Bijlage 9 Evidence tabellen

Evidence tabellen behorende bij de oorspronkelijke uitgangsvragen die in deze richtlijn via de GRADE-methodiek zijn uitgewerkt.

Uitgangsvraag 1: Psycho-educatie
Wat zijn de effecten van psycho-educatie in vergelijking met geen psycho-educatie op vermoeidheid, kwaliteit van leven en (fysiek) functioneren bij patiënten met vermoeidheid bij kanker in de palliatieve fase?

Patiënten Patiënten met vermoeidheid bij kanker in de palliatieve fase
Interventie Psycho-educatie, psycho-education, nursing intervention, energy conservation
Comparator Geen psycho-educatie, geen niet-nursing interventie met potentieel effect op de outcome measurements, geen energy conservation
Outcome Vermoeidheid, kwaliteit van leven, (fysiek) functioneren

Systematic reviews

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and all other outcomes	VII Critical appraisal of study quality
1. Reference	1. Study design 2. Source of funding/conflicts of interest 3. Setting 4. Sample size 5. Duration of the Study	1. Eligibility criteria 2. Patient characteristics 3. Group comparability	1. Intervention(s) 2. Comparator(s)	1. Effect size primary outcome	1. Effect size secondary outcome(s) 2. Effect size all other outcomes, endpoints	1.Level of evidence 2. Dropouts 3. Results critical appraisal
First author Journal Publication year	Specify the type of study Trial number Specify the source of funding	Inclusion criteria Exclusion criteria Age Gender (M:F)	including dose, length, regimen and timing if relevant	Functioning Fatigue Quality of life Participation	Brief description of secondary outcome(s) and p values. including adverse effects, toxicity	Classification of intervention studies. Number of dropouts/withdrawals in each group

	presence of declaration of interest. Number of centers Countries Setting Randomized Inclusion dates	Tumor Stage Palliative stage p for group comparability.	Duration of intervention	Other (primary as defined in the study)		Cochrane Score
Chan Journal of Pain and Symptom Management 2011	Design: RCT Funding: government Hong Kong Health Service Research Fund. Number of centers: 1 Country: Hong-Kong Setting: Outpatient Radiotherapy unit n=140 Inclusion dates: NR	Eligibility criteria: Age 16 years or older; Stage 3 or 4 lung cancer; scheduled to receive palliative RT of an average of 4.3 Gy/fraction; the ability to communicate in Chinese; signed informed consent; an Abbreviated Mental Test score of 8 or above indicating normal cognitive ability; Karnofsky Performance Status score of 60% or above Excluded: known psychiatric morbidity	Intervention: A 40-minute educational package plus coaching of Progressive muscle relaxation (PMR) was delivered to patients within one week prior to the beginning of the course of RT, and reinforced three weeks after commencing RT. The education package consisted of leaflets and discussion on the selected symptoms	Fatigue showed a significant difference (p=0.011) in the pattern of change between baseline and 6 weeks favouring intervention (time x group effect), with a small effect size (partial eta squared 0.033). Breathlessness showed a significant difference (p=0.002) in the pattern of change between baseline and 6 weeks favouring intervention (time x group effect), with small effect size (partial eta squared 0.04). Anxiety showed a significant difference (p=0.001) in the pattern of changeetween baseline and 6 weeks favouring		RCT Dropout at three months: Ex: 11%, C: 43% (all due to death) Cochrane score 3/7 downgraded for blinding, unclear allocation concealment, incomplete outcomes

		and/or involvement in other clinical trials. Mean age: NR M:F: NR Tumor types: lung cancer Tumor stages: III/IV Palliative stage: Disease directed treatment No information about group comparability	and their self-care management 4 weeks Control: Usual care	intervention (time x group effect), with small effect size (partial eta-squared 0.051)		

Uitgangsvraag 2: Corticosteroïden

Wat is het effect van corticosteroïden (dexamethason, predniso(lo)n, methylprednisolon) op vermoeidheid, kwaliteit van leven en functioneren ten opzichte van placebo, geen behandeling of andere (medicamenteuze) behandeling bij patiënten met vermoeidheid bij kanker in de palliatieve fase?

Patiënten Patiënten met vermoeidheid en kanker in de palliatieve fase
Interventie Corticosteroïden, dexamethason, predniso(lo)n methylprednisolon
Comparator Placebo, geen behandeling of andere (medicamenteuze) behandeling
Outcome Vermoeidheid, kwaliteit van leven, functioneren

Systematic reviews

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and all other outcomes	VII Critical appraisal of study quality
1. Reference	1. Study design 2. Source of funding/conflicts of interest 3. Setting 4. Sample size 5. Duration of the Study	1. Eligibility criteria 2. Patient characteristics 3. Group comparability	1. Intervention(s) 2. Comparator(s)	1. Effect size primary outcome	1. Effect size secondary outcome(s) 2. Effect size all other outcomes, endpoints	1.Level of evidence 2. Dropouts 3. Results critical appraisal
Mücke Cochrane Database of Systematic Reviews 2015	Design: Cochrane review Funding: None Databases: Medline, EMBASE, CINAHL, Cochrane register of controlled trials, conference proceedings. Study designs: RCT Setting: Palliative care	Eligibility criteria: RCT; full reports; fatigue; palliative care; focus on pharmacological treatment (psychostimulants (amphetamines, modafinil, armodafinil, methylphenidate, pemoline), amantadine, corticosteroids (dexamethasone, prednisone, methylprednisolone),	Intervention: Dexamethasone 4 mg; Medroxyprogesterone 500mg twice daily; Methylprednisolone 125 mg/day, 8 weeks Other interventions in the review: psychostimulants (amphetamines, modafinil, armodafinil, methylphenidate, pemoline), amantadine, corticosteroids	One study showed that dexamethasone was significantly superior for fatigue to placebo. No significant difference in the improvement of individual symptoms on the ESAS, psychological distress, HADS or HADS depression scores. Methylprednisolone (125 mg/day for eight weeks) was used with significant		Systematic review Dropouts: NR Amstar score: 11/11

	N included studies: 45 (18 studies on cancer; dexamethasone 1 study, methylprednisolon 1 study, medroxyprogesteron 1 study) Search date: April 2014	donepezil, antidepressants such as selective serotonin reuptake inhibitors (SSRIs; paroxetine), acetylsalicylic acid, megestrol acetate, alfacalcidol and acetyl-L-carnitine.); primary outcome had to be fatigue (or related terms such as asthenia); diseases requiring palliative care or diseases at an advanced, life-threatening stage. Excluded: primary target of clinical conditions such as depression or anxiety; focus on physiological deficiencies such as lack of haemoglobin, nor did we focus on drugs targeting specific cytokines; studies comparing different types of cancer-modifying treatment and the effect on prognosis and quality of life; studies which did not focus on	(dexamethasone, prednisone, methylprednisolone), donepezil, antidepressants such as selective serotonin reuptake inhibitors (SSRIs; paroxetine), acetylsalicylic acid, megestrol acetate, alfacalcidol and acetyl-L-carnitine. Control: Placebo	effect in only one study of 403 participants with cancer related fatigue (Della Cuna 1989). Medroxyprogesterone was tested in only one study of 134 participants EORTC-QLQC30 questionnaire. The use of 500mg twice a day over 12 weeks showed no significant effect.		

		pharmacological treatment; studies on fatigue related to antineoplastic treatment (e.g. chemotherapy, radiotherapy, surgical intervention). Mean age: NR M:F: NR Tumor types: all Tumor stages: advanced stage Palliative stage: NR No information about group comparability				

Primairy studies

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and all other outcomes	VII Critical appraisal of study quality
1. Reference	1. Study design 2. Source of funding/conflicts of interest 3. Setting 4. Sample size 5. Duration of the Study	1. Eligibility criteria 2. Patient characteristics 3. Group comparability	1. Intervention(s) 2. Comparator(s)	1. Effect size primary outcome	1. Effect size secondary outcome(s) 2. Effect size all other outcomes, endpoints	1.Level of evidence 2. Dropouts 3. Results critical appraisal
First author Journal Publication year	Specify the type of study Trial number Specify the source of funding presence of declaration of interest. Number of centers	Inclusion criteria Exclusion criteria Age Gender (M:F) Tumor Stage Palliative stage	including dose, length, regimen and timing if relevant Duration of intervention	Functioning Fatigue Quality of life Participation Other (primary as defined in the study)	Brief description of secondary outcome(s) and p values. including adverse effects, toxicity	Classification of intervention studies. Number of dropouts/withdrawals in each group Cochrane Score

	Countries Setting Randomized Inclusion dates	p for group comparability.				
Chow International Journal of Radiation Oncology 2015	Design: RCT NCT01248585 Funding: not governmental organization NCIC CTG's programmatic grant from the Canadian Cancer Society Research Institute Number of centers: 23 Country: Canada Setting: Cancer center n=298 Inclusion dates: May 2011 to Dec 2014	Eligibility criteria: Radiologically confirmed bone metastases; pain correspondingly; >=18 years; BPI pain >= 2/10; stable dose and schedule of narcotic medications prescribed; planning to receive a single 8 Gy fraction of palliative radiotherapy to one or two target volumes Excluded: haematological malignancies; concurrent use or use within 7 days of the study period of any corticosteroid medication other than topical or inhaled preparations; medical contraindications to corticosteroids such as uncontrolled diabetes, uncontrolled hypertension, or active peptic ulcer;	Intervention: Dexamethasone; 8 mg; two 4 mg tablets; oral; at least 1 h before the start of radiotherapy (day 0) and then every day for 4 days after radiotherapy (days 1–4) 5 days Control: Placebo	EORTC QLQ-C15-PAL Physical change from baseline to day 10: Ex: -1.6 (23.4), C: -3.4 (19.0), p=0.392 EORTC QLQ-C15-PAL Fatigue, change from baseline to day 10: Ex: 5.1 (27.7), C: 4.1 (23.4), p=0.995 Pain flare on days 0–10: Ex: 39/148 (26%), C: 53/150 (35%), absolute difference 8.9% (lower 95%CI bound: 0.0, one-sided p=0.05); Pain flare on days 0–5: Ex: 29/148 (20%), C: 46/150 (31%), absolute difference 11.1% (lower 95%CI bound: 2.8, one-sided p=0.03).	Patients in the dexamethasone group had significantly reduced nausea and functional interference, and improved appetite at day 10 compared with baseline. Grade 3-5 AE: Ex: 19 (bloating 1, fatigue 2, bone pain 11, anorexia 1, hyperglycaemia 3, constipation 1), C: 24 (fatigue 3, bone pain 20, anorexia 1)	RCT Dropouts: Ex: 20 (1 death, 2 declined, 13 missing data, 4 withdrew), C: 21 (1 death, 5 declined, 9 missing data, 5 withdrawn), ITT performed Cochrane score 7/7

		hypokalaemia <3.0 mmol/L; random glucose concentration of >=13.9 mmol/L ; KPS <40; plans to receive cytotoxic chemotherapy within 10 days of radiotherapy. clinical or radiological evidence of spinal cord compression, a pathological fracture, or an impending fracture needing surgical fixation; treatment with a non-steroidal anti-inflammatory drug (NSAID), but patients treated with daily low-dose aspirin for anti-platelet therapy were eligible; received previous radiotherapy to study site or sites were also ineligible Median age: Ex: 68 (58.5 to 75), C: 70 (61 to 77) M:F: 170:128 Tumor types: all (breast, prostate, lung, other) Tumor stages: Bone Metastases				

		Palliative stage: Symptom oriented palliation No information about group comparability				
Eguchi Palliative Support Care 2015	Design: RCT Funding: not governmental organization Epidemiological and Clinical Research Information Network (ECRIN) Number of centers: 22 Country: Finland Setting NR n=35 Inclusion dates: NR	Eligibility criteria: >18 years;advanced cancer confirmed on a histological or cytological examination; life expectancy > 4 months; no future plans for chemotherapy, radiotherapy, or surgical treatment; CRF refractory to other treatments; able to receive medications orally; being treated in a hospital; ALT level <=300 U/ ml, an aspartate aminotransferase (AST) level £300 U/ ml, a creatinine level <=3.0 mg/ dl, and a total bilirubin level <= 3.0 mg/ dl. Excluded: severe heart disease; diabetes mellitus; active gastrointestinal ulcers; viral hepatitis; infectious	Intervention: Methylprednisolone 16 mg; oral; twice daily 7 days Control: Placebo	VAS fatigue, mean difference in change from baseline: -7.50 (–29.13), p=0.484; VAS fatigue, mean change from baseline to day 7: Ex: –1.56 (32.5), C: –9.06 (27.2), p=0.484 Questionnaire for Cancer Patients Treated with Anticancer Drugs (QoL–ACD): A trend toward improvement was evident in the MP group, not significantly different compared with the placebo group.	> grade 3 AE: no significant differences between the two groups: Ex: 3 (diarrhea, peripheral sensory neuropathy, and dyspnea), C: 3 (dyspnea, headache, and fever)	RCT Dropouts: C: 1 withdrawal Cochrane score 7/7

		disease; tuberculosis; received radiotherapy or chemotherapy in the prior four weeks; surgery for cancer in the previous two weeks; history of corticosteroid allergy; administered corticosteroids in the last two weeks; required corticosteroids for other diseases; no adequate understanding of condition. Median age: 69 (46 to 84) M:F: 21:13 Tumor types: all (lung, breast, stomach, colorectal HBP, other) Tumor stages: advanced stage, metastatic Palliative stage: Symptom oriented palliation The demographic and clinical characteristics of the two groups were not significantly different at baseline, though the number of patients with poor performance status was higher in the MP group				

Mercadante American Journal of Palliative care 2007	Design: RCT Funding: NR Number of centers: NR Country: Italy Setting: Palliative care unit n=76 Inclusion dates: NR	Eligibility criteria: Advanced cancer; age 18 to 80 years; presence of cancer pain requiring opioids; moderate to severe pain; admitted to a palliative care unit with facilities for follow-up until death. Excluded: contraindications for using corticosteroids, including severe hypertension, hyperglycemia, fluid retention, and known gastric lesions; important liver or renal involvement; cognitive impairment at referral; received corticosteroids in the previous month; or who presented with a clear indication for the use of corticosteroids other than pain; life expectancy of less than 2 weeks Mean age: Ex: 69 (64-74), C: 67 (62–71) M:F: NR Tumor types: all	Intervention: Dexamethasone; Oral; 8 mg daily; along with their opioid medication as in control group Until death Control: Usual care (continued treatment with strong opioids, including morphine, fentanyl, and methadone)	Well-being (QoL) at 2 weeks: Ex: 4.2 (3.3 to 5.1), C: 2.7 (1.8 to 3.6), p=0.01 Pain intensity at 2 weeks: 1.9 (1.6 to 2.1), C: 2.2 (1.8 to 2.7), p=ns	No evident adverse effects attributed to corticosteroids were found, and no patient stopped the treatment.	RCT Dropouts: 10 (5 death <2 weeks, 2 protocol violation, 2 incomplete, 1 lost) Cochrane score 2/7 downgraded for randomization, allocation concealment, blinding, incomplete outcome data

		Tumor stages: advanced stage Palliative stage: Terminal phase The 2 groups were comparable in terms of gender, age, performance status, survival, primary cancer, principal mechanism of pain, and adjuvant medication				
Paulsen Journal of Clinical Oncology 2014	Design: RCT NCT00676936 Funding: public research funds, government Telemark Hospital Trust and the South-Eastern Norway Regional Health Authority. Number of centers: 5 Country: Norway Setting: palliative care units and outpatient oncology services n=50 Inclusion dates: April 2008 to January 2012	Elligibility criteria: Patients with cancer; age >=18 years with average NRS pain >=4 NRS; >4 weeks expected survival; receiving an opioid for moderate or severe cancer pain Excluded:excruciating pain, NRS >=8 in last 24 hours; use of corticosteroids in the last 4 weeks; diabetes mellitus; peptic ulcer disease; concurrent medication with nonsteroidal anti-inflammatory drugs; radiotherapy or systemic cancer treatment;	Intervention: Methylprednisolone 16 mg; twice daily 7 days Control: Placebo	Fatigue, Mean change from baseline to day 7: Ex : -16.7 (95%CI - 27.0 to -6.3, C 3.3 (95%CI -4.5 to 11.1), p=0.003; Fatigue Baseline: Ex: 77.1 (95%CI 68.3 to 85.9), C: 67.2 (95%CI 56.3 to 78.1) p=0.15; Fatigue Day 7: Ex: 60.4 (95%CI 49.7 to 71.2), C: 70.5 (95%CI 61.4 to 79.6), p=0.16 NRS pain intensity, mean difference in average at day 7: - 0.08 (95%CI -0.97 to 1.13), p=0.50; MRS pain	There were no differences between number of AEs (average Ex: 1.08 (95%CI 0.52 to 1.64), C: 1.55 (95%CI 0.85 to 2.24), p=0.28; Ex: 27 (Oral symptoms 6, restlessness 6, physic change 2, anxiety 2, edema 1, muscle weakness 1, sleepnessless 4, dyspepsia 4, other 2), C: 34 (Oral symptoms 7, restlessness 3, physic change 3, anxiety 3, edema 5, muscle weakness 3, sleepnessless 3, dyspepsia 3, other 3)	RCT Dropouts: Ex: 1 (discontinued), C: 2 (not allocated, discontinued) Cochrane score 7/7

		started <4 weeks before entering the study or planned to start within the study period; spinal cord compression or need of bone surgery; severe cognitive impairment Mean age: Ex: 62.5 (95%CI 59.0 to 65.9), C: 66.0 (95%CI 60.8 to 71.2) M:F: 25:24 Tumor types: all (breast, prostate, GI, Lung, Gyneacologic, other), with metastases Tumor stages: advanced stage; metastatic Palliative stage: NR The two treatment groups had some minor differences in characteristics at baseline, these were corrected for in the data analyses.		intensity, mean average: Ex: 3.6 (95%CI 2.8 to 4.4), C: 3.7 (95%CI 3.0 to 4.4), p=088; NRS pain intensity, mean difference in average change from baseline at day 7: Ex: -0.48 (95%CI -1.43 to 0.47), Ex: -1.16 (95%CI -1.96 to - 0.35), C: - 0.68 (95%CI, -1.28 to -0.08), p=0 .50; NRS pain intensity, corrected mean difference in average change from baseline at day 7: -0.33 (95%CI,- 1.33 to 0.67).		

Uitgangsvraag 3: Psychostimulantia

Wat is het effect van psychostimulantia op vermoeidheid, kwaliteit van leven en functioneren ten opzichte van placebo, geen behandeling of andere (medicamenteuze) behandeling bij patiënten met vermoeidheid bij kanker in de palliatieve fase?

Patiënten Patiënten met vermoeidheid bij kanker in de palliatieve fase
Interventie Psychostimulantia, methylfenidaat, dexamfetamine, modafinil
Comparator Placebo, geen behandeling of andere (medicamenteuze) behandeling
Outcome Vermoeidheid, kwaliteit van leven, functioneren.

Systematic reviews

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and all other outcomes	VII Critical appraisal of study quality
1. Reference	1. Study design 2. Source of funding/conflicts of interest 3. Setting 4. Sample size 5. Duration of the Study	1. Eligibility criteria 2. Patient characteristics 3. Group comparability	1. Intervention(s) 2. Comparator(s)	1. Effect size primary outcome	1. Effect size secondary outcome(s) 2. Effect size all other outcomes, endpoints	1.Level of evidence 2. Dropouts 3. Results critical appraisal
First author Journal Publication year	Specify the type of study Registration number Specify the source of funding	Inclusion criteria Exclusion criteria Age Gender (M:F) Tumor	including dose, length, regimen and timing if relevant	Functioning Fatigue Quality of life Participation	Brief description of secondary outcome(s) and p values. including adverse effects, toxicity	Amstar score

	presence of declaration of interest. Databases Study designs Setting Search date	Stage Palliative stage		Other (primary as defined in the study)		
Mücke Cochrane Database of Systematic Reviews 2015	Design: Cochrane review Funding: None Databases: Medline, EMBASE, CINAHL, Cochrane register of controlled trials, conference proceedings. Study designs: RCT Setting: Palliative care N included studies: 45 (18 studies on cancer, 5 for methylphenidate in palliative cancer, 2	Eligibility criteria: RCT; full reports; fatigue; palliative care; focus on pharmacological treatment (psychostimulants (amphetamines, modafinil, armodafinil, methylphenidate, pemoline), amantadine, corticosteroids (dexamethasone, prednisone, methylprednisolone), donepezil, antidepressants such as selective serotonin reuptake inhibitors (SSRIs; paroxetine), acetylsalicylic acid, megestrol acetate, alfacalcidol and acetyl-L-carnitine.); primary outcome had to be fatigue (or related terms such as asthenia); diseases requiring palliative care or diseases at an advanced, life-threatening stage. Excluded: primary target of clinical conditions such as depression or anxiety; focus on physiological deficiencies such as lack of	Intervention: Methylphenidate, Modafinil 100 to 200 mg/day Other interventions in the review: psychostimulants (amphetamines, modafinil, armodafinil, methylphenidate, pemoline), amantadine, corticosteroids (dexamethasone, prednisone, methylprednisolone), donepezil, antidepressants such as selective serotonin reuptake inhibitors (SSRIs; paroxetine), acetylsalicylic acid, megestrol acetate, alfacalcidol and acetyl-L-carnitine. Control: Placebo	Meta-analysis of 2 studies showed slightly superior effect of methylphenidate compared to placebo: standardised mean difference (SMD) 0.49, 95%CI 0.15 to 0.83. 2 of 3 other studies using other fatigue outcomes showed a significant difference. Modafinil 2 studies of 704 patients with cancer. One showed a significant interaction between treatment condition (modafinil 200mg/day) and baseline fatigue, where patients with severe baseline fatigue benefited from modafinil and patients with mild or moderate fatigue did not. A recent study		Systematic review Dropouts: NR Amstar score: 11/11

	available for meta-analysis) Search date: April 2014	haemoglobin, nor did we focus on drugs targeting specific cytokines; studies comparing different types of cancer-modifying treatment and the effect on prognosis and quality of life; studies which did not focus on pharmacological treatment; studies on fatigue related to antineoplastic treatment (e.g. chemotherapy, radiotherapy, surgical intervention). Mean age: NR M:F: NR Tumor types: all Tumor stages: advanced stage Palliative stage: NR No information about group comparability		demonstrated that both modafinil (100 to 200 mg/day) and placebo led to a clinically significant improvement in FACIT-F scores (Spathis 2014).However, there was no significant difference between placebo and modafinil.		

Primary studies

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and all other outcomes	VII Critical appraisal of study quality
1. Reference	1. Study design 2. Source of funding/conflicts of interest 3. Setting 4. Sample size 5. Duration of the Study	1. Eligibility criteria 2. Patient characteristics 3. Group comparability	1. Intervention(s) 2. Comparator(s)	1. Effect size primary outcome	1. Effect size secondary outcome(s) 2. Effect size all other outcomes, endpoints	1.Level of evidence 2. Dropouts 3. Results critical appraisal
First author Journal Publication year	Specify the type of study Trial number Specify the source of funding presence of declaration of interest. Number of centers Countries Setting Randomized Inclusion dates	Inclusion criteria Exclusion criteria Age Gender (M:F) Tumor Stage Palliative stage p for group comparability.	including dose, length, regimen and timing if relevant Duration of intervention	Functioning Fatigue Quality of life Participation Other (primary as defined in the study)	Brief description of secondary outcome(s) and p values. including adverse effects, toxicity	Classification of intervention studies. Number of dropouts/withdrawals in each group Cochrane Score
Bruera	Design: RCT	Eligibility criteria: advanced cancer; ESAS fatigue score of 4; MMSE normal score (24 of 30);	Intervention: Methylphenidate 5-mg; orally; up to 4	FACIT-F, median changes at day 8 from baseline:	HADS anxiety, median differences in changes:	RCT

Journal of Clinical Oncology 2013	Funding: Government National Institutes of Health National Institute of Nursing Research Number of centers: 2 Country: US Setting: Outpatient palliative care clinics n=190 Inclusion dates: NR	hemoglobin level of 8 g/dL within 2 weeks of enrollment Excluded: history of tachycardia, arrhythmia, uncontrolled hypertension, glaucoma, severe anxiety disorders, major depression, or substance abuse; no current treatment with monoamine oxidase inhibitors, tricyclic antidepressants, clonidine, warfarin, or erythropoietin; pregnant and lactating women Median age: 57.5 (25 to 84) M:F: 62:128 Tumor types: Gastrointestinal, Lung, Breast, Genitourinary, Melanoma, Hematologic, other Tumor stages: advanced stage, at palliative care unit Palliative stage: Symptom oriented palliation No significant differences on baseline characteristics between both groups were found	times daily; Nested allocation to NTI or CTI phone calls four to six times; 2 weeks 14 days Control: Placebo; orally; every 2 hours; up to 4 times daily; Nested allocation to NTI or CTI phone calls four to six times; 2 weeks	Methylfenidaat: 6.0 IQR 0 to 16.0, Placebo: 7.0, IQR, 0.5 to 12.0,p=0 .87; FACIT-F, median changes at day 15 from baseline: Methylphenidate: 5.5 IQR -1.0 to 11.0, Placebo: 6.0, IQR, 2.0 to 11.0 ,p=0 .69; ESAS-Fatigue, median changes at day 8 from baseline: Methylphenidate: -2.0 IQR -3.0 to 0, Placebo: -2.0, IQR, 0-3 to 0,p=0 .98; ESAS-Fatigue, median changes at day 15 from baseline: Methylphenidate: -2.0 IQR -4.0 to 0, Placebo: -2.0, IQR, -5.0 to 0 ,p=0 .86	Methylphenidate: 0.5 IQR -3 to 1, Placebo: -1, IQR, -3 to 1,p=0 .32; HADS depression, median differences in changes: Methylphenidate: 0 IQR -1 to 2, Placebo: -1, IQR, -2.5 to 1,p=0 .08; PSQI, median differences in changes: Methylphenidate: 0 IQR -3 to 1, Placebo: -2, IQR -3 to 1,p=0 .31 The difference in the number of grade 3 adverse events between the MP and PL groups was not statistically significant (40 of 93 patients v 29 of 97 patients, respectively; P .06).	Dropouts: Ex: 23, C: 24 Cochrane score 4/7 (downgraded due to unclear randomization and incomplete outcome assessment)
Butler Brain	Design: RCT	Elligibility criteria: Aged >=18 years, metastatic brain tumor (histologic confirmation of	Intervention: d-MPH 5-mg tablets	FACIT-F fatigue subscale score baseline, the mean (SE)	NR	RCT Dropouts: NR

2007	Funding: healthcare industry or other (give name of organization or corporation) National Cancer Institute/Division of Cancer Prevention CCOP Research Base Grant 1 U10CA81851 and Celgene Corporation. Number of centers: 4 Country: US Setting: Cancer center, University medical center n=68 Inclusion dates: NR	primary or metastatic cancer), or histologically confirmed primary brain tumor (glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic mixed oligoastrocytoma, low-grade glioma, meningioma, or ependymoma); Karnofsky Performance Scale (KPS) >=70; life expectancy >=3 months; hemoglobin >=10.0, white blood cell count >=1,500, and platelets >=75,000; and planned brain RT (partial or whole brain) >=2500 cGy. Patients may have had previous chemotherapy and/or irradiation to sites other than the brain and were allowed to receive chemotherapy concomitantly with the brain irradiation. Excluded: Serious medical or psychiatric illness that would prevent informed consent, completion of protocol therapy, or completion of QOL questionnaires; history of hypersensitivity to d,l-methylphenidate or d-MPH (Ritalin or generic equivalent); patients with a history of steroid psychosis; patients with a history of or who were currently taking	During RT + 8 weeks Control: Matched placebo	Ex: 34.7 (1.4), C: 33.3 (2.4) (p=0.61); 8 weeks post-RT, the least squares estimated means (SEs) adjusted for patient characteristics, Ex: 33.7 (2.3) C: 35.6 (2.5), (p=0.64); Effect 8 weeks post RT –1.9 (95%CI –9.6 to 5.8). No differences in overall QOL measured by the FACT, brain QOL measured by the subscale score, depression measured by the CESD, and global cognition assessed by the MMSE differed significantly by treatment arm at 8 weeks posttreatment or across the entire follow-up period.		Cochrane score 5/7 downgraded for allocation concealment, incomplete outcome assessment

		medications for attention-deficit disorder, anxiety disorder, schizophrenia, or substance abuse; patients taking antidepressants for any reason; patients with a family history of or active Tourette's syndrome; patients with history of or active glaucoma; patients who have received prior brain RT, including stereotactic radiosurgery; patients undergoing craniospinal axis irradiation; patients with hypertension or other cardiovascular disease requiring antihypertensives or other cardiovascular medications; and patients who are pregnant or breast-feeding. Median age: 57.5 (25 to 84) M:F: Ex: 20:14, C: 17:17 Tumor types: Brain tumor (metastatic brain tumor (histologic confirmation of primary or metastatic cancer), or histologically confirmed primary brain tumor (glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic mixed oligoastrocytoma, low-				

		grade glioma, meningioma, or ependymoma);) Tumor stages: NR Palliative stage: NR Patient characteristics are similar for the two groups.				
Hovey Support Care Cancer 2014	Design: RCT Funding: healthcare industry or other (give name of organization or corporation) Sanofi Australia Pty Ltd. Number of centers: 25 Country: Australia Setting: Hospitals (Urban) n=84 Inclusion dates: June 2009 to march 2011	Eligibility criteria: metastatic prostate or breast cancer; undergoing outpatient docetaxel-based chemotherapy every 3 weeks at a minimum dose of 50 mg/m2 who had already received at least 2 cycles of docetaxel and were expected to receive at least two further cycles; MDASI fatigue score ≥4/10 during their previous chemotherapy cycle; 'clinically significant' fatigue, ≥3 on the Somatic and Psychological Health Report somatic subscale, worsening of fatigue after the commencement of docetaxel chemotherapy; hemoglobin level ≥10 g/dL within 2 weeks of study randomization. Excluded: docetaxel dose reduction to less than 50 mg/m2 before cycle three; history of	Intervention: Modafinil 200 mg/day; for a period of 15 days during each 21-day docetaxel chemotherapy 4 periods of 15 days Control: Placebo	The primary endpoint of MDASI fatigue score AUC day 3 – day 10 during TP1 and TP2 was not statistically different between the two treatment arms (p=0.15). MDASI fatigue score AUC day 3 – day 10 for all four TPs combined was not statistically significant (p=0.12). A statistically significant difference in favor of modafinil during TP2 (p=0.03) and TP4 (p=0.03) was noted, suggesting a delayed effect for modafinil.	Grade 3 or 4 AE: Modafinil 17, placebo 4. 1 AE was possibly related to modafinil, 11 to doxecatel, 9 to neither treatment. Nausea and vomiting: modafinil 45.4 %, placebo 25 %. Discontinuation due to AE: modafinil 8 (14.3 %), placebo 4 (14.3 %)). Withdrawal due to AE modafinil: 8, 6 possibly related to modafinil (insomnia, agitation, headache, severe fatigue). Deaths; all placebo (3=prostate cancer)	RCT Dropouts: Ex: 14, C: 4; ITT performed Cochrane score 7/7

		chronic fatigue; uncontrolled hypertension; known hypersensitivity/ intolerance to modafinil or any of the excipients; pregnancy; a psychological or social condition that did not permit treatment or medical follow-up and/or prohibited compliance with the study protocol; serious concomitant illness that would preclude participation in the study Mean age: Ex: 66.4 (10.6, C: 68.0 (10.7) M:F: 65:18 Tumor types: Prostate or breast cancer Tumor stages: metastatic Palliative stage: Disease directed treatment No information about group comparability				
Lundorff Palliative Medicine	Design: RCT	Eligibility criteria: Advanced cancer; Age > 18 years; ESAS tiredness score > 50mm; KPS 40–70%; hemoglobin level >=	Intervention: Modafinil 200mg once; Oral	ESAS Fatigue, difference between	ESAS Depression and drowsiness were statistically significantly	Cross-over RCT Dropouts: Ex: 2

2009	Funding: NR Number of centers: 1 Country: Denmark Setting: Department of Palliative care, general hospital n=28 Inclusion dates: April 2005 to July 2007	6.5 mmol/l; creatinine < 150 mmol/l; total S-calcium < 2.7 mmol/l. Excluded: women who were pregnant or lactating; history of severe anxiety disorders, significant arterial hypertension or untreated tachycardia; CNS metastases; significant hepatic or renal dysfunction; administration of ethinylestradiol, triazolam and monoamine oxidase inhibitors. Median age: 62 (40 to 79) M:F: 16:12 Tumor types: Gastrointestinal, Lung, Breast, Genitourinary, Head/neck Hematologic, other Tumor stages: advanced stage, at palliative care unit Palliative stage: NR There were no statistically significant differences between the two study arms regarding demographics, primary cancer disease and performance status at baseline assessment.	4 days Control: Placebo	groups - 0.857 (2.953), favouring modafinil,p=0.111 Finger Tapping Test (FTT) with the dominant hand and TMT were statistically significantly improved on modafinil treatment compared with placebo (P values. 0.006 and 0.042, respectively). ESAS difference between groups (negative favouring modafinil): Pain -0.071 (2.035), p=0.863; Fatigue - 0.857 (2.953), p=0.111; Nausea -0.286 (0.854), p=0.138; Depression - 1.071 (1.538), p=<0.001; Anxiety 0.250 (2.012), p=0.672; Drowsiness -1.357 (3.423), p=0.038; Shortness of breath - 0.571 (2.098), p=0.089; Appetite -0.607 (3.071), p=0.398; Feeling of well-being - 1.214 (3.489),	improved on modafinil treatment compared with placebo (P values. 0.001 and 0.038, respectively). The frequency and intensity of side effects were similar on both treatments, and there were no statistically significant differences.	Cochrane score 7/7

				p=0.069; Constipation 0.037 (2.139), p=0.874		

Uitgangsvraag 4: Antidepressiva

Wat is het effect van antidepressiva op vermoeidheid, kwaliteit van leven, functioneren ten opzichte van placebo, geen behandeling of andere (medicamenteuze) behandeling bij patiënten met vermoeidheid bij kanker in de palliatieve fase?

Patiënten Patiënten met vermoeidheid bij kanker in de palliatieve fase
Interventie Antidepressiva, paroxetine, of andere (selectieve) serotonineheropnameremmer (SSRI)
Comparator Placebo, geen behandeling of andere (medicamenteuze) behandeling
Outcome Vermoeidheid, kwaliteit van leven, functioneren

Systematic reviews

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and all other outcomes	VII Critical appraisal of study quality
1. Reference	1. Study design 2. Source of funding/conflicts of interest 3. Setting 4. Sample size 5. Duration of the Study	1. Eligibility criteria 2. Patient characteristics 3. Group comparability	1. Intervention(s) 2. Comparator(s)	1. Effect size primary outcome	1. Effect size secondary outcome(s) 2. Effect size all other outcomes, endpoints	1.Level of evidence 2. Dropouts 3. Results critical appraisal
First author Journal Publication year	Specify the type of study Registration number Specify the source of funding presence of declaration of interest.	Inclusion criteria Exclusion criteria Age Gender (M:F) Tumor	including dose, length, regimen and timing if relevant	Functioning Fatigue Quality of life Participation	Brief description of secondary outcome(s) and p values. including adverse effects, toxicity	Amstar score

	Databases Study designs Setting Included studies Search date	Stage Palliative stage		Other (primary as defined in the study)		
Mucke Cochrane Database of Systematic Reviews 2015	Design: Cochrane review Funding: None Databases: Medline, EMBASE, CINAHL, Cochrane register of controlled trials, conference proceedings. Study designs: RCT Setting: Palliative care N included studies: 45 Search date: April 2014	Elligibility criteria: RCT; full reports; fatigue; palliative care; focus on pharmacological treatment (psychostimulants (amphetamines, modafinil, armodafinil, methylphenidate, pemoline), amantadine, corticosteroids (dexamethasone, prednisone, methylprednisolone), donepezil, antidepressants such as selective serotonin reuptake inhibitors (SSRIs; paroxetine), acetylsalicylic acid, megestrol acetate, alfacalcidol and acetyl-L-carnitine.); primary outcome had to be fatigue (or related terms	Intervention: Paroxetine Other interventions in the review: psychostimulants (amphetamines, modafinil, armodafinil, methylphenidate, pemoline), amantadine, corticosteroids (dexamethasone, prednisone, methylprednisolone), donepezil, antidepressants such as selective serotonin reuptake inhibitors (SSRIs; paroxetine), acetylsalicylic acid, megestrol acetate, alfacalcidol and acetyl-L-carnitine.	Paroxetine was tested in a study of 479 patients with cancer without significant effects. However, the Center for Epidemiological Studies Depression (CESD) score, controlling baseline depression scores, confirmed that the dose of paroxetine provided was more effective than placebo in reducing depression (p=0.001).		Systematic review Dropouts: NR Amstar score: 11/11

		such as asthenia); diseases requiring palliative care or diseases at an advanced, life-threatening stage. Excluded: primary target of clinical conditions such as depression or anxiety; focus on physiological deficiencies such as lack of haemoglobin, nor did we focus on drugs targeting specific cytokines; studies comparing different types of cancer-modifying treatment and the effect on prognosis and quality of life; studies which did not focus on pharmacological treatment; studies on fatigue related to antineoplastic treatment (e.g. chemotherapy, radiotherapy, surgical intervention). Mean age: NR	Control: Placebo			

		M:F: NR Tumor types: all Tumor stages: advanced stage Palliative stage: NR No information about group comparability				

Primary studies

I Study ID	II Method	III Patient characteristic	IV Intervention(s)	V Results primary outcome	VI Results secondary and all other outcomes	VII Critical appraisal of study quality
1. Reference	1. Study design 2. Source of funding/conflicts of interest 3. Setting 4. Sample size 5. Duration of the Study	1. Eligibility criteria 2. Patient characteristics 3. Group comparability	1. Intervention(s) 2. Comparator(s)	1. Effect size primary outcome	1. Effect size secondary outcome(s) 2. Effect size all other outcomes, endpoints	1.Level of evidence 2. Dropouts 3. Results critical appraisal
First author Journal Publication year	Specify the type of study Trial number Specify the source of funding presence of declaration of interest. Number of centers Countries Setting Randomized Inclusion dates	Inclusion criteria Exclusion criteria Age Gender (M:F) Tumor Stage Palliative stage p for group comparability.	including dose, length, regimen and timing if relevant Duration of intervention	Functioning Fatigue Quality of life Participation Other (primary as defined in the study)	Brief description of secondary outcome(s) and p values. including adverse effects, toxicity	Classification of intervention studies. Number of dropouts/withdrawals in each group Cochrane Score
Stockler Lancet Oncology 2007	Design: RCT Funding: Government, Non-governmental organization, healthcare industry or other (give name of organization or corporation) The Cancer Councils of New South Wales and South Australia; The National Health and Medical Research Council of Australia;	Eligibility criteria: Advanced cancer defined by the presence of metastatic disease; treatment with palliative intent; >=4 of 10 on scales for depression, anxiety, fatigue, or low energy from the Patient Disease And Treatment Assessment Form (Pt DATA Form; ECOG 0–2; life expectancy >3	Intervention: Sertraline 50 mg; once a day; given orally; to be continued indefiitely. Indefinitely Control: Placebo	FACT-F: Sertaline: 56.8, Placebo: 57.1, Difference 0.3, (95%CI –4·3 to 4·9), p=0·9 FACT-G: Sertaline: 71.9, Placebo: 70.2, diff: 1.7 (95%CI –1.3 to 4.7), p=0.2 Depression scores: CES-D: Sertaline: 23.3, Placebo: 23.7, diff: 0.4,	No other statistically significant differences were observed. Frequency and severity of most AE and all SAE were much the same in both groups. Mild rash or pruritus, and grade 2 or 3 vomiting were more common with sertraline than with placebo; mild oedema was less	RCT Dropouts: 8 weeks: Sertaline: 4 deaths, 25 no quest.; 6 stopped intervention; Placebo: 3 deaths, 10 no quest.; 9 stopped intervention Cochrane score 6/7 downgraded for incomplete outcome

	Pfizer Australia; Pfizer International; and by the Clinical Trials Partnership of the Cancer Institute New South Wales and the NHMRC Clinical Trials Centre Number of centers: 24 Country: Australia Setting: Cancer center, general hospital (Urban) n=189 Inclusion dates: July 2001 to Februari 2006	months; serum creatinine <200 µmol/L; bilirubin <30 µmol/L; ability to complete baseline quality-of-life questionnaires; Excluded: major depression; delirium; coexisting disorders that contraindicated treatment with selective serotonin reuptake inhibitors (eg, hypersensitivity or carcinoid tumour); history of schizophrenia or bipolar aff ective disorder; treatment with antidepressants (including St John's wort) or procarbazine within the past 4 weeks, or with tramadol within the past 7 days. Mean age: NR M:F: 111:78 Tumor types: all Tumor stages: advanced stage; metastatic Palliative stage: Disease directed treatment No information about group comparability		(95%CI –2.6 to 3.4), p=0.8: HADS-D: Sertaline: 24.1, Placebo: 25.4, diff: 1.4, (95%CI –2.2 to 5.0), p=0.4; Pt DATA Form: Sertaline: 19.1, Placebo: 21.1, diff: 2.0, (95%CI –3.8 to 7.8), p=0.5; UBQ-C: Sertaline: 16.9, Placebo: 19.5, diff: 2.6, (95%CI –2.4 to 7.6), p=0.3	common with sertraline than with placebo	

Uitgangsvraag 5: Beweging/lichamelijke activiteit

Wat zijn de effecten van beweging/lichamelijke training op vermoeidheid, kwaliteit van leven en (fysiek) functioneren in vergelijking met geen beweging/lichamelijke training bij patiënten met vermoeidheid bij kanker in de palliatieve fase?

Patiënten Patiënten met vermoeidheid bij kanker in de palliatieve fase
Interventie Beweging/lichamelijke training
Comparator Geen beweging/lichamelijke training
Outcome Vermoeidheid, kwaliteit van leven en (fysiek) functioneren

Systematic reviews

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and all other outcomes	VII Critical appraisal of study quality
1. Reference	1. Study design 2. Source of funding/conflicts of interest 3. Setting 4. Sample size 5. Duration of the Study	1. Eligibility criteria 2. Patient characteristics 3. Group comparability	1. Intervention(s) 2. Intervention 2 2. Comparator(s)	1. Effect size primary outcome	1. Effect size secondary outcome(s) 2. Effect size all other outcomes, endpoints	1.Level of evidence 2. Dropouts 3. Results critical appraisal
First author Journal Publication year	Specify the type of study Registration number Specify the source of funding	Inclusion criteria Exclusion criteria Age Gender (M:F) Tumor	including dose, length, regimen and timing if relevant	Functioning Fatigue Quality of life Participation	Brief description of secondary outcome(s) and p values. including adverse effects, toxicity	Amstar score

	presence of declaration of interest. Databases Study designs Setting Included studies Search date	Stage Palliative stage		Other (primary as defined in the study)		
Dittus Preventive Medicine 2017	Design: Systematic review (Non-Cochrane) NR Funding: Government NIH Databases: PubMed, Ovid Medline and CINHAL Study designs: RCTs, single-arm pre/post interventions, pragmatic studies and prospective cohort studies evaluating programs Setting NR	Eligibility criteria: English language articles; RCTs, single-arm pre/post interventions, pragmatic studies and prospective cohort studies; evaluating programs; testing an intervention with a component of exercise and where at least one third of the sample population had advanced cancer; parameters of physical capacity including aerobe fitness, strength and standard measures of physical function, fatigue and overall QOL.	Interventions: Sixteen focused on exercise (62%) and ten (38%) were multi-modality interventions that included exercise. Interventions varied in length, intensity, exercise activity included, location, and supervision. NR or 6-16 weeks Control: diverse, mostly usual care	Three RCTs showed significant improvement in functional tests compared to controls, not significantly different between groups in one RCT, Another RCT reported significantly better self-reports of physical function compared to control (not tested) Three RCTs identified a significant reduction in fatigue between groups who did and did not receive an exercise intervention; One RCT, in individuals with metastatic breast cancer receiving chemotherapy,	NR NR	Systematic review Dropouts: NR Amstar score: 4/11 (downgraded for lack of protocol, descriptions, quality assessment, publication bias, grey literature)

	N included studies: 26 (14 RCT) Search date: March 2017	Excluded: NR Mean age: NR NR Tumor types: Mixed population of advanced cancer patients 58% of studies (n=15), single cancer type 42% of studies (n = 11, of which 7 lung) Tumor stages: advanced stage Palliative stage: NR No information about group comparability		identified a significant difference in fatigue between the two groups, using chair exercise; Six RCTs observed no significant difference in fatigue between groups. In summary RCT trials did not clearly identify improved fatigue with exercise interventions compared to controls Three RCTs (n=367 participants) identified significant improvements in QOL compared to controls; Six RCTs (n = 231 participants) reported no improvements in QOL compared to controls.		
Salakari Acta Oncologica 2015	Design: Systematic review (Non-Cochrane) NR Funding: NR NR	Eligibility criteria: Advanced cancer or palliative care and rehabilitation; 2009-2014; RCT; adults; abstract and full text available Excluded: Incomplete studies; non-English;	Intervention: Physical exercise; Physical exercise and massage; football training; Resistance training and aerobe exercise	Exercise improves physical performance and has positive effects on several other domains of QoL. Effective rehabilitation	NR We found no adverse effects related to or caused by rehabilitation.	Systematic review NR Amstar score 5/11 downgraded for lack of protocol, grey literature, quality assessment, assessment of publication

	Databases: Medline, Cochrane Study designs: RCT Setting NR N included studies: 13 RCT Search date: September 2014	non-controlled; non-randomized; case reports; clinical practice presentation; treatment protocols and models Mean age: NR NR Tumor types: all Tumor stages (RCTs): Advanced cancer and palliative care and rehabilitation Palliative stage: NR No information about group comparability	NR Control: Variable, but not systematically reported	also improves the overall QoL.		bias, and conflict of interest information
Albrecht CLIN J Oncol Nurs 2012	Design: Systematic review (Non-Cochrane) NR Funding: Public research funds, government National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of	Eligibility criteria: English, published after 1991, and focus on adult participants with advanced-stage cancer, and examine the effects of a form of PA. No exclusion criteria Mean age: NR NR	Intervention: Any form of additional physical movement that resulted in increased energy expenditure (e.g., physical aerobe activity, group exercise, rehabilitation exercises) NR	Seated exercise intervention showed statistically lower fatigue scores compared to the usual care group (p=0.02; 1 study). The intervention group showed clinically significant improvements when compared to the	The intervention group was more likely to be discharged home (p= 0.05; 1 study) and die at home (p=0.01; 1 study).	Systematic review Amstar score: 4/11 (downgraded for lack of protocol, descriptions, quality assessment, publication bias, grey literature)

	Health (#5-K07-AT002943). Databases: Ovid, MEDLINE, CINAHL, and PubMed Study designs: retrospective chart reviews, feasibility studies, case studies, and randomized trials Setting NR N included studies: 16 (2 RCT) Search date: NR	Tumor types: all types Tumor stages: advanced stage Palliative stage: NR Group comparability not reported	Comparators: None or Usual care	standard care group (p-values NR; 1 study). Seated exercise had a slower decrease in reported HRQOL through four cycles of chemotherapy, with trends toward significance than usual care (p=0.07; 1 study)		
Beaton Physiotherapy Canada 2009	Design: Systematic review (Non-Cochrane) NR Funding: NR No conflict of interest (stated) Databases: MEDLINE, EMBASE, CINAHL, PsycINFO, the Cochrane Central Register of Controlled Trials, the Cochrane Databases of	Eligibility criteria: (1) population: persons with metastatic, advanced, or palliative cancer; (2) intervention: exercise as the intervention or a component of the intervention; (3) publication in a peer-reviewed journal. Excluded: Studies of persons with lymphoma, melanoma, or myeloma (these are not considered to be	Intervention: Either (2 studies) 12 weeks exercise, as seated repetitive motion exercises based on a fitness video at home; individualized resistance program with warm-up and cool-down periods, in public facility, or (1 study) 3 weeks, 2-3 /per week Exercise interventions in cancer center involved group-based conditioning and	No aggregate analysis	No aggregate analysis Three of the eight studies specifically reported on adverse effects, and no adverse effects occurred.	Systematic review Amstar score 7/11 downgraded for lack of protocol, grey literature, publication bias. Included RCT scores 8/11

	Systematic Reviews (EBM Reviews—Ovid), and PEDro Study designs: Case series and RCT Setting NR N included studies: 8 (3 RCT) Search date: May 2008	metastatic cancers) and studies in which results of those with metastatic cancer could not be separated from those with non-metastatic cancer; Studies in languages other than English or French, newspaper editorials, critical reviews of individual articles, and qualitative research studies; less than one-third of the sample had metastatic or advanced cancer. Mean age: NR NR Tumor types: all types Tumor stages (RCTs): Advanced and palliative intent Palliative stage: NR Group comparability not reported	relaxation combined with cognitive, social, emotional, and spiritual interventions. 3 weeks (1 study); 12 weeks (2 studies) Control intervention: usual level of care (3 studies); plus, waitlisted with an offer to participate in the exercise intervention at a later date (1 study).			
Lowe	Design: Systematic review (Non-Cochrane)	Eligibility criteria: examine physical activity intervention;	Interventions: Aerobe exercise interventions,	No significant difference (1 RCT)	NR	Systematic review

Journal of Supportive Oncology 2009	NR Funding: NR No conflict of interest (stated) Databases: NR Study designs: all Setting NR N included studies: 6 (1 RCT) Search date: NR	palliative care patients; >18 years; PROMs QoL physical functioning or fatigue Excluded: mixed populations without subgroup analysis Mean age: NR NR Tumor types: all Tumor stages: NR Palliative stage: NR No information about group comparability	mix of aerobe and resistance training 4-52 weeks Control: NR	NR Slower decrease of well-being for intervention (1 RCT) NR NR	NR	Dropouts: NR Amstar score 6/11 downgraded for lack of protocol, search information, grey literature, publication bias.

Primary studies

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and all other outcomes	VII Critical appraisal of study quality
1. Reference	1. Study design 2. Source of funding/conflicts of interest 3. Setting 4. Sample size 5. Duration of the Study	1. Eligibility criteria 2. Patient characteristics 3. Group comparability	1. Intervention(s) 2. Intervention 2 2. Comparator(s)	1. Effect size primary outcome	1. Effect size secondary outcome(s) 2. Effect size all other outcomes, endpoints	1.Level of evidence 2. Dropouts 3. Results critical appraisal
First author Journal Publication year	Specify the type of study Trial number Specify the source of funding presence of declaration of interest. Number of centers Countries Setting Randomized Inclusion dates	Inclusion criteria Exclusion criteria Age Gender (M:F) Tumor Stage Palliative stage p for group comparability.	including dose, length, regimen and timing if relevant Duration of intervention	Functioning Fatigue Quality of life Participation Other (primary as defined in the study)	Brief description of secondary outcome(s) and p values. including adverse effects, toxicity	Classification of intervention studies. Number of dropouts/withdrawals in each group Cochrane Score
Bourke European Urology 2014	Design: RCT ISRCTN88605738 Funding: None No conflict of interest (stated) Number of centers: NR Country: UK Setting NR n=100	Eligibility criteria: ADT; locally advanced or metastatic prostate cancer; sedentary (ie, exercising < 90 min per week at a moderate intensity); receiving continuous ADT for a minimum of 6 mo prior to recruitment; planned long-term retention on ADT	Intervention: Combined tapered (ie, a tapering of supervised support for behaviour change) 30 min aerobe (stationary cycles, rowing ergometers, and treadmills) and resistance exercise and dietary advice intervention delivered with integrated behaviour change	FACT-F: 12 weeks adjusted MD: 5.3 points; 95%CI, 2.7–7.9, p<0.001; 6 months: adjusted MD: 3.9 points; 95%CI, 1.1–6.8, p=0.007	No other differences for other secondary outcomes, except better aerobe exercise tolerance at 6 months for intervention group Ex: atrial fibrillation (n=1); C: death (n=1);	RCT Dropouts: 85% of the cohort completing 12-wk follow-up and 68% of men attending follow-up at 6 mo. Cochrane Score 4/7 downgraded for blinding and possible selective reporting

	Inclusion dates: 2008 to 2011	Excluded: Unstable angina; uncontrolled hypertension; recent myocardial infarction; pacemakers; painful or unstable bony metastases Mean age: 71 M:F: 100:0 Tumor types: Prostate cancer Tumor stages: Locally advanced or metastatic Palliative stage: Disease directed treatment There were no significant differences between groups at baseline (p > 0.05 for all variables).	support; supervised by an exercise physiologist. Twice a week from weeks 1–6, and once per week from weeks 7–12. self-directed independent exercise session once a week from weeks 1–6, and twice per week from weeks 7–12. Small-group healthy eating seminars, lasting approximately 20 min, were carried out every 2 w. 12 weeks Control: Usual care	FACT-G: 12 weeks adjusted MD: 8.9 points; 95%CI, 3.7–14.2, p=0.001; 6 months: adjusted MD: 3.3 points; 95%CI, 2.6 to 9.3, p=0.27	no skeletal related adverse events	
Cheville Cancer 2010	Design: RCT NR Funding: NR No conflict of interest (stated) Number of centers: 1 Country: US Setting: Mixed n=103 Inclusion dates: NR	Eligibility criteria: Adult advanced cancer patients; scheduled to undergo radiation therapy; diagnosis within the last 12 months; an expected survival time of at least 6 months; a 5-year survival probability of no more than 50%; and a treatment recommendation of radiation therapy of at least 2 weeks Excluded: previous radiation therapy; recurrent disease after a disease-free period of greater than 6 months; previous cancer diagnosis within 5 years; Mini Mental Status Examination score of less than 20; ECOG performance score of 3 or more; active alcohol or substance dependence (except nicotine); active thought disorder; suicidal plans; were	Intervention: Structured, multidisciplinary intervention; 8 sessions delivered by a PT and a psychiatrist or psychologist with cofacilitation provided by an advanced practice nurse, licensed social worker, or certified hospital chaplain depending on the theme; 3-day-per week schedule for 90 mins; truncal and upper-limb strengthening exercises; Lower limb strengthening activities 4 weeks Control: Usual care	LASA fatigue (change from baseline): 4 weeks: Ex: -8.3 (23.2), C: 6.3 (29.9), p=0.72; 8 weeks: Ex: -6.6 (27.1), C: -5.1 (28.8), p=0.96; 27 weeks Ex: -9.5 (27.1), C: -6.5 (26.27), p=0.92 LASA overall QoL (mean): 4 weeks: Ex: 72.8 (20.62), C: 64.1 (22.53), p=0.0469; 8 weeks: Ex: 71.9 (19.41), C: 68.4 (23.48), p=0.42; 27 weeks Ex: 72.1	NR NR	RCT Dropouts: Ex: 6 lost; C: 3 lost Cochrane score 3/7 downgraded for randomization, allocation concealment and blinding

		participating in another psychosocial research trial Mean age: 59.5 (range 31-85) M:F: 66:37 Tumor types: all types Tumor stages: advanced stage Palliative stage: Disease directed treatment There were no significant differences between the groups at baseline		(19.49), C: 72.1 (18.97), p=0.99		
Cheville Journal of Pain and Symptom Management 2013	Design: RCT NCT01334983 Funding: Government National Institutes of Health grant KL2 RR024151-01. Number of centers: 1 Country: US Setting: Oncology clinic (Urban) n=66 Inclusion dates: May 2010 to July 2010	Eligibility criteria: Patients with pathology-confirmed Stage IV lung and colorectal cancers; Ambulatory Post Acute Care (AM-PAC) Computer Adaptive Test (CAT) scores between 50 and 75 Excluded: Folstein Mini-Mental State Examination score of 25 or less; inadequate English proficiency, hospice enrollment; an average pain numeric rating scale score of>= 6 of 10 Mean age: Ex: 63.8 (12.5; C: 65.5 (8.9) M:F: 35:31 Tumor types: lung and colorectal Tumor stages: IV Palliative stage: Mixed The groups were well balanced with respect to demographic, cancer type, and treatment characteristics	Intervention: Instructional session in REST as well as a pedometer-based walking program; bimonthly telephone calls; delivered by two PTs; wo sets of five-exercise routines, one targeting the upper and the other the lower body; participants were instructed to perform 10 repetitions of each REST exercise in the upper and lower body routines at least twice a week for a total of four sessions (two upper and two lower body); participants gradually increased their repetitions to 15; pedometers; participants were instructed to walk briskly. 8 weeks Control: Nothing	There was no difference in activity short form (mean change from 0 to 8 week): Ex: 1.56 (5.53) 95%CI -0.72 to 3.84); C: 0.94 (5.91) 95%CI -1.26 to 3.14; p=0.74 FACT-F favored the intervention group (mean change from 0 to 8 week): Ex: 4.46 (8.56) 95%CI0.81 to 8.11); C: -0.79 (9.11) 95%CI -4.26 to 2.67; p=0.03 There was no difference in FACT-G (mean change from 0 to 8 week): Ex: 1.07 (11.60) 95%CI -5.97 to 3.83); C: 0.12 (10.22)	Sleep favored the intervention group (mean change from 0 to 8 week): Ex: 1.46 (1.88) 95%CI 0.70 to 2.22); C: -0.10 (1.71) 95%CI -0.74 to 0.54; p=0.002; There was no difference in pain (mean change from 0 to 8 week): Ex: -0.62 (2.59) 95%CI -1.66 to 0.43); C: -0.50 (2.01) 95%CI -1.25 to 0.25; p=0.87 Deaths Ex: 5, C: 2; no adverse events occurred during or within hours of performing the REST exercises or the walking program.	RCT Dropouts: Ex: 7 lost (5 died); C: 3 lost (2 died) Cochrane score 5/7 downgraded for blinding

				95%CI -3.19 to 4.74; p=0.54 Mobility short form favored the intervention group (mean change from 0 to 8 week): Ex: 4.88 (4.66) 95%CI 2.96 to 6.80); C: 0.23 (5.22) 95%CI -1.76 to 2.22; p=0.002		
Cormie Prostate Cancer and Prostatic Disease 2013	Design: RCT NR Funding: Government Cancer Council of Western Australia. Author supported by Movember through the Prostate Cancer Foundation Number of centers: 1 Country: Australia Setting: Urban n=20 Inclusion dates: July 2011 to July 2012	Eligibility criteria: Histological diagnosis of prostate cancer, established bone metastatic disease as determined by a whole-body bone scan Excluded: Moderate–severe bone pain that limited activities of daily living (i.e., National Cancer Institute's Common Terminology Criteria for Adverse Events grade 2–3 bone pain19) or had musculoskeletal, cardiovascular and/or neurological disorders that could inhibit them from exercising Mean age: Ex: 73.1 (7.5), C: 71.2 (6.9) M:F: 20:0 Tumor types: Prostate cancer Tumor stages: Bone Metastases Palliative stage: NR	Intervention: Twice-weekly resistance exercise sessions for 12 weeks in an exercise clinic; small groups of one to five participants; supervised by accredited exercise physiologists; 60 min sessions, eight exercises that target the major muscle groups of the upper and lower body 12 weeks Control: Usual care	SF-36 physical functioning (group difference in mean change): 0.0 (95%CI -4.2 to 4.2), p=0.996 Fatigue (MFSI-SF) (group difference in mean change): -4.2 (95%CI -17.6 to 9.2), p=0.521 SF-36 general health (group difference in mean change): 1.9 (95%CI -4.1 to 7.9), p=0.508; SF-36 physical health composite (group difference in mean change): -0.1 (95%CI -4.6 to 4.4), p=0.957; SF-36 mental health	No differences in other SF-36, fatigue outcomes (MSFI-SF), BSI; Significant difference in leg extension (p=0.016), 400m walk (p=0.010), 6m walk (p=<0.001); whole body lean mass (p=0.026), appendicular lean mass (p=0.003) No adverse events or skeletal complications occurred during the exercise sessions; Ex: 1 fracture due to fall; Ex: 3 (advancing disease requiring chemotherapy, increased bone pain	RCT Dropouts: Only some assessments missing Cochrane score 5/7 downgraded for blinding

		The two groups were well balanced, with no significant differences in characteristics at baseline or in any of the outcome measures assessed.		composite (group difference in mean change): 2.8 (95%CI -5.3 to 11.0), p=0.475	and fall); C: 1 (advancing disease requiring chemotherapy); P=0.264	
Dhillon Annals of Oncology 2017	Design: RCT ACTRN12609000971235 Funding: Non-governmental organization Lance Armstrong Foundation/National Lung Cancer Alliance Partnership as a Young Investigator Award (no grant number) to JV; the Vojakovic Fellowship from Slater and Gordon Asbestos Research Fund (no grant number); Cancer Institute NSW Clinical Fellowships (05/CRF/1-06, 2006; 09/RIG1-13, 2010) to JV; the ALTG to HD (no grant number), and PoCoG to HD (no grant number) Number of centers: 5 Country: Australia Setting: