

# Effects of Exercise Intervention on Persons with Metastatic Cancer: A Systematic Review

Rebekah Beaton, Wendy Pagdin-Friesen, Christa Robertson, Cathy Vigar, Heather Watson, Susan R. Harris

## ABSTRACT

**Purpose:** To systematically review and synthesize results of studies that examined the effects of exercise on persons with metastatic cancer.

**Methods:** Databases searched were MEDLINE, EMBASE, CINAHL, PsycINFO, and Cochrane Central Register of Controlled Trials. Search terms used were “metastatic or advanced or palliative AND cancer or neoplasms AND exercise or physical activity or exercise therapy or physical fitness.” The search identified 8 studies published in 10 articles between 2000 and 2007. Two quality-assessment tools were used, and levels of evidence were assigned according to the Oxford Centre for Evidence-Based Medicine (CEBM) guidelines.

**Results:** Of the eight studies, three were randomized controlled trials (RCTs) and five were case series. Because three of the RCTs were based on the same sample, only one was included in the results and discussion sections. CEBM levels of evidence ranged from 2b to 4. Two overall recommendations were made, one grade A and one grade C. Exercise interventions ranged from aerobic exercise and strength training to multidimensional programmes with exercise as one component. All studies used physical and/or quality-of-life outcome measures.

**Conclusions:** Review findings suggest that exercise may be beneficial for persons with metastatic cancer. Future research should clarify optimal exercise dose parameters.

**Key Words:** exercise, metastatic cancer, physical activity, quality of life, systematic review

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## RÉSUMÉ

**Objectif :** Effectuer une étude méthodique et une synthèse des résultats des études ayant analysé les effets de l'exercice sur les personnes souffrant d'un cancer métastatique.

**Méthodes :** Les bases de données dans lesquelles des recherches ont été réalisées sont MEDLINE, EMBASE, CINAHL, PsycINFO et le Registre Cochrane des essais contrôlés. Les mots clés utilisés pour la recherche étaient les suivants : « metastatic or advanced or palliative AND cancer or neoplasms AND exercise or physical activity or exercise therapy or physical fitness », soit, en français, *métastatique* ou *avancé* ou *palliatif* ET *cancer* ou *néoplasmes* ET *exercice* ou *activité physique* ou *thérapie par l'exercice* ou *forme physique*. La recherche a permis de trouver huit études, publiées dans 10 articles de 2000 à 2007. Deux instruments d'évaluation de la qualité ont été utilisés et les niveaux de preuve ont été assignés suivant les directives énoncées par le Centre for Evidence-Based Medicine (CEBM) de l'Université d'Oxford.

**Résultats :** Des huit études, trois étaient des essais aléatoire contrôlés (EAC) et cinq étaient des analyses descriptives. Puisque trois des EAC reposaient sur le même échantillon, un seul des trois a été inclus dans la section résultats et celle de discussion. Les niveaux de preuve du CEBM se chiffraient de 2b à 4. Deux recommandations d'ensemble ont été formulées, une de grade A et une de grade C. Les interventions au chapitre de l'exercice variaient de l'exercice aérobique et l'entraînement en force, jusqu'aux programmes à dimensions multiples dont une composante était l'exercice. Toutes les études ont utilisé des mesures de résultats de condition physique et/ou de qualité de vie.

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**Conclusions:** Une revue des constatations de ces études semble indiquer que l'exercice pourrait être profitable pour les personnes souffrant d'un cancer métastatique. Des études ultérieures devraient avoir lieu en vue de clarifier les paramètres portant sur la quantité optimale d'exercice à effectuer.

**Mots clés:** activité physique, cancer métastatique, exercice, qualité de vie, revue systématique

The Canadian Cancer Society estimates that 171,000 new diagnoses of cancer and 75,300 cancer-related deaths will occur in Canada in 2009.<sup>1</sup> Among patients with a new cancer diagnosis, 30% already have metastases.<sup>2</sup> Frequent sites of metastasis include lung, liver, breast, and bone;<sup>3</sup> once metastasis has occurred, prognosis is generally poor. However, persons with metastatic cancer are now living longer. For example, for breast cancer patients, the average survival period following metastasis is 18 to 24 months, and many patients exceed this period.<sup>4</sup>

Most persons with metastatic cancer encounter different challenges than those with local or regional cancer, in that they are living with a terminal disease.<sup>5-9</sup> Associated with this are declines in quality of life (QOL), psychological barriers, and fatigue.<sup>5-9</sup> The prevalence of metastatic cancer, increased longevity, and compromised QOL suggest the need for research on interventions aimed at improving QOL. To date, there has been no systematic review on the effects of exercise for persons with metastatic cancer.

Completed systematic reviews in the cancer literature have focused on exercise interventions for persons with local or regional cancer.<sup>10-14</sup> Researchers tend to explore types of exercise interventions implemented both during and after cancer diagnosis. Many reviews have investigated the impact of exercise on fatigue,<sup>8,10-15</sup> an important symptom given that 90% of persons with cancer experience cancer-related fatigue.<sup>7</sup> Cancer-related fatigue has also been linked to symptoms of anxiety and depression.<sup>7</sup> Physical exercise has been identified as an effective intervention to improve QOL and fatigue in patients whose cancer has not metastasized.<sup>8,10-15</sup>

Furthermore, recent observational studies have shown that physical activity may actually decrease the risk of recurrence and prolong overall survival in women with primary breast cancer.<sup>16,17</sup>

Evidence is now emerging on the potential benefits of exercise for persons with metastatic cancer.<sup>6,8,18,19</sup> Although persons with metastatic cancer have traditionally been encouraged to rest, it is now generally accepted that rest is not an effective intervention for cancer-related fatigue.<sup>8</sup> Patients and their families are being educated that fatigue is a normal symptom of cancer and a normal side effect of cancer treatments.<sup>7</sup> An unavoidable complication with longitudinal research in this area is the high attrition rates due to mortality and potentially rapid declines in health.<sup>6</sup> Because of these differences between

persons living with local or regional cancer (in remission) and those living with metastatic disease, results of previous systematic reviews involving the former group are not generalizable to persons with metastatic cancer. This systematic review therefore seeks to provide a synthesis of the evidence on the effects of exercise for persons with metastatic cancer.

