REVIEW

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Body weight and composition endpoints in cancer cachexia clinical trials: Systematic Review 4 of the cachexia endpoints series

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Abstract

Significant variation exists in the outcomes used in cancer cachexia trials, including measures of body composition, which are often selected as primary or secondary endpoints. To date, there has been no review of the most commonly selected measures or their potential sensitivity to detect changes resulting from the interventions being examined. The aim of this systematic review is to assess the frequency and diversity of body composition measures that have been used in cancer cachexia trials. MEDLINE, Embase and Cochrane Library databases were systematically searched between January 1990 and June 2021. Eligible trials examined adults (≥18 years) who had received an intervention aiming to treat or attenuate the effects of cancer cachexia for >14 days. Trials were also of a prospective controlled design and included body weight or at least one anthropometric, bioelectrical or radiological endpoint pertaining to body composition, irrespective of the modality of intervention (e.g., pharmacological, nutritional, physical exercise and behavioural) or comparator. Trials with a sample size of <40 patients were excluded. Data extraction used Covidence software, and reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance. This review was prospectively registered (PROSPERO: CRD42022276710). A total of 84 clinical trials, comprising 13 016 patients, were eligible for inclusion. Non-small-cell lung cancer and pancreatic cancer were studied most frequently. The majority of trial interventions were pharmacological (52%) or nutritional (34%) in nature. The most frequently reported endpoints were assessments of body weight (68 trials, n = 11 561) followed by bioimpedance analysis (BIA)-based estimates (23 trials, n = 3140). Sixteen trials (n = 3052) included dual-energy X-ray absorptiometry (DEXA)-based endpoints, and computed tomography (CT) body composition was included in eight trials (n = 841). Discrepancies were evident when comparing the efficacy of interventions using BIA-based estimates of lean tissue mass against radiological assessment modalities. Body weight, BIA and DEXA-based endpoints have been most frequently used in cancer cachexia trials. Although the optimal endpoints cannot be determined from this review, body weight,

alongside measurements from radiological body composition analysis, would seem appropriate. The choice of radiological modality is likely to be dependent on the trial setting, population and intervention in question. CT and magnetic resonance imaging, which have the ability to accurately discriminate tissue types, are likely to be more sensitive and provide greater detail. Endpoints are of particular importance when aligned with the intervention's mechanism of action and/or intended patient benefit.

Keywords body composition; cachexia; cancer cachexia; clinical trials

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Introduction

Cancer cachexia is a complex multifactorial syndrome characterized by loss of muscle and body fat.[1] These changes are strongly associated with poorer quality of life, increased morbidity and worse survival.[2] The 2011 consensus definition for cancer cachexia provided diagnostic and staging criteria that have been instrumental in aiding cachexia trial design.[1] At present, there is no similar consensus regarding endpoints, and significant variations remain amongst the clinical assessments used in cancer cachexia trials.

A comprehensive patient assessment of cachexia would consider changes in body composition, dietary intake, biomarkers of the pathophysiological drivers of cachexia, physical function and quality of life, and the influence on associated oncological outcomes. Depending on the mechanism of a given clinical trial intervention, particular weighting may be assigned to chosen measures within this broad range. Selected endpoints must be both sensitive enough to detect change and specific enough not to be readily influenced by other conditions or treatments. Furthermore, it is imperative that they convey clinical relevance.

Endpoints pertaining to body weight and composition are amongst the most frequently reported in cachexia trials and will be the focus of this review. Anthropometric measurements and electric bioimpedance analysis (BIA) are simple modalities that, although inexpensive and non-invasive, are prone to confounders and provide finite levels of detail. Dual-energy X-ray absorptiometry (DEXA) is widely available and can provide estimates of regional/whole-body fat or lean tissue mass. However, DEXA is unable to discriminate between different types of 'lean tissue' (e.g., skeletal muscle vs. organs) or anatomical locations (e.g., visceral vs. subcutaneous adipose tissue).[3] While cachexia research has traditionally focused on the loss of muscle, it is now known that adipose tissue also plays an important role in cachexia pathophysiology, and different mechanisms underpin the loss of each tissue type.[4] As such, the ability of modalities to distinguish between body tissue compartments is of increasing relevance. Computed tomography (CT) and magnetic resonance imaging (MRI) scans are considered the 'gold-standard' assessment modalities for body composition owing to their specificity in discriminating tissue identities and their precision.[5] Comparison of the two has shown high levels of agreement in assessments of muscle quantity and quality[6]; however, CT has been more frequently utilized in cachexia research owing to its more widespread use in routine clinical practice.

At present, it is not known what the best endpoints for cancer cachexia trials are. This may have resulted in sub-optimal clinical trial design, which could have in turn hindered the development of effective therapies. An appraisal of the endpoints currently used would seem like a logical starting point. The aim of this systematic review is to assess the frequency and diversity of measures that have been used to assess body weight and body composition in cancer cachexia trials.

Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[7] The review protocol was prospectively registered at the International Prospective Register of Systematic Reviews: PROSPERO (CRD42022276710).[8]

This review will address assessments of body weight, alongside anthropometric, bioelectrical or radiological endpoints pertaining to body composition. It is one of a series of six that will comprehensively evaluate the endpoints examined in cancer cachexia trials. Given the breadth of outcome measures in the literature, these were categorized broadly under the following domains: physical function,[9] quality of life, appetite and dietary intake, body weight and composition, oncological outcomes and biomarkers.

Search strategy

A systematic search of MEDLINE (Ovid), Embase (Ovid) and Cochrane Central Register of Controlled Trials databases

was conducted by a senior research librarian (University of Oslo). All published studies from 1 January 1990 to 2 June 2021 were eligible. Search results were synthesized and managed using the web-based systematic review software 'Covidence' (Veritas Health Innovations, Melbourne, Australia), and duplicates were removed. A detailed search strategy is outlined in *Appendix A*.

Study eligibility criteria

Prospective clinical trials that considered an intervention aiming to treat or attenuate the effects of cachexia in adult patients (≥18 years) with cancer were considered for eligibility. Inclusion was irrespective of the site of primary malignancy, modality of intervention (e.g., pharmacological, nutritional and physical exercise) or choice of comparator. Articles were excluded if they studied fewer than 40 patients and/or if the intervention lasted <14 days. Studies in which patients underwent surgery during the assessment period were excluded. All included full-text articles were written in the English language.

Data selection and extraction

The titles and abstracts of the identified studies were independently reviewed by three authors (OD, TSS and BJAL). Those selected were subsequently subject to full-text review (LRB and MSS). In instances of discrepancies between reviewers regarding an article's inclusion, consensus was reached through consultation between reviewers or with the wider authorship group. A pre-defined data extraction table was developed and pilot-tested before relevant data points were extracted independently by the lead authors (LRB and MSS).

Relevant outcome measures

Endpoints considered by this review were those pertaining to assessments of body weight and other modalities that aim to assess changes in body composition. These shall be categorized as anthropometric (e.g., body weight, circumference or skinfold measurements), bioelectrical (e.g., BIA) or radiological (e.g., DEXA, CT or MRI) measure of body composition.

Assessment of methodology and risk of bias

The methodological quality of each study was independently assessed by four reviewers (JS, JM, OD and BJAL) using the modified Downs and Black checklist.[10] This tool assesses several criteria including study design, internal and external validity, and reporting standards.

Data analysis

Study characteristics, patient details and disease demographics were reported descriptively. The aim of this review was to describe the body weight and composition outcomes used, rather than estimate treatment effects. As such, quantitative meta-analysis was not performed. Furthermore, the heterogenous nature of the trials and interventions studied made meta-analysis of treatment effects on each endpoint impractical. Analyses and visualization were conducted using RStudio Version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) with packages including *maps* and *tidyverse*.

Results

Overall, 8166 studies were identified following systematic searches of MEDLINE (Ovid), Embase (Ovid) and Cochrane Central Register of Controlled Trials databases (*Appendix A*). Following the removal of duplicates (*n* = 2191), further screening of the title and abstract for 5975 studies was performed. Of these, 5606 articles were excluded and 369 were retrieved for full-text review. Following detailed screening against the chosen inclusion and exclusion criteria, 84 clinical trials were eligible for inclusion. The PRISMA flow chart is detailed in *Figure 1*.

Study characteristics

Between 1990 and 2021, a total of 84 prospective clinical trials (*n* = 13 016 participants) included body weight or measure(s) of body composition as an endpoint. While numerous primary tumour sites were considered, pancreatic cancer (*n* = 11 trials) and non-small-cell lung cancer (*n* = 10 trials) were the most frequently studied. Cohorts ranged in size, with the largest cohort being 979 patients studied by the ROMANA 1 and 2 trials.[11] Pharmacological interventions (*n* = 43 trials) were most evaluated, followed by nutritional (*n* = 28 trials), multi-modal (*n* = 9 trials) and exercise-based modalities (*n* = 4 trials). The key characteristics of the included trials are detailed in *Table 1*.

Figure 2 depicts the geographical distribution of the included cancer cachexia clinical trials. For multicentre or multinational trials (*n* = 12 studies), coordinates for the

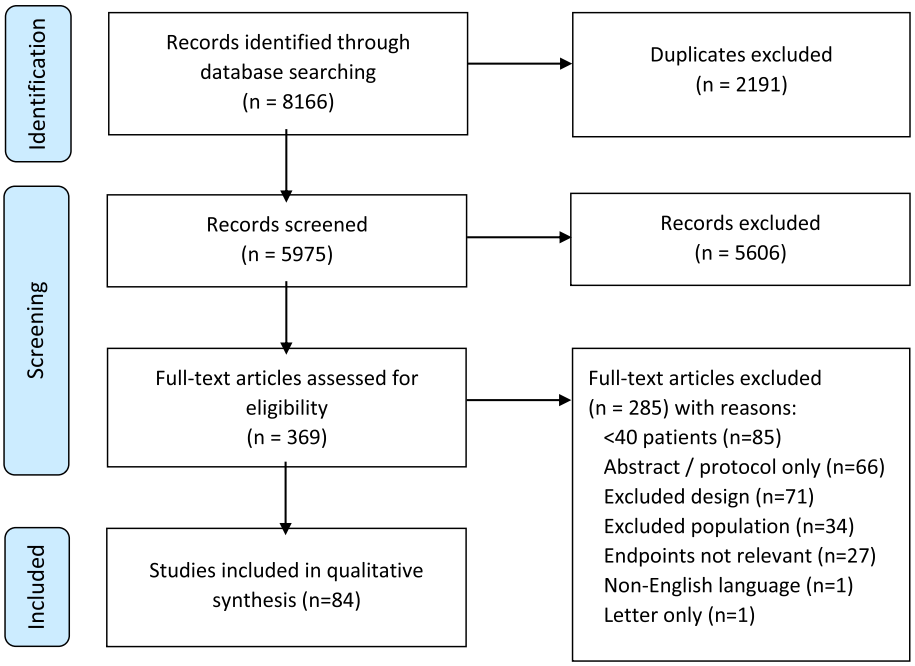

Figure 1 PRISMA flow chart.

institution of the corresponding author were used. It was noted that limited research has been conducted in Eastern Europe, Africa or South America.

Temporal trends in body composition endpoint selection

The relative use of body weight and body composition assessments over time is depicted in *Figure 3*. The proportion of trials that included assessments of body weight or body mass index (BMI) as an endpoint measure did not vary particularly over the time frame considered. Other anthropometric measures (e.g., skinfold thickness or arm circumference) have been less utilized in recent years with only three trials in the last decade reporting these endpoints. BIA has been used with relative consistency during the last 20 years, whereas DEXA-based estimates of body composition were included in only two trials before 2010, when its use increased. The reporting of CT body composition analysis in clinical trials is more contemporary with only eight trials, all conducted within the last decade, having included this assessment modality.

Body weight and other anthropometric endpoints

Seventy-five trials (*n* = 12 056 participants) measured body weight or other anthropometric endpoints pertaining to body composition (*Table 1* and *Appendix B*). Assessments of body weight (68 trials, *n* = 11 561 participants) were utilized in pharmacological (*n* = 37), nutritional (*n* = 22), multi-modal (*n* = 8) and exercise-based (*n* = 1) clinical trials. A body weight assessment was selected as the (co-)primary endpoint in 32 (47.1%) of these trials and was a secondary/exploratory outcome for the other 36 (52.9%). Analyses were based on absolute change in body weight in 48 trials (70.6%) and percentage change from baseline in 16 trials (23.5%) with 4 trials considering both (5.9%). The ACT-ONE trial analysed the rate (slope) of absolute and percentage weight change.[62] Body weight was handled as an ordinal variable by three trials[19,32,54] where comparison was drawn between proportions of weight-gaining, weight-stable and weight-losing participants. Over one third of the trials that considered body weight (38.2%, *n* = 4735) noted significant differences between trial groups (*Figure 4* and *Table 2*). BMI was reported as an endpoint for 13 trials, most commonly in addition to body weight (6/13 trials). The majority of studies that chose BMI as an endpoint employed a nutritional intervention (61.5%). It was the primary endpoint in only one of these trials (7.7%). Fourteen trials included anthropometric measures of the arm as endpoints (*n* = 1901 participants). Eight of these evaluated pharmacological interventions (57.1%), five were nutritional (35.7%) and one was multi-modal (7.1%). Measurements of mid-arm circumference, and other derived upper arm measures such as muscle and fat areas, were selected as endpoints in 12 trials (*n* = 1324, *Appendix B*). Skinfold thickness was also used commonly as an endpoint

Table 1 Key characteristics of included clinical trials

Author (reference)	Year	Sample size	Study design	Study quality	Primary cancer site	Intervention	Comparator	Body composition outcomes[a]
Kardinal et al.[12]	1990	293	RCT	8	Any malignancy (not brain)	Cyproheptadine (**pharmacological**)	Placebo	Body weight[c] (*primary*)
Loprinzi et al.[13]	1990	133	RCT	9	Any malignancy (not brain/breast/ endometrial)	Megestrol acetate (**pharmacological**)	Placebo	**Body weight**[b,c] (*primary*)
Feliu et al.[14]	1992	150	RCT	5	Any malignancy (not hormone dependent)	Megestrol acetate (**pharmacological**)	Placebo	Body weight[b] (*primary*)
Downer et al.[15]	1993	60	RCT	1	Any malignancy	Medroxyprogesterone acetate (**pharmacological**)	Placebo	Body weight[b] (*primary*) Mid-arm circumference Triceps skinfold thickness
Loprinzi et al.[16]	1993	342	Phase III RCT	8	Any malignancy (not breast/endometrial)	Megestrol acetate 1280 mg or megestrol acetate 800 mg (**pharmacological**)	Megestrol acetate 480 mg or megestrol acetate 160 mg	Body weight[c] (*primary*)
Ovesen et al.[17]	1993	105	RCT	8	Small-cell-lung/ovarian/ breast	Nutritional counselling (**nutritional**)	Standard care	Body weight[b] (*primary*) Arm muscle area **Triceps skinfold thickness**
Goldberg et al.[18]	1995	70	RCT	8	Any malignancy (not primary brain tumour)	Pentoxifylline (**pharmacological**)	Placebo	Body weight[c] (*primary*)
Gebbia et al.[19]	1996	122	RCT	6	Any malignancy (not hormone dependent)	Megestrol acetate 320 mg (**pharmacological**)	Megestrol acetate 160 mg	Body weight (*primary*)
Lissoni et al.[20]	1996	100	RCT	7	Any solid tumour	Melatonin (**pharmacological**)	Standard care	**Body weight**[b] (*primary*)
Simons et al.[21]	1996	206	RCT	7	Any malignancy (not hormone dependent)	Medroxyprogesterone acetate (**pharmacological**)	Placebo	**Body weight**[b] (*primary*)
Beller et al.[22]	1997	240	RCT	4	Any malignancy (not hormone dependent)	Megestrol acetate 480 mg or megestrol acetate 160 mg (**pharmacological**)	Placebo	Body weight[b] (*primary*) Mid-arm circumference Mid-arm fat and muscle area Triceps skinfold thickness
Chen et al.[23]	1997	129	RCT	8	Head and neck	Megestrol acetate or prepulside (**pharmacological**)	Placebo	**Body weight**[b] (*primary*)
Daneryd et al.[24]	1998	180	RCT	7	Any malignancy	Indomethacin + erythropoietin (**pharmacological**)	Indomethacin	Lean body mass—DEXA **Body weight**[b]
De Conno et al.[25]	1998	42	RCT	6	Any malignancy (not hormone dependent)	Megestrol acetate (**pharmacological**)	Placebo	**Body weight**[b] (*primary*)
Vadell et al.[26]	1998	150	RCT	5	Any malignancy	Megestrol acetate 480 mg or megestrol acetate 160 mg (**pharmacological**)	Placebo	**Body weight**[b] (*primary*) Mid-arm circumference **Triceps skinfold thickness**
Loprinizi et al.[27]	1999	496	RCT	8			Fluoxymesterone	Body weight[c]

(*Continues*)

Table 1 (continued)

