were the most common reason for withdrawal in both groups (exercise groups: $n=71$ withdrawals; usual care: $n=46$ withdrawals; see Supplementary content 5 for all reasons for withdrawals).

Exercise adherence: Adherence to the scheduled number of exercise sessions was reported in 13 trials [32, 33, 35, 40–42, 45, 46, 48, 50–52, 54]. Median adherence rate was 69% (range: 44–93%, $n=13$ trials), therefore not meeting the pre-defined criterion of ≥ 75%.

Table 2 Adverse events by grade of severity described for those in the exercise and usual care groups

AE grade[1]	Exercise intervention 115 total adverse events out of 959 participants (4 exercise-related adverse events out of 959 participants)	Usual care 74 total adverse events out of 929 participants
1	Grade 1 adverse events: $n=9$	Grade 1 adverse events: $n=0$
	Back or muscle soreness (exercise related) $n=4$ Minor fall $n=1$ Minor unspecified events $n=4$	$n=0$
2	Grade 2 adverse events: $n=12$	Grade 2 adverse events: $n=7$
	Fever/dizziness/pain/bodily discomfort $n=5$ Pain $n=2$ Neutropenia $n=2$ Infection $n=2$ Rectal bleeding $n=1$	Pain $n=2$ Neutropenia $n=2$ Infection $n=2$ Gastrointestinal stricture, intrahepatic duct $n=1$
3[2]	Grade 3 adverse events: $n=36$	Grade 3 adverse events: $n=22$
	Illness or too unwell $n=8$ Infections $n=7$ Bone marrow suppression $n=4$ Other health problems $n=3$ Increased bone pain $n=3$ Hospitalised $n=2$ Physical impairment $n=2$ Health deterioration $n=1$ Fall (leading to withdrawal) $n=1$ Anaemia $n=1$ Myalgia $n=1$ Asthenia $n=1$ Pneumonia $n=1$ Chemotherapy side effect $n=1$	Illness or too unwell $n=5$ Bone marrow suppression $n=4$ physical impairment $n=4$ Infections $n=2$ Health deterioration $n=2$ Anaemia $n=2$ Increased bone pain $n=1$ Leucopoenia $n=1$ Worsening psychiatric condition $n=1$
4	Grade 4 adverse events: $n=18$	Grade 4 adverse events: $n=15$
	Disease progression $n=16$ Pathological fracture $n=1$ Fractured rib $n=1$	Disease progression $n=15$
5	Grade 5 adverse events: $n=40$	Grade 5 adverse events: $n=30$
	Death $n=40$	Death $n=30$

AE, adverse events

[1]Adverse events were classified using the Common Terminology Criteria as grade 1: asymptomatic or mild symptoms; grade 2: moderate, minimal, local or non-invasive intervention indicated and limiting age-appropriate instrumental activities of daily living; grade 3: severe or medically significant but not immediately life-threatening; grade 4: life-threatening consequences and urgent intervention indicated or grade 5: death

[2]Adverse events in which the severity was not reported were considered grade 3 or higher if the event led to study withdrawal

Meta-analyses results: exercise versus usual care

Compared with usual care, there were small to moderate effects (all $p<0.05$) in favour of exercise for QOL (SMD = 0.27 (95% CI = 0.14, 0.39)), fatigue (SMD = 0.30 (95% CI = 0.13, 0.47)), aerobic fitness (SMD = 0.30 (95% CI = 0.12, 0.49)) and lower-body strength (SMD = 0.48 (95% CI = 0.12, 0.84); Fig. 3). No overall effects were observed for upper-body strength (SMD = 0.45 (95% CI = −0.09, 0.98), $p=0.10$), pain (SMD = 0.24 (95% CI = −0.01, 0.48), $p=0.06$), depression (SMD = 0.33 (95% CI = −0.07, 0.72), $p=0.10$) and anxiety (SMD = 0.11 (95% CI = −0.13, 0.35), $p=0.36$). No significant subgroup effects of exercise mode, supervision, duration and cancer type were observed (Supplementary content 6).