## REVIEW QUESTIONS

The following questions guided this systematic review:

1. What exercise interventions are being used for persons with metastatic cancer?
2. What is the effect of these interventions on QOL and physical outcome measures?
3. What attrition rates and adverse effects were documented in these studies?
4. What research needs to be completed in the future?

## METHODS

For this review, the term *metastatic cancer* is defined as "the spread of cancer from one part of the body to another."<sup>3</sup> This definition includes Stage IV cancer, the stage at which "the cancer has spread to another organ."<sup>20</sup> Staging is determined by "location of the primary tumor; tumor size and number of tumors; lymph node involvement, cell type and tumor grade; and presence or absence of metastasis."<sup>20</sup> Other equivalent terms used in the research literature are "advanced"<sup>6</sup> or "palliative"<sup>8</sup> cancer. *Advanced cancer* is defined as cancer that has spread to other places in the body and usually cannot be cured or controlled with treatment.<sup>21</sup> It is important to note, however, that not all persons with metastatic or advanced cancer are in the palliative or end-of-life phase. These distinctions will be made when the reviewed studies are described in detail.

## Data Sources and Search Strategy

The search strategy included searching electronic databases, hand-searching reference lists, and communicating with experts in the field. Electronic databases selected were those cited previously in previous systematic reviews<sup>9,10-14</sup> on persons with local or regional cancer and exercise: MEDLINE, EMBASE, CINAHL, PsycINFO, the Cochrane Central Register of Controlled Trials, the Cochrane Databases of Systematic Reviews (EBM Reviews—Ovid), and PEDro.

The search was conducted up to and including May 8, 2008, using the following keywords: *metastatic* or *palliative* or *advanced* AND *cancer* or *neoplasm* AND *exercise* or *physical activity* or *exercise therapy* or *physical fitness*. The search strategy was modified for each database and exploded, when possible, in order to maximize sensitivity and produce a comprehensive search. These search terms were chosen from an examination of search terms used in similar reviews and modified after consultation with a health sciences reference librarian. Terms were searched for title, abstract, and subject heading.

**Study Selection: Inclusion and Exclusion Criteria**

Articles were included at the title stage based on (1) *population*: persons with metastatic, advanced, or palliative cancer; and (2) *intervention*: exercise as the intervention or a component of the intervention. Titles that were unclear were also included at this stage. Abstracts of the selected studies were included based on population, intervention, and (3) *publication* in a peer-reviewed journal. Following these steps, full texts were reviewed using these inclusion criteria. Because of the lack of studies involving persons with metastatic cancer, articles were not screened based on comparisons, control groups, or outcome measures, in order to include as many relevant studies as possible.

Throughout the search process, exclusion criteria were (1) *population*: studies of persons with lymphoma, melanoma, or myeloma (these are not considered to be metastatic cancers)<sup>3</sup> and studies in which results of those with metastatic cancer could not be separated from those with non-metastatic cancer; and (2) *type*: studies in languages other than English or French, newspaper editorials, critical reviews of individual articles, and qualitative research studies. In addition, studies were excluded if less than one-third of the sample had metastatic or advanced cancer.

Two independent reviewers (WPF, RB) screened all titles, abstracts, and full texts. Disagreements between

the reviewers were resolved by consensus. Arbitration by a third reviewer (CR) was used for unresolved disagreements.

**Levels of Evidence**

Levels of evidence from the Oxford Centre for Evidence-Based Medicine (CEBM)<sup>22</sup> were assigned to each study by one reviewer (HW) and then checked by a second reviewer (CR; see Table 1).

**Study Quality Assessment**

Two quality-assessment tools were used, depending on study design. Randomized controlled trials (RCTs) were assessed using criteria from van Tulder et al.<sup>23</sup> (see Table 2); case series were assessed using the case-series criteria<sup>24</sup> (see Table 3).

**Table 2** Methodological Quality Assessment Tool for Randomized Controlled Trials<sup>23</sup>

Description	Yes/ No/ Not Sure	Page Found
A. Was the method of randomization adequate?		
B. Was the treatment allocation concealed from the groups or individuals?		
C. Was the patient blinded to the intervention?		
D. Were the groups similar at baseline regarding the most important prognostic indicators?		
E. Was the therapist providing treatment blinded to the intervention?		
F. Was the outcome assessor blinded to the intervention?		
G. Were co-interventions avoided or similar?		
H. Was the compliance acceptable in all groups?		
I. Was the dropout rate described and acceptable?		
J. Was the timing of the outcome assessment in all groups similar?		
K. Did the analysis include an intention to treat analysis?		
Total /11		

Source: van Tulder M, Furlan A, Bombardier C, Bouter L, Editorial Board of the Cochrane Collaboration Back Review Group. Updated method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group. Spine. 2003;28:1290-9. Reproduced by permission.

**Table 1** Oxford Centre for Evidence-Based Medicine Levels of Evidence for Therapy/Prevention, Aetiology/Harm (May 2001)<sup>22</sup>

Level	Types of Studies: Therapy/Prevention, Aetiology/Harm
1a	SR (with homogeneity) of RCTs
1b	Individual RCT (with narrow confidence interval)
1c	“All or none” <sup>22</sup>
2a	SR (with homogeneity) of cohort studies
2b	Individual cohort study, including low-quality RCT (e.g., <80% follow-up)
2c	“Outcomes” research and ecological studies
3a	SR (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case series and poor-quality cohort and case-control studies
5	Expert opinion without explicit critical appraisal or based on physiology, bench research, or “first principles”

RCT = randomized controlled trial; SR = systematic review  
Adapted from Phillips et al.<sup>22</sup>

**Table 3** Methodological Quality Assessment Tool for Case Series<sup>24</sup>

Description	Yes/ No/ Not Sure	Page Found
1. Is the study based on a representative sample from a relevant population?		
2. Are the criteria for inclusion explicit?		
3. Did all individuals enter the survey at a similar point in their disease progression?		
4. Was the follow-up long enough for important events to occur?		
5.1. Were the outcomes assessed using objective criteria?		
5.2. Was blinding used?		
Total /5		

Adapted from Kahn et al.<sup>24</sup>

**Table 4** Oxford Centre for Evidence-based Medicine—Grades of Recommendation (May 2001)<sup>22</sup>

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies Extrapolations* from level 1 studies
C	Level 4 studies Extrapolations* from level 2/3 studies
D	Level 5 evidence Troublingly inconsistent/inconclusive studies of any level

\*The term “extrapolations” indicates that data are used in a situation that has clinically important differences from the original study situation.