Author (reference)	Year	Sample size	Study design	Study quality	Primary cancer site	Intervention	Comparator	Body composition outcomes[a]
					Any malignancy (not breast/prostate/ovarian/ endometrial)	Megestrol acetate or dexamethasone (**pharmacological**)		(*primary*)
McMillan et al.[28]	1999	73	RCT	7	Gastrointestinal	Megestrol acetate + ibuprofen (**pharmacological**)	Megestrol acetate + placebo	**Body weight**[b] (*primary*) **Mid-arm circumference** Triceps skinfold thickness Biceps skinfold thickness
Westman et al.[29]	1999	255	RCT	7	Other mixed	Megestrol acetate (**pharmacological**)	Placebo	Body weight[b] (*primary*)
Jatoi et al.[30]	2002	469	RCT	10	Any malignancy (not brain/breast/ovarian/ endometrial)	Megestrol acetate + dronabinol or megestrol acetate + placebo (**pharmacological**)	Dronabinol + placebo	**Body weight**[c] (*primary*)
Persson et al.[31]	2002	144	RCT	6	Breast/colorectal/gastric/ prostate	Individual nutritional counselling or individual and group nutritional counselling (**nutritional**)	Group nutritional counselling or standard care	**Body weight**[c] (*primary*)
Ulutin et al.[32]	2002	119	RCT	9	NSCLC	Megestrol acetate 320 mg (**pharmacological**)	Megestrol acetate 160 mg	**Body weight** (increase vs. stable vs. decrease)
Bruera et al.[33]	2003	91	RCT	7	Any malignancy	Fish oil capsules (**nutritional**)	Placebo	Lean body mass—BIA Body weight[b] Mid-arm muscle circumference Triceps skinfold thickness Subscapular skinfold thickness
Fearon et al.[34]	2003	200	RCT	8	Pancreatic	*n*-3 fatty acid and antioxidant-enriched supplement (**nutritional**)	Supplement without *n*-3 fatty acid and antioxidants	Lean body mass—BIA Body weight[b]
Isenring et al.[35]	2004	60	RCT	8	Gastrointestinal/head and neck	Nutrition counselling and protocol (**nutritional**)	Standard care	Fat-free mass—BIA **Body weight**[b]
Lundholm et al.[36]	2004	309	RCT	5	Any solid tumour	Indomethacin + erythropoietin + nutritional support + home total parenteral nutrition (**multi-modal**)	Indomethacin + erythropoietin	Fat mass—DEXA Lean body mass—DEXA Body weight[b] Mid-arm muscle circumference Triceps skinfold thickness
Gonçalves Dias et al.[37]	2005	64	Non-randomized trial	1	Head and neck	Home enteral (nasogastric) feeding or oral diet + nutritional supplements (**nutritional**)	Oral diet	Body weight[b] BMI Mid-arm circumference Mid-arm muscle area Triceps skinfold thickness

(*Continues*)

Table 1 (continued)

Author (reference)	Year	Sample size	Study design	Study quality	Primary cancer site	Intervention	Comparator	Body composition outcomes[a]
Gordon et al.[38]	2005	50	RCT	10	Pancreatic	Thalidomide (**pharmacological**)	Placebo	**Body weight**[b] (*primary*) **Bone-free arm muscle area**
Fearon et al.[39]	2006	518	RCT	8	Gastrointestinal/lung	EPA 2 g or EPA 4 g (**pharmacological**)	Placebo	Lean body mass—BIA Body weight[b]
Berk et al.[40]	2008	472	RCT	9	Any solid tumour	Nutritional supplement (**nutritional**)	Placebo	Lean body mass—BIA (*primary*) Body weight[c] Various skinfold thickness
Wiedenmann et al.[41]	2008	86	Phase II RCT	7	Pancreatic	Infliximab 5 mg/kg or infliximab 3 mg/kg (**pharmacological**)	Placebo	Lean body mass—BIA (*primary*)
Beijer et al.[42]	2009	100	RCT	8	Any malignancy	Adenosine 5′-triphosphate (**pharmacological**)	Standard care	**Triceps skinfold thickness** (*primary*) Body weight[b] Mid-arm circumference
Mantovani et al.[43]	2010	332	Phase III RCT	7	Any malignancy	Megestrol acetate or EPA-enriched nutritional supplement or L-carnitine or thalidomide (**pharmacological**)	Megestrol acetate + EPA-enriched nutritional supplement + L-carnitine + thalidomide	**Lean body mass—DEXA** (*primary*) Lean body mass—BIA (*primary*) **Lean body mass—CT** (*primary*)
Navari et al.[44]	2010	80	RCT	7	Gastrointestinal/lung	Megestrol acetate + olanzapine (**pharmacological**)	Megestrol acetate	**Body weight**[c] (*primary*)
Baldwin et al.[45]	2011	358	RCT	8	Gastrointestinal/NSCLC/ mesothelioma	Nutritional supplement + nutritional counselling or nutritional supplement (**nutritional**)	Nutritional counselling or standard care	Body weight[b]
Kraft et al.[46]	2012	72	RCT	10	Pancreatic	L-Carnitine supplement (**nutritional**)	Placebo	**Fat mass—BIA** **BMI**
Macciò et al.[47]	2012	144	Phase III RCT	8	Gynaecological	Megestrol acetate + L-carnitine + celecoxib + antioxidants (**pharmacological**)	Megestrol acetate	**Lean body mass—DEXA** (*primary*)
Madeddu et al.[48]	2012	60	Phase III RCT	7	Any malignancy	L-Carnitine + celecoxib + megestrol acetate (**pharmacological**)	L-Carnitine + celecoxib	Lean body mass—DEXA (*primary*) Lean body mass—CT (*primary*) Lean body mass—BIA (*primary*)
Silander et al.[49]	2012	134	RCT	6	Head and neck	Prophylactic PEG (**nutritional**)	Standard care	Body weight[c] (*primary*) BMI

(*Continues*)

Table 1 (continued)

Author (reference)	Year	Sample size	Study design	Study quality	Primary cancer site	Intervention	Comparator	Body composition outcomes[a]
Wen et al.[50]	2012	102	RCT	5	Any malignancy	Megestrol acetate + thalidomide (**pharmacological**)	Megestrol acetate	**Body weight**[b] (*primary*)
Del Fabbro et al.[51]	2013	73	RCT	10	Gastrointestinal/lung	Melatonin (**pharmacological**)	Placebo	Body weight[b] (*primary*) Lean body mass—BIA Fat-free mass—BIA
Dobs et al.[52]	2013	159	Phase II RCT	8	Other mixed	Enobosarm 1 mg or enobosarm 3 mg (**pharmacological**)	Placebo	**Lean body mass—DEXA** (*primary*) Body weight[b] Fat mass—DEXA
Kanat et al.[53]	2013	69	RCT	8	Any malignancy	Megestrol acetate + meloxicam or megestrol acetate + EPA-enriched nutritional supplement (**pharmacological**)	Meloxicam + EPA-enriched nutritional supplement	Body weight[b] (*primary*) Lean body mass—BIA (*primary*) BMI
Poulsen et al.[54]	2013	61	RCT	5	Oesophageal/gastric/ gynaecological	Nutritional counselling (**nutritional**)	Standard care	**Body weight** (loss vs. maintenance) (*primary*) Fat mass—BIA Fat-free mass—BIA
Bourdel-Marchasson et al.[55]	2014	336	RCT	10	Other mixed	Nutritional counselling (**nutritional**)	Standard care	Body weight[b]
Pottel et al.[56]	2014	85	Exploratory RCT	8	Head and neck	Echium oil (**nutritional**)	Sunflower oil	Body weight[c] (*primary*) Lean body mass—DEXA Lean body mass—BIA Fat mass—DEXA Fat mass—BIA Fat-free mass—BIA
Focan et al.[57]	2015	53	RCT	7	Any malignancy	Dietetic and psychological mindfulness workshops (**multi-modal**)	Standard care	**BMI** (*primary*) **Body weight**[b]
Garcia et al.[58]	2015	82	Phase II RCT	7	Any malignancy	Anamorelin 50 mg (**pharmacological**)	Placebo	**Lean body mass—DEXA** (*primary*) **Appendicular LBM– DEXA** **Total body mass—DEXA** Fat mass—DEXA
Capozzi et al.[59]	2016	60	Exploratory RCT	8	Head and neck	Early 'lifestyle intervention' (individualized exercise with education and support) (**exercise**)	Delayed 'lifestyle intervention' (individualized exercise with education and support)	Lean body mass—DEXA Fat mass—DEXA BMI
Kapoor et al.[60]	2016	63	RCT	8	Any malignancy	Improved atta (nutritional supplement) + nutritional counselling (**nutritional**)	Nutritional counselling	Body weight[b] Mid-arm circumference Various skinfold thickness
Mehrzad et al.[61]	2016	70	RCT	8		Pentoxifylline	Placebo	Body weight[b]

(*Continues*)

Table 1 (continued)

Author (reference)	Year	Sample size	Study design	Study quality	Primary cancer site	Intervention	Comparator	Body composition outcomes[a]
					Any malignancy (not brain)	(**pharmacological**)		Mid-arm circumference
Stewart Coats et al.[62]	2016	87	Phase II RCT	10	NSCLC/colorectal	Espindolol 10 mg or espindolol 2.5 mg (**pharmacological**)	Placebo	**Body weight**[b,c] (*primary*) **Lean body mass—DEXA** Fat mass—DEXA
Takayama et al.[63]	2016	181	Phase II RCT	8	NSCLC	Anamorelin 100 mg or anamorelin 50 mg (**pharmacological**)	Placebo	**Lean body mass—DEXA** (*primary*) Lean body mass—BIA **Fat mass—DEXA** **Fat mass—BIA** **Body weight**[b]
Temel et al.[11]	2016	979	Phase III RCT	8	NSCLC	Anamorelin (**pharmacological**)	Placebo	**Lean body mass—DEXA** (*primary*) **Body weight**[b] **Total body mass—DEXA** **Fat mass—DEXA** **Appendicular LBM—DEXA**
Woo et al.[64]	2016	67	Phase II RCT	9	Pancreatic	Pancreatic exocrine replacement therapy (**nutritional**)	Placebo	Body weight[b,c] (*primary*)
Currow et al.[65]	2017	513	Phase III RCT	8	NSCLC	Anamorelin (**pharmacological**)	Placebo	**Body weight**[b]
Jatoi et al.[66]	2017	302	RCT	8	Any malignancy (not primary brain tumour)	Creatine monohydrate (**nutritional**)	Placebo	Body weight[c] (*primary*)
Leedo et al.[67]	2017	40	RCT	8	Lung	Home meal delivery (**nutritional**)	Standard care	Body weight[b]
Sandmael et al.[68]	2017	41	Pilot RCT	9	Head and neck	Exercise and nutrition intervention during radiotherapy treatment (**multi-modal**)	Exercise and nutrition intervention after radiotherapy treatment	Skeletal muscle index—CT Body weight[b]
Solheim et al.[69]	2017	46	Phase II RCT	8	NSCLC/pancreatic	Exercise, celecoxib + nutritional supplements (**multi-modal**)	Standard care	**Body weight**[b,c] Skeletal muscle area—CT
Werner et al.[70]	2017	60	RCT	7	Pancreatic	Fish oil (**nutritional**)	Marine phospholipids	Body weight[c] BMI
Ziętarska et al.[71]	2017	95	RCT	6	Colorectal	Nutritional supplements (**nutritional**)	Standard care	BMI
Golan et al.[72]	2018	125	Phase II RCT	7	Pancreatic	Anti-myostatin antibody 300 mg or anti-myostatin antibody 100 mg (**pharmacological**)	Placebo	Thigh muscle volume—CT Skeletal muscle area—CT Adipose tissue area—CT Lean body mass—DEXA Fat mass—DEXA
Katakami et al.[73]	2018	174	Phase III RCT	8	NSCLC	Anamorelin (**pharmacological**)	Placebo	**Lean body mass—DEXA** (*primary*) **Body weight**[b]
Kouchaki et al.[74]	2018	90	Phase III RCT	8	Gastrointestinal	Megestrol acetate + celecoxib	Megestrol acetate + placebo	Body weight[b,c] (*primary*)

(*Continues*)

Table 1 (continued)

Author (reference)	Year	Sample size	Study design	Study quality	Primary cancer site	Intervention	Comparator	Body composition outcomes[a]
						(**pharmacological**)		
Schink et al.[75]	2018	131	Pilot non-randomized trial	9	Any solid tumour	Whole-body electromyostimulation + nutritional counselling (**multi-modal**)	Nutritional counselling	**Lean body mass—BIA** (*primary*) Fat mass—BIA **Body weight**[b]
Uster et al.[76]	2018	58	RCT	9	Gastrointestinal/lung	Exercise programme + nutritional counselling (**multi-modal**)	Standard care	Body weight[b]
Xie et al.[77]	2018	54	RCT	8	Lung	Thalidomide + cinobufagin (**pharmacological**)	Cinobufagin	Body weight[b] Mid-arm circumference
Akita et al.[78]	2019	62	RCT	8	Pancreatic	EPA-enriched nutritional supplement (**nutritional**)	Standard care	Lean body mass—BIA Fat mass—BIA Psoas muscle area—CT BMI
Britton et al.[79]	2019	307	RCT	7	Head and neck	Psychological nutritional intervention (**nutritional**)	Standard care	**Body weight**[c]
Cereda et al.[80]	2019	166	RCT	8	Other mixed	Whey protein isolate supplement + nutritional counselling (**nutritional**)	Nutritional counselling	**Fat-free mass index—BIA** **Body weight**[b]
Laviano et al.[81]	2019	55	Pilot RCT	8	NSCLC	Targeted medical nutrition supplement (**nutritional**)	Isocaloric comparator drink	Skeletal muscle area—CT Visceral fat area—CT Appendicular LBM—DEXA Fat mass—DEXA Body weight[b]
Obling et al.[82]	2019	47	RCT	7	Gastrointestinal	Supplemental home parenteral nutrition and nutritional counselling (**nutritional**)	Nutritional counselling	**Fat-free mass—BIA** (*primary*) **Fat-free mass index—BIA** (*primary*)
Stuecher et al.[83]	2019	44	RCT	8	Gastrointestinal	Walking exercise programme (**exercise**)	Standard care	**Lean body mass—BIA**
Wiskemann et al.[84]	2019	65	RCT	5	Pancreatic	Supervised resistance training or home-based resistance training (**exercise**)	Standard care	Body weight[c] (*primary*)
Boulec et al.[85]	2020	111	RCT	7	Any malignancy	Parenteral nutrition (**nutritional**)	Oral feeding	Body weight[b]
Huang et al.[86]	2020	119	RCT	7	Nasopharyngeal	Nutritional supplements (**nutritional**)	Standard care	Body weight[b]
Kamel et al.[87]	2020	40	RCT	7	Pancreatic	Resistance training (**exercise**)	Standard care	**Appendicular LBM—DEXA** **Fat mass—DEXA**
Movahed et al.[88]	2020	100	RCT	8	Oesophageal	Supplements ± enteral or parenteral nutrition ± pharmacotherapy + nutritional counselling (**multi-modal**)	Nutritional counselling	Fat mass—BIA Fat-free mass index—BIA Body weight[b] BMI

(*Continues*)

Table 1 (continued)

Author (reference)	Year	Sample size	Study design	Study quality	Primary cancer site	Intervention	Comparator	Body composition outcomes[a]
Qiu et al.[89]	2020	96	RCT	6	Oesophageal	Nutritional counselling (**nutritional**)	Standard care	BMI
Storck et al.[90]	2020	52	RCT	10	Other mixed	Protein supplement + nutritional counselling + exercise programme (**multi-modal**)	Standard care	Lean body mass—BIA Fat mass—BIA BMI
Currow et al.[91]	2021	190	Phase III RCT	6	Any malignancy	Megestrol acetate or dexamethasone (**pharmacological**)	Placebo	Body weight[b]
Hunter et al.[92]	2021	120	Phase III RCT	7	Any solid tumour	Mirtazapine (**pharmacological**)	Placebo	Lean body mass—BIA Body weight[b]
Kutz et al.[93]	2021	58	RCT	7	Head and neck	Nutritional counselling (**nutritional**)	Standard care	BMI Fat-free mass—BIA
Tobberup et al.[94]	2021	120	Non-randomized trial	9	NSCLC	Fish oil + nutritional counselling + exercise programme (**multi-modal**)	Standard care (historical comparator)	Skeletal muscle area—CT Body weight[b]

Note: Sample sizes are reported as per 'intention to treat'. Abbreviations: BIA, bioimpedance analysis; BMI, body mass index; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; EPA, eicosapentaenoic acid; LBM, lean body mass; NSCLC, non-small-cell lung cancer; PEG, percutaneous endoscopic gastrostomy; RCT, randomized controlled trial.
[a]Endpoints that are bold underlined had a statistically significant difference between groups.
[b]Endpoint expressed as change in absolute value from baseline.
[c]Endpoint expressed as percentage change from baseline.