Discussion

The aim of this systematic review and meta-analysis was to evaluate the safety, feasibility and effectiveness of physical exercise for people with advanced cancer in the palliative care phase. It was identified that structured exercise programs were in general safe based on the current findings: there were no differences in adverse event risk between exercise and usual care. Only 3% of adverse events were exercise related, which were low severity. Exercise was feasible in terms of recruitment and retention; however, adherence (69%) did not meet the pre-specified criteria of > 75%. It remains important to consider that this specific cohort of cancer patients experiences a high disease burden. Therefore, an adherence rate of 69% still represents a positive outcome in terms to exercise adoption and adherence. A small to moderate effect (all $p<0.05$) was observed in favour of exercise for QOL, fatigue, aerobic fitness and lower-body strength. Caution with exercise prescription remains relevant because all included studies did not comprehensively report adverse event monitoring and recording procedures. This highlights the need for standardised monitoring and reporting of adverse events to be incorporated into the design of exercise oncology RCTs. This review highlights the importance of considering exercise for people diagnosed with advanced cancer in

Subgroup	Studies (n=)	Participants (n=)	Heterogeneity (%)	SMD (95% CI)	P-value
Exercise mode					
Aerobic exercise	2	121	0	0.02 [-0.06, 0.10]	0.61
Resistance exercise	5	312	0	0.01 [-0.02, 0.05]	0.46
Mixed-mode exercise	13	1344	13	0.01 [-0.01, 0.03]	0.25
Other exercise	1	63	NA	0.00 [-0.07, 0.07]	1.00
Supervision					
Supervised	16	1500	16	0.01 [-0.01, 0.03]	0.18
Unsupervised	5	340	0	0.01 [-0.03, 0.05]	0.60
Duration					
Less than 12 weeks	13	1198	24	0.02 [-0.01, 0.04]	0.16
12 weeks or more	8	642	0	0.01 [-0.02, 0.04]	0.65
Cancer					
Breast	3	178	0	0.01 [-0.04, 0.06]	0.72
Colorectal	0	0	NA	NA	NA
Prostate	2	77	0	0.11 [-0.03, 0.24]	0.12
Leukemia	0	0	NA	NA	NA
Mixed	11	1152	29	0.01 [-0.01, 0.03]	0.26
Lung	5	433	0	0.01 [-0.04, 0.06]	0.68
Multiple myeloma	0	0	NA	NA	NA
Overall	21	1840	0	0.01 [-0.01, 0.02]	0.24

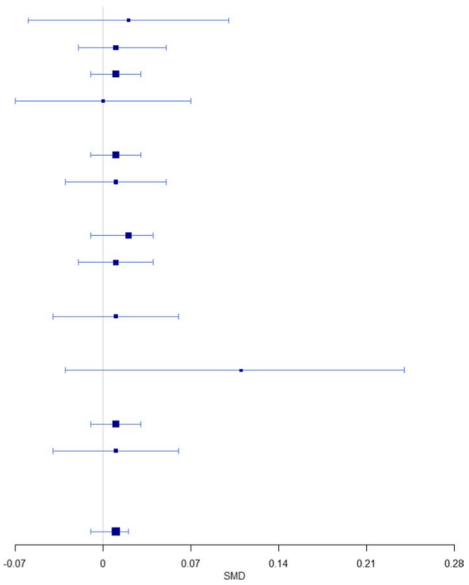

Fig. 2 Meta-analysis of adverse events between exercise and usual care with subgroup analysis results

Outcome	Studies (n=)	Participants (n=)	Heterogeneity (%)	SMD (95% CI)	P-value
Quality of life	11	975	0	0.27 [0.14, 0.39]	<0.0001
Fatigue	20	1746	61	0.30 [0.13, 0.47]	0.0004
Aerobic fitness	15	1312	57	0.30 [0.12, 0.49]	0.002
Upper-body strength	7	939	93	0.45 [-0.09, 0.98]	0.10
Lower-body strength	10	1044	85	0.48 [0.12, 0.84]	0.01
Pain	10	717	52	0.24 [-0.01, 0.48]	0.06
Anxiety	5	472	30	0.11 [-0.13, 0.35]	0.36
Depression	4	412	66	0.33 [-0.07, 0.72]	0.10