Quality assessment for the included studies was performed by four reviewers (WPF, CR, RB, CV); each reviewer assessed quality for two or three of the studies, and the results were then checked by a second reviewer. Each reviewer evaluated the full text of the articles, answering the appropriate list of questions with a “yes,” “no,” or “not reported.” A point was granted only for a “yes.” Disagreements were resolved via discussion and consensus.

Grades of recommendation (see Table 4) from the Oxford CEBM<sup>22</sup> were summarized for the studies by one reviewer (HW) and then checked by a second (CR).

#### Data Extraction

A data-extraction tool was developed and pilot-tested on three studies. Pilot testing was completed by two independent reviewers (RB, CR), and amendments were made where necessary. Once no new additions or modifications were forthcoming, pilot testing was deemed complete.

Data extraction for the 10 included articles<sup>5,8,18,25–31</sup> was performed by four reviewers (RB, WPF, CR, CV); each reviewer extracted data for two or three of the articles, and the results were then checked by a second reviewer. Disagreements were resolved via discussion and consensus.

#### Data Synthesis

A summary of findings for each study was compiled to depict study quality, level of evidence, design type, sample characteristics, intervention type, outcomes, and results (see Table 5).

## RESULTS

### Search Summary

An initial search of the databases produced a total of 674 articles; the total was reduced to 224 after title screening. Screening of abstracts yielded 27 articles with agreement as measured by the kappa statistic ( $\kappa = 0.69$ ). Evaluation of full texts resulted in 12 articles being initially chosen for inclusion ( $\kappa = 0.92$ ). Two of

these articles (both case reports) were subsequently excluded because of their low level of evidence. Following the full-text review, it was determined that the articles written by Brown et al.,<sup>5</sup> Lapid et al.,<sup>25</sup> and Rummans et al.<sup>26</sup> were based on the same study sample. To demonstrate the breadth of literature available on the topic, all of these articles are listed in the characteristics table (Table 5), but only the details of Rummans et al.<sup>26</sup> are included in the Results and Discussion sections. The following sections therefore describe 8 studies rather than 10.

### Study Designs and Levels of Evidence

Three of the included studies<sup>18,26,28</sup> were RCTs with an Oxford CEBM<sup>22</sup> evidence level of 2b; the other five studies<sup>8,27,29–31</sup> were case series with an evidence level of 4.

### Summary of Study Characteristics

The study characteristics are summarized using the PICO format: patients or participants (P), intervention (I), comparison or control group (C), and outcomes (O).

#### Patients or Participants

Three of the studies included only persons with metastatic cancer, described as “advanced cancer” in two studies<sup>18,26</sup> and as “metastatic cancer” in the third study.<sup>31</sup> The remaining five studies included samples in which between 39% and 80% of the participants were described as having “advanced”<sup>29,30</sup> or “metastatic” cancer<sup>8,27</sup> or as receiving treatment with “palliative intent.”<sup>28</sup> The remaining participants in these five studies were described as having local or regional cancer and/or as receiving adjuvant treatment (see Table 5).

#### Interventions

The exercise interventions used in the studies involving persons with metastatic cancer were heterogeneous with respect to type, frequency, and intensity.

*Exercise as Sole Intervention.* In four of the eight studies, the effects of exercise as the sole intervention were examined, although several different types of exercise were used in each study.<sup>8,18,27,28</sup> Exercise interventions involved walking, arm exercises in a chair, marching, and dancing;<sup>8</sup> seated repetitive motion exercises based on a fitness video;<sup>18</sup> group-based circuit training for upper- and lower-extremity strength, standing balance, and aerobic endurance;<sup>27</sup> and an individualized resistance programme with warm-up and cool-down periods.<sup>28</sup> Exercises were carried out at home,<sup>8,18</sup> in a hospital gym,<sup>27</sup> or in a public facility.<sup>28</sup> The frequency of exercise ranged from twice per week<sup>27</sup> to several sessions per day<sup>8</sup> for durations ranging from 2 weeks<sup>8</sup> to 12 weeks.<sup>18,28</sup>