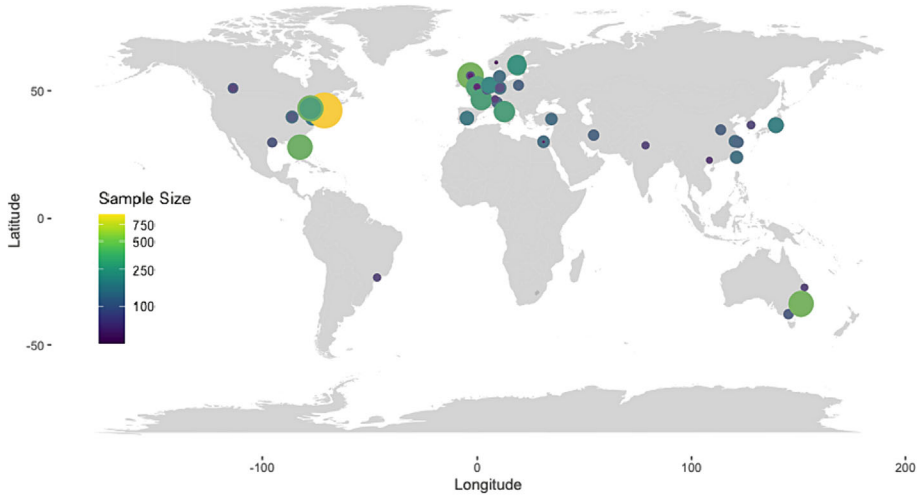

Figure 2 Geographical distribution of included cancer cachexia trials.

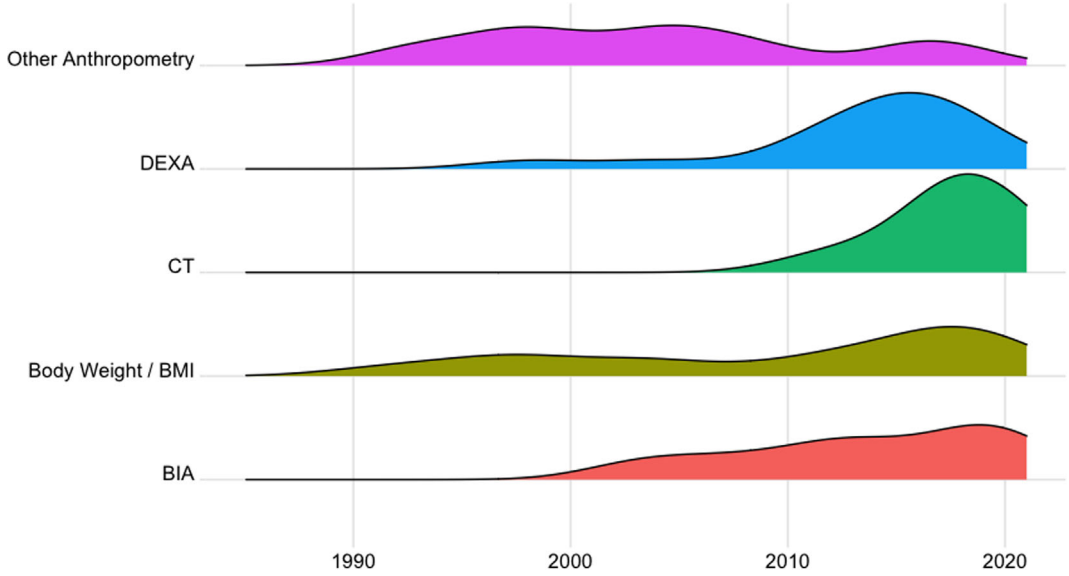

Figure 3 Temporal trends in relative use of body weight and body composition assessments. BIA, bioimpedance analysis; BMI, body mass index; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry.

(11 trials, *n* = 1727 participants). All of these 11 trials measured the triceps skinfold, and some also considered skinfold thickness at the biceps, subscapular skinfold and other sites. Triceps skinfold thickness was the primary endpoint for one trial, where arm anthropometry was used as a secondary/exploratory outcome for all other trials.

All studies that included arm-based anthropometric measurements also included body weight as an endpoint. Of these, 9 (64.3%) identified no statistically significant difference between groups using any selected outcome measure. Two trials[17,42] identified statistically significant improvements in triceps skinfold thickness but no corresponding change in body weight. Conversely, McMillan et al.'s trial led to increased body weight (5.1 kg median difference between trial arms) and mid-arm circumference measurement (1 cm median difference between trial arms), but no change in skinfold thickness measurements.[28]

Bioelectrical body composition endpoints

Endpoints based on assessment with BIA were used in 23 trials (*n* = 3140 participants, *Table 1* and *Appendix C*). The interventions tested were commonly nutritional (11 trials, 47.8%) or pharmacological (9 trials, 39.1%). BIA-based endpoints were selected as a (co-)primary endpoint in 6 trials (26.1%)

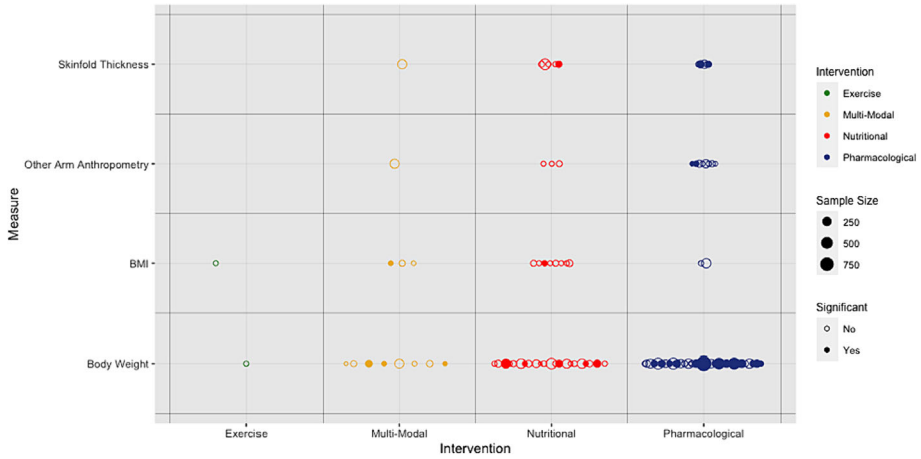

Figure 4 Summary of anthropometric measures of body composition by intervention modality. BMI, body mass index.

and a secondary/exploratory endpoint in the remaining 17 (73.9%). The most frequently included endpoint was estimated whole-body lean body mass (LBM) (16 trials, *n* = 2576 participants), with fat-free mass (FFM) or fat-free mass index (FFMI) calculated as alternative endpoints by 8 trials (*n* = 650 participants). Fat mass (FM) was estimated using BIA in eight trials (*n* = 744 participants).

Fourteen studies (60.9%) that used BIA did not detect statistically significant differences between trial groups with any of their selected endpoints (including those not BIA-based) (*Table 2* and *Figure 5*). In two trials, improvements were identified in BIA estimates of LBM/FFM that were congruent with increased body weight.[75,80] A statistically significant increase in body weight was identified in two trials of nutritional counselling[35,54] but there were no accompanying changes in BIA estimates of LBM. Two of the seven trials (28.6%) that estimated FM using BIA demonstrated a statistically significant increase with their intervention that was congruent with body weight gain.[46,63]

Radiological body composition endpoints

DEXA was used in 16 trials (*n* = 3052) with LBM (*n* = 2957 participants) and FM (*n* = 2162) being the most frequently reported endpoints (*Table 1* and *Appendix C*). Appendicular lean mass was used as an alternative endpoint in two trials[81,87] and alongside whole-body LBM in another two trials[58,65] (*Figure 6*). Pharmacological interventions were used for most trials that used DEXA (68.8%). DEXA-based measures were used as the primary endpoint for 50% (*n* = 8) of these trials.

Five trials included in this review compared the effects of anamorelin against placebo (*n* = 1929 participants). Of these, four evaluated LBM using DEXA, and all identified a statistically significant increase compared to placebo with congruent increases in overall body weight.[11,58,63,73] Of note, Takayama et al.'s relatively large (*n* = 181) placebo-controlled trial identified significant improvements in body weight alongside increased FM using both DEXA and BIA, but only a significant improvement in LBM when measured with DEXA (mean difference vs. placebo: 1.15 kg [95% confidence interval—CI: 0.11–2.18]), not with BIA-based estimates (mean difference vs. placebo: 0.78 kg [95% CI: −0.35 to 1.90]).[63]

Only eight trials included endpoints based on CT body composition (*n* = 841, *Table 1* and *Appendix C*), with two of these (25%) considering it a (co-)primary endpoint. All but one[43] of these had relatively small sample sizes (≤125 patients). Four measured the cross-sectional area of skeletal muscle (*n* = 346) at the third (L3)[68,69,94] or fourth/fifth lumbar vertebral level.[72] One of these studies reported the L3 cross-sectional area of muscle as normalized for height, termed skeletal muscle index (SMI).[68] Others included the L3 cross-sectional area of psoas major[78] or derived estimates of LBM (kg) based on L3 muscularity.[43,48] CT estimates of adipose tissue were also reported by two trials.[72,81] Six of the included trials noted no significant differences for any of their selected endpoints.

The five-arm phase III randomized controlled trial (RCT) (*n* = 332) by Mantovani et al.[43] identified improved LBM using DEXA (mean difference: 2.1 kg) and CT estimates (mean difference: 2.6 kg) in one of the trial arms but detected no difference using BIA (mean difference: 1.2 kg, *P* = 0.609). Similarly, Madeddu et al.[48] found improvements in LBM across both trial arms based on DEXA and CT estimates, but not with BIA.

Discussion

This systematic review summarizes the frequency and diversity of endpoints examining body weight and composition in cancer cachexia clinical trials. It is one of six systematic

Table 2 Utilization of body composition endpoints

Endpoint	No. of studies	Years of publication	Total sample size	Intervention type	Statistically significant results (between trial groups)	Intervention type
Anthropometric measures						
Body weight	68	1990–2021	11 561	Pharmacological: 37 Nutritional: 22 Exercise: 1 Multi-modal: 8	Yes: 26 No: 42	Pharmacological: 18 Nutritional: 5 Exercise/lifestyle: Multi-modal: 3
Skinfold thickness	11	1993–2016	1727	Pharmacological: 5 Nutritional: 5 Multi-modal: 1	Yes: 3 No: 8	Pharmacological: 2 Nutritional: 1
Other arm anthropometry	12	1993–2018	1321	Pharmacological: 8 Nutritional: 3 Multi-modal: 1	Yes: 2 No: 10	Pharmacological: 2
Body mass index (BMI)	13	2005–2021	917	Pharmacological: 1 Nutritional: 8 Exercise: 1 Multi-modal: 3	Yes: 2 No: 11	Nutritional: 1 Multi-modal: 1
BIA body composition						
Lean body mass	16	2003–2021	2576	Pharmacological: 8 Nutritional: 5 Exercise: 1 Multi-modal: 2	Yes: 2 No: 14	Exercise: 1 Multi-modal: 1
Fat mass	8	2012–2020	744	Pharmacological: 1 Nutritional: 4 Multi-modal: 3	Yes: 2 No: 5	Pharmacological: 1 Nutritional: 1
Fat-free mass	6	2004–2021	384	Pharmacological: 1 Nutritional: 5	Yes: 1 No: 5	Nutritional: 1
Fat-free mass index	3	2019–2020	313	Nutritional: 2 Multi-modal: 1	Yes: 2 No: 1	Nutritional: 2
DEXA body composition						
Lean body mass	14	1998–2018	2957	Pharmacological: 11 Nutritional: 1 Exercise: 1 Multi-modal: 1	Yes: 8 No: 6	Pharmacological: 8
Fat mass	11	2004–2020	2162	Pharmacological: 6 Nutritional: 2 Exercise: 2 Multi-modal: 1	Yes: 2 No: 9	Pharmacological: 2
Appendicular lean body mass	4	2015–2020	1156	Pharmacological: 2 Nutritional: 1 Exercise: 1	Yes: 3 No: 1	Pharmacological: 2 Exercise/lifestyle: 1
Total body mass	2	2015–2016	1061	Pharmacological: 2	Yes: 2	Pharmacological: 2
CT body composition						
Estimated lean body mass (L3)	2	2010–2012	392	Pharmacological: 2	Yes: 1 No: 1	Pharmacological: 1
Skeletal muscle area (L3/L4/L5)	4	2017–2021	346	Pharmacological: 1 Nutritional: 1 Multi-modal: 2	No: 4	N/A
Thigh muscle volume	1	2018	125	Pharmacological: 1	No: 1	N/A
Fat area (L4/L5)	1	2018	125	Pharmacological: 1	No: 1	N/A
Skeletal muscle index	1	2017	41	Multi-modal: 1	No: 2	N/A
Psoas muscle area (L3)	1	2019	62	Nutritional: 1	No: 1	N/A
Visceral fat area	1	2019	55	Nutritional: 1	No: 1	N/A

Note: Sample sizes are reported as per 'intention to treat'. Abbreviations: BIA, bioimpedance analysis; BMI, body mass index; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; L3/L4/L5, third/fourth/fifth lumbar vertebral level.

reviews being undertaken, with others considering physical function,[9] quality of life, appetite and dietary intake, biomarkers and oncology/survival endpoints. Assessments of body weight were the most commonly reported endpoint, used by over 80% of the included trials. Other anthropometric measures, such as skinfold thickness measurements and arm circumference, were less frequently used, especially in more contemporary trials. BIA-based estimates were often included but have been largely superseded by DEXA, especially in larger trials, and more recently by CT body composition analyses.

Body weight is the simplest and most widely available assessment that can indicate alterations to body composition and has long been regarded as a central tenet of cachexia.

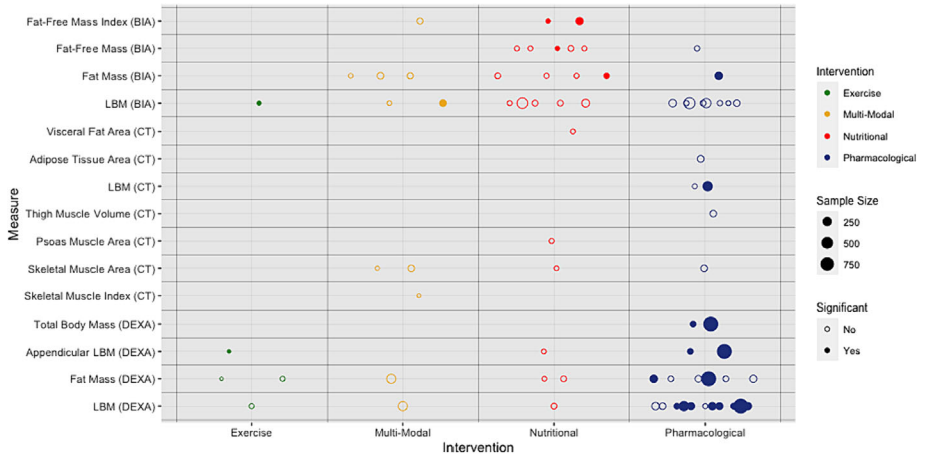

Figure 5 Summary of bioelectrical/radiological measures of body composition by intervention modality. BIA, bioimpedance analysis; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; LBM, lean body mass.

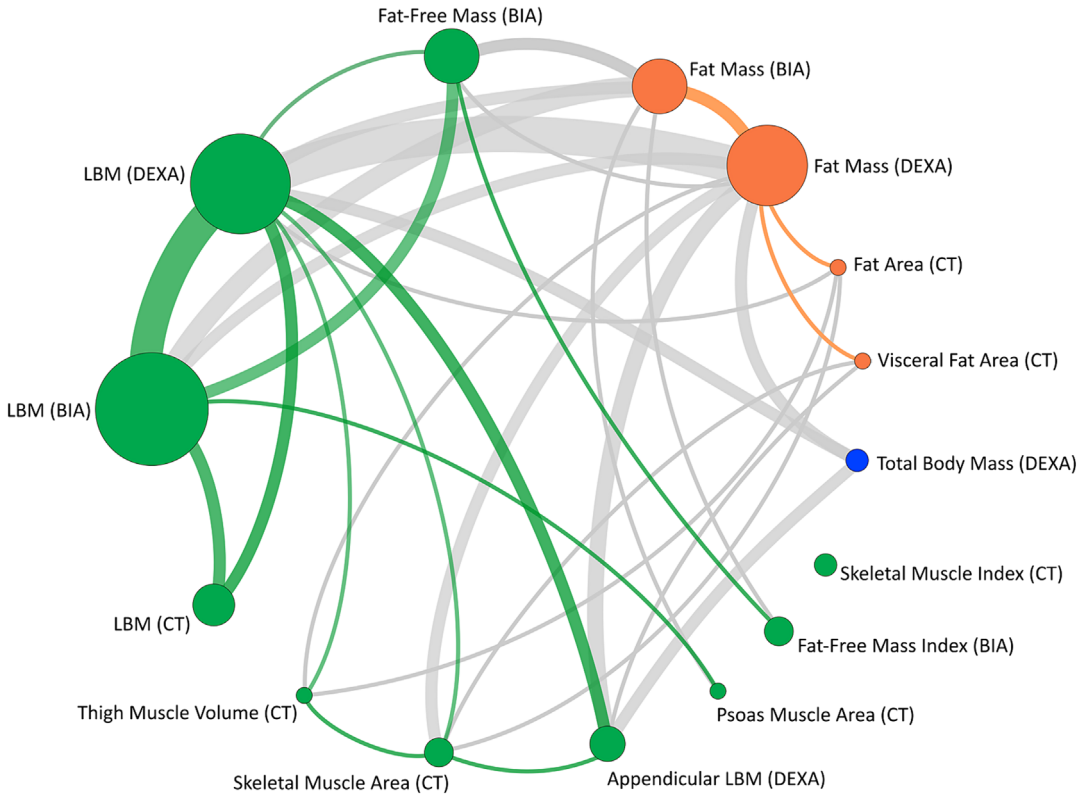

Figure 6 A network diagram illustrating combinations of reported bioelectrical/radiological endpoints. Endpoints pertaining to muscle are highlighted in green. Endpoints pertaining to fat are highlighted in orange. Green connecting lines highlight the use of two measures of muscle in the same trial. Similarly, orange lines highlight the use of two measures of fat, while grey lines indicate combinations of muscle and fat measures. The size of the nodes reflects the number of studies that have reported the endpoint. The thickness of the connecting line reflects the number of studies reporting each pair of measures. BIA, bioimpedance analysis; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; LBM, lean body mass.

