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OPEN

Exercise Medicine in the Management of Pancreatic Cancer

A Systematic Review

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Abstract: The aim of this study was to examine the health-related effects of exercise in patients with pancreatic cancer (PanCa) through a systematic review of current evidence. Studies were obtained through searching PubMed, Web of Science, PsycINFO, Embase, CINAHL Plus, and Cochrane Library databases with additional hand searches. All intervention-based studies were included if it involved (1) adult patients with PanCa, (2) exercise training, and (3) findings in quality of life, cancer-related fatigue, psychological distress, and physical function. The review protocol was registered in PROSPERO: CRD42020154684. Seven trials described in 9 publications were included consisting of 201 patients with early-stage and advanced PanCa. Participants were required to perform supervised and/or home-based, low- to moderate-intensity resistance and/or aerobic exercise for 12 to 35 weeks or duration of neoadjuvant therapy. There were no exercise-related adverse events with a reported retention rate of 71% to 90% and exercise attendance of 64% to 96%. The programs were consistently associated with improvements in cancer-related fatigue, psychological distress, and physical function, with mixed effects on quality of life. Exercise training seems to be safe and feasible and may have a beneficial effect on various physical and psychological outcomes in patients with PanCa. Further work with rigorous study designs is required to consolidate and advance current findings.

Key Words: pancreatic cancer, exercise, quality of life, cancer-related fatigue, psychological distress, physical function

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Pancreatic cancer (PanCa) remains one of the most aggressive malignancies with a 5-year survival rate ranging from 5% to 15%[1] and a rising incidence rate globally.[2,3] Current treatment options for PanCa including surgery, chemotherapy, and radiotherapy provide limited survival benefits yet impose considerable physical and psychological burden. Patients with PanCa during and after treatments are predisposed to experience loss of skeletal muscle mass, impaired physical function, and increased fatigue and psychological distress.[4–9] In addition, PanCa is typically diagnosed in patients at an older age (median age, ~70 years) and with advanced disease.[3,10] Comorbidities such as sarcopenia and cachexia are prevalent in patients with PanCa,[11,12] along with various other debilitating symptoms including pain, insomnia, vomiting, and nausea.[13,14] These health conditions resulting from PanCa treatments and the disease can severely compromise patients' physical functioning and overall quality of life (QoL).[10,15,16] Given the relatively short survival time in patients with PanCa after diagnosis (median survival, ~3–26 months),[10,17] QoL is of paramount importance and is an independent predictor of overall survival.[16,18,19] Therefore, strategies that enhance QoL and attenuate decline in physical and psychological function in this patient group are of clinical importance.

Exercise training is increasingly recognized as an effective therapy for patients after cancer diagnosis across the disease spectrum, improving quality and, possibly, quantity of life; reducing treatment side effects; enhancing fitness and health in preparation for surgery and other treatments; and rehabilitating function and structure after treatment. Numerous systematic reviews and meta-analyses indicate that regular exercise can result in improvements in QoL, physical function, cancer-related fatigue (CRF) and psychological health in patients with cancer before, during, and after treatment.[20–24] In addition, exercise (in particular resistance training) is recommended as an essential intervention component to treat cancer cachexia.[25] Initial evidence suggests that individualized exercise interventions can be well accepted by patients with cancer (including PanCa) with cachexia or in the precachexia stage and is associated with promising efficacy on body mass when delivered concomitantly with nutritional support and anti-inflammatory medications.[26,27] The substantial benefits of exercise in patients with cancer have prompted the development of various international guidelines[28–30] recommending patients with cancer to stay physically active according to their clinical needs, personal circumstances, and preferences. However, most patients involved in current exercise oncology research are diagnosed with common types of solid tumors including breast, prostate, lung, and colorectal, and with early-stage disease.[31]

A small but growing number of exercise trials in patients with PanCa have been published; however, to date, the research findings regarding the health-related effects of exercise in this patient group have not been systematically appraised and synthesized. Although a recent systematic review[32] has discussed the effects of exercise on physical function and physical activity level in patients with resectable or potentially resectable liver and pancreatic tumors, only 2 experimental studies in patients with PanCa were included. In addition, the effects of exercise on other important health-related outcomes that commonly deteriorate as a result of PanCa and its treatments have not been addressed, including QoL, CRF, and psychological distress.

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Therefore, we conducted a systematic review to examine the health-related effects of exercise training in patients with PanCa. The primary end point was the reported change in QoL outcomes measured at different follow-up periods. In addition, the effects of exercise training on CRF, psychological distress, and objectively measured physical function (including muscle strength, cardiovascular fitness, functional ambulation, and balance) were also evaluated. When available, the magnitude of change in the outcome measure was checked for clinical meaningfulness based on an established minimal important difference (MID) (Supplemental Table 1, http://links.lww.com/MPA/A854).

MATERIALS AND METHODS

This review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,[33] and the review protocol was registered with the International Prospective Register of Systemic Reviews (PROSPERO ID: CRD42020154684).

Eligibility Criteria

Studies were considered eligible and included in the review if they met the following criteria regarding participants (*P*), intervention (*I*), comparator (*C*), outcomes (*O*), and study design (*S*):

P—adult men or women (age ≥18 years) diagnosed with PanCa (stages I–IV) who were before or after surgical resection irrespective of therapy administration (such as chemotherapy, radiotherapy, and chemoradiation) or in palliative care;

I—any form of exercise training including supervised or home-based programs with varied volumes and intensities;

C—with or without a control group undertaking standard care or distinct exercise training from the intervention;

O—including at least pre- and postintervention measurements for one or more outcomes of interest (ie, QoL, physical function, CRF, and psychological distress) in patients with PanCa undertaking exercise training; and

S—all intervention-based studies including randomized controlled trials (RCTs)/nonrandomized controlled trials and uncontrolled trials.

Studies were excluded if (i) participants consisted of non-PanCa patients unless separate data were available (however, participants with periampullary and ampullary adenocarcinoma were considered if they were treated similarly to those with pancreatic tumors in the trial); (ii) intervention included only stretch activity (exercise intervention complemented by nonexercise components was considered, such as diet and/or nutritional supplements); (iii) no data regarding the outcomes of interest were articulately reported; or (iv) only qualitative research was conducted.

Search Strategy

Electronic searching of all available records up until January 31, 2020, was undertaken in PubMed, Web of Science, PsycINFO, Embase, CINAHL Plus, and Cochrane Library databases using controlled vocabulary and free-text terms (Supplemental Table 2, http://links.lww.com/MPA/A854). Standardized thesaurus terms for the major concepts regarding population and intervention in each database were identified through respective subject headings search tool. Free-text terms were developed based on the predefined review question. All search terms and their combinations were piloted in the selected databases to ensure retrieval of as many relevant studies as possible. No limitations were imposed on search fields during electronic searching. In addition, a rerun of literature searching was conducted before data extraction and synthesis to identify any relevant late-published studies. Beyond database searching, additional methods of literature searching were also used to ensure further identification of eligible studies. For example, the reference lists of identified original studies and reviews were checked. Moreover, publication alerts were set up in PubMed in October 2019 using MeSH terms (ie, pancreatic neoplasms) and 2 groups of free-text terms for population and intervention, respectively.

Selection Strategy

Records yielded from electronic searching were exported and stored in EndNote (X9.3.2, Clarivate, London, UK). Duplicates were removed either automatically (using EndNote) or manually. After deduplication, the titles and abstracts of the remaining records were first reviewed by H.L. to exclude irrelevant articles. Subsequently, peer-reviewed journal articles with full text and published in English were further reviewed by H.L. and D.R.T. independently for eligibility against the predefined inclusion and exclusion criteria. A third reviewer (C.T.) was used when disagreement occurred, and consensus among the 3 reviewers was achieved.

Data Extraction

Data extraction of all included articles was performed by 2 reviewers (H.L. and P.L.) independently using a preestablished form that was developed based on a template recommended by the Cochrane Effective Practice and Organization of Care group.[34] This form was pilot tested by H.L. to ensure all relevant information could be captured. The following data were extracted from all included articles: general study information (such as name of the first author, country, and year of publication), study design, study setting, participant and intervention characteristics, data collection methods, and outcomes of interest for each group/participant. Any discrepancies on extracted data were resolved by discussion between H.L. and P.L., and an agreement was achieved for all data items.

Risk of Bias (Methodological Quality) Assessment

Risk of bias assessment of all included studies was evaluated using the McMaster University Critical Appraisal Tool (CAT) for Quantitative Studies[35] due to the diversified quantitative research designs of the included studies. The CAT includes 14 questions that cover the domains of study purpose, literature review, study sample, outcome measure, intervention, results, and conclusions. Each question was rated as "yes," "no," or "not addressed" depending on how well the study met the criterion of the question, in which "yes" was conferred 1 point, whereas "no" and "not addressed" equaled 0 points (pts). A sum score was calculated for each study based on the applicable questions in the CAT, with higher scores indicating higher methodological quality.[36–38] The risk of bias assessment for all included studies was performed independently by 2 reviewers (H.L. and P.L.). Any disagreements between H.L. and P.L. were resolved by consensus through discussion with a third reviewer (D.R.T.).

RESULTS

Study Selection

A total of 6498 records were identified through all sources, and the process of study selection is shown in Figure 1. After deduplication with EndNote, 5671 records were screened by titles and abstracts. After removal of irrelevant records (n = 5239) and further deduplication manually (n = 389), the full text of 43 articles were evaluated for eligibility. Of these, 34 articles were excluded based on the predefined inclusion and exclusion criteria. No additional records were identified through a rerun of database searching undertaken before the data extraction and synthesis. Therefore, 9 articles[39–47] based on 7 trials were finally included

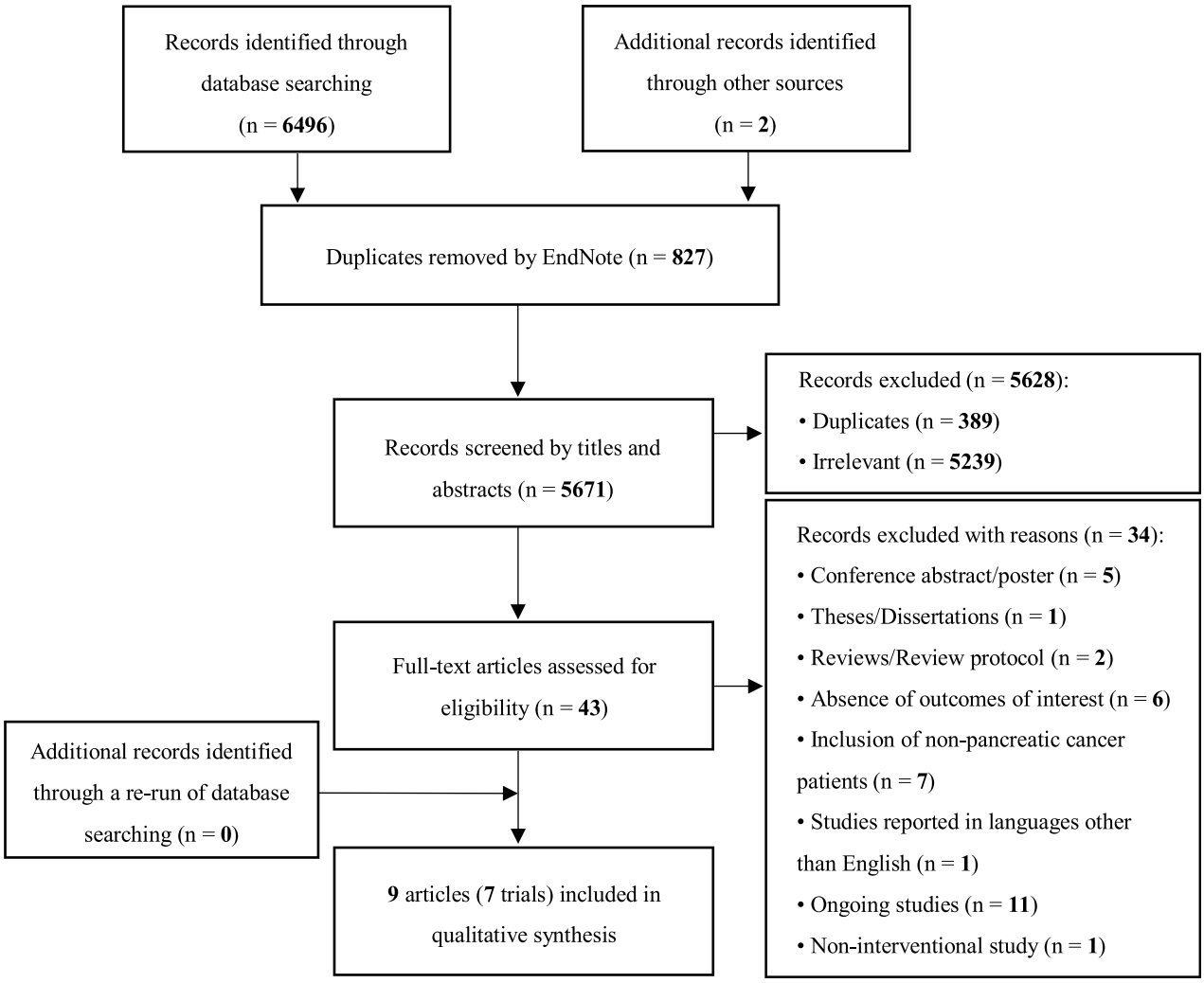

FIGURE 1. Flow diagram of study selection.

in this review, in which 2 trials[41,44] reported the outcomes of interest separately in 2 articles.[41,44,45,47]

Risk of Bias Assessment

The risk of bias assessment of the included trials is presented in Table 1. For trials with more than one publication included,[41,44,45,47] the risk of bias was appraised based on the information provided in the first published article.[41,44] In accordance with the questions applicable to different research designs in the McMaster CAT, there were various levels of bias in all of the included trials except for the trial by Yeo et al[39] that scored 14 of 14 pts (100%). Regardless of research design, all included trials[39–47] satisfied the criteria regarding study purpose, research justification, participants and intervention description, data analysis methods, and clinical significance. In addition, 6[39–45,47] of the 7 included trials scored positively in items 4a (reliability of outcome measures), 4b (validity of outcome measures), and 7 (appropriateness in conclusion). In contrast, the major methodological concerns were observed in items 3b (justification of sample size) and 5c (control of cointervention), which were present in 3[43–46] and 5[40–43,46,47] of the included trials, respectively.

Study Characteristics

Study characteristics of the included publications are presented in Table 2. The findings of the included trials were published between 2012 and 2019, with 3 trials conducted in the United States,[39,41,43] 2 in Germany,[42,44] and 1 in Australia[40] and the United Kingdom,[46] respectively. Of the 7 trials, 2 were RCTs,[39,44] 1 a single-arm trial,[41] 3 were case reports,[40,42,46] and 1 was a case series.[43] In addition, the included trials were conducted either before[41,43,46] or after surgery,[39,40,44] except for the case report by Niels et al,[42] which was undertaken across different settings (ie, palliative care, neoadjuvant and adjuvant settings).

Participant Characteristics

The number of participants in the case series,[43] single-arm trial,[41] and RCTs[44,45] ranged from 3 to 102 with both men and women included, whereas each of the 3 case reports[40,42,46] included only 1 male patient. In addition, the sample size involved in the trial by Ngo-Huang et al[41] differed in its 2 published articles (ie, n = 20[41] and 50[47]) due to further recruitment after the initial publication. The age range of participants was 38 to 91 years.[39,40,42,43,46] However, 2 trials with 4 publications[41,44,45,47] only reported the mean age standard deviation (SD) of the group.

TABLE 1. Risk of Bias Assessment of Included Trials

Study, Year	Design	1	2	3a	3b	4a	4b	5a	5b	5c	6a	6b	6c	6d	7	Overall Score (%)
Yeo et al, 2012[39]	RCT	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	14/14 (100)
Cormie et al, 2014[40]	CR	Y	Y	Y	Y	Y	Y	Y	N/A	N	N/A	Y	Y	N/A	Y	10/11 (91)
Ngo-Huang et al, 2017[41]*	SAT	Y	Y	Y	Y	Y	Y	Y	N/A	N	Y	Y	Y	Y†	Y	12/13 (92)
Ngo-Huang et al, 2019[47]*																
Niels et al, 2018[42]	CR	Y	Y	Y	Y	Y	Y	Y	N/A	N	N/A	Y	Y	N/A	Y	10/11 (91)
Marker et al, 2018[43]	CS	Y	Y	Y	N	Y	Y	Y	N/A	Not Ad	N/A	Y	Y	N/A	Y	9/11 (82)
Wiskemann et al, 2019[44]‡	RCT	Y	Y	Y	N§	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14 (93)
Steindorf et al, 2019[45]‡																
McLaughlin et al, 2019[46]	CR	Y	Y	Y	Not ad	Not ad	Not ad	Y	N/A	Not ad	N/A	Y	Y	N/A	N	6/11 (55)

Item: 1: Was the purpose stated clearly? 2: Was relevant background literature reviewed? 3a: Was the sample described in detail? 3b: Was sample size justified? 4a: Were outcome measures reliable? 4b: Were outcome measures valid? 5a: Was intervention described in detail? 5b: Was contamination avoided? 5c: Was cointervention avoided? 6a: Were results reported in terms of statistical significance? 6b: Were the analysis method(s) appropriate? 6c: Was clinical importance reported? 6d: Were dropouts reported? 7: Were conclusions appropriate given study methods and results?

*Same trial with different sample size involved, outcome measures and data reported.

†The report of dropouts was not addressed in the companion paper (Ngo-Huang et al, 2019) from the same trial.

‡Same trial with different outcome measures and data reported.

§The justification of sample size was provided in the companion article (Steindorf et al, 2019) from the same trial.

CR indicates case report; CS, case series; N, no; N/A, not applicable; Not Ad, not addressed; SAT, single-arm trial; Y, yes.

The included trials[39–44,46] comprised patients with stage I–IV PanCa. Of them, however, only 2 patients were diagnosed with metastatic disease, with 1 in the case report by Niels et al[42] and 1 in the RCT by Wiskemann et al.[44] Two trials[39,44] contained 5 patients with ampullary or periampullary cancer out of a sample size of 102[39] and 43,[44] respectively, including ampullary ductal, bile duct, and duodenal adenocarcinoma. Three trials[43,44,47] consisted of patients with cancer cachexia or sarcopenia (with or without frailty) based on relevant diagnostic criteria. Specifically, Wiskemann et al[44] reported that more than half (55.8%) of the participants were cachectic, experiencing a weight loss of 10% or higher in the last 6 months before the baseline assessment.[48] Similarly, in the case series by Marker et al,[43] 2 of the 3 participants were reported as cachectic, having a weight loss of greater than 2% and an appendicular skeletal muscle index consistent with sarcopenia.[48] In addition, Ngo-Huang et al[47] reported that 56% (n = 28) of the participants were sarcopenic,[49] and of these, 8 were classed as frail (as per Fried's phenotype criteria for frailty[50]).