**Table 5** Characteristics of Included Studies

Author(s)	Design & Evidence Level	Participants	Exercise Intervention	Outcome Measures	Results
Adamsen et al. (2003) <sup>29</sup>	Case series Level 4	Baseline participants: <i>n</i> = 27 Participants completed: <i>n</i> = 23 M:F 9:14 Age (yrs): range = 18–63; median = 40 Cancer status ( <i>n</i> = 23): 57% advanced, 43% adjuvant Primary cancer site/type ( <i>n</i> ): colon (6), breast (5), haematological (4), ovary (2), testes (2), sarcoma (1), SCLC (1), cervix (1), unknown (1)	Frequency: 3×/wk over 6 wks Intensity: 85–95% 1RM (5–8 repetitions), 150–250 W equivalent to 60–100% HR max Type of exercise: group warm-up exercises, resistance training, stationary bike Session duration: 1.5 hrs Concurrent intervention: relaxation, massage, body-awareness training	Physical: 1. 1RM 2. VO <sub>2</sub> max 3. Physical activity level QOL: 1. EORTC QLQ-C30 2. SF-36 3. HADS	Physical: 1. S ↑ kg ( <i>p</i> = 0.000) 2. S ↑ l/min ( <i>p</i> = 0.001) 3. NS ↑ QOL: 1. NS ↑ 6/15 domains. 2. S ↑ role physical ( <i>p</i> = 0.02); NS ↑ or no change in remaining domains 3. NS ↓ anxiety, ↑ depression
Adamsen et al. (2006) <sup>30</sup>	Case series Level 4	Baseline participants: <i>n</i> = 115 Participants completed: <i>n</i> = 82 M:F 26:66 Age (yrs): range = 18–63; median = 40 Cancer status ( <i>n</i> = 82): 56% advanced, 44% adjuvant Primary cancer site/type ( <i>n</i> ): breast (27), haematological (16), ovary (14), colon (8), testes (3), sarcoma (3), unknown (2), SCLC (2), cervix (2), esophageal (2), rhinopharynx (1), oral (1), gastric (1)	Frequency: 3×/wk over 6 wks Intensity: 85–95% 1RM (5–8 repetitions), 70–250 W equivalent to 60–100% HR max Type of exercise: group warm-up exercises, resistance training, stationary bike Session duration: 1.5 hrs Concurrent intervention: relaxation, massage, body-awareness training	Physical: 1. 1RM 2. VO <sub>2</sub> max 3. Physical activity level QOL: 1. SF-36 2. EORTC QLQ-C30	Physical: 1. S ↑ kg ( <i>p</i> = 0.001) 2. S ↑ l/min ( <i>p</i> = 0.001) 3. S ↑ ( <i>p</i> = 0.001) QOL: 1. S ↑ 7/10 domains ( <i>p</i> = 0.001) 2. S ↑ 8/15 domains ( <i>p</i> = 0.001)
Carson et al. (2007) <sup>31</sup>	Pre-to-post, multilevel outcome analysis Level 4	Baseline participants: <i>n</i> = 21 Participants completed: <i>n</i> = 13 M:F 0:13 Age (yrs): range = 44–75; median = 59 Cancer status ( <i>n</i> = 13): 100% metastatic Primary cancer site/type ( <i>n</i> ): breast (13)	Frequency: group session = 1×/wk over 8 wks; individual practice = 7×/wk over 8 wks Intensity: gentle Type of exercise: yoga Session duration: group sessions for 120 min; individual home practice for an average of 21 min/day Concurrent intervention: breathing exercises, meditation, didactic presentations, group interchange	QOL: 1. Multilevel random effects estimates (a) Effect of treatment (time) (b) Same-day outcomes (c) Next-day outcomes	QOL: Daily levels of (a) S ↑ invigoration ( <i>p</i> < 0.01); S ↑ acceptance ( <i>p</i> < 0.02); NS ↓ pain, ↑ relaxation, ↓ fatigue, ↓ distress (b) S ↑ invigoration ( <i>p</i> < 0.01); S ↑ acceptance ( <i>p</i> < 0.02); S ↓ pain ( <i>p</i> < 0.01); NS ↑ relaxation, ↓ fatigue, ↓ distress (c) S ↑ invigoration ( <i>p</i> = 0.03); S ↑ acceptance ( <i>p</i> = 0.02); S ↓ pain ( <i>p</i> = 0.03); S ↑ relaxation ( <i>p</i> = 0.03); NS ↓ fatigue and distress
Headley et al. (2004) <sup>18</sup>	RCT Level 2b	Intervention: Baseline participants: <i>n</i> = 19 Participants completed: <i>n</i> = 16 M:F 0:16 Age (yrs): range = 37–73; median = 52.25 Cancer status ( <i>n</i> = 16): 100% advanced Primary cancer site/type ( <i>n</i> ): breast (16) Control: Baseline participants: <i>n</i> = 19 Participants completed: <i>n</i> = 16 M:F 0:16 Age (yrs): range = 37–73; median = 50 Cancer status ( <i>n</i> = 16): 100% advanced Primary cancer site/type ( <i>n</i> ): breast (16)	Intervention: Frequency: 3×/wk over 12 wks Intensity: moderate Type of exercise: seated fitness video consisting of repetitive motion exercises Session duration: 30 min Concurrent intervention: n/d Control: Continue usual physical activity	QOL: 1. FACIT-F (a) QOL total (b) Fatigue (c) Physical well-being (d) Social well-being (e) Emotional well-being (f) Functional well-being	QOL: (a) Intervention group had slower rate of decline in total score ( <i>p</i> = 0.02) (b) S less ↑ in intervention group ( <i>p</i> = 0.008) (c) S less ↓ in intervention group ( <i>p</i> = 0.02) (d) NS (e) NS (f) NS

(Continued)

**Table 5** Characteristics of Included Studies

Author(s)	Design & Evidence Level	Participants	Exercise Intervention	Outcome Measures	Results
Oldervoll et al. (2006) <sup>27</sup>	Case series Level 4	Baseline participants: <i>n</i> = 52 Participants completed: <i>n</i> = 34 M:F 15:19 Age (yrs): range = 40–82; median = 65 Cancer status ( <i>n</i> = 34): 80% metastatic, 20% not described Primary cancer site/type ( <i>n</i> ): GI (16), other (7), breast (5), genitourinary (5), lung (1)	Frequency: 2×/wk over 6 wks Intensity: low intensity as able according to supervising physiotherapist Type of exercise: circuit training for UE and LE strength, standing balance, aerobic endurance Session duration: 50 min Concurrent intervention: none	Physical: 1. BMI 2. Body weight 3. 6MWT 4. STS 5. Functional reach QOL: 1. FQ (a) Physical fatigue (b) Mental fatigue (c) Total fatigue 2. EORTC QLQ-C30	Physical: 1. NS ↓ score 2. NS ↓ kg 3. S ↑ walk length ( <i>p</i> = 0.007) S ↓ time ( <i>p</i> = 0.001) NS ↑ reach QOL: 1. (a) S ↓ physical fatigue ( <i>p</i> = 0.04) (b) NS change in mental fatigue (c) NS ↓ in total fatigue 2. S ↑ in role, emotional, social and dyspnea ( <i>p</i> = 0.02, 0.002, 0.008, 0.006); NS ↓ in fatigue; NS change in physical functioning and global QOL; NS improvement in physical, cognitive, nausea/vomiting, pain, sleep disturbance, loss of appetite, constipation, diarrhoea, financial impact
Porock et al. (2000) <sup>8</sup>	Case series Level 4	Baseline participants: <i>n</i> = 9 Participants completed: <i>n</i> = 6 M:F 3:6 Age (yrs): range = 51–77; median = 59.87 Cancer status ( <i>n</i> = 6): 78% metastatic, 22% not described Primary cancer site/type ( <i>n</i> ): bowel (4), pancreas (2), melanoma (1), breast (1), oral (1)	Frequency: several sessions 7×/wk over 2–4 wks Intensity: monitored HR for intensity but authors do not report HR zone Type of exercise: Duke Energizing Exercise plan (individualized, e.g., walking, arm exercises in chair with rubber band, marching, dancing) Session duration: started at 50% of what the participant can comfortably tolerate Concurrent intervention: none	QOL: 1. MFI 2. SDS 3. HADS 4. QOL scale	QOL: 1. Minimal fluctuation in subscale scores (NS) 2. Within same range of scores as others in this population (NS) 3. Majority of participants not classified as depressed; possible trend of ↓ anxiety levels 4. ↑ QOL day 0–14 (NS)
Rummans et al. (2006) <sup>26</sup> Brown et al. (2006) <sup>5</sup> Lapid et al. (2007) <sup>25</sup>	RCT Level 2b	Intervention: Baseline participants: <i>n</i> = 49 Participants completed: <i>n</i> = 39 M:F 29:20 Age (yrs): range = 31–85; median = 59.7 Cancer status ( <i>n</i> = 39): 100% advanced Primary cancer site/type ( <i>n</i> ): GI (18), lung (9), other (8), head/neck (7), brain (6), ovary (1) Control: Baseline participants: <i>n</i> = 54 Participants completed: <i>n</i> = 43 M:F 37:17 Age (yrs): range = 36–82; median = 59.4 Cancer status ( <i>n</i> = 43): 100% advanced Primary cancer site/type ( <i>n</i> ): GI (21), head/neck (11), other (10), lung (6), brain (6), ovary (0)	Intervention: Frequency: 8 sessions over 3 wks Intensity: n/d Type of exercise: conditioning, relaxation Session duration: 20 min condition, 10–20 min relax Concurrent intervention: 50–60 min cognitive, social, emotional, and spiritual interventions Control: Usual level of care, consisting of regular outpatient visits with primary oncologist, radiation oncologist, and other allied health care providers	QOL: 1. LASA (a) QOL (b) Overall spiritual well-being 2. Spitzer Uniscale 3. SDS 4. POMS (a) Emotional distress score (b) Total score 5. FACIT-SWB	QOL: 1. (a) S ↑ QOL in intervention > control group @ 4 wks ( <i>p</i> = 0.047); NS @ 8 & 27 wks (b) S ↑ overall spiritual well-being intervention > control ( <i>p</i> = 0.003) 2. Results n/d 3. NS between groups 4. (a) S ↑ emotional distress in the control group ( <i>p</i> = 0.042) (b) NS between groups for total score 5. NS between groups * Note: intervention participants maintained QOL; controls gradually decreased to baseline at 6-mo follow-up.