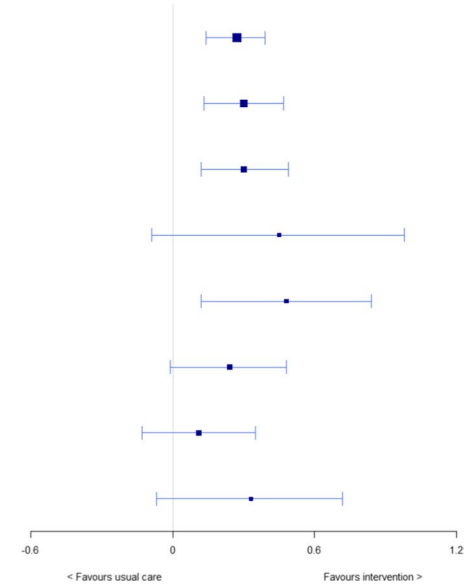

Fig. 3 Meta-analysis results of the effects of exercise versus usual care for health-related outcomes

the palliative care phase as part of the holistic approach to their individual care.

Given that exercise was shown to be safe within this review, it is recommended from the findings that careful consideration be given to the type of exercise prescribed for people with advanced cancer. Exercise programs were noted to be safe; however, the vulnerability of this population must be considered when determining and prescribing these programs. In this review, 16 (73%) out of the 22 studies were fully supervised by an exercise professional and a further three were partially supervised (Table 3). Three studies were home-based studies with additional safety consideration, for example Coleman et al. provided individual exercise programs based on patients' health and exercise history, strength levels and aerobic capacity which was determined in the initial testing session [44]. The home-based study by

Dhillon et al. required medical clearance and participation in the Physical Activity Readiness questionnaire along with individually prescribed weekly sessions with an exercise provider [34]. Given these findings and the complexities of the disease and the potential treatment effects, an initial comprehensive physical history and assessment would safeguard the participant when undertaking exercise [57]. An additional consideration is a risk that certain exercise would not be suitable for people with advanced illness. Combining these notions will allow clinicians to focus on the risks and the potential benefits and match it to the needs of the patient. For example, if cancer has metastasised to the bones patients may have compromised bone strength (high impact and heavy load exercise may not be appropriate) and if they have cachexia, weakness and wasting of the muscles due to their illness, they may have reduced energy levels, strength and QOL (exercise must begin at a much lower intensity and load). Depending on individual circumstances impact sports and heavier resistance training programs may be more suitable for people without bone metastases, whereas a seated exercise program with light resistance bands or a lighter intensity program (such as light yoga or light resistance banded exercise) may be more suitable for patients experiencing cachexia [58].

The interventions in this review were feasible, but there are noted limitations to adherence. Diminished adherence to exercise could be contributed to by several factors, not the least of which would be illness or treatment-related changes for participants with advanced cancer. Additional factors such as the location of the exercise program varied in the studies; the setting was noted to be a significant barrier to exercise participation in prior studies [15]. Although not seen in the current review, qualitative evidence has also reported that patients who have previously been comfortable attending the gym pre-cancer were not comfortable within the gym environment due to their change in health status. The safety of exercise was of significant importance to participants, although being in a supervised gym-like environment did not always equate with additional feelings of safety [59, 60]. Notions of both the setting and safety were important to people approaching the end of their life in these interviews and should be studied further to help support current exercise evidence in this population. This review found that overall exercise was safe for people with advanced cancer to participate in. Given that this is true and that the studies presented exercised cautionary approaches to exercise supervision, safety should be carefully considered when prescribing exercise. It is suggested that best practice should involve supervision by a qualified exercise professional with experience in cancer care such as an Accredited Exercise Physiologist or Physiotherapist [61], at least in the first instance. The mode, setting and supervision of exercise may have an impact on adherence in people with advanced cancer given that adherence levels were lower when compared with other cancer populations; these factors are easily modifiable and should be considered for this population. In the current review, Yee et al. reported a 100% compliance to the resistance-based exercise program compared to 25% in the aerobic-based program highlighting that for the population within this study the aerobic prescription may not have been appropriate [55].