Intervention Characteristics

The characteristics of the exercise interventions are shown in Table 2. Four trials[40,42,43,46] offered supervised combined resistance and aerobic exercise, 1 trial[44] used supervised or home-based resistance training, and 2 trials[39,41] prescribed structured home-based walking with or without resistance training. However, in the case reports by Cormie et al[40] and McLaughlin et al,[46] patients were also encouraged to perform additional home-based aerobic exercise to supplement clinic sessions with the goal of accumulating weekly 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity exercise.[51] Moreover, in the case report by McLaughlin et al,[46] low-intensity (60% of maximum heart rate) ergometer cycling during the 12 weeks of chemotherapy infusion was performed.

The length of the exercise interventions ranged from 12 to 35 weeks[39–42,44,46] or was reported as spanning the period of neoadjuvant therapy.[43] All trials except for Yeo et al[39] required participants to exercise 2 to 3 times per week with the sessional duration of at least 60 minutes. Resistance training was reported as completing 5 to 10 exercises in each session using machines or resistance bands that cover the major muscle groups of the upper and lower body.[40–42,44,46] In addition, 1 to 3 sets of 6 to 20 repetitions/set were performed for each resistance exercise at an intensity of 50% to 85% of 1 repetition maximum (1RM) or a rating of perceived exertion (RPE) of 12 to 16 (Borg 6–20 Scale).[40–42,44,46] With regard to the aerobic exercise component, 8 to 20 minutes of interval or continuous exercise training (such as walking and cycling) were performed at an intensity of 65% to 80% of maximum heart rate or an RPE of 11 to 13.[40–42,46]

In addition to the exercise program, 3 trials[41,43,44] offered participants complementary nutritional support/counseling. Of them, however, only the trial by Ngo-Huang et al[41] provided a detailed description of their nutritional support that included at least 20 g of protein intake via a high-protein meal or snack within an hour after completion of the resistance training session and guidance on food selection.

Outcomes of Interest

The effects of the interventions on QoL, CRF, psychological distress, and physical function are shown in Table 2.

Quality of Life

All included trials[39,40,42,43,45–47] examined QoL using various scales. Of these trials, inconsistent findings were reported in the RCTs[39,45] and the single-arm trial.[47] Yeo et al[39] measured QoL using the 36-item Short Form Health Survey (version 2.0) (SF-36) physical component summary (PCS) and mental component summary (MCS), and reported statistically ($P \leq 0.05$) and clinically significant changes in the PCS (5 pts) and MCS (6 pts)[52–54] in the exercise group. In the three-arm RCT reported by Steindorf et al,[45] the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core module (EORTC QLQ-C30) and the PanCa specific module (QLQ-PAN26) were used, with no significant difference observed at the end of the 6-month study. However, at 3 months, there was a significant difference ($P = 0.016$) in the QLQ-C30 global health status/QoL scale between the pooled exercise groups and the

TABLE 2. Characteristics of Included Publications

Study, Year, Country	Design	Study Setting	Sample Size by Group, Sex, Age/Mean Age (SD) (Range), Type (% of PanCa), and Staging	Exercise Program	Outcomes: Time Points	Outcomes: Measures (Clinically Relevant Changes)*	Outcomes: Results	Feasibility Profile
Controlled trials								
Yeo et al, 2012,[39] United States	RCT	ADJ	*Ex*: 54, M & F, 66 y (38–87 y), PanCa (96%), bile duct and duodenal, stage I–III *UC*: 48, M & F, 67 y (48–91 y), PanCa (94%), bile duct and duodenal, stage I–III	*Type*: Walking *Length*: 3 mo *Frequency*: progress to 3–5 sessions/wk *Duration:* progress to 20–40 min/session *Volume*: progress to 10–30 min of brisk walking/session *Intensity*: not predetermined and untracked *Setting*: home *Supervision*: no	Postsurgery (baseline), and 3–6 mo after discharge	– SF-36 (PCS ↑5 pts, MCS ↑6 pts) – FACIT-F (total score ↑9 pts); FVAS (↓1.3 pts)	– QoL↑[†] – CRF↓[†]	No intervention-related AEs; *Recruitment rate*: 93% *Retention rate*: 76% (Ex) vs 73% (UC)
Wiskemann et al, 2019,[44‡] Germany	RCT	ADJ	*Ex1*: 9, M & F, 63 (6.4) y, PanCa (78%) and bile duct, stage I–II *Ex2*: 20, M & F, 61 (8.7) y, PanCa (95%) and bile duct stage I–IV *UC*: 14, M & F, 58 (8.2) y, PanCa (86%), bile duct and ampullary ductal, stage I–II	*Type*: resistance training *Length*: 6 mo *Frequency*: 2 sessions/wk *Duration*: 60 min/session *Volume*: 5–8 exercises, 1–3 sets/exercise with 8–20 repetitions/set *Intensity*: 50%–80% of 1RM (Ex1) or an RPE of 14–16 (Borg 6–20 scale) (Ex2) *Setting*: exercise facility (Ex1) or home (Ex2) *Supervision*: yes (Ex1) or no (Ex2)	Pre- and postintervention	– Isokinetic and handheld dynamometer – CPET (VO2max ↑0.1 L/min and ↑0.2 L/min in Ex1 and Ex2, respectively); 6MWT	– Muscle strength↑[§] – Cardiovascular fitness↔	No intervention-related AEs; *Recruitment rate*: 21%, *Retention rate*: 75% (Ex1) vs 71% (Ex2) vs 77% (UC), *Attendance rate*: 64% (Ex1) vs 78% (Ex2)
Steindorf et al, 2019,[45‡] Germany	RCT	ADJ	As above (see Wiskemann et al, 2019)	As above (see Wiskemann et al, 2019)	Preintervention (baseline), 3 (T1) and 6 mo (T2)	– EORTC QLQ-C30 (the global health status/QoL scale ↑11.5 pts at T1 for the pooled Ex group); EORTC QLQ-PAN26 (pancreatic pain: ↓10.3 pts (T1) and ↓8.3 pts (T2) for Ex2; indigestion: ↓9.3 pts (T1) and ↓16.7 pts (T2) for Ex1; body image: ↓10.8 pts (T1) and ↓11.9 pts (T2) for Ex2) – MFI (for the pooled exercise group physical fatigue ↓3.3 pts (T1) and ↓2.6 pts (T2), and reduced activity ↓2.1 pts (T1)	– QoL[‖] ↑[§](T1), ↔(T2) – General fatigue ↔ (T1), ↔(T2); physical fatigue ↑[§](T1), ↔(T2); mental fatigue ↔(T1), ↔(T2); reduced activity ↑[§](T1), ↔(T2); reduced motivation ↑[§](T1), ↔(T2)	As above (see Wiskemann et al, 2019) except for retention rate (=68%) in Ex2 reported differently