<p>Segal et al. (2003)<sup>28</sup></p>	<p>RCT Level 2b</p>	<p>Intervention: Baseline participants: <i>n</i> = 82 (33 in palliative group, 49 in curative group) Participants completed: <i>n</i> = 82 (33 in palliative group, 49 in curative group) M:F 82:0 Age (yrs): mean (SD) for entire group = 68.2 (7.9) Cancer status: 40.2% = “treatment with palliative intent” Primary cancer site (<i>n</i>): prostate (82) Control: Baseline participants: <i>n</i> = 73 (27 in palliative group, 46 in curative group) Participants completed: <i>n</i> = 73 (27 in palliative group, 46 in curative group) M:F 73:0 Age (yrs): mean (SD) for entire group = 67.7 (7.5) Cancer status: 37.0% = “treatment with palliative intent” Primary cancer site (<i>n</i>): prostate (73)</p>	<p>Intervention: Frequency: 3×/wk over 12 wks Intensity: 60–70% of predicted 1RM Type of exercise: personalized resistance program with warm-up and cool-down Session duration: 2 sets, 8–12 repetitions of each of 9 exercises Concurrent intervention: none Control: Waitlist</p>	<p>Physical: 1. Chest press load test 2. Leg press load test 3. Body weight 4. BMI 5. WC 6. Sum of skin folds QOL: 1. FACT-F 2. FACT-P</p>	<p>Physical: 1. S benefit of UE resistance exercise for palliative intervention group (<i>p</i> = 0.012) 2. S LE fitness enhanced in palliative intervention group (<i>p</i> = 0.015) 3–6: No differences between groups QOL: 1. NS ↑ score in palliative intervention group, ↓ score in palliative control group (<i>p</i> = 0.052) 2. S ↑ score in palliative intervention group, ↓ score in palliative control group (<i>p</i> = 0.020)</p>
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AROM = active range of motion; BMI = body mass index; ECG = electrocardiogram; ECHO = echocardiogram; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version; FACT-F = Functional Assessment of Cancer Therapy: Fatigue; FACT-P = Functional Assessment of Cancer Therapy: Prostate; FACIT-SWB = Functional Assessment of Chronic Illness Therapy—Spiritual Well-Being; FEV1 = forced expiratory volume in one second; FQ = Fatigue Questionnaire; FVC = forced vital capacity; GI = gastrointestinal; GIQLI = Gastrointestinal Quality of Life Index; HADS = Hospital Anxiety Depression Scale; HR = heart rate; HR max = heart rate maximum; LASA = Linear Analogue Self Assessment; LE = lower extremity; MFI = Multidimensional Fatigue Inventory; n/a = not applicable; n/d = not documented; NKC = natural killer cells; NS = not significant; POMS = Profile of Mood States; QOL = quality of life; RCT = randomized controlled trial; S = significant; SCLC = small cell lung cancer; SDS = Symptom Distress Scale; SF-36 = Short Form 36-item Health Survey; STS = timed sit-to-stand; UE = upper extremity; VC = vital capacity; VO<sub>2</sub> max = maximal oxygen uptake; W = watt; WC = waist circumference; 1RM = one-repetition maximum; 6MWT = 6-Minute Walk Test

**Exercise Combined with Other Interventions.** The other four studies assessed the effects of exercise as a component of a multidimensional intervention.<sup>26,29-31</sup> Exercise interventions involved group-based conditioning and relaxation combined with cognitive, social, emotional, and spiritual interventions;<sup>26</sup> group warm-up exercises, resistance training, and riding a stationary bicycle combined with relaxation, massage, and body-awareness training;<sup>29,30</sup> and group-based yoga combined with breathing exercises, meditation, didactic presentations, and group interchange.<sup>31</sup> These combined interventions took place at a cancer centre,<sup>26</sup> a hospital gym,<sup>29,30</sup> or a medical centre.<sup>31</sup> Exercise frequency ranged from once per week<sup>31</sup> to two to three times per week<sup>26,29,30</sup> for durations of 3,<sup>26</sup> 6,<sup>29,30</sup> or 8 weeks.<sup>31</sup>