Adherence to exercise was low (69%) in this study compared to other clinical populations such as people with mild cognitive impairment or dementia (70%) and people with heart failure (87%) [62, 63]. An additional element for consideration which could impact adherence for people with advanced cancer is program duration and intensity. Some studies showed lower compliance [46, 64] and it seemed likely that the intensity of the exercise, program duration and type of exercise may have played a role. For example, exercise at a higher intensity and longer duration may not be suitable and some people with advanced illness demonstrating less compliance. Some study participants in this review also identified that their preference was to participate in individualised programs [64]. While this is an area which requires additional study, the development of exercise programs which are designed and targeted to an individual's goals and context and flexible to the potential need for changes due to their current and ever-changing physiological capacity should be taken into consideration.

This review found that exercise benefits in QOL, fitness and strength; some programs also resulted in additional benefits such as improvements in fatigue; similar findings have been reported across the cancer population [22, 28, 29]. Due to the nature of advanced disease, cancer patients suffer from a severe physical decline in areas such as QOL, mobility, strength and overall physical functioning [65]. During treatments such as chemotherapy and radiotherapy, patients can experience significant long-lasting side effects such as nausea, cancer-related fatigue, peripheral neuropathies and pain [66–68]. As the illness progresses, these issues remain and maintaining physical function through exercise could be extremely important in supporting good QOL for patients [69]. Exercise interventions with safety precautions (such as supervision) and considerations for the individual's health status have been shown in this review to support people with cancer in the palliative care phase.

The exercise showed a moderate effect in reducing fatigue and no significant effect in reducing pain in those who participated in the studies compared to the control groups in this review. Controlling or reducing physical symptoms such as fatigue and pain are crucial in preserving a comfortable QOL in this population [70]. Fatigue is a debilitating symptom that many patients in the palliative care phase experience during their illness and treatment. Studies in earlier stage cancer report improvements in fatigue levels, after participating in

Table 3 Overview of samples and exercise details of included studies

	Sample size and cancer type	Treatment	Exercise type	Exercise location and supervision	Primary outcome(s) result
Adamsen 2009	$n=269$ ovaries, testes, oesophagus, brain, cervix, pharynx, pancreas, stomach	Undergoing chemotherapy	Type: aerobic + resistance Frequency: 3 days/week Intensity: aerobic: 85–95% HR max, 3.75 MET hours/session; resistance: 3 sets of 5–8 repetitions, 70–100 & 1 RM, 4 MET hours/session Duration: 90 min Intervention length: 6 weeks	Exercise at supervised venue	Fatigue: ↓
Brown 2006	$N=115$ brain, head, neck, lungs, ovarian, gastrointestinal	Undergoing radiation therapy	Type: resistance Frequency: 2 days/week Intensity: not reported Duration: 90 min Intervention length: 4 weeks	Exercise at supervised venue	Fatigue: ↔
Cheville 2010	$n=103$ gastrointestinal, head, neck, lungs, brain, other	Undergoing radiation therapy	Type: aerobic + resistance Frequency: 3 days/week Intensity: 10–20 repetitions using TheraBand Duration: 90 min Intervention length: 4 weeks	Exercise at supervised venue	Fatigue: ↔ Physical well-being: ↑ Vigor activity: ↔ Fatigue intertia: ↔
Cheville 2013	$N=66$ lungs, colorectal	Previous or undergoing chemotherapy, hormonal therapy and/or other	Type: aerobic + resistance Frequency: 2–7 days/week Intensity: aerobic: 3.5 METS; Resistance: 10–15 repetitions per exercise Duration: 30–60 min Intervention length: 8 weeks	At home (unsupervised)—initial session supervised	Mobility: ↑
Cormie 2013	$N=20$ prostate	Previous AST, radiation and/or surgery	Type: resistance Frequency: 2 days/week Intensity: 12–8 RM, 2–4 sets per exercise Duration: 60 min Intervention length: 12 weeks	Exercise at supervised venue	Adverse events: $n=0$ Attendance (out of 24 sessions): 20.2 ± 7.6 Compliance (%): 93.2 ± 6.3 Session RPE: 13.8 ± 1.5 Perceived tolerance (1–7 scale): 6.1 ± 0.7 Severity of bone pain (VAS): 0.6 ± 0.7
Coleman 2003	$N=26$ multiple myeloma	Undergoing chemotherapy	Type: aerobic + resistance Frequency: 3 days/week Intensity: aerobic: 12–15 RPE; resistance: 2 sets of 8 repetitions per exercise Duration: 20 min Intervention length: 6 months	At home (unsupervised)	Lean body weight: ↑ Fatigue: ↔ Mood disturbance: ↔ Sleep: ↔