Included trials have used it to create various endpoints (e.g., absolute/percentage differences from baseline or comparison between weight-stable, weight-gaining and weight-losing groups). Further study is likely required to establish consensus on which of these specific body weight endpoints is most informative. While BMI is likely a helpful baseline descriptor, given the relevance of obesity as a prognostic variable in patients with cachexia and/or sarcopenia,[95–97] the use of BMI as

an endpoint instead of, or alongside, body weight does not add value. Other simple anthropometric measures, such as triceps skinfold thickness or other arm anthropometry, were featured in earlier cachexia trials but have been used less in recent years. All of these methods pose practical advantages, such as low cost, widespread availability and ease of measurement, but provide limited information when compared with radiological methods.

Estimates of body composition using BIA have been featured as chosen endpoints for a number of the included trials. BIA measures the electrical properties of tissues (resistance and reactance), and these values can be used in equations to approximate FM/FFM/LBM. Previous studies have shown that BIA is prone to overestimation for lean mass and underestimation of FM[98] and has poor agreement with comparable DEXA[99] and CT-based measures.[100] Indeed, some of the included studies identified significant differences between trial groups on DEXA and/or CT estimates of body composition that were not evident using BIA-based estimates.[43,48,63] However, it must be noted that BIA does have several practical advantages. It uses equipment that is portable and non-invasive, making it perhaps a more attractive option for assessments in frail, incurable cachexia populations or in community-based studies where assessments may take place in non-clinical locations. As such, BIA may remain an appropriate option for particular trial settings despite its limitations.

DEXA has been widely used for assessment of lean and adipose tissue in cachexia trials to date, including amongst many of the larger studies included in this review.[11,36,43] It does not routinely feature during the clinical staging pathway for patients with cancer but is an attractive research imaging adjunct owing to its modest cost, low radiation dose and short imaging time. While DEXA estimates of LBM have shown excellent correlation with both MRI and CT,[101] there is some evidence that measures of adipose tissue using DEXA can tend towards underestimation.[102] It also lacks the specificity to assess changes in individual muscle groups and is unable to identify myosteatosis, which appears to be an important prognostic feature on CT[103] and MRI body composition analyses[6] via observational studies.

CT body composition analysis was used in eight contemporary cancer cachexia trials (2010 onwards). Within the broader literature, a large number of observational studies have evaluated the impact of low muscle quantity[104] or radiodensity[103] as per CT body composition analysis, with consistently adverse prognostication noted for patients with cancer. While only one of the included trials identified significant differences between groups using CT-based endpoints, it must be noted that similar negative findings were seen on other concurrent endpoints (including body weight, DEXA and BIA) in all but one study.[69] This is therefore likely reflective of the efficacy of the interventions used, rather than the sensitivity of the endpoint measured. Furthermore, some of the trials that included CT-based assessments used muscle groups or vertebral levels that have not yet been adequately validated to the same standard as the use of L3 cross-sectional area.[3] Other assessments, such as radiodensity or volumetric body composition analysis, remain unexplored in the cachexia trial setting. CT is a very pragmatic imaging modality for some patient groups, owing to its routine use in the clinical staging and follow-up of cancer patients. However, when research imaging requirements are in excess of clinical need, the issue of associated ionizing radiation must be duly considered. Furthermore, trial timepoints may not align with the clinical pathway. Balancing this alongside finite resources and the need to limit patient burden can be challenging. Despite the dose reductions achieved with improved technology and focused scanning,[105] the necessary radiation exposure from CT still often exceeds that of DEXA.[106] As such, when clinical imaging is not available, other assessment modalities such as MRI may be more appropriate.

Non-significant findings may result from an intervention that lacks efficacy, a trial that is inadequately powered relative to the chosen outcome or a measurement that lacks the precision to detect a true effect. With this in mind, limited inferences may be drawn regarding how a trial's significant or non-significant results may reflect on the selected endpoint(s), particularly if these are secondary endpoints that were not featured during sample size calculations. When comparing methods of body composition assessment, it is useful to consider several key measurement characteristics: reliability, validity, responsiveness to change, minimally important clinical difference and sensibility.

Reliability refers to the consistency and repeatability of a measurement when applied under similar conditions. One could consider intra-rater reliability (agreement of measures by a single evaluator on different occasions) or inter-rater reliability (agreement between different evaluators). Body weight would be expected to have excellent inter-rater reliability, owing to ease of measurement. However, achieving intra-rater reliability is dependent on consistent patient factors (e.g., clothing or fasting and hydration status) and use of the calibrated instruments. While good intra-rater and inter-rater reliability has been demonstrated for BIA, this also requires adherence to strict standardization of measurement conditions,[107] which may be difficult to achieve in real-world settings. DEXA and CT assessments of body composition may previously have been subject to lower levels of reliability, owing to their need for manual segmentation of anatomical features or regions of interest, but technological and software advancements have led to more reliable measurements now being obtained.[108] Furthermore, CT performs well during tests of precision; the ability of a measurement technique to reproduce results when performed in an identical manner.[109]

Validity refers to a method's accuracy in assessing what it is intended to measure. In the case of cachexia, researchers

are likely to be interested in changes in quantities of muscle and/or fat. This may present an obvious limitation with body weight, as it cannot inform us regarding the alterations to body composition that have led to any change in weight. This limits its use in isolation. Furthermore, the potential for fluid accumulations (e.g., ascites/peripheral oedema/hydration status) to influence body weight, BIA or even DEXA could lead to these modalities providing less valid assessments.[110] While most studies of CT body composition extrapolate single-slice measurements to estimate whole-body composition, it is not known whether wasting occurs uniformly throughout the body.[109] Analyses conducted over larger regions of interest may yet improve the validity of CT body composition.[111]

Responsiveness to change is a measure's ability to detect meaningful differences over time and is crucial for monitoring responses to trial interventions. Multiple factors can influence these parameters, and in the setting of cachexia clinical trials, it can be challenging to assess efficacy independent of confounders. While single axial slice CT (e.g., L3) and whole-body measurements are known to be highly correlated,[3] this may not hold true when assessing changes over time.[109]

A minimal clinically important difference (MCID) describes the smallest change that could be considered clinically significant. Such a metric may be determined with consideration of how changes in body composition endpoints relate to other outcomes. For example, what change in muscle mass is required to influence quality of life or survival? As has been observed with muscle mass and function,[112] the relationships between endpoints may be non-linear, and this must be acknowledged when considering responsiveness to change. The minimum body weight change that is considered clinically important for an individual's health is more commonly studied in the field of obesity than in cachexia. Semaglutide (glucagon-like peptide-1 [GLP-1] receptor agonist) was granted Food and Drug Administration (FDA) approval based on $>$5% weight loss being regarded as clinically meaningful.[113] A $>$5% weight gain may be considered an equivalent MCID for treatment of cachexia, yet such precedent has not been set thus far.

Measurements should have sensibility (or interpretability) so they can be understood with ease. Body weight is meaningful and can be easily interpreted by clinicians, researchers and even patients. Conversely, bioelectrical estimates of body composition are less well known, and as such, the sensibility of these is limited. With improved consensus regarding effective assessment methods and endpoints, it should be anticipated that relevant stakeholders will become more informed regarding their chosen measurement techniques and how their findings relate to patients.

It is evident that no single assessment method currently fulfils all requirements. Rather, researchers should choose appropriate endpoints to align with their study aims and the cohort in question. What represents the 'gold-standard' measure would be dependent on the choice of intervention and its underlying mechanism. Assessment of body weight alongside dietary intake may be reasonable when assessing an appetite stimulant and has the added advantage of having regulatory approval in the obesity arena. Similarly, assessing DEXA or CT-based body composition would be sensible when trialling an exercise intervention aimed to improve lean mass. The practicalities, including cost and participant burden, mean that assessing these in clinical trials may be aspirational, despite a clear need.

A large volume of data has been compiled through each of the six reviews undertaken within this series. While there was a need to give a detailed appraisal within each of these, further work is ongoing to examine the relationships between these parameters. The findings presented are likely to have even greater value when considered in the context of other endpoints. For example, how do improvements in lean mass relate to physical function? The group aspires towards achieving a wider consensus alongside the identification and prioritization of areas for future research. Key strengths of this review include the broad search criteria and the robust methodological approach and appraisal process. However, the eligibility criteria could be considered a limitation, as balance was sought between the need to find trials of sufficient quality against having to appraise an impractical number of manuscripts. Although a specific time period was defined for the purposes of this work, it is accepted that trials published before 1990 may have yielded additional data, though this would pre-date the use of most endpoints considered by this review. The sample size cut-off was felt to be appropriate, as trials with $<$40 participants were expected to be insufficiently powered to assess changes in the endpoints being assessed. Furthermore, the minimum intervention time of 14 days was selected as interventions conducted for a shorter duration were felt unlikely to influence the disease course of cachexia. It should be acknowledged, however, that these restrictions may have precluded the inclusion of some informative trials. While the focus of this review was prospective, interventional trials, it is also acknowledged that many high-quality studies of other designs may yet inform the process of establishing a consensus regarding the optimum endpoints for cachexia trials, and future review of these would also be informative.

Endpoints should be intrinsically linked to inclusion criteria and vice versa. Changes in body composition are a key feature of cancer cachexia and, therefore, by definition, often feature as a baseline descriptive criterion (and, thus, outcome measure) in cachexia intervention trials. The Global Leadership Initiative on Malnutrition (GLIM) consensus criteria[114] were not designed to be used for the diagnosis of cachexia; however, they are intended to complement the existing cachexia literature, acknowledging that all patients with cachexia would meet their diagnosis of malnutrition. This group agreed that a body composition-based phenotypical criterion (weight loss,

low BMI or reduced muscle mass) and an aetiological criterion (reduced food intake/assimilation or inflammation) are required for a diagnosis of malnutrition. Their recommendation for methods of estimating low muscle mass was for DEXA or 'corresponding standards using other body composition methods like BIA, CT or MRI'. The group also stated that anthropometric measures, such as arm muscle circumference, may be used as an alternative when radiological imaging is unavailable. Similarly, broad assessment methodology was proposed by the European consensus definition for sarcopenia,[5] with DEXA, BIA, CT and MRI all listed as options for evaluating 'muscle quantity or quality'. As shown in this present review, the range of modalities within the guidance is reflective of the heterogeneity within the existing literature.

Conclusions

Based on the findings presented herein, the use of body weight alongside a radiological modality for body composition analysis would seem like suitable endpoints for cancer cachexia trials. Thus far, body weight has been reported in a variety of ways, and further consensus is required regarding the specific body weight endpoint that should be used for future trials. The choice of radiological modality is likely to be dependent on the trial setting, population and intervention in question. When available, CT imaging is a well-validated and often pragmatic option that provides good levels of detail regarding body composition. Through ongoing exploration of this, and other assessment methods such as MRI,[110] further evidence is likely to emerge that will help standardize the appraisal of body composition. Endpoint heterogeneity in cancer cachexia clinical trials has greatly contributed to the lack of approved treatments by regulatory authorities.[115] Moreover, discrepancies between clinicians, regulatory industries and patients' perspectives regarding the most clinically relevant endpoints in cancer cachexia remain challenging. It is vital that consensus is achieved to ensure reporting consistency and maximize the efficacy of upcoming trials aiming to counteract the devastating effects of cancer cachexia.

Conflict of interest statement

LRB, MSS, MSY, VEB, DCM, AB, TRB, OD, RDD, MTF, CG, MJH, GJ, MM, JM, IOO, IP, JS, MRS, OMV and TSS have none to declare. JA has received lecture fees from Baxter and Danone. RJES has received personal fees for consultancy from Avidity Biosciences, Actimed, Faraday and Helsinn. BJAL has received personal fees for consultancy from Artelo, Actimed, Faraday, Kyowa Kirin and Toray.

References

1. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;**12**:489–495.
2. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. *Nat Rev Dis Primers* 2018;**4**:17105.
3. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* 2008;**33**:997–1006.
4. Fearon KCH. Cancer cachexia and fat–muscle physiology. *N Engl J Med* 2011; **365**:565–567.
5. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019;**48**:16–31.
6. Faron A, Sprinkart AM, Kuetting DLR, Feisst A, Isaak A, Endler C, et al. Body composition analysis using CT and MRI: intra-individual intermodal comparison of muscle mass and myosteatosis. *Sci Rep* 2020;**10**:11765.
7. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *BMJ* 2009; **339**.
8. Solheim T, Laird B, Skipworth RJE, Fallon M, Kaasa S, Dajani O. *A systematic literature review examining endpoints for cancer cachexia trials*. PROSPERO; 2022. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022276710.
9. McDonald J, Sayers J, Anker SD, Arends J, Balstad TR, Baracos V, et al. Physical function endpoints in cancer cachexia clinical trials: Systematic Review 1 of the cachexia endpoints series. *J Cachexia Sarcopenia Muscle* 2023;**14**:13321.
10. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;**52**:377–384.
11. Temel JS, Abernethy AP, Currow DC, Friend J, Duus EM, Yan Y, et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. *Lancet Oncol* 2016;**17**:519–531.
12. Kardinal CG, Loprinzi CL, Schaid DJ, Curtis Hass A, Dose AM, Athmann LM, et al. A controlled trial of cyproheptadine in cancer patients with anorexia and/or cachexia. *Cancer* 1990;**65**:2657–2662.
13. Loprinzi CL, Ellison NM, Schaid DJ, Krook JE, Athmann LM, Dose AM, et al. Controlled trial of megestrol acetate for the treatment of cancer anorexia and cachexia. *JNCI J Natl Cancer Inst* 1990;**82**: 1127–1132.
14. Feliu J, González-Barón M, Berrocal A, Artal A, Ordóñez A, Garrido P, et al. Usefulness of megestrol acetate in cancer cachexia and anorexia: a placebo-controlled study. *Am J Clin Oncol* 1992;**15**:436–440.
15. Downer S, Joel S, Allbright A, Plant H, Stubbs L, Talbot D, et al. A double blind placebo controlled trial of medroxyprogesterone acetate (MPA) in cancer cachexia. *Br J Cancer* 1993;**67**:1102–1105.
16. Loprinzi CL, Michalak JC, Schaid DJ, Mailliard JA, Athmann LM, Goldberg RM, et al. Phase III evaluation of four doses of megestrol acetate as therapy for patients with cancer anorexia and/or cachexia. *JCO* 1993;**11**:762–767.
17. Ovesen L, Allingstrup L, Hannibal J, Mortensen EL, Hansen OP. Effect of dietary counseling on food intake, body weight, response rate, survival, and qual-