Uncontrolled trials								
Cormie et al, 2014,[40] Australia	CR	ADJ	*Ex*: 1, M, 49 y, PanCa (100%), stage II No control arm	*Type*: resistance (R) + aerobic (A) exercise *Length*: 6 mo *Frequency*: 2 sessions/wk *Duration*: 60 min/session *Volume*: (R) 10 exercises, 2–3 sets/exercise; (A) 15–20 min walking and cycling *Intensity*: (R) 6–12RM; (A) 65%–80% MHR with an RPE of 11–13 (Borg 6–20 scale) *Setting*: exercise clinic and home (accumulating additional 150 min of walking and/or cycling per wk) *Supervision*: mixed¶	Preintervention (baseline), 3 (T1) and 6 mo (T2)	– SF-36 (PCS ↑8.3 pts and ↑12.3 pts, MCS ↑11 pts and ↑17.9 pts at T1 and T2, respectively); FACT-Hep (total score ↑31 pts and ↑37 pts at T1 and T2, respectively) – FACIT-F (total score ↑28 pts and ↑39 pts at T1 and T2, respectively) – BSI-18 – 400-m walk test (time ↓43.3 s at T2) - Leg press 1RM test - 5STS (time ↓2 s and ↓3.2 s at T1 and T2, respectively) - Stairclimb test; usual- and fast-pace 6-m walk tests - 6-m backward walk; Sensory Organization Test	– QoL ↑(T1), ↑(T2) – CRF ↓(T1), ↓(T2) – Psychological distress ↓ (T1), ↓(T2) – Cardiovascular fitness ↑ (T1), ↑(T2) – Muscle strength ↑(T1), ↑(T2) – Muscle power ↑(T1), ↑(T2) – Functional ambulation ↑ (T1), ↑(T2) – Balance ↑(T1), ↑(T2)	No intervention-related AEs; *Attendance rate*: 73%
Ngo-Huang et al, 2017,[41#] United States	SAT	NAJ	*Ex*: 20, M & F, 64 (9.9) y, PanCa (100%), potentially resectable No control arm	*Type*: resistance training (R) + walking (W) *Length*: median of 17 wk (range, 5–35 wk) over the preoperative period *Frequency*: at least 2 (R) or 3 (W) d/wk *Duration*: at least 60 min/d *Volume*: (R) 8 exercises, 3 sets/exercise, 8–12 repetitions/set; (W) at least 20 min/d *Intensity*: RPE of 12–13 (Borg 6–20 scale) *Setting*: home *Supervision*: no	Baseline (T0), and pre- (T1) and postsurgery (T2)	– 10-m walk test (gait speed ↑0.18 m/s at T1); Dynamic Gait Index (total score ↑1.2 pts at T1) – 5STS	– Functional ambulation ↔(T1), ↔(T2); Balance ↔(T1), ↔(T2) – Muscle power ↔(T1), ↔(T2)	No intervention-related AEs; *Retention rate at T1*: 75% (50% at T2 because patients not amendable to surgery were excluded from postintervention assessment)

(Continued on next page)

TABLE 2. *(Continued)*

Study, Year, Country	Design	Study Setting	Sample Size by Group, Sex, Age/Mean Age (SD) (Range), Type (% of PanCa), and Staging	Exercise Program	Outcomes: Time Points	Outcomes: Measures (Clinically Relevant Changes)*	Outcomes: Results	Feasibility Profile
Niels et al, 2018,[42] Germany	CR	Palliative + NAJ + ADJ	*Ex*: 1, M, 46 y, PanCa (100%), stage IV No control arm	*Type*: resistance (R) + aerobic (A) exercise *Length*: approximately 7 mo *Frequency*: 2 sessions/wk *Duration*: unspecified *Volume*: (R) 6 exercises, 2 sets/exercise, 8–12 repetitions/set; (A) 2 sets of ergometer training, 4–10 min/set *Intensity*: (R) 70%–80% of 1RM; (A) 70%–80% MHR with an RPE of 6–7 (Borg 0–10 scale) *Setting*: unspecified *Supervision*: yes	Baseline (T0), 3 (T1), and 7 mo (T2)	– EORTC QLQ-C30 (the global health status/QoL ↑16.6 pts at T1 and T2) – HADS (depression subscale score ↓3 pts and ↓4 pts at T1 and T2, respectively) – 1RM test (leg extension strength ↑26.7 kg at T1 and T2, chest press strength ↑15.6 kg and ↑17.7 kg at T1 and T2, respectively); – CPET (maximal cycle excise capacity ↑35w and ↑45w at T1 and T2, respectively)	– QoL ↑(T1), ↑(T2) – Depression ↓(T1), ↓(T2); anxiety ↓(T1), ↓(T2) – Muscle strength ↑(T1), ↑(T2) – Cardiovascular fitness ↑(T1), ↑(T2)	No intervention-related AEs
Marker et al, 2018,[43] United States	CS	NAJ	*Ex*: 3, M & F, 71 (1.9) y (70–74 y), PanCa (100%), borderline resectable No control arm	*Type*: resistance + aerobic exercise *Length*: over the neoadjuvant therapy *Frequency*: 2–3 sessions/wk *Duration*: 60 min/session *Volume*: 45 min of combined aerobic and resistance exercises *Intensity*: ≤85% of heart-rate reserve or RPE of 7 (Borg 0–10 scale) *Setting*: fitness facility *Supervision*: yes	Baseline (T0), presurgery (T1), and 6 wk after discharge (T2)	– FACT-G (total score ↑16.5 pts and ↑12 pts at T1 and T2, respectively) – FACIT-F (total score ↑5 pts at T1 and T2) – CES-D – 400-m walk test – Usual- and fast-pace 10-meter walk test – Grip strength dynamometry – 30STS (↑6 repetitions at T1)	– QoL ↑(T1), ↑(T2) – CRF ↓(T1), ↓(T2) – Depression ↓(T1), ↓(T2) – Cardiovascular fitness ↑(T1), ↑(T2) – Functional ambulation ↑(T1), ↓(T2) – Muscle strength ↑(T1), ↓(T2) – Muscle power ↑(T1), ↑(T2)	Information or data regarding AEs was not provided; *No. eligible patients recruited within 8 mo*: 3; *Percentage of wk with at least 2 sessions attended weekly against the total wk involved*: 85%
McLaughlin et al, 2019,[46] United Kingdom	CR	NAJ	*Ex*: 1, M, 47 y, PanCa (100%), stage III No control arm	*Type*: resistance (R) + aerobic (A) exercise *Length*: 12 wk *Frequency*: 2 sessions/wk *Duration*: unspecified *Volume*: (R) 8 exercises, 3 sets/exercise, 12 repetitions/set; (A) 15 min of continuous cycling *Intensity*: (R) 60% of 1RM; (A) 70% of MHR *Setting*: gym, home (accumulating additional 150-min of moderate intensity or 75-min of vigorous intensity exercise per week), and hospital (40 min of cycling during infusion at 60% of MHR) *Supervision*: mixed¶	Baseline (T0), 4 (T1), 8 (T2), and 12 wk (T3)	– FACT-Hep – FACIT-F – BSI-18 – Submaximal Astrand test – 12RM tests – 5STS – Stairclimb test; usual- and fast-pace 6-meter walk test – 6-m backward walk	– QoL ↑(T1), ↑(T2), ↑(T3) – CRF ↓(T1), ↓(T2), ↓(T3) – Psychological distress ↓(T1), ↓(T2), ↓(T3) – Aerobic capacity ↑(T1), ↑(T2), ↑(T3) – Muscle strength ↑(T1), ↑(T2), ↑(T3) – Muscle power ↑(T1), ↑(T2), ↑(T3) – Functional ambulation ↑(T1), ↑(T2), ↑(T3) – Balance ↑(T1), ↑(T2), ↑(T3)	No intervention-related AEs; *Attendance rate*: 96% (gym-based exercise sessions), *Program adherence rate*: 100% and 69% (gym-based exercise sessions in nonchemotherapy and chemotherapy weeks, respectively) and 83% (cycling during infusion)

Ngo-Huang et al, 2019,[47#] United States	SAT	NAJ	*Ex*: 50, M & F, 66 (8) y, PanCa (100%), potentially resectable No control arm	As above (see Ngo-Huang et al, 2017), except for the length of the intervention reported as mean duration of 16 wk (SD, 9 wk)	Baseline and postintervention (before surgery)	– FACT-Hep – 6MWT (distance ↑25.7 m) – 5STS	– QoL↔ – Cardiovascular fitness† – Muscle power†,¶	No intervention-related AEs; *Retention rate:* 90%

*When there was clinical meaningfulness based on the relevant MID provided in Supplementary Table 1.
†Statistically significant from baseline.
‡Same trial with different outcome measures and data reported.
§Statistically significant from control group.
‖Based on the global health status/QoL score in EORTC QLQ-C30.
¶Supervised + unsupervised.
#Same trial with different sample size involved, outcome measures, and data reported.
↔ indicates no statistical significance; ↑, increase; ↓, decrease; 5STS, 5-repetition sit-to-stand; 6MWT, 6-minute walk test; 30STS, 30-second sit-to-stand test; ADJ, adjuvant; BSI-18, Brief Symptom Inventory-18; CES-D; Center for Epidemiologic Studies Depression Scale; CR, case report; Ex, exercise group; F, female; FACT-G, Functional Assessment of Cancer Therapy–General questionnaire; M, male; MFI, Multidimensional Fatigue Inventory; MHR, maximum heart rate; NAJ, neoadjuvant; PAN 26, pancreatic cancer specific module; SAT, single-arm trial; UC, usual care control group; VO2max, maximum oxygen uptake.

controls,[45] and the improvements exceeded the MID of 10 pts.[55,56] In addition, there were clinically significant improvements in the QLQ-PAN26 symptom scales for the supervised and home-based exercise groups,[45] including pancreatic pain (>8 pts), indigestion (>9 pts), and body image (>10 pts).[57] However, in the single-arm trial by Ngo-Huang et al[47] that used the Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep) questionnaire, no significant improvements were observed.

In the case reports[40,42,46] and case series,[43] positive changes in QoL outcomes were consistently reported. Cormie et al[40] used the SF-36 and the FACT-Hep questionnaires, and clinically relevant improvements were observed in the SF-36 PCS (>8 pts) and MCS (≥11 pts),[52–54] as well as in the FACT-Hep total score (≥31 pts).[58] Niels et al[42] used the QLQ-C30 with an improvement of ~17 pts in the global health status/QoL scale, suggesting a clinically meaningful improvement in the participant's QoL.[55,56] In addition, Marker et al[43] and McLaughlin et al[46] assessed QoL using the FACT-General and the FACT-Hep questionnaire, respectively. Both trials[43,46] reported a numerical or percentage increase in the total score of the questionnaire at various follow-up periods, and the increments (≥12 pts) in the trial by Marker et al[43] were of clinical significance.[59]

Cancer-Related Fatigue

Five trials[39,40,43,45,46] examined CRF using different scales. Yeo et al[39] used the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale and the Fatigue Visual Analog Scale (FVAS, 0–10), and reported statistically ($P \leq 0.05$) and clinically significant changes in the exercise group for both measures (FACIT-F: 9 pts[59]; FVAS: 1.3 pts[60]). At the midpoint of the 6-month trial by Steindorf et al,[45] there were significant group differences ($P < 0.03$) in various fatigue dimensions measured by the Multidimensional Fatigue Inventory, including physical fatigue, reduced activity, and reduced motivation. In addition, the improvements in physical fatigue (>2.5 pts) and reduced activity (>2 pts) for the pooled exercise groups of the trial[45] were clinically significant.[61] In the remaining 3 trials,[40,43,46] CRF was assessed using the FACIT-F, and all reported a higher score after the exercise intervention compared with baseline, indicating a reduction in fatigue, with the magnitude of change in the trials by Cormie et al[40] (≥28 pts) and Marker et al[43] (5 pts) being clinically important.[59]

Psychological Distress

Four trials[40,42,43,46] examined variables associated with psychological distress (including anxiety, depression, and somatization) using varied questionnaires that included the Brief Symptom Inventory-18, the Hospital Anxiety and Depression Scale (HADS), and the Center for Epidemiologic Studies Depression Scale. All of these trials[40,42,43,46] reported an improvement in the related symptom scales across various time points, and the change score in the depression subscale of the HADS (≥3 pts) in the case report by Niels et al[42] was clinically meaningful.[62]

Physical Function

A wide array of objectively-measured physical function parameters were examined in 6 trials,[40–44,46,47] including muscle strength and power, cardiovascular fitness, functional ambulation, and balance. Five trials[40,42–44,46] evaluated muscle strength using various methods. Wiskemann et al[44] used an isokinetic dynamometer and a handheld dynamometer in their 3-armed trial, with a significant group difference ($P = 0.04$) in isometric strength observed for knee extension favoring the home-based exercise group. In addition, the authors[44] also reported a significantly greater isokinetic force of elbow flexors ($P = 0.02$) and elbow

extensors ($P = 0.01$) in the supervised exercise group compared with controls. The remaining 4 trials[40,42,43,46] used either a 1RM, a 12RM, or a grip strength test, with three[40,42,46] reporting enhanced muscle strength across various follow-up periods, and the case report by Niels et al[42] reporting a clinically relevant improvement in chest press (>15.6 kg) and leg extension (26.7 kg) strength.[63] In addition, Marker et al[43] in their case series of 3 patients exercising during neoadjuvant therapy (chemotherapy and radiotherapy) reported an improvement in grip strength before surgery.

Four trials[40,43,46,47] measured lower-limb muscle power using either the 5-repetition sit-to-stand (5STS) or the 30-second sit-to-stand test (30STS), and all reported an improvement. Within these trials, Ngo-Huang et al[47] reported a statistically significant improvement ($P = 0.049$) in participants after preoperative exercise (mean duration of 16 weeks); however, the change was not significant in their first publication,[41] which involved a smaller sample size. In addition, clinically relevant improvements were observed in Cormie et al[40] using the 5STS (time reduced ≥2 seconds)[64] and in Marker et al[43] using the 30STS (6 more repetitions)[65] at varying time points.

All trials but one[39] examined cardiovascular fitness using either a performance-based test or a laboratory test alone or in combination and reported varying magnitudes of gains. Ngo-Huang et al[47] reported a significant within-group change ($P = 0.001$) in the 6-minute walk test, with the improvement of 25.7 m clinically meaningful.[66] In addition, in the 3-arm RCT by Wiskemann et al,[44] the improvement in maximal oxygen uptake for the exercise groups (0.1 and 0.2 L/min) measured by the cardiopulmonary exercise test (CPET) also exceeded the MID of 0.05 L/min,[67,68] although the gains were not statistically significant. Of the remaining 4 trials,[40,42,43,46] clinically relevant improvements were observed by Cormie et al[40] using the 400-m walk test (time reduced by 43.3 seconds)[69] and Niels et al[42] using the CPET (>35-W improvement in maximal cycling capacity).[67,68]

Four trials[40,41,43,46] assessed functional ambulation using either the 10-m walk test alone or multiple tests (including stair climb, and usual- and fast-pace 6- and 10-m walk). All of the trials[40,41,43,46] reported an improvement at midpoint assessments, and 2[40,46] also demonstrated gains at postintervention. In addition, there was a clinically relevant improvement in the 10-m walk test (0.18 m/s faster)[70] in the single-arm trial by Ngo-Huang et al,[41] although the change was not statistically significant.

With regard to balance ability, 3 trials[40,41,46] assessed dynamic balance with either the 6-m backward walk or the Dynamic Gait Index. In addition, Cormie et al[40] also measured postural balance using the Sensory Organization Test. All trials[40,41,46] demonstrated an improvement in balance, and the trial by Ngo-Huang et al[41] also showed a clinically meaningful improvement in the Dynamic Gait Index (1.2 pts).[71]

Feasibility Profile

An overview of the feasibility profiles of the exercise interventions is presented in Table 2. All included trials explicitly reported no intervention-related adverse events (AEs)[39–42,44–47] or did not provide relevant description in the article.[43] However, there was a range of non–intervention-related AEs in some of the included trials mainly due to the aggressive nature of PanCa and treatment-related side effects. For example, multiple events of death (n = 18) and disease progression (n = 3) were reported in the trials by Yeo et al[39] and Wiskemann et al.[44] In addition, AEs/symptoms including incisional hernia (n = 1), fracture (n = 1), deep vein thrombosis (n = 1), constipation (n = 1), nausea and vomiting (n = 1), and mucositis (n = 1) were reported in 3 trials.[42,44,46] All of the AEs resulted in temporary or permanent discontinuance of the exercise programs[39,42,44] or a reduction in the prescribed exercise intensity.[46]

Apart from the incidence of AEs, other feasibility metrics were provided in the included trials. Yeo et al[39] and Wiskemann et al[44] reported a recruitment rate of 93% and 21%, respectively. In addition, Marker et al[43] also reported that only 3 participants were enrolled during an 8-month recruitment period, and as a result, the study was reported as a case series. The included RCTs[39,44] and single-arm trial[41] reported dropouts, and the retention rates for the exercise groups were 76%,[39] 75% and 71% (for supervised and home-based exercise groups, respectively),[44] and 75%[41] (reported as 90% in the later published article[47] from the trial). However, reasons for dropouts were only provided in the RCTs, including death,[39,44] disease progression,[44] treatment-related side effects,[44] further resection required,[44] and withdrawal.[39,44] Participants' attendance to the planned exercise sessions was reported in 3 trials,[40,44,46] and the attendance rates were 73%,[40] 64% and 78% (for supervised and home-based sessions, respectively),[44] and 96%.[46] In addition, Marker et al[43] reported that for 85% of the prescribed weeks, participants attended at least 2 sessions per week. Only McLaughlin et al[46] reported the participant's actual completed exercise intensity, that is, 100% and 69% for supervised sessions in nonchemotherapy and chemotherapy weeks, respectively, and 83% for exercise during infusion.

DISCUSSION

This is the first systematic review examining the multifaceted health-related effects of exercise in patients with PanCa. Given the current evidence, exercise training seems to be safe and feasible and may have a favorable effect on various physical and psychological outcomes in this patient group.

Despite a high number of non–intervention-related AEs, exercise training seems to be safe in patients with PanCa with no exercise-related AEs reported across the studies. The high incidence of non–intervention-related AEs is not unexpected given the aggressive nature of PanCa and cumulative toxicities from cancer therapies. Importantly, the feasibility profile seemed favorable with a reported retention rate of 71% to 90% and exercise attendance of 64% to 96%. These findings are similar to a systematic review of exercise interventions in patients with advanced cancer[72] and an exercise study consisting of patients with malignant pleural mesothelioma,[73] suggesting that patients with PanCa should not be excluded from exercise. However, the relatively short life expectancy and substantial adverse effects from treatment regimens highlight the need for regular and shorter assessment intervals in this patient group so that the shorter-term benefits of exercise can be determined. This may also facilitate the necessary modifications in an exercise program being made in a timely fashion.

Among the efficacy outcomes in current evidence, we found that exercise training was most consistently associated with improvements in psychological distress. Combined resistance and aerobic exercise reduced symptoms of depression and anxiety irrespective of the disease stage and study setting.[40,42,43,46] This finding is in line with several systematic reviews and meta-analyses of patients with common cancers (predominantly breast).[74–76] Similarly, a recent study in patients with pleural mesothelioma also reported decreased anxiety after a short-term, home-based program that included resistance and aerobic exercise.[73] It has been well established that exercise and, in particular, aerobic exercise are associated with less rates of psychological distress symptoms.[77,78] This may be associated with improved self-efficacy beliefs after exercise training, which is recognized as a positive contributor to high levels of mental health and psychological functioning.[79]

In addition, a range of biological hypotheses have been proposed for the emotional benefits of exercise, including increase in body temperature and cerebral blood flow, and higher levels of endorphins.[80]

The evidence also suggests that exercise may be effective in attenuating CRF in patients with PanCa; however, the beneficial effect may be moderated by exercise mode. Aerobic exercise with or without resistance training lowered fatigue levels across varying follow-up periods, whereas the improvements in various dimensions of fatigue did not persist throughout the study period in the trial by Steindorf et al,[45] which only provided resistance training. Cancer-related fatigue is one of the most common symptoms during chemotherapy and is suggested to be influenced by many constitutional, clinical, and environmental factors in patients with PanCa.[81] There is no clear mechanistic explanation yet regarding the role of exercise in regulating CRF during active cancer treatment, although some reports suggest the possible association with improvements in chemotherapy-induced anemia[82] and cardiorespiratory capacity[83] after exercise training.

The effect of exercise on physical function seems promising. Various improvements were observed in muscle strength and power, cardiovascular fitness, functional ambulation, and balance. This is generally in concordance with exercise studies in other poor prognostic patients with cancer (including mesothelioma and esophageal) receiving active cancer treatments, where enhanced aerobic capacity and lower-limb muscle function were observed.[73,84] The declines in muscle strength, balance, and functional ambulation at the postsurgery assessments in the single-arm trial[41] and the case series[43] may be associated with detraining and incomplete recovery after surgery. In addition, the nonsignificant finding in 5STS in the initial paper by Ngo-Huang et al[41] is likely due to the small sample size, as a similar improvement was reported in the subsequent report[47] with a larger sample size and was statistically significant.

Regarding the effect of exercise on QoL, the current findings are somewhat mixed. Most of the included studies demonstrated statistically or clinically significant improvements in various QoL scales.[39,40,42,43,45,46] However, no effect was observed by Ngo-Huang et al in their single-arm trial.[47] In addition, Steindorf et al[45] only reported improvement of overall QoL at the midpoint of their 6-month trial. The inconsistent findings in the current evidence may be explained by the complex determinants of QoL in patients with PanCa. Evidence indicates that disease progression is associated with a deterioration of QoL in this patient group.[85] There are also a number of other factors identified that may contribute to a worsening in QoL, such as treatments, comorbidities, and various demographic factors (including ethnicity, age, and educational level).[16] Although the benefits of exercise in QoL for various patients with cancer (including advanced disease) have been well established,[22,24,86,87] its effect for patients with PanCa requires further work and clarification.

There are some limitations of this systematic review. First, more than half of the trials included were uncontrolled studies, with 3 being case reports and 1 being a case series. Thus, caution should be taken when interpreting the findings of this review. In addition, a meta-analysis was not undertaken as less than 2 RCTs provided sufficient data on the same outcome measure, and the heterogeneity in exercise programs and measurement tools/instruments of the included studies was substantial. Lastly, the MID values of the outcome measures in patients with PanCa were limited, so the relevant values for patients with other cancers or clinical conditions were used to determine clinical significance. Nevertheless, the MID values used provide an indication of the meaningfulness of the changes observed in the outcome measures.

Despite these limitations, the preliminary benefits observed with current evidence may provide valuable insights for the management of PanCa. Of importance, the improvements in muscle strength and/or muscle power were reported in 3 studies,[43,44,47] which consisted of a large proportion of patients with cachexia or sarcopenia and administrated a multimodal intervention (ie, exercise training in combination with nutritional support). The disorders of cancer cachexia and sarcopenia have been well documented leading to progressive muscle weakness and functional impairments[88] and are usually difficult to treat in patients with PanCa due to their complex pathophysiology.[89]

The promising initial findings warrant additional RCTs with larger sample sizes in patients with PanCa. It is particularly important to examine the effects of exercise on cancer-related outcomes to reinforce the role of exercise in this patient group. To date, there is only one study published reporting exercise being associated with normalized tumor vasculature.[90] In addition, standardized reporting of AEs in ongoing trials and, in particular, in patients with advanced disease remains essential to confirm the safety of exercise in patients with PanCa. It would also be worthwhile to improve reporting of key exercise variables that are actually delivered (including volume, intensity, frequency, type, and duration) so that compliance can be determined, which is increasingly considered pivotal in exercise oncology research.[91,92] Lastly, initial evidence suggests that sport-based programs are also associated with various benefits in patients with cancer (mainly prostate and breast).[93] Therefore, investigating alternative physical activities other than traditional exercise training modes may prove beneficial in providing a wider array of activities in which patients with PanCa can safely participate to derive physical and psychological benefits and enhance QoL.

CONCLUSIONS

The current evidence suggests that exercise training is safe and feasible and has a beneficial effect on various physical and psychological outcomes in patients with PanCa. However, as patients with PanCa are an understudied patient group in current exercise oncology research, only a small number of trials were included in this review, with more than half of them being a case report or case series. In addition, there was vast heterogeneity of exercise programs and measurement instruments in the included studies. Therefore, additional RCTs with high methodological quality and homogeneous measurement instruments are required to consolidate and advance our findings.

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