Table 3 (continued)

	Sample size and cancer type	Treatment	Exercise type	Exercise location and supervision	Primary outcome(s) result
Dhillon 2017	*N* = 112 lungs	Previous or undergoing chemotherapy or targeted therapy	Type: aerobic + resistance Frequency: 1 day per week Intensity: increase by > 3 MET h/week from baseline Duration: 30–45 min per session Intervention length: 8 weeks	At home (unsupervised)	Fatigue: ↔ Quality of life: ↔
Galvao 2018	*N* = 57 prostate	Current ADT	Type: aerobic + resistance Frequency: 3 days per week Intensity: aerobic: 60–85% HRmax; resistance: 3 sets per exercise, 8–12 RM Duration: 60 min Intervention length: 12 weeks	Exercise at supervised venue	Physical function: ↑
Henke 2014	*N* = 46 lungs	Undergoing palliative chemotherapy	Type: aerobic + resistance Frequency: 5–7 days per week Intensity: aerobic: 55–70% HRR; resistance: 50% maximal capacity, 10 repetitions per exercise (TheraBand, 4.6 lbs) Duration: 30–40 min Intervention length: 12 weeks	Exercise at supervised venue	Barthel index (activities of daily living): ↑
Hwang 2012	*N* = 24 lungs	Undergoing targeted therapy	Type: aerobic Frequency: 3 days per week Intensity: 60–80% VO2peak (11–17 RPE) Duration: 30–40 min Intervention length: 8 weeks	Exercise at supervised venue	VO2peak: ↑
Jastrzebski 2015	*N* = 20 lungs	Undergoing chemotherapy	Type: aerobic Frequency: 5 days per week Intensity: 70% HRmax Duration: 45 min Intervention length: 8 weeks	Exercise at supervised venue	Dyspnoea/breathlessness: ↓
Ligibel 2016	*N* = 101 breast	Previous or undergoing chemotherapy, endocrine therapy and/or biologic therapy	Type: aerobic Frequency: 3–7 days per week Intensity: 11–14 RPE Duration: 150 min per week Intervention length: 16 weeks	Exercise at supervised venue	Minutes of weekly exercise: ↔ Bruce ramp treadmill test: ↔
Oldervoll 2011	*N* = 231 gastrointestinal, breast, lungs, urological, gynaecological, haematological	Undergoing chemotherapy, radiotherapy, hormonal or targeted therapy	Type: aerobic + resistance Frequency: 2 days per week Intensity: not reported Duration: 50 min Intervention length: 8 weeks	Exercise at supervised venue	Global quality of life: ↔ 6-min walk test: ↑ Timed-repeated sit to stand: ↓ Functional reach: ↔

Table 3 (continued)