ity of life in cancer patients undergoing chemotherapy: a prospective, randomized study. *JCO* 1993;**11**: 2043–2049.
18. Goldberg RM, Loprinzi CL, Mailliard JA, O'Fallon JR, Krook JE, Ghosh C, et al. Pentoxifylline for treatment of cancer anorexia and cachexia? A randomized, double-blind, placebo-controlled trial. *JCO* 1995;**13**:2856–2859.
19. Gebbia V, Testa A, Gebbia N. Prospective randomised trial of two dose levels of megestrol acetate in the management of anorexia-cachexia syndrome in patients with metastatic cancer. *Br J Cancer* 1996; **73**:1576–1580.
20. Lissoni P, Paolorossi F, Tancini G, Barni S, Ardizzoia A, Brivio F, et al. Is there a role for melatonin in the treatment of neoplastic cachexia? *Eur J Cancer* 1996;**32**: 1340–1343.
21. Simons JP, Aaronson NK, Vansteenkiste JF, ten Velde GP, Muller MJ, Drenth BM, et al. Effects of medroxyprogesterone acetate on appetite, weight, and quality of life in advanced-stage non-hormone-sensitive cancer: a placebo-controlled multicenter study. *JCO* 1996;**14**: 1077–1084.
22. Beller E, Tattersall M, Lumley T, Levi J, Dalley D, Olver I, et al. Improved quality of life with megestrol acetate in patients with endocrine-insensitive advanced cancer: a randomised placebo-controlled trial. *Ann Oncol* 1997;**8**:277–283.
23. Chen HC, Leung SW, Wang CJ, Sun LM, Fang FM, Hsu JH. Effect of megestrol acetate and prepulsid on nutritional improvement in patients with head and neck cancers undergoing radiotherapy. *Radiother Oncol* 1997;**43**:75–79.
24. Daneryd P, Svanberg E, Körner U, Lindholm E, Sandström R, Brevinge H, et al. Protection of metabolic and exercise capacity in unselected weight-losing cancer patients following treatment with recombinant erythropoietin: a randomized prospective study. *Cancer Res* 1998;**58**: 5374–5379.
25. De Conno F, Martini C, Zecca E, Balzarini A, Venturino P, Groff L, et al. Megestrol acetate for anorexia in patients with far-advanced cancer: a double-blind controlled clinical trial. *Eur J Cancer* 1998; **34**:1705–1709.
26. Vadell C, Seguí MA, Giménez-Arnau JM, Morales S, Cirera L, Bestit I, et al. Anticachectic efficacy of megestrol acetate at different doses and versus placebo in patients with neoplastic cachexia. *Am J Clin Oncol* 1998;**21**:347–351.
27. Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, Krook JE, Wilwerding MB, et al. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *JCO* 1999;**17**: 3299–3306.
28. McMillan DC, Wigmore SJ, Wigmore KCH, O'Gorman P, Wright CE, McArdle CS. A prospective randomized study of megestrol acetate and ibuprofen in gastrointestinal cancer patients with weight loss. *Br J Cancer* 1999;**79**:495–500.
29. Westman G, Bergman B, Albertsson M, Kadar L, Gustavsson G, Thaning L, et al. Megestrol acetate in advanced, progressive, hormone-insensitive cancer. Effects on the quality of life: a placebo-controlled, randomised, multicentre trial. *Eur J Cancer* 1999;**35**:586–595.
30. Jatoi A, Windschitl HE, Loprinzi CL, Sloan JA, Dakhil SR, Mailliard JA, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *JCO* 2002;**20**: 567–573.
31. Persson CR, Johansson BBK, Sjoden PO, Glimelius BLG. A randomized study of nutritional support in patients with colorectal and gastric cancer. *Nutr Cancer* 2002; **42**:48–58.
32. Ulutin HC, Arpaci F, Pak Y. Megestrol acetate for cachexia and anorexia in advanced non-small cell lung cancer: a randomized study comparing two different doses. *Tumori* 2002;**88**:277–280.
33. Bruera E, Strasser F, Palmer JL, Willey J, Calder K, Amyotte G, et al. Effect of fish oil on appetite and other symptoms in patients with advanced cancer and anorexia/cachexia: a double-blind, placebo-controlled study. *J Clin Oncol* 2003;**21**: 129–134.
34. Fearon KCH, von Meyenfeldt MF, Moses AGW, van Geenen R, Roy A, Gouma DJ, et al. Effect of a protein and energy dense n-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. *Gut* 2003;**52**:1479–1486.
35. Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer* 2004;**91**:447–452.
36. Lundholm K, Daneryd P, Bosaeus I, Körner U, Lindholm E. Palliative nutritional intervention in addition to cyclooxygenase and erythropoietin treatment for patients with malignant disease: effects on survival, metabolism, and function: a randomized prospective study. *Cancer* 2004; **100**:1967–1977.
37. Gonçalves Dias MC, de Fátima Nunes Marucci M, Nadalin W, Waitzberg DL. Nutritional intervention improves the caloric and proteic ingestion of head and neck cancer patients under radiotherapy. *Nutr Hosp* 2005;**20**:320–325.
38. Gordon JN, Trebble TM, Ellis RD, Duncan HD, Johns T, Goggin PM. Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. *Gut* 2005;**54**:540–545.
39. Fearon KCH, Barber MD, Moses AG, Ahmedzai SH, Taylor GS, Tisdale MJ, et al. Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. *JCO* 2006;**24**:3401–3407.
40. Berk L, James J, Schwartz A, Hug E, Mahadevan A, Samuels M, et al. A randomized, double-blind, placebo-controlled trial of a β-hydroxyl β-methyl butyrate, glutamine, and arginine mixture for the treatment of cancer cachexia (RTOG 0122). *Support Care Cancer* 2008;**16**: 1179–1188.
41. Wiedenmann B, Malfertheiner P, Friess H, Ritch P, Arseneau J, Mantovani G, et al. A multicenter, phase II study of infliximab plus gemcitabine in pancreatic cancer cachexia. *J Support Oncol* 2008;**6**:18–25.
42. Beijer S, Hupperets PS, van den Borne BE, Eussen SR, van Henten AM, van den Beuken-van EM, et al. Effect of adenosine 5'-triphosphate infusions on the nutritional status and survival of preterminal cancer patients. *Anticancer Drugs* 2009; **20**:625–633.
43. Mantovani G, Macciò A, Madeddu C, Serpe R, Massa E, Dessì M, et al. Randomized phase III clinical trial of five different arms of treatment in 332 patients with cancer cachexia. *Oncologist* 2010;**15**: 200–211.
44. Navari RM, Brenner MC. Treatment of cancer-related anorexia with olanzapine and megestrol acetate: a randomized trial. *Support Care Cancer* 2010;**18**: 951–956.
45. Baldwin C, Spiro A, McGough C, Norman AR, Gillbanks A, Thomas K, et al. Simple nutritional intervention in patients with advanced cancers of the gastrointestinal tract, non-small cell lung cancers or mesothelioma and weight loss receiving chemotherapy: a randomised controlled trial. *J Hum Nutr Diet* 2011;**24**:431–440.
46. Kraft M, Kraft K, Gärtner S, Mayerle J, Simon P, Weber E, et al. L-Carnitine-supplementation in advanced pancreatic cancer (CARPAN)—a randomized multicentre trial. *Nutr J* 2012;**11**:52.
47. Macciò A, Madeddu C, Gramignano G, Mulas C, Floris C, Sanna E, et al. A randomized phase III clinical trial of a combined treatment for cachexia in patients with gynecological cancers: evaluating the impact on metabolic and inflammatory profiles and quality of life. *Gynecol Oncol* 2012;**124**:417–425.
48. Madeddu C, Dessì M, Panzone F, Serpe R, Antoni G, Cau MC, et al. Randomized phase III clinical trial of a combined treatment with carnitine + celecoxib ± megestrol acetate for patients with cancer-related anorexia/cachexia syndrome. *Clin Nutr* 2012;**31**:176–182.
49. Silander E, Nyman J, Bove M, Johansson L, Larsson S, Hammerlid E. Impact of prophylactic percutaneous endoscopic gastrostomy on malnutrition and quality of life in patients with head and neck cancer—a randomized study. *Head Neck* 2012;**34**:1–9.
50. Wen HS, Li X, Cao YZ, Zhang CC, Yang F, Shi YM, et al. Clinical studies on the treatment of cancer cachexia with megestrol acetate plus thalidomide. *Chemotherapy* 2012;**58**:461–467.
51. Del Fabbro E, Dev R, Hui D, Palmer L, Bruera E. Effects of melatonin on appetite and other symptoms in patients with ad-

vanced cancer and cachexia: a double-blind placebo-controlled trial. *JCO* 2013; **31**:1271–1276.
52. Dobs AS, Boccia RV, Croot CC, Gabrail NY, Dalton JT, Hancock ML, et al. Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. *Lancet Oncol* 2013;**14**: 335–345.
53. Kanat O, Cubukcu E, Avci N, Budak F, Ercan I, Canhoroz M, et al. Comparison of three different treatment modalities in the management of cancer cachexia. *Tumori* 2013;**99**:229–233.
54. Poulsen GM, Pedersen LL, Østerlind K, Bæksgaard L, Andersen JR. Randomized trial of the effects of individual nutritional counseling in cancer patients. *Clin Nutr* 2014;**33**:749–753.
55. Bourdel-Marchasson I, Blanc-Bisson C, Doussau A, Germain C, Blanc JF, Dauba J, et al. Nutritional advice in older patients at risk of malnutrition during treatment for chemotherapy: a two-year randomized controlled trial. Wong V, editor. *PLoS ONE*. 2014;**9**(9):e108687.
56. Pottel L, Lycke M, Boterberg T, Pottel H, Goethals L, Duprez F, et al. Echium oil is not protective against weight loss in head and neck cancer patients undergoing curative radio(chemo)therapy: a randomised-controlled trial. *BMC Complement Altern Med* 2014;**14**:382.
57. Focan C, Houbiers G, Gilles L, Steeland TV, Georges N, Maniglia A, et al. Dietetic and psychological mindfulness workshops for the management of cachectic cancer patients. A randomized study. *Anticancer Res* 2015;**3**:5.
58. Garcia JM, Boccia RV, Graham CD, Yan Y, Duus EM, Allen S, et al. Anamorelin for patients with cancer cachexia: an integrated analysis of two phase 2, randomised, placebo-controlled, double-blind trials. *Lancet Oncol* 2015;**16**: 108–116.
59. Capozzi LC, McNeely ML, Lau HY, Reimer RA, Giese-Davis J, Fung TS, et al. Patient-reported outcomes, body composition, and nutrition status in patients with head and neck cancer: results from an exploratory randomized controlled exercise trial. *Cancer* 2016;**122**:1185–1200.
60. Kapoor N, Naufahu J, Tewfik S, Bhatnagar S, Garg R, Tewfik I. A prospective randomized controlled trial to study the impact of a nutrition-sensitive intervention on adult women with cancer cachexia undergoing palliative care in India. *Integr Cancer Ther* 2017;**16**:74–84.
61. Mehrzad V, Afshar R, Akbari M. Pentoxifylline treatment in patients with cancer cachexia: a double-blind, randomized, placebo-controlled clinical trial. *Adv Biomed Res* 2016;**5**:60.
62. Stewart Coats AJ, Ho GF, Prabhash K, Haehling S, Tilson J, Brown R, et al. Espindolol for the treatment and prevention of cachexia in patients with stage III/IV non-small cell lung cancer or colorectal cancer: a randomized, double-blind, placebo-controlled, international multicentre phase II study (the ACT-ONE trial). *J Cachexia Sarcopenia Muscle* 2016;**7**:355–365.
63. Takayama K, Katakami N, Yokoyama T, Atagi S, Yoshimori K, Kagamu H, et al. Anamorelin (ONO-7643) in Japanese patients with non-small cell lung cancer and cachexia: results of a randomized phase 2 trial. *Support Care Cancer* 2016; **24**:3495–3505.
64. Woo SM, Joo J, Kim SY, Park SJ, Han SS, Kim TH, et al. Efficacy of pancreatic exocrine replacement therapy for patients with unresectable pancreatic cancer in a randomized trial. *Pancreatology* 2016;**16**: 1099–1105.
65. Currow D, Temel JS, Abernethy A, Milanowski J, Friend J, Fearon KC. ROMANA 3: a phase 3 safety extension study of anamorelin in advanced non-small-cell lung cancer (NSCLC) patients with cachexia. *Ann Oncol* 2017;**28**: 1949–1956.
66. Jatoi A, Steen PD, Atherton PJ, Moore DF, Rowland KM, Le-Lindqwister NA, et al. A double-blind, placebo-controlled randomized trial of creatine for the cancer anorexia/weight loss syndrome (N02C4): an Alliance trial. *Ann Oncol* 2017;**28**: 1957–1963.
67. Leedo E, Gade J, Granov S, Mellemgaard A, Klausen TW, Rask K, et al. The effect of a home delivery meal service of energy- and protein-rich meals on quality of life in malnourished outpatients suffering from lung cancer: a randomized controlled trial. *Nutr Cancer* 2017;**69**: 444–453.
68. Sandmael JA, Bye A, Solheim TS, Stene GB, Thorsen L, Kaasa S, et al. Feasibility and preliminary effects of resistance training and nutritional supplements during versus after radiotherapy in patients with head and neck cancer: a pilot randomized trial. *Cancer* 2017;**123**: 4440–4448.
69. Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. *J Cachexia Sarcopenia Muscle* 2017;**8**: 778–788.
70. Werner K, Küllenberg de Gaudry D, Taylor LA, Keck T, Unger C, Hopt UT, et al. Dietary supplementation with n-3-fatty acids in patients with pancreatic cancer and cachexia: marine phospholipids versus fish oil—a randomized controlled double-blind trial. *Lipids Health Dis* 2017; **16**:104.
71. Ziętarska M, Krawczyk-Lipiec J, Kraj L, Zaucha R, Małgorzewicz S. Chemotherapy-related toxicity, nutritional status and quality of life in precachectic oncologic patients with, or without, high protein nutritional support. A prospective, randomized study. *Nutrients* 2017;**9**:1108.
72. Golan T, Geva R, Richards D, Madhusudan S, Lin BK, Wang HT, et al. LY2495655, an antimyostatin antibody, in pancreatic cancer: a randomized, phase 2 trial. *J Cachexia Sarcopenia Muscle* 2018;**9**: 871–879.
73. Katakami N, Uchino J, Yokoyama T, Naito T, Kondo M, Yamada K, et al. Anamorelin (ONO-7643) for the treatment of patients with non-small cell lung cancer and cachexia: results from a randomized, double-blind, placebo-controlled, multicenter study of Japanese patients (ONO-7643-04). *Cancer* 2018;**124**:606–616.
74. Kouchaki B, Janbabai G, Alipour A, Ala S, Borhani S, Salehifar E. Randomized double-blind clinical trial of combined treatment with megestrol acetate plus celecoxib versus megestrol acetate alone in cachexia-anorexia syndrome induced by GI cancers. *Support Care Cancer* 2018; **26**:2479–2489.
75. Schink K, Herrmann HJ, Schwappacher R, Meyer J, Orlemann T, Waldmann E, et al. Effects of whole-body electromyostimulation combined with individualized nutritional support on body composition in patients with advanced cancer: a controlled pilot trial. *BMC Cancer* 2018;**18**:886.
76. Uster A, Ruehlin M, Mey S, Gisi D, Knols R, Imoberdorf R, et al. Effects of nutrition and physical exercise intervention in palliative cancer patients: a randomized controlled trial. *Clin Nutr* 2018;**37**: 1202–1209.
77. Xie M, Chen X, Qin S, Bao Y, Bu K, Lu Y. Clinical study on thalidomide combined with cinobufagin to treat lung cancer cachexia. *J Can Res Ther* 2018;**14**:226–232.
78. Akita H, Takahashi H, Asukai K, Tomokuni A, Wada H, Marukawa S, et al. The utility of nutritional supportive care with an eicosapentaenoic acid (EPA)-enriched nutrition agent during pre-operative chemoradiotherapy for pancreatic cancer: prospective randomized control study. *Clin Nutr ESPEN* 2019;**33**:148–153.
79. Britton B, Baker AL, Wolfenden L, Wratten C, Bauer J, Beck AK, et al. Eating As Treatment (EAT): a stepped-wedge, randomized controlled trial of a health behavior change intervention provided by dietitians to improve nutrition in patients with head and neck cancer undergoing radiation therapy (TROG 12.03). *Int J Radiat Oncol*Biology*Phys* 2019;**103**:353–362.
80. Cereda E, Turri A, Klersy C, Cappello S, Ferrari A, Filippi AR, et al. Whey protein isolate supplementation improves body composition, muscle strength, and treatment tolerance in malnourished advanced cancer patients undergoing chemotherapy. *Cancer Med* 2019;**8**: 6923–6932.
81. Laviano A, Calder PC, Schols AMWJ, Lonnqvist F, Bech M, Muscaritoli M. Safety and tolerability of targeted medical nutrition for cachexia in non-small-cell lung cancer: a randomized, double-blind, controlled pilot trial. *Controlled Pilot Trial Nutr Cancer* 2020;**72**:439–450.
82. Obling SR, Wilson BV, Pfeiffer P, Kjeldsen J. Home parenteral nutrition increases fat free mass in patients with incurable

gastrointestinal cancer. Results of a randomized controlled trial. *Clin Nutr* 2019; **38**:182–190.
83. Stuecher K, Bolling C, Vogt L, Niederer D, Schmidt K, Dignaß A, et al. Exercise improves functional capacity and lean body mass in patients with gastrointestinal cancer during chemotherapy: a single-blind RCT. *Support Care Cancer* 2019;**27**: 2159–2169.
84. Wiskemann J, Clauss D, Tjaden C, Hackert T, Schneider L, Ulrich CM, et al. Progressive resistance training to impact physical fitness and body weight in pancreatic cancer patients: a randomized controlled trial. *Pancreas* 2019;**48**:257–266.
85. Bouleuc C, Anota A, Cornet C, Grodard G, Thiery-Vuillemin A, Dubroeucq O, et al. Impact on health-related quality of life of parenteral nutrition for patients with advanced cancer cachexia: results from a randomized controlled trial. *Oncologist* 2020;**25**:e843–e851.
86. Huang S, Piao Y, Cao C, Chen J, Sheng W, Shu Z, et al. A prospective randomized controlled trial on the value of prophylactic oral nutritional supplementation in locally advanced nasopharyngeal carcinoma patients receiving chemo-radiotherapy. *Oral Oncol* 2020;**111**:105025.
87. Kamel FH, Basha MA, Alsharidah AS, Salama AB. Resistance training impact on mobility, muscle strength and lean mass in pancreatic cancer cachexia: a randomized controlled trial. *Clin Rehabil* 2020; **34**:1391–1399.
88. Movahed S, Seilanian Toussi M, Pahlavani N, Motlagh AG, Eslami S, Nematy M, et al. Effects of medical nutrition therapy compared with general nutritional advice on nutritional status and nutrition-related complications in esophageal cancer patients receiving concurrent chemoradiation: a randomized controlled trial. *MNM* 2020;**13**:265–276.
89. Qiu Y, You J, Wang K, Cao Y, Hu Y, Zhang H, et al. Effect of whole-course nutrition management on patients with esophageal cancer undergoing concurrent chemoradiotherapy: a randomized control trial. *Nutrition* 2020;**69**:110558.
90. Storck LJ, Ruehlin M, Gaeumann S, Gisi D, Schmocker M, Meffert PJ, et al. Effect of a leucine-rich supplement in combination with nutrition and physical exercise in advanced cancer patients: a randomized controlled intervention trial. *Clin Nutr* 2020;**39**:3637–3644.
91. Currow DC, Glare P, Louw S, Martin P, Clark K, Fazekas B, et al. A randomised, double blind, placebo-controlled trial of megestrol acetate or dexamethasone in treating symptomatic anorexia in people with advanced cancer. *Sci Rep* 2021;**11**: 2421.
92. Hunter CN, Abdel-Aal HH, Elsherief WA, Farag DE, Riad NM, Alsirafy SA. Mirtazapine in cancer-associated anorexia and cachexia: a double-blind placebo-controlled randomized trial. *J Pain Symptom Manage* 2021;**62**:1207–1215.
93. Kutz LM, Abel J, Schweizer D, Tribius S, Krüll A, Petersen C, et al. Quality of life, HPV-status and phase angle predict survival in head and neck cancer patients under (chemo)radiotherapy undergoing nutritional intervention: results from the prospective randomized HEADNUT-trial. *Radiother Oncol* 2022;**166**:145–153.
94. Tobberup R, Carus A, Rasmussen HH, Falkmer UG, Jorgensen MG, Schmidt EB, et al. Feasibility of a multimodal intervention on malnutrition in patients with lung cancer during primary anti-neoplastic treatment. *Clin Nutr* 2021;**40**:525–533.
95. Gao Q, Hu K, Gao J, Shang Y, Mei F, Zhao L, et al. Prevalence and prognostic value of sarcopenic obesity in patients with cancer: a systematic review and meta-analysis. *Nutrition* 2022;**101**:111704.
96. Donini LM, Busetto L, Bischoff SC, Cederholm T, Ballesteros-Pomar MD, Batsis JA, et al. Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO consensus statement. *Clin Nutr* 2022;321–335.
97. Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. *JCO* 2015; **33**:90–99.
98. McLester CN, Nickerson BS, Kliszczewicz BM, McLester JR. Reliability and agreement of various InBody body composition analyzers as compared to dual-energy X-ray absorptiometry in healthy men and women. *J Clin Densitom* 2020;**23**:443–450.
99. Buckinx F, Reginster JY, Dardenne N, Croisiser JL, Kaux JF, Beaudart C, et al. Concordance between muscle mass assessed by bioelectrical impedance analysis and by dual energy X-ray absorptiometry: a cross-sectional study. *BMC Musculoskelet Disord* 2015;**16**:60.
100. Hansen C, Tobberup R, Rasmussen HH, Delekta AM, Holst M. Measurement of body composition: agreement between methods of measurement by bioimpedance and computed tomography in patients with non-small cell lung cancer. *Clin Nutr ESPEN* 2021;**44**:429–436.
101. Buckinx F, Landi F, Cesari M, Fielding RA, Visser M, Engelke K, et al. Pitfalls in the measurement of muscle mass: a need for a reference standard. *J Cachexia Sarcopenia Muscle* 2018;**9**:269–278.
102. Kullberg J, Brandberg J, Angelhed JE, Frimmel H, Bergelin E, Strid L, et al. Whole-body adipose tissue analysis: comparison of MRI, CT and dual energy X-ray absorptiometry. *BJR* 2009;**82**:123–130.
103. Aleixo GFP, Shachar SS, Nyrop KA, Muss HB, Malpica L, Williams GR. Myosteatosis and prognosis in cancer: systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2020;**145**:102839.
104. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: a meta-analysis and systematic review. *Eur J Cancer* 2016;**57**:58–67.
105. Smith-Bindman R, Wang Y, Chu P, Chung R, Einstein AJ, Balcombe J, et al. International variation in radiation dose for computed tomography examinations: prospective cohort study. *BMJ* 2019;**2**:k4931.
106. Blake GM, Naeem M, Boutros M. Comparison of effective dose to children and adults from dual X-ray absorptiometry examinations. *Bone* 2006;**38**:935–942.
107. Koch B, Miller A, Glass NA, Owen E, Kirkpatrick T, Grossman R, et al. Reliability of multifrequency bioelectrical impedance analysis to quantify body composition in patients after musculoskeletal trauma. *Iowa Orthop J* 2022;**42**:75–82.
108. Cespedes Feliciano EM, Popuri K, Cobzas D, Baracos VE, Beg MF, Khan AD, et al. Evaluation of automated computed tomography segmentation to assess body composition and mortality associations in cancer patients. *J Cachexia Sarcopenia Muscle* 2020;**11**:1258–1269.
109. Arribas L, Sabaté-Llobera A, Domingo MC, Taberna M, Sospedra M, Martin L, et al. Assessing dynamic change in muscle during treatment of patients with cancer: precision testing standards. *Clin Nutr* 2022;**41**:1059–1065.
110. Han J, Harrison L, Patzelt L, Wu M, Junker D, Herzig S, et al. Imaging modalities for diagnosis and monitoring of cancer cachexia. *EJNMMI Res* 2021;**11**:94.
111. Anyene I, Caan B, Williams GR, Popuri K, Lenchik L, Giri S, et al. Body composition from single versus multi-slice abdominal computed tomography: concordance and associations with colorectal cancer survival. *J Cachexia Sarcopenia Muscle* 2022;**13**:13080.
112. Ramage MI, Skipworth RJE. The relationship between muscle mass and function in cancer cachexia: smoke and mirrors? *Curr Opin Support Palliat Care* 2018;**12**: 439–444.
113. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021; **384**:989–1002.
114. Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition—a consensus report from the global clinical nutrition community. *J Cachexia Sarcopenia Muscle* 2019;**10**: 207–217.
115. Fearon K, Argiles J, Baracos V, Bernabei R, Coats A, Crawford J, et al. Request for regulatory guidance for cancer cachexia intervention trials. *J Cachexia Sarcopenia Muscle* 2015;**6**:272–274.

Appendix A: Literature search strategy

1 Documentation on the literature search for 'What is the optimal endpoint to evaluate effect of interventions aiming to treat cancer cachexia?'

The following databases were searched:

Database	Number of retrieved references for trials	Number of retrieved references for cohort/longitudinal studies
MEDLINE (Ovid)	3812	1918
Embase (Ovid)	2033	2031
Cochrane Central Register of Controlled Trials	1923	
Number of references before de-duplication	8166	3949
Number of references after de-duplication	5998	3190

All searches were done on 2 June 2021 by Gunn Kleven, senior librarian at the Library of Medicine and Science, University of Oslo.

Number of hours spent: 30

Ovid MEDLINE® ALL 1946 to 1 July 2021

Date searched: 2 June 2021

Search strategy:

#	Searches	Results
1	exp Neoplasms/or (neoplasm* or cancer* or tumor* or tumour* or oncol* or malign* or carcinom* or adenocarcinom* or adenoma or metasta*).ti,ab,kf.	4 606 655
2	Cachexia/ or Emaciation/ or Malnutrition/ or Starvation/ or Wasting syndrome/ or Thinness/ or Sarcopenia/ or Anorexia/or *Weight Loss/	63 432
3	and/1-2	9650
4	((cachexia or cachexic or anorexia or anorectic or emaciat* or malnutrition or underweight or starvation* or thiness or leanness or sarcopenia or wasting syndrome* or wasting disease* or weightloss* or ((appetite* or weight) adj2 (loss or loosing or losing))) adj4 (neoplasm* or cancer* or tumor* or tumour* or oncol* or malign* or carcinom* or adenocarcinom* or adenoma or metasta*)).ti,ab,kf.	7231
5	((cachexia or cachexic or anorexia or anorectic or emaciat* or malnutrition or underweight or starvation* or thiness or leanness or sarcopenia or wasting syndrome* or wasting disease* or weightloss* or ((appetite* or weight) adj2 (loss or loosing or losing))) and (neoplasm* or cancer* or tumor* or tumour* or oncol* or malign* or carcinom* or adenocarcinom* or adenoma or metasta*)).ti.	4253
6	or/3-5	13 924
7	randomized controlled trial.pt.	536 354
8	controlled clinical trial.pt.	94 265
9	randomized.ab.	525 221
10	placebo.ab.	219 320
11	drug therapy.fs.	2 343 029
12	randomly.ab.	360 557
13	trial.ab.	557 904
14	groups.ab.	2 213 680
15	or/7-14	5 047 938
16	exp animals/not humans.sh.	4 855 037
17	15 not 16	4 388 865
18	6 and 17	4078
19	limit 18 to yr = '1990-Current'	3812
20	cohort studies/ or follow-up studies/ or longitudinal studies/ or 'national longitudinal study of adolescent health'/ or prospective studies/or retrospective studies/	2 168 707
21	(cohort* or longitudinal or prospective* or retrospective*).tw.	2 098 508
22	or/20-21	3 012 965
23	and/6,22	3215
24	limit 23 to yr = '1990-Current'	3139
25	24 not 19	1918
26	19 or 24	5730

Embase Classic + Embase 1947 to 1 July 2021
Date searched: 2 June 2021
Search strategy:

#	Searches	Results
1	exp neoplasm/or (neoplasm* or cancer* or tumor* or tumour* or oncol* or malign* or carcinom* or adenocarcinom* or adenoma or metasta*).ti,ab,kw.	6 400 926
2	cachexia/ or emaciation/ or *malnutrition/ or starvation/ or wasting syndrome/ or *anorexia/ or sarcopenia/or *weight loss/	93 608
3	and/1-2	20 654
4	((cachexia or cachexic or anorexia or anorectic or emaciat* or malnutrition or underweight or starvation* or thiness or leanness or sarcopenia or wasting syndrome* or wasting disease* or weightloss* or ((appetite* or weight) adj2 (loss or loosing or losing))) adj3 (neoplasm* or cancer* or tumor* or tumour* or oncol* or malign* or carcinom* or adenocarcinom* or adenoma or metasta*)).ti,ab,kw.	9798
5	((cachexia or cachexic or anorexia or anorectic or emaciat* or malnutrition or underweight or starvation* or thiness or leanness or sarcopenia or wasting syndrome* or wasting disease* or weightloss* or ((appetite* or weight) adj2 (loss or loosing or losing))) and (neoplasm* or cancer* or tumor* or tumour* or oncol* or malign* or carcinom* or adenocarcinom* or adenoma or metasta*)).ti.	6437
6	or/3-5	24 964
7	Randomized controlled trial/	666 248
8	Controlled clinical trial/	463 928
9	random$.ti,ab.	1 691 555
10	randomization/	91 413
11	intermethod comparison/	272 763
12	placebo.ti,ab.	330 754
13	(compare or compared or comparison).ti.	571 937
14	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	2 334 019
15	(open adj label).ti,ab.	88 467
16	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	251 401
17	double blind procedure/	187 924
18	parallel group$1.ti,ab.	27 750
19	(crossover or cross over).ti,ab.	112 863
20	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	359 989
21	(assigned or allocated).ti,ab.	424 479
22	(controlled adj7 (study or design or trial)).ti,ab.	385 967
23	(volunteer or volunteers).ti,ab.	264 717
24	human experiment/	550 005
25	trial.ti.	340 818
26	or/7-25	5 516 795
27	(random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)	8736
28	Cross-sectional study/not (randomized controlled trial/ or controlled clinical study/ or controlled study/or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)	273 554
29	(((case adj control$) and random$) not randomi?ed controlled).ti,ab.	18 641
30	(Systematic review not (trial or study)).ti.	179 350
31	(nonrandom$ not random$).ti,ab.	17 184
32	Random field$.ti,ab.	2525
33	(random cluster adj3 sampl$).ti,ab.	1368
34	(review.ab. and review.pt.) not trial.ti.	902 488
35	we searched.ab. and (review.ti. or review.pt.)	37 332
36	update review.ab.	116
37	(databases adj4 searched).ab.	43 700
38	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/	1 113 420
39	Animal experiment/not (human experiment/or human/)	2 339 504
40	or/27-39	3 735 626
41	26 not 40	4 907 360
42	and/6,41	3904
43	limit 42 to yr = '1990-Current'	3674
44	limit 43 to conference abstracts	1641
45	43 not 44	2033

(*Continues*)

#	Searches	Results
46	cohort analysis/ or follow up/ or longitudinal study/ or 'national longitudinal study of adolescent health'/ or prospective study/or retrospective study/	3 499 550
47	((cohort adj (study or studies)) or cohort analy* or longitudinal).tw.	705 575
48	or/46-47	3 722 608
49	and/6,48	4417
50	limit 49 to yr = '1990-Current'	4387
51	limit 50 to conference abstracts	1639
52	50 not 51	2748
53	52 not 45	2031

Cochrane Central Register of Controlled Trials

Date searched: 2 June 2021

Search strategy:

#	Searches	Results
1	[mh Neoplasms]	82 548
2	((neoplasm* or cancer* or tumor* or tumour* or oncol* or malign* or carcinom* or adenocarcinom* or adenoma or metasta*)):ti,ab,kw (Word variations have been searched)	232 559
3	#1 or #2	241 300
4	[mh Cachexia] or [mh ^Emaciation] or [mh ^Malnutrition] or [mh Starvation] or [mh ^'Wasting syndrome'] or [mh Thinness] or [mh Sarcopenia] or [mh Anorexia]	2665
5	MeSH descriptor: [Weight Loss] this term only	6360
6	#3 and (#4 or #5)	1017
7	(((cachexia or cachexic or anorexia or anorectic or emaciat* or malnutrition or underweight or starvation* or thiness or leanness or sarcopenia or 'wasting syndrom' or 'wasting syndromes' or 'wasting disease' or 'wasting diseases' or weightloss* or ((appetite* or weight) near/2 (loss or loosing or losing))) near/3 (neoplasm* or cancer* or tumor* or tumour* or oncol* or malign* or carcinom* or adenocarcinom* or adenoma or metasta*))):ti,ab,kw	1475
8	(((cachexia or cachexic or anorexia or anorectic or emaciat* or malnutrition or underweight or starvation* or thiness or leanness or sarcopenia or 'wasting syndrome' or 'wasting syndromes' or 'wasting disease' or 'wasting diseases' or weightloss* or ((appetite* or weight) near/2 (loss or loosing or losing))) and (neoplasm* or cancer* or tumor* or tumour* or oncol* or malign* or carcinom* or adenocarcinom* or adenoma or metasta*))):ti (Word variations have been searched)	758
9	#6 or #7 or #8 with Publication Year from 1990 to 2021, in Trials	2345

Appendix B: Included studies considering anthropometric assessments of body composition

Author (reference)	Year	Sample size	Study design	Study quality	Primary cancer site	Intervention	Comparator	Body composition outcomes[b]
Body weight								
Kardinal et al.[12]	1990	293	RCT	8	Any malignancy (not brain)	Cyproheptadine (pharmacological)	Placebo	Body weight[d] (*primary*)
Loprinzi et al.[13]	1990	133	RCT	9	Any malignancy (not brain/breast/ endometrial)	Megestrol acetate (pharmacological)	Placebo	**Body weight**[c,d] (*primary*)
Feliu et al.[14]	1992	150	RCT	5	Any malignancy (not hormone dependent)	Megestrol acetate (pharmacological)	Placebo	Body weight[c] (*primary*)
Downer et al.[15a]	1993	60	RCT	1	Any malignancy	Medroxyprogesterone acetate (pharmacological)	Placebo	Body weight[c] (*primary*) Mid-arm circumference Triceps skinfold thickness
Loprinzi et al.[16]	1993	342	Phase III RCT	8	Any malignancy (not breast/endometrial)	Megestrol acetate 1280 mg or megestrol acetate 800 mg (pharmacological)	Megestrol acetate 480 mg or megestrol acetate 160 mg	Body weight[d] (*primary*)
Ovesen et al.[17a]	1993	105	RCT	8	Small-cell-lung/ovarian/ breast	Nutritional counselling (nutritional)	Standard care	Body weight[c] (*primary*) Arm muscle area **Triceps skinfold thickness**
Goldberg et al.[18]	1995	70	RCT	8	Any malignancy (not primary brain tumour)	Pentoxifylline (pharmacological)	Placebo	Body weight[d] (*primary*)
Gebbia et al.[19]	1996	122	RCT	6	Any malignancy (not hormone dependent)	Megestrol acetate 320 mg (pharmacological)	Megestrol acetate 160 mg	Body weight (*primary*)
Lissoni et al.[20]	1996	100	RCT	7	Any solid tumour	Melatonin (pharmacological)	Standard care	**Body weight**[c] (*primary*)
Simons et al.[21]	1996	206	RCT	7	Any malignancy (not hormone dependent)	Medroxyprogesterone acetate (pharmacological)	Placebo	**Body weight**[c] (*primary*)
Beller et al.[22a]	1997	240	RCT	4	Any malignancy (not hormone dependent)	Megestrol acetate 480 mg or megestrol acetate 160 mg (pharmacological)	Placebo	Body weight[c] (*primary*) Mid-arm circumference Mid-arm fat area Mid-arm muscle area Triceps skinfold thickness
Chen et al.[23]	1997	129	RCT	8	Head and neck	Megestrol acetate or prepulside (pharmacological)	Placebo	**Body weight**[c] (*primary*)
Daneryd et al.[24]	1998	180	RCT	7	Any malignancy	Indomethacin + erythropoietin (pharmacological)	Indomethacin	Lean body mass—DEXA **Body weight**[c]

(*Continues*)

Author (reference)	Year	Sample size	Study design	Study quality	Primary cancer site	Intervention	Comparator	Body composition outcomes[b]
De Conno et al.[25]	1998	42	RCT	6	Any malignancy (not hormone dependent)	Megestrol acetate (pharmacological)	Placebo	**Body weight**[c] (*primary*)
Vadell et al.[26a]	1998	150	RCT	5	Any malignancy	Megestrol acetate 480 mg or megestrol acetate 160 mg (pharmacological)	Placebo	**Body weight**[c] (*primary*) Mid-arm circumference **Triceps skinfold thickness**
Loprinizi et al.[27]	1999	496	RCT	8	Any malignancy (not breast/prostate/ovarian/ endometrial)	Megestrol acetate or dexamethasone (pharmacological)	Fluoxymesterone	Body weight[d] (*primary*)
McMillan et al.[28a]	1999	73	RCT	7	Gastrointestinal	Megestrol acetate + ibuprofen (pharmacological)	Megestrol acetate + placebo	**Body weight**[c] (*primary*) **Mid-arm circumference** Triceps skinfold thickness Biceps skinfold thickness
Westman et al.[29]	1999	255	RCT	7	Other mixed	Megestrol acetate (pharmacological)	Placebo	Body weight[c] (*primary*)
Jatoi et al.[30]	2002	469	RCT	10	Any malignancy (not brain/breast/ovarian/ endometrial)	Megestrol acetate + dronabinol or megestrol acetate + placebo (pharmacological)	Dronabinol + placebo	**Body weight**[d] (*primary*)
Persson et al.[31]	2002	144	RCT	6	Breast/colorectal/gastric/ prostate	Individual nutritional counselling or individual and group nutritional counselling (nutritional)	Group nutritional counselling or standard care	**Body weight**[d] (*primary*)
Ulutin et al.[32]	2002	119	RCT	9	NSCLC	Megestrol acetate 320 mg (pharmacological)	Megestrol acetate 160 mg	**Body weight** (increase vs. stable vs. decrease)
Bruera et al.[33a]	2003	91	RCT	7	Any malignancy	Fish oil capsules (nutritional)	Placebo	Lean body mass—BIA Body weight[c] Mid-arm muscle circumference Triceps skinfold thickness Subscapular skinfold thickness
Fearon et al.[34]	2003	200	RCT	8	Pancreatic	*n*-3 fatty acid and antioxidant-enriched supplement (nutritional)	Supplement without *n*-3 fatty acid and antioxidants	Lean body mass—BIA Body weight[c]
Isenring et al.[35]	2004	60	RCT	8	Gastrointestinal/head and neck	Nutrition counselling and protocol (nutritional)	Standard care	Fat-free mass—BIA **Body weight**[c]
Lundholm et al.[36a]	2004	309	RCT	5	Any solid tumour	Indomethacin + erythropoietin + nutritional support + home total parenteral nutrition (multi-modal)	Indomethacin + erythropoietin	Fat mass—DEXA Lean body mass—DEXA Body weight[c] Mid-arm muscle circumference Triceps skinfold thickness

(*Continues*)

Author (reference)	Year	Sample size	Study design	Study quality	Primary cancer site	Intervention	Comparator	Body composition outcomes[b]
Gonçalves Dias et al.[37a]	2005	64	Non-randomized trial	1	Head and neck	Home enteral (nasogastric) feeding or oral diet + nutritional supplements (nutritional)	Oral diet	Body weight[c] BMI Mid-arm circumference Mid-arm muscle area Triceps skinfold thickness
Gordon et al.[38a]	2005	50	RCT	10	Pancreatic	Thalidomide (pharmacological)	Placebo	**Body weight**[c] (*primary*) **Bone-free arm muscle area**
Fearon et al.[39]	2006	518	RCT	8	Gastrointestinal/lung	EPA 2 g or EPA 4 g (pharmacological)	Placebo	Lean body mass—BIA Body weight[c]
Berk et al.[40a]	2008	472	RCT	9	Any solid tumour	Nutritional supplement (nutritional)	Placebo	Lean body mass—BIA (*primary*) Body weight[d] Various skinfold thickness
Beijer et al.[42a]	2009	100	RCT	8	Any malignancy	Adenosine 5′-triphosphate (pharmacological)	Standard care	**Triceps skinfold thickness** (*primary*) Body weight[c] Mid-arm circumference
Navari et al.[44]	2010	80	RCT	7	Gastrointestinal/lung	Megestrol acetate + olanzapine (pharmacological)	Megestrol acetate	**Body weight**[d] (*primary*)
Baldwin et al.[45]	2011	358	RCT	8	Gastrointestinal/NSCLC/ mesothelioma	Nutritional supplement + nutritional counselling or nutritional supplement (nutritional)	Nutritional counselling or standard care	Body weight[c]
Silander et al.[49a]	2012	134	RCT	6	Head and neck	Prophylactic PEG (nutritional)	Standard care	Body weight[d] (*primary*) BMI
Wen et al.[50]	2012	102	RCT	5	Any malignancy	Megestrol acetate + thalidomide (pharmacological)	Megestrol acetate	**Body weight**[c] (*primary*)
Del Fabbro et al.[51]	2013	73	RCT	10	Gastrointestinal/lung	Melatonin (pharmacological)	Placebo	Body weight[c] (*primary*) Lean body mass—BIA Fat-free mass—BIA
Dobs et al.[52]	2013	159	Phase II RCT	8	Other mixed	Enobosarm 1 mg or enobosarm 3 mg (pharmacological)	Placebo	**Lean body mass—DEXA** (*primary*) Body weight[c] Fat mass—DEXA
Kanat et al.[53a]	2013	69	RCT	8	Any malignancy	Megestrol acetate + meloxicam or megestrol acetate + EPA-enriched nutritional supplement (pharmacological)	Meloxicam + EPA-enriched nutritional supplement	Body weight[c] (*primary*) Lean body mass—BIA (*primary*) BMI
Poulsen et al.[54]	2013	61	RCT	5	Oesophageal/gastric/ gynaecological	Nutritional counselling (nutritional)	Standard care	**Body weight** (loss vs. maintenance)

(*Continues*)

Author (reference)	Year	Sample size	Study design	Study quality	Primary cancer site	Intervention	Comparator	Body composition outcomes[b]
								(*primary*) Fat mass—BIA Fat-free mass—BIA
Bourdel-Marchasson et al.[55]	2014	336	RCT	10	Other mixed	Nutritional counselling (nutritional)	Standard care	Body weight[c]
Pottel et al.[56]	2014	85	Exploratory RCT	8	Head and neck	Echium oil (nutritional)	Sunflower oil	Body weight[d] (*primary*) Lean body mass—DEXA Lean body mass—BIA Fat mass—DEXA Fat mass—BIA Fat-free mass—BIA
Focan et al.[57a]	2015	53	RCT	7	Any malignancy	Dietetic and psychological mindfulness workshops (multi-modal)	Standard care	**BMI** (*primary*) **Body weight**[c]
Kapoor et al.[60a]	2016	63	RCT	8	Any malignancy	Improved atta (nutritional supplement) + nutritional counselling (nutritional)	Nutritional counselling	Body weight[c] Mid-arm circumference Various skinfold thickness
Mehrzad et al.[61a]	2016	70	RCT	8	Any malignancy (not brain)	Pentoxifylline (pharmacological)	Placebo	Body weight[c] Mid-arm circumference
Stewart Coats et al.[62]	2016	87	Phase II RCT	10	NSCLC/colorectal	Espindolol 10 mg or espindolol 2.5 mg (pharmacological)	Placebo	**Body weight**[c,d] (*primary*) **Lean body mass—DEXA** Fat mass—DEXA
Takayama et al.[63]	2016	181	Phase II RCT	8	NSCLC	Anamorelin 100 mg or anamorelin 50 mg (pharmacological)	Placebo	**Lean body mass—DEXA** (*primary*) Lean body mass—BIA **Fat mass—DEXA** **Fat mass—BIA** **Body weight**[c]
Temel et al.[11]	2016	979	Phase III RCT	8	NSCLC	Anamorelin (pharmacological)	Placebo	**Lean body mass—DEXA** (*primary*) **Body weight**[c] **Total body mass—DEXA** **Fat mass—DEXA** **Appendicular LBM—DEXA**
Woo et al.[64]	2016	67	Phase II RCT	9	Pancreatic	Pancreatic exocrine replacement therapy (nutritional)	Placebo	Body weight[c,d] (*primary*)
Currow et al.[65]	2017	513	Phase III RCT	8	NSCLC	Anamorelin (pharmacological)	Placebo	**Body weight**[c]
Jatoi et al.[66]	2017	300	RCT	8	Any malignancy (not primary brain tumour)	Creatine monohydrate (nutritional)	Placebo	Body weight[d] (*primary*)
Leedo et al.[67]	2017	40	RCT	8	Lung	Home meal delivery (nutritional)	Standard care	Body weight[c]
Sandmael et al.[68]	2017	41	Pilot RCT	9	Head and neck			Skeletal muscle index—CT

(*Continues*)

Author (reference)	Year	Sample size	Study design	Study quality	Primary cancer site	Intervention	Comparator	Body composition outcomes[b]
						Exercise and nutrition intervention during radiotherapy treatment (multi-modal)	Exercise and nutrition intervention after radiotherapy treatment	Body weight[c]
Solheim et al.[69]	2017	46	Phase II RCT	8	NSCLC/pancreatic	Exercise, celecoxib + nutritional supplements (multi-modal)	Standard care	**Body weight**[c,d] Skeletal muscle area—CT
Werner et al.[70]	2017	60	RCT	7	Pancreatic	Fish oil (nutritional)	Marine phospholipids	Body weight[d] BMI
Katakami et al.[73]	2018	174	Phase III RCT	8	NSCLC	Anamorelin (pharmacological)	Placebo	**Lean body mass—DEXA** (*primary*) **Body weight**[c]
Kouchaki et al.[74]	2018	90	Phase III RCT	8	Gastrointestinal	Megestrol acetate + celecoxib (pharmacological)	Megestrol acetate + placebo	Body weight[c,d] (*primary*)
Schink et al.[75]	2018	131	Pilot non-randomized trial	9	Any solid tumour	Whole-body electromyostimulation + nutritional counselling (multi-modal)	Nutritional counselling	**Lean body mass—BIA** (*primary*) Fat mass—BIA **Body weight**[c]
Uster et al.[76]	2018	58	RCT	9	Gastrointestinal/lung	Exercise programme + nutritional counselling (multi-modal)	Standard care	Body weight[c]
Xie et al.[77a]	2018	54	RCT	8	Lung	Thalidomide + cinobufagin (pharmacological)	Cinobufagin	Body weight[c] Mid-arm circumference
Britton et al.[79]	2019	307	RCT	7	Head and neck	Psychological nutritional intervention (nutritional)	Standard care	**Body weight**[d]
Cereda et al.[80]	2019	166	RCT	8	Other mixed	Whey protein isolate supplement + nutritional counselling (nutritional)	Nutritional counselling	**Fat-free mass index—BIA** **Body weight**[c]
Laviano et al.[81]	2019	55	Pilot RCT	8	NSCLC	Targeted medical nutrition supplement (nutritional)	Isocaloric comparator drink	Skeletal muscle area—CT Visceral fat area—CT Appendicular LBM—DEXA Fat mass—DEXA Body weight[c]
Wiskemann et al.[84]	2019	65	RCT	5	Pancreatic	Supervised resistance training or home-based resistance training (exercise)	Standard care	Body weight[d] (*primary*)
Boulec et al.[85]	2020	111	RCT	7	Any malignancy	Parenteral nutrition (nutritional)	Oral feeding	Body weight[c]
Huang et al.[86]	2020	119	RCT	7	Nasopharyngeal	Nutritional supplements (nutritional)	Standard care	Body weight[c]
Movahed et al.[88]	2020	100	RCT	8	Oesophageal	Supplements ± enteral or parenteral nutrition ± pharmacotherapy + nutritional counselling	Nutritional counselling	Fat mass—BIA Fat-free mass index—BIA Body weight[c] BMI

(*Continues*)

Author (reference)	Year	Sample size	Study design	Study quality	Primary cancer site	Intervention	Comparator	Body composition outcomes[b]
						(multi-modal)		
Currow et al.[91]	2021	190	Phase III RCT	6	Any malignancy	Megestrol acetate or dexamethasone (pharmacological)	Placebo	Body weight[c]
Hunter et al.[92]	2021	120	Phase III RCT	7	Any solid tumour	Mirtazapine (pharmacological)	Placebo	Lean body mass—BIA Body weight[c]
Tobberup et al.[94]	2021	120	Non-randomized trial	9	NSCLC	Fish oil + nutritional counselling + exercise programme (multi-modal)	Standard care (historical comparator)	Skeletal muscle area—CT Body weight[c]
BMI								
Gonçalves Dias et al.[37a]	2005	64	Non-randomized trial	1	Head and neck	Home enteral (nasogastric) feeding or oral diet + nutritional supplements (nutritional)	Oral diet	Body weight[c] BMI Mid-arm circumference Mid-arm muscle area Triceps skinfold thickness
Kraft et al.[46]	2012	72	RCT	10	Pancreatic	L-Carnitine supplement (nutritional)	Placebo	**Fat mass—BIA** **BMI**
Silander et al.[49a]	2012	134	RCT	6	Head and neck	Prophylactic PEG (nutritional)	Standard care	Body weight[d] (*primary*) BMI
Kanat et al.[53a]	2013	69	RCT	8	Any malignancy	Megestrol acetate + meloxicam or megestrol acetate + EPA-enriched nutritional supplement (pharmacological)	Meloxicam + EPA-enriched nutritional supplement	Body weight[c] (*primary*) Lean body mass—BIA (*primary*) BMI
Focan et al.[57a]	2015	53	RCT	7	Any malignancy	Dietetic and psychological mindfulness workshops (multi-modal)	Standard care	**BMI** (*primary*) **Body weight**[c]
Capozzi et al.[59]	2016	60	Exploratory RCT	8	Head and neck	Early 'lifestyle intervention' (individualized exercise with education and support) (exercise)	Delayed 'lifestyle intervention' (individualized exercise with education and support)	Lean body mass—DEXA Fat mass—DEXA BMI
Werner et al.[70]	2017	60	RCT	7	Pancreatic	Fish oil (nutritional)	Marine phospholipids	Body weight[d] BMI
Ziętarska et al.[71]	2017	95	RCT	6	Colorectal	Nutritional supplements (nutritional)	Standard care	BMI
Akita et al.[78]	2019	62	RCT	8	Pancreatic	EPA-enriched nutritional supplement (nutritional)	Standard care	Lean body mass—BIA Fat mass—BIA Psoas muscle area—CT BMI
Movahed et al.[88]	2020	100	RCT	8	Oesophageal	Supplements ± enteral or parenteral nutrition ± pharmacotherapy + nutritional counselling (multi-modal)	Nutritional counselling	Fat mass—BIA Fat-free mass index—BIA Body weight[c] BMI
Qiu et al.[89]	2020	96	RCT	6	Oesophageal	Nutritional counselling	Standard care	BMI

(*Continues*)

Author (reference)	Year	Sample size	Study design	Study quality	Primary cancer site	Intervention	Comparator	Body composition outcomes[b]
						(nutritional)		
Storck et al.[90]	2020	52	RCT	10	Other mixed	Protein supplement + nutritional counselling + exercise programme (multi-modal)	Standard care	Lean body mass—BIA Fat mass—BIA BMI
Kutz et al.[93]	2021	58	RCT	7	Head and neck	Nutritional counselling (nutritional)	Standard care	BMI Fat-free mass—BIA
Other anthropometry								
Downer et al.[15a]	1993	60	RCT	1	Any malignancy	Medroxyprogesterone acetate (pharmacological)	Placebo	Body weight[c] (*primary*) Mid-arm circumference Triceps skinfold thickness
Ovesen et al.[17a]	1993	105	RCT	8	Small-cell-lung/ovarian/ breast	Nutritional counselling (nutritional)	Standard care	Body weight[c] (*primary*) Arm muscle area **Triceps skinfold thickness**
Beller et al.[22a]	1997	240	RCT	4	Any malignancy (not hormone dependent)	Megestrol acetate 480 mg or megestrol acetate 160 mg (pharmacological)	Placebo	Body weight[c] (*primary*) Mid-arm circumference Mid-arm fat area Mid-arm muscle area Triceps skinfold thickness
Vadell et al.[26a]	1998	150	RCT	5	Any malignancy	Megestrol acetate 480 mg or megestrol acetate 160 mg (pharmacological)	Placebo	**Body weight**[c] (*primary*) Mid-arm circumference **Triceps skinfold thickness**
McMillan et al.[28a]	1999	73	RCT	7	Gastrointestinal	Megestrol acetate + ibuprofen (pharmacological)	Megestrol acetate + placebo	**Body weight**[c] (*primary*) **Mid-arm circumference** Triceps skinfold thickness Biceps skinfold thickness
Bruera et al.[33a]	2003	91	RCT	7	Any malignancy	Fish oil capsules (nutritional)	Placebo	Lean body mass—BIA Body weight[c] Mid-arm muscle circumference Triceps skinfold thickness Subscapular skinfold thickness
Gonçalves Dias et al.[37a]	2005	64	Non-randomized trial	1	Head and neck	Home enteral (nasogastric) feeding or oral diet + nutritional supplements (nutritional)	Oral diet	Body weight[c] BMI Mid-arm circumference Mid-arm muscle area Triceps skinfold thickness
Lundholm et al.[36a]	2004	309	RCT	5	Any solid tumour	Indomethacin + erythropoietin + nutritional support + home total parenteral nutrition	Indomethacin + erythropoietin	Fat mass—DEXA Lean body mass—DEXA Body weight[c] Mid-arm muscle circumference

(*Continues*)

Author (reference)	Year	Sample size	Study design	Study quality	Primary cancer site	Intervention	Comparator	Body composition outcomes[b]
Gordon et al.[38a]	2005	50	RCT	10	Pancreatic	(multi-modal) Thalidomide (pharmacological)	Placebo	Triceps skinfold thickness **Body weight**[c] (*primary*) **Bone-free arm muscle area**
Berk et al.[40a]	2008	472	RCT	9	Any solid tumour	Nutritional supplement (nutritional)	Placebo	Lean body mass—BIA (*primary*) Body weight[d] Various skinfold thickness
Beijer et al.[42a]	2009	100	RCT	8	Any malignancy	Adenosine 5′-triphosphate (pharmacological)	Standard care	**Triceps skinfold thickness** (*primary*) Body weight[c] Mid-arm circumference
Kapoor et al.[60a]	2016	63	RCT	8	Any malignancy	Improved atta (nutritional supplement) + nutritional counselling (nutritional)	Nutritional counselling	Body weight[c] Mid-arm circumference Various skinfold thickness
Mehrzad et al.[61a]	2016	70	RCT	8	Any malignancy (not brain)	Pentoxifylline (pharmacological)	Placebo	Body weight[c] Mid-arm circumference
Xie et al.[77a]	2018	54	RCT	8	Lung	Thalidomide + cinobufagin (pharmacological)	Cinobufagin	Body weight[c] Mid-arm circumference

Note: Sample sizes are reported as per 'intention to treat'. Abbreviations: BIA, bioimpedance analysis; BMI, body mass index; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; EPA, eicosapentaenoic acid; NSCLC, non-small-cell lung cancer; PEG, percutaneous endoscopic gastrostomy; RCT, randomized controlled trial.

[a]Considered more than one anthropometric estimate of body composition.

[b]Endpoints that are bold underlined had a statistically significant difference between groups.

[c]Endpoint expressed as change in absolute value from baseline.

[d]Endpoint expressed as percentage change from baseline.

Appendix C: Included studies considering bioelectrical or radiological assessments of body composition

Author (reference)	Year	Sample size	Study design	Quality score	Primary cancer site	Intervention	Comparator	Body composition outcomes[b]
BIA body composition								
Bruera et al.[33]	2003	91	RCT	7	Any malignancy	Fish oil capsules (nutritional)	Placebo	Lean body mass—BIA Body weight Mid-arm muscle circumference Triceps skinfold thickness Subscapular skinfold thickness
Fearon et al.[34]	2003	200	RCT	8	Pancreatic	*n*-3 fatty acid and antioxidant-enriched supplement (nutritional)	Supplement without *n*-3 fatty acid and antioxidants	Lean body mass—BIA Body weight
Isenring et al.[35]	2004	60	RCT	8	Gastrointestinal/head and neck	Nutrition counselling and protocol (nutritional)	Standard care	Fat-free mass—BIA **Body weight**
Fearon et al.[39]	2006	518	RCT	8	Gastrointestinal/lung	EPA 2 g or EPA 4 g (pharmacological)	Placebo	Lean body mass—BIA Body weight
Berk et al.[40]	2008	472	RCT	9	Any solid tumour	Nutritional supplement (nutritional)	Placebo	Lean body mass—BIA (*primary*) Body weight Various skinfold thickness
Wiedenmann et al.[41]	2008	86	Phase II RCT	7	Pancreatic	Infliximab 5 mg/kg or infliximab 3 mg/kg (pharmacological)	Placebo	Lean body mass—BIA (*primary*)
Mantovani et al.[43a]	2010	332	Phase III RCT	7	Any malignancy	Megestrol acetate or EPA-enriched nutritional supplement or L-carnitine or thalidomide (pharmacological)	Megestrol acetate + EPA-enriched nutritional supplement + L-carnitine + thalidomide	**Lean body mass—DEXA** (*primary*) Lean body mass—BIA (*primary*) **Lean body mass—CT** (*primary*)
Kraft et al.[46]	2012	72	RCT	10	Pancreatic	L-Carnitine supplement (nutritional)	Placebo	**Fat mass—BIA** **BMI**
Madeddu et al.[48a]	2012	60	Phase III RCT	7	Any malignancy	L-Carnitine + celecoxib + megestrol acetate (pharmacological)	L-Carnitine + celecoxib	Lean body mass—DEXA (*primary*) Lean body mass—CT (*primary*) Lean body mass—BIA (*primary*)
Del Fabbro et al.[51]	2013	73	RCT	10	Gastrointestinal/lung	Melatonin (pharmacological)	Placebo	Body weight (*primary*) Lean body mass—BIA Fat-free mass—BIA

(*Continues*)

Author (reference)	Year	Sample size	Study design	Quality score	Primary cancer site	Intervention	Comparator	Body composition outcomes[b]
Kanat et al.[53]	2013	69	RCT	8	Any malignancy	Megestrol acetate + meloxicam or megestrol acetate + EPA-enriched nutritional supplement (pharmacological)	Meloxicam + EPA-enriched nutritional supplement	Body weight (*primary*) Lean body mass—BIA (*primary*) BMI
Poulsen et al.[54]	2013	61	RCT	5	Oesophageal/gastric/ gynaecological	Nutritional counselling (nutritional)	Standard care	**Body weight** (*primary*) Fat mass—BIA Fat-free mass—BIA
Pottel et al.[56a]	2014	85	Exploratory RCT	8	Head and neck	Echium oil (nutritional)	Sunflower oil	Body weight (*primary*) Lean body mass—DEXA Fat mass—DEXA Lean body mass—BIA Fat mass—BIA Fat-free mass—BIA
Takayama et al.[63a]	2016	181	Phase II RCT	8	NSCLC	Anamorelin 100 mg or anamorelin 50 mg (pharmacological)	Placebo	**Lean body mass—DEXA** (*primary*) **Fat mass—DEXA** Lean body mass—BIA **Fat mass—BIA** **Body weight**
Schink et al.[75]	2018	131	Pilot non-randomized trial	9	Any solid tumour	Whole-body electromyostimulation + nutritional counselling (multi-modal)	Nutritional counselling	**Lean body mass—BIA** (*primary*) Fat mass—BIA
Akita et al.[78a]	2019	62	RCT	8	Pancreatic	EPA-enriched nutritional supplement + nutritional guidance (nutritional)	Nutritional guidance	**Body weight** Lean body mass—BIA Fat mass—BIA Psoas muscle area—CT BMI
Cereda et al.[80]	2019	166	RCT	8	Other mixed	Whey protein isolate supplement + nutritional counselling (nutritional)	Nutritional counselling	**Fat-free mass index—BIA** **Body weight**
Obling et al.[82]	2019	47	RCT	7	Gastrointestinal	Supplemental home parenteral nutrition and nutritional counselling (nutritional)	Nutritional counselling	**Fat-free mass—BIA** (*primary*) **Fat-free mass index—BIA** (*primary*)
Stuecher et al.[83]	2019	44	RCT	8	Gastrointestinal	Walking exercise programme (exercise)	Standard care	**Lean body mass—BIA**
Movahed et al.[88]	2020	100	RCT	8	Oesophageal	Supplements ± enteral or parenteral nutrition ± pharmacotherapy + nutritional counselling (multi-modal)	Nutritional counselling	Fat mass—BIA Fat-free mass index—BIA Body weight BMI

(*Continues*)

Author (reference)	Year	Sample size	Study design	Quality score	Primary cancer site	Intervention	Comparator	Body composition outcomes[b]
Storck et al.[90]	2020	52	RCT	10	Other mixed	Whey protein supplement + nutritional counselling + exercise programme (multi-modal)	Standard care	Lean body mass—BIA Fat mass—BIA BMI
Hunter et al.[92]	2021	120	Phase III RCT	7	Any solid tumour	Mirtazapine (pharmacological)	Placebo	Lean body mass—BIA Body weight
Kutz et al.[93]	2021	58	RCT	7	Head and neck	Nutritional counselling (nutritional)	Standard care	BMI Fat-free mass—BIA
DEXA body composition								
Daneryd et al.[24]	1998	180	RCT	7	Any malignancy	Indomethacin + erythropoietin (pharmacological)	Indomethacin	Lean body mass—DEXA **Body weight**
Lundholm et al.[36]	2004	309	RCT	5	Any solid tumour	Indomethacin + erythropoietin + nutritional support + home total parenteral nutrition (multi-modal)	Indomethacin + erythropoietin	Fat mass—DEXA Lean body mass—DEXA Body weight Mid-arm muscle circumference Triceps skinfold thickness
Mantovani et al.[43a]	2010	332	Phase II RCT	9	Any malignancy	Megestrol acetate or EPA-enriched nutritional supplement or L-carnitine or thalidomide (pharmacological)	Megestrol acetate + EPA-enriched nutritional supplement + L-carnitine + thalidomide	**Lean body mass—DEXA** (*primary*) Lean body mass—BIA (*primary*) **Lean body mass—CT** (*primary*)
Macciò et al.[47]	2012	144	Phase III RCT	8	Gynaecological	Megestrol acetate + L-carnitine + celecoxib + antioxidants (pharmacological)	Megestrol acetate	**Lean body mass—DEXA** (*primary*)
Madeddu et al.[48a]	2012	60	Phase III RCT	7	Any malignancy	L-Carnitine + celecoxib + megestrol acetate (pharmacological)	L-Carnitine + celecoxib	Lean body mass—DEXA (*primary*) Lean body mass—CT (*primary*) Lean body mass—BIA (*primary*)
Dobs et al.[52]	2013	159	Phase II RCT	8	Other mixed	Enobosarm 1 mg or enobosarm 3 mg (pharmacological)	Placebo	**Lean body mass—DEXA** (*primary*) Body weight Fat mass—DEXA
Pottel et al.[56a]	2014	85	Exploratory RCT	8	Head and neck	Echium oil (nutritional)	Sunflower oil	Body weight (*primary*) Lean body mass—DEXA Lean body mass—BIA Fat mass—DEXA Fat mass—BIA Fat-free mass—BIA

(*Continues*)

Author (reference)	Year	Sample size	Study design	Quality score	Primary cancer site	Intervention	Comparator	Body composition outcomes[b]
Garcia et al.[58]	2015	82	Phase II RCT	7	Any malignancy	Anamorelin 50 mg (pharmacological)	Placebo	**Lean body mass—DEXA** (*primary*) **Appendicular LBM—DEXA** **Total body mass—DEXA** Fat mass—DEXA
Capozzi et al.[59]	2016	60	Exploratory RCT	8	Head and neck	Early 'lifestyle intervention' (individualized exercise with education and support) (exercise)	Delayed 'lifestyle intervention' (individualized exercise with education and support)	Lean body mass—DEXA Fat mass—DEXA BMI
Stewart Coats et al.[62]	2016	87	Phase II RCT	10	NSCLC/colorectal	Espindolol 10 mg or espindolol 2.5 mg (pharmacological)	Placebo	**Body weight** (*primary*) **Lean body mass—DEXA** Fat mass—DEXA
Takayama et al.[63a]	2016	181	Phase II RCT	8	NSCLC	Anamorelin 100 mg or anamorelin 50 mg (pharmacological)	Placebo	**Lean body mass—DEXA** (*primary*) **Fat mass—DEXA** Lean body mass—BIA **Fat mass—BIA** **Body weight**
Temel et al.[11]	2016	979	Phase III RCT	8	NSCLC	Anamorelin (pharmacological)	Placebo	**Lean body mass—DEXA** (*primary*) **Body weight** **Total body mass—DEXA** **Fat mass—DEXA** **Appendicular LBM—DEXA**
Katakami et al.[73]	2018	174	Phase III RCT	8	NSCLC	Anamorelin (pharmacological)	Placebo	**Lean body mass—DEXA** (*primary*) **Body weight**
Golan et al.[72a]	2018	125	Phase II RCT	7	Pancreatic	Anti-myostatin antibody 300 mg or anti-myostatin antibody 100 mg (pharmacological)	Placebo	Thigh muscle volume—CT Skeletal muscle area—CT Adipose tissue area—CT Lean body mass—DEXA Fat mass—DEXA
Laviano et al.[81a]	2019	55	Pilot RCT	8	NSCLC	Targeted medical nutrition supplement (nutritional)	Isocaloric comparator drink	Skeletal muscle area—CT Visceral fat area—CT Appendicular LBM—DEXA Fat mass—DEXA Body weight
Kamel et al.[87]	2020	40	RCT	7	Pancreatic	Resistance training (exercise)	Standard care	**Appendicular LBM—DEXA** **Fat mass—DEXA**

(*Continues*)

Author (reference)	Year	Sample size	Study design	Quality score	Primary cancer site	Intervention	Comparator	Body composition outcomes[b]
CT body composition								
Mantovani et al.[43a]	2010	332	Phase III RCT	7	Any malignancy	Megestrol acetate or EPA-enriched nutritional supplement or L-carnitine or thalidomide (pharmacological)	Megestrol acetate + EPA-enriched nutritional supplement + L-carnitine + thalidomide	**Lean body mass—DEXA** (*primary*) Lean body mass—BIA (*primary*) **Lean body mass—CT** (*primary*)
Madeddu et al.[48a]	2012	60	Phase III RCT	7	Any malignancy	L-Carnitine + celecoxib + megestrol acetate (pharmacological)	L-Carnitine + celecoxib	Lean body mass—DEXA (*primary*) Lean body mass—CT (*primary*) Lean body mass—BIA (*primary*)
Sandmael et al.[68]	2017	41	Pilot RCT	9	Head and neck	Exercise and nutrition intervention during radiotherapy treatment (multi-modal)	Exercise and nutrition intervention after radiotherapy treatment	Skeletal muscle index—CT Body weight
Solheim et al.[69]	2017	46	Phase II RCT	8	NSCLC/pancreatic	Exercise, celecoxib + nutritional supplements (multi-modal)	Standard care	**Body weight** Skeletal muscle area—CT
Golan et al.[72a]	2018	125	Phase II RCT	7	Pancreatic	Anti-myostatin antibody 300 mg or anti-myostatin antibody 100 mg (pharmacological)	Placebo	Thigh muscle volume—CT Skeletal muscle area—CT Adipose tissue area—CT Lean body mass—DEXA Fat mass—DEXA
Akita et al.[78a]	2019	62	RCT	8	Pancreatic	EPA-enriched nutritional supplement + nutritional guidance (nutritional)	Nutritional guidance	Lean body mass—BIA Fat mass—BIA Psoas muscle area—CT BMI
Laviano et al.[81a]	2019	55	Pilot RCT	8	NSCLC	Targeted medical nutrition supplement (nutritional)	Isocaloric comparator drink	Skeletal muscle area—CT Visceral fat area—CT Appendicular LBM—DEXA Fat mass—DEXA Body weight
Tobberup et al.[94]	2021	120	Non-randomized trial	9	NSCLC	Fish oil + nutritional counselling + exercise programme (multi-modal)	Standard care (historical comparator)	Skeletal muscle area—CT Body weight

Note: Sample sizes are reported as per 'intention to treat'.
Abbreviations: BIA, bioimpedance analysis; BMI, body mass index; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; EPA, eicosapentaenoic acid; LBM, lean body mass; NSCLC, non-small-cell lung cancer; RCT, randomized controlled trial.
[a]Considered more than one radiological or bioelectrical estimate of body composition.
[b]Endpoints that are bold underlined had a statistically significant difference between groups.