### Control or Comparison Groups

The control groups in the three RCTs<sup>18,26,28</sup> received the usual level of care; in one RCT,<sup>28</sup> the control group was waitlisted with an offer to participate in the exercise intervention at a later date. In four of the studies,<sup>27-30</sup> both physical and QOL changes were measured, whereas only QOL was assessed in the other four studies.<sup>8,18,26,31</sup>

### Outcome Measures

While the outcome tools varied across studies, the physical measures used most frequently included one-repetition maximum (1RM)<sup>29,30</sup> and maximal oxygen uptake (VO<sub>2</sub> max),<sup>29,30</sup> while the QOL measures used most frequently included the European Organization for Research and Treatment of Cancer QOL Questionnaire C30 (EORTC QLQ-30)<sup>27,29,30</sup> and the 36-Item Short Form Health Survey (SF 36).<sup>29,30</sup>

### Inclusion and Exclusion Criteria of the Studies

Inclusion and exclusion criteria differed across studies with respect to life expectancy, comorbidities, and mental health status. Four studies documented inclusion and exclusion criteria based on life expectancy.<sup>8,26,27,31</sup> Rummans et al.<sup>26</sup> included persons with a five-year survival probability of less than 50%; Oldervoll et al.<sup>27</sup> included persons with a 3- to 12-month life expectancy; Porock et al.<sup>8</sup> included persons with a life expectancy of at least 1 month; and Carson et al.<sup>31</sup> excluded persons with less than 6 months' life expectancy. Five studies<sup>8,18,28-30</sup> used exclusion criteria based on

comorbidities, and all but Porock et al.<sup>8</sup> excluded persons based on the presence of bone metastases or lesions. Four of the studies<sup>8,26,29,31</sup> stated exclusion criteria based on mental health status; for example, Adamsen et al.<sup>29</sup> excluded persons with dementia and persons with psychotic conditions.

### Similarity of Study Groups at Baseline

Across all eight studies, baseline information collected included age, gender, cancer status, primary cancer site and/or cancer type, and medical treatment. The mean ages of the samples ranged from 40 to 68 years. Five studies<sup>8,26,27,29,30</sup> included both male and female participants, whereas two<sup>18,31</sup> included only female participants and one<sup>28</sup> included only male participants. With respect to the classification of cancer status, four studies<sup>18,26,29,30</sup> used the term "advanced" cancer, three<sup>27,28,31</sup> used the term "metastatic," and one<sup>28</sup> used the term "treated with palliative intent." Primary sites and types of cancer varied across the review and within studies: participants in two studies<sup>18,31</sup> were diagnosed with primary breast cancer and those in one study<sup>28</sup> with prostate cancer, while participant samples for the remaining studies<sup>8,26,27,29,30</sup> included at least five different primary cancer sites. Six studies<sup>18,27-31</sup> included some proportion of persons undergoing concurrent chemotherapy treatment; in three of those studies,<sup>18,29,30</sup> all participants were undergoing concurrent chemotherapy. Two of the eight studies<sup>8,26</sup> included some persons undergoing concurrent radiation therapy (11% of the sample in Porock et al.<sup>8</sup> and 89% in Rummans et al.<sup>26</sup>).

### Attrition, Adherence, and Adverse Effects

In two RCTs, attrition rates were documented. Rummans et al.<sup>26</sup> documented an overall attrition rate of 7%, while Headley et al.<sup>18</sup> documented an overall attrition rate of 16%. In the five case-series studies,<sup>8,27,29-31</sup> attrition rates ranged from 14% to 35%. Only four studies<sup>18,27,30,31</sup> included adherence measures for the population of interest; these ranged from 75% to 88%. Three of the eight studies<sup>18,27,31</sup> specifically reported on adverse effects, and no adverse effects occurred.

### Quality Assessment

All three RCTs<sup>18,26,28</sup> scored 8/11 using the van Tulder et al. criteria (see Table 6).<sup>23</sup> None of the RCTs fulfilled

**Table 6** Methodological Quality Assessment: Randomized Controlled Trials<sup>22\*</sup>

Study	A	B	C	D	E	F	G	H	I	J	K	Total Score
Headley et al. <sup>18</sup>	Y	N	N	Y	Y	Y	Y	Y	Y	Y	N	8/11
Rummans et al. <sup>26</sup>	Y	N	N	Y	N	Y	Y	Y	Y	Y	Y	8/11
Segal et al. <sup>28</sup>	Y	N	N	Y	N	Y	Y	Y	Y	Y	Y	8/11

Y = yes / met criteria; N = no / did not meet criteria

\*See Table 2 for a description of quality-assessment criteria A-K.

**Table 7** Methodological Quality Assessment: Case Series<sup>23\*</sup>

Study	1	2	3	4	5.1	5.2	Total Score
Adamsen et al. <sup>29</sup>	N	Y	Y	Y	Y	N	3.5/5
Adamsen et al. <sup>30</sup>	N	Y	Y	Y	Y	N	3.5/5
Carson et al. <sup>31</sup>	N	N	Y	Y	Y	N	2.5/5
Olervoll et al. <sup>27</sup>	N	Y	Y	Y	Y	N	3.5/5
Porock et al. <sup>8</sup>	N	Y	Y	Y	Y	N	3.5/5

Y = yes / met criteria; N = no / did not meet criteria

\*See Table 3 for a description of methodological quality indicators 1–5.2.

criterion B, the concealment of treatment allocation, or criterion C, the blinding of the patient to the intervention. Furthermore, two RCTs<sup>26,28</sup> did not fulfil criterion E, the blinding of the therapist to the intervention; because the third RCT involved home-based exercises,<sup>18</sup> the outcome assessors were blinded to the participants' status (i.e., intervention vs. control group). Headley et al.<sup>18</sup> did not fulfil criterion K, the intention to treat analysis.

Using the case series assessment criteria (see Table 3), four case series<sup>8,27,29,30</sup> scored 3.5/5 and the fifth<sup>31</sup> scored 2.5/5 (see Table 7). In all five case-series studies,<sup>8,27,29–31</sup> criterion 6, the comparison of sub-series, did not apply. Therefore, studies were scored out of a possible total of 5. None of these studies fulfilled criterion 5.2 (blinding) or criterion 1 (representative sampling). Carson et al.<sup>31</sup> did not fulfil criterion 2, as the study's inclusion criteria were not explicit.

### Recommendations with Grades of Recommendation

Based on consistent results from the three RCTs (Table 4),<sup>18,26,28</sup> the following recommendations can be made. Grade A recommendation: Exercise interventions resulted in improved QOL.<sup>24</sup> In the study by Rummans et al.,<sup>26</sup> the intervention group experienced an increase in overall spiritual well-being, while there was an increase in emotional distress in the control group. In the study by Headley et al.,<sup>18</sup> the intervention group experienced a slower decline in total QOL. Segal et al. reported significantly improved QOL in those men with prostate cancer who were treated with palliative intent.<sup>28</sup> Improvements in QOL were also reported in several of the case-series studies.<sup>8,27,30,31</sup> These included increased levels of invigoration and acceptance;<sup>31</sup> decreased physical fatigue with increased role, emotional, social, and dyspnea sub-scales;<sup>27</sup> improved role-physical score on the SF-36;<sup>29</sup> decreased anxiety with increased QOL;<sup>8</sup> and a general increase in QOL.<sup>30</sup>

Based on results from one RCT<sup>28</sup> and three case-series studies,<sup>27,29,30</sup> the following grade C recommendation is provided: Exercise interventions resulted in improved measures of physical performance (i.e., upper- and lower-extremity muscle endurance;<sup>28</sup> increased muscle strength and aerobic fitness;<sup>29,30</sup> increased walking distance and faster sit-to-stand<sup>27</sup>).

## DISCUSSION

Cancer is increasingly prevalent among Canadians.<sup>1</sup> Persons with cancer report symptoms of fatigue, emotional stress, and declining QOL.<sup>5–9</sup> Chemotherapy and radiation therapy contribute to the fatigue experienced by persons being treated for cancer, but fatigue is even more pronounced in persons with metastatic cancer, whose treatment with these modalities is often long-term.

Although systematic reviews have been published on the effects of exercise for persons with local or regional cancer,<sup>9,12–16</sup> no systematic review has yet isolated the effects of exercise interventions for persons with metastatic cancer. This systematic review included 10 articles<sup>5,8,18,25–31</sup> with Oxford CEBM<sup>22</sup> levels of evidence ranging from 2b to 4. All of these studies are included in Table 5 above, but only eight studies<sup>8,18,26–31</sup> were used in the final data synthesis, as three of the studies<sup>5,25,26</sup> used the same study sample.

With respect to the first question guiding this systematic review, the exercise interventions used for people with metastatic cancer were extremely variable, ranging from yoga to aerobic exercise to resistance exercise. With respect to our second guiding question, exercise was shown to have positive effects on QOL (grade A recommendation) and physical outcomes (grade C recommendation). Our third guiding question related to attrition rates and adverse effects. Attrition rates were reported, and were less than 50%, across all the studies reviewed. Adverse effects were documented in only three of the eight studies, but none were found within those studies. The need for future research, the fourth guiding question, will be discussed in a later section.

## LIMITATIONS

The main limitation of this review is the heterogeneity of the study samples, exercise interventions, and outcome measures. Therefore, caution must be used in generalizing these findings. The results of this review may not have high external validity, as they may not accurately represent persons with metastatic cancer. In five of the studies,<sup>8,28–31</sup> only 39% to 80% of the sample had metastatic cancer. The samples also varied with respect

to age, primary cancer site or type, cancer status, and medical treatment.

Because the exercise interventions were so diverse, it is not possible to draw conclusions about optimal frequency, intensity, exercise type, or session duration for this population. In addition, intensity measures were not documented in four of the eight studies.<sup>18,26,27,31</sup> Where subjects participated in a multidimensional intervention, it was not possible to isolate the effects of physical exercise. For example, the studies by Adamsen et al.<sup>29,30</sup> incorporated massage, relaxation, and body-awareness training along with physical exercise. Some of the positive effects seen may be attributable to these additional components.

All eight studies<sup>8,18,26–31</sup> used QOL measures as a dependent variable. Four studies<sup>27–30</sup> also used physical outcome measures. However, 16 different QOL measures and 19 different physical measures were used across the eight studies. The wide diversity of these measures also contributed to our inability to quantitatively pool results.

### Reliability and Validity of Outcome Measures

The diversity of the outcome measures used in these studies may be due to the fact that no single measure for QOL covers the physical, psychological, and spiritual domains in a format that would provide sufficient and reliable information.<sup>32</sup> As a result, a combination of assessments must be used to achieve a more thorough assessment of QOL specific to the purpose of the research. The EORTC QLQ-C30, the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System, the Symptom Distress Scale (SDS), and the SF-36 are valid and reliable for the advanced cancer population.<sup>32–35</sup> For assessment of fatigue, Hagelin<sup>36</sup> found the EORTC QLQ-C30, the Multidimensional Fatigue Inventory (MFI 20), and the Hospital Anxiety and Depression Scales (HADS) valid and reliable for this population. Six of the eight studies<sup>8,18,26,27,29,30</sup> used at least one of these six outcome measures.

In a systematic review of QOL measures used in palliative care studies, Jordhoy et al.<sup>37</sup> reported that physical function assessment represented only a small portion of palliative care QOL outcome measures. This may explain why only four<sup>27–30</sup> of eight studies included a physical measure in conjunction with QOL measures. Jordhoy et al.<sup>37</sup> called for clear definitions and conceptualization of physical function, as well as consensus on relevant aspects to include in improved instruments.

The two most commonly used physical measures across the included studies were one repetition maximum (1RM) and maximal oxygen uptake (VO<sub>2</sub> max). 1RM is a reliable and safe method for dosing and evaluation of muscle strength training programmes for elderly people,<sup>38</sup> making it appropriate for the wide age range

(18–63 years) of participants in the included studies. With respect to VO<sub>2</sub> max, however, Jones et al. suggested recently that sub-maximal testing, without gas-exchange measurement, might be “useful in clinical oncology,” since “maximum tests are not used for cardiac or pulmonary diagnostic purposes in the cancer setting.”<sup>39(p.760)</sup>

Consistency of outcome measures for QOL, fatigue, and physical function would allow for comparability of results across studies and future meta-analyses.

### Attrition and Adherence

Retention of participants is a challenge for any study, but this is particularly the case when the participants have a shorter life expectancy and experience very debilitating symptoms. In a review article on cachexia,<sup>40</sup> attrition rates of 50% over an 8-week period were not uncommon among persons with cancer. A study examining barriers to participation by persons in palliative care found that an intervention of more than 1 month is generally not feasible for palliative populations, as many of the participants will have died or become too unwell to participate.<sup>41</sup> Thus, it might be expected that any study, especially one longer than 1 month, that examines the effect of a physical exercise intervention for persons with metastatic disease would have higher than normal attrition rates. In addition, the persons included in these studies experience not only the usual barriers to initial participation (e.g., travel distance, lack of interest, and other demands) but also the additional barriers of not feeling well enough to participate,<sup>26</sup> family objections, or protection of patients by staff members.<sup>41</sup>

All included studies had attrition rates of less than 50%, even though six of the eight studies<sup>18,27–31</sup> had durations longer than 1 month, suggesting that the participants tolerated the exercise interventions well, despite their poor health status. Four studies had attrition rates higher than 20%.<sup>8,27,30,31</sup> In their 28-day study, Porock et al.<sup>8</sup> documented an attrition rate of 33%, whereas Adamsen et al.<sup>30</sup> reported an attrition rate of 29% for medical reasons (12%) or other reasons not specified by the authors (17%). Carson et al.<sup>31</sup> reported an attrition rate of 28% without documenting reasons; Oldervall et al.<sup>27</sup> noted an attrition rate of 34.6% due to sudden death or to medical and social reasons.

Four studies<sup>18,26,28,29</sup> documented attrition rates of less than 20%. Adamsen et al. reported an attrition rate of only 14.8%, “despite the demanding nature of the program,”<sup>29(p.712)</sup> which included extremely high intensity exercises. Participants completed three sets of five to eight repetitions at 85–95% of 1RM, two to three times per week for large muscle groups. The authors explained the high completion rate as a function of group formation, suggesting that participants experienced a sense of belonging to their respective groups and that this social connection led to a high level of commitment.<sup>29</sup>

Attrition rates of less than 20% were also reported in the three RCTs,<sup>18,26,28</sup> a rate lower than those of the case-series studies.

Adherence rates ranged from 75% to 88% but were documented in only four of the eight studies,<sup>18,27,30,31</sup> none of the authors commented specifically on potential reasons for these rates. We speculate that individualized programming, group participation, or even noticeable improvements may have motivated adherence to the specified exercise prescriptions. However, given the lack of information on reasons for adherence, this should be a topic for future research.

Adverse effects were documented in only three of the eight studies,<sup>18,27,31</sup> and no adverse effects were reported. Participants in the Headley et al. study<sup>18</sup> were 32 women with stage IV breast cancer who were undergoing outpatient chemotherapy; the intervention group completed a home-based, seated exercise programme. The sites of the participants' metastases were not described. In the study by Oldervoll and colleagues,<sup>27</sup> which involved 34 participants, the intervention group took part in twice-weekly 50-minute sessions consisting of warm-up; circuit training focusing on upper- and lower-limb strengthening, balance, and aerobic activities; and relaxation/stretching. Twenty participants in the sample were from the palliative care unit or the outpatient oncology clinic at a hospital, and the other 14 from a hospice setting; their life expectancy was described as "more than 3 months and less than 1 year."<sup>27(p.422)</sup> Metastatic disease was reported in 80% of the sample; the most common sites were bone, lymphatic system, and lung. Participants in the Carson et al. study were women with metastatic breast cancer who participated in an 8-week yoga programme.<sup>31</sup> Patients with a life expectancy of less than 6 months were excluded from participation.<sup>31</sup> Sites of metastases were not described.

Because adverse events were documented in only three of the eight studies reviewed and only 100 participants were involved (with a variety of different types of cancer), it would be premature to suggest that exercise is unequivocally "safe" for persons with metastatic or advanced cancer.

### Implications for Practice

The findings of this systematic review provide some support for exercise as an effective intervention for persons with metastatic cancer. While our findings do not provide specific exercise prescription for this group, they have shown that exercise had a positive effect on QOL (grade A recommendation) and physical status (grade C recommendation). These results are important to communicate to patients and their families, who may understandably be concerned that exercise will increase symptoms, including fatigue and discomfort. It is important also to clearly communicate the goals of exercise

(i.e., to maintain or improve function in order to retain independence with mobility and transfers). As always, it is essential to form treatment goals in conjunction with the patient and family and to provide education regarding best practice.

### Implications for Future Research

Future research should clarify optimal exercise prescription, investigate all metastatic cancer sub-groups, determine acceptable attrition rates in this population, use valid and reliable outcome measures and consistent terminology in defining cancer status, and clearly document adverse effects. As recommended by authors in the included studies,<sup>27,29,30</sup> larger and more rigorous RCTs are needed to investigate current gaps in the literature. It would also be of interest to determine whether exercise could improve survival time in persons with metastatic cancer, as shown in observational studies of physical activity for women who have had breast cancer.<sup>16,17</sup>

With respect to exercise prescription, future research should establish the minimal exercise dose, investigate the effects of longer intervention periods, and compare exercise types. While a combination of aerobic and resistance training was used in two of the studies,<sup>27,28</sup> no study compared the benefits of an aerobic programme to those of a resistance programme. Future studies are also needed to develop exercise prescription parameters for all metastatic cancer sub-groups to clarify whether the response to exercise varies according to metastatic cancer types.

Finally, to allow meta-analysis of the effects of exercise on persons with metastatic cancer, outcome measures should be more homogeneous (i.e., the same combination of valid and reliable outcome measures should be used to cover the multiple aspects of QOL and physical status).

### CONCLUSIONS

This systematic review synthesized the available literature on the impact of exercise interventions for persons with metastatic cancer. One grade A recommendation supports the effects of exercise in enhancing QOL, while one grade C recommendation provides some support for exercise effects in improving physical performance outcomes. Clinicians working with persons with metastatic cancer should consider the implications of these findings but should use caution in their application, as there is currently no agreement on optimal exercise parameters and only limited evidence as to the safety of exercise for this population. Additional research using large-scale RCTs could identify optimal and safe exercise parameters for this population.

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