	Sample size and cancer type	Treatment	Exercise type	Exercise location and supervision	Primary outcome(s) result
Poort 2020	*N* = 134 breast, colorectal, prostate, renal cell, ovarian, bladder, melanoma	Undergoing chemotherapy, hormone therapy, targeted therapy or immunotherapy	Type: aerobic + resistance Frequency: 1 day per week Intensity: aerobic: 35–80% HRR; resistance: 60–80% 1 RM, 3 sets of 8–12 repetitions Duration: 120 min Intervention length: 12 weeks	Exercise at supervised venue	Fatigue: ↓
Porter 2019	*N* = 63 breast cancer	Previous or current chemotherapy, radiotherapy and/or surgery	Type: other Frequency: 1 day per week Intensity: not reported Duration: 120 min Intervention length: 8 weeks	Exercise at supervised venue	50% of eligible patients enrolled; 87% completed post-intervention surveys; 65% attended ≥ 4 sessions; 80% were highly satisfied
Pyszora 2016	*n* = 60 alimentary, urogenital, lung, central nervous system, mammary gland, haematological, mouth	NR	Type: resistance exercise + myofascial release proprioceptive neuromuscular facilitation Frequency: 3 days per week Intensity: Not reported Duration: 30 min Intervention length: 2 weeks	At home (unsupervised)—initial session supervised	Fatigue: ↓
Quist 2020	*n* = 218 advanced inoperable lung cancer	Undergoing chemotherapy	Type: aerobic + resistance Frequency: 2 days per week Intensity: aerobic: 60–80% HRmax; Resistance: 3 sets of 5–8 repetitions, 70–90% of 1RM Duration: 90 min Intervention length: 12 weeks	Exercise at supervised venue	VO2peak: ↔
Rief 2014	*N* = 60 lungs, breast, prostate, melanoma, renal	Undergoing radiation therapy	Type: resistance exercise Frequency: daily Intensity: not reported Duration: 30 min Intervention length: 2 weeks	Exercise at supervised venue	Survival: ↔
Rutkowska 2019	*N* = 30 lung cancer	Undergoing chemotherapy	Type: aerobic + resistance Frequency: 5 days per week Intensity: aerobic: 30–80% peak work rate; resistance: 40–70% 1 RM Duration: 30–60 min Intervention length: 4 weeks	Exercise at supervised venue	St. George's Respiratory Questionnaire Global: ↔ Short Form-36: ↔ Functional Assessment of Cancer Therapy-Lung: ↔

Table 3 (continued)

	Sample size and cancer type	Treatment	Exercise type	Exercise location and supervision	Primary outcome(s) result
Schuler 2017	*N* = 70 haematological, brain, gastrointestinal, lung, head, neck, testicle, breast, sarcoma	Undergoing chemotherapy or radiotherapy	Type: aerobic + resistance Frequency: 3–5 days per week Intensity: ≥ 13 RPE Duration: 30–60 min Intervention length: 12 weeks	At home (unsupervised)—initial session supervised or with supervision 2 ×/week	Fatigue: ↔
Solheim 2017	*n* = 46 lung, pancreatic	Undergoing chemotherapy	Type: aerobic + Resistance Frequency: 2–5 days per week Intensity: not reported Duration: 60 min Intervention length: 6 weeks	At home exercise—no supervision	Recruitment: 11.5% Attrition: 11% Compliance: 60%
Yee 2019	*n* = 14 breast cancer	Previous or undergoing hormone therapy or chemotherapy	Type: aerobic + resistance Frequency: 2 days per week Intensity: aerobic: 11–13 RPE; Resistance: 2 sets of 10–12 repetitions, 6–7 OMNI perceived exertion scale Duration: 60 min Intervention length: 8 weeks	Supervised home exercise	Recruitment: 93% Adherence: aerobic = 25%; resistance = 100% *N* = 0 adverse events

HRmax, heart rate max; *HRR*, hear rate reserve; *METs*, metabolic equivalents; *RM*, repetition maximum; *RPE*, rating of perceived exertion; *VO2max*, maximal oxygen consumption; *VO2peak*, peak oxygen consumption

an exercise intervention [71–74]; in this review, fatigue either did not get worse [34, 44, 48, 50] or improved across the studies [45, 49, 53]. Pain is also a common symptom experienced by advanced cancer patients, which severely affects QOL. Although pain levels can negatively impact compliance with an exercise program as seen in Vanderbyl et al. [75], where they used qigong, pain levels were shown to dramatically reduce immediately after taking part in resistance exercise [76]. Additional studies on exercise and pain reduction, specifically the type of exercise that would help to reduce pain levels, are needed within this population.

The current review shows that muscle strength was maintained and, in some cases, increased with exercise. Cachexia is a common physical concern for advanced cancer patients [77]. Cachexia may be positively impacted by maintaining good nutrition and activating the muscles through exercise. Solheim et al. [46] and Cheville et al. [47] reported an increase in their participants' body weight after a multimodal intervention, while Schink et al. (78) reported the maintenance of body weight in their intervention group, compared to weight loss in the control group. A qualitative study by Sheill et al. [17] reported that the men they studied found that the symptoms of their metastatic prostate cancer and the effects of treatments including fatigue and pain negatively impacted their participation in exercise. Participants reported weight loss in overweight individuals due to exercise in this study, followed by an increase in energy levels. They also reported that it had improved their well-being and increased their overall energy levels. The physiological changes reported in this review signify the extremely important role that physical exercise could have on advanced-stage cancer patients in improving overall well-being and quality of life.

Strength and limitations

This study demonstrates a robust and comprehensive review and meta-analysis of the outcomes of exercise in patients with advanced cancer in the palliative care phase. The meta-analysis allowed for a more comprehensive interpretation of the benefits of exercise within this population. While the papers included people with incurable cancer, some inclusion criteria (such as low Eastern Cooperative Oncology Group (ECOG) performance scores) included people who were earlier in their palliative care trajectory. Moreover, 41% ($n=9$) of studies excluded individuals based on the presence of comorbidities and/or medical reasons. Therefore, the present findings may be less generalisable to those with a higher disease burden and multiple comorbidities. The relevance of these interventions for populations who are deteriorating and with poorer prognoses requires additional study. Similarly, the best setting, ideal timing of exercise interventions and the maintenance dosing and duration of benefit for participants with advanced cancer remain unclear. While the studies included in this review were from varied localities, the broadly represented countries are from the global north. The relevance, feasibility and outcomes of similar programs in other cultural and socio-economic settings need further investigation. A further limitation is that due to the current absence of previous evidence around exercise adherence specifically for patients during palliative care, the criterion value we used for adherence (75%) was based on a walking exercise intervention, where approximately one-quarter of the sample had stage IV disease [29]. It is also important to recognise that our subgroup analyses were exploratory, and due to the small number of studies, a lack of power may have prevented us from identifying associations that are present but not identified in our results.

Conclusion

In this review, exercise was shown to be safe and feasible with physical and psychosocial benefits experienced by the participants. Improvements from exercise were apparent in QOL, fitness, strength and fatigue. Through the analysis of the current literature in this review, physical exercise was shown to be a valuable tool for individuals living with advanced-stage cancer in the stable palliative care phase. Given the health circumstances of people in palliative care for cancer, more research is required to understand the most appropriate approach to exercise programming based on the individual's needs. Consideration needs to be given to the location of the exercise and the type of exercise that should be undertaken so that the people feel safe and supported in the chosen environment. An important clinical consideration is that due to the complexities that people with advanced cancer experience, they should be seen by an exercise professional with experience in cancer care (such as an Accredited Exercise Physiologist/Physiotherapist) for the best advice based on their individual exercise needs.

In this review, it is important to acknowledge that if exercise was to be included in the palliative care phase, it may constitute an important step toward best quality holistic care. Exercises have the potential for healing and the hope that participants may experience from it, despite their advanced illness, is a fundamental element of the palliative care phase [78]. A greater exercise rehabilitative focus within palliative care for people with advanced cancer may enable hope and a sense of meaning, while also delaying or improving declines, limiting symptoms, preventing unnecessary hospitalisations and enabling further treatments [79]. Within the clinical setting, a larger focus on exercise, acknowledging the growing evidence base, may accelerate the necessary integration of

additional care options to improve the experience of people with advanced cancer within the palliative care phase.

Directions for future research

Based on this review, further research is needed to determine the benefits of individually driven and prescribed exercise programs. Research should also be considered to explore group exercise programs (that have the benefits of social connectedness) that can be undertaken in different settings such as online and in the patients' home. These options could minimise the stress of adding an extra appointment into an already busy time for people. Further study of the optimal timing and dosing of exercise interventions for people with advanced cancer in the palliative care phase and the outcomes of people with more significant functional decline and poorer prognoses is required.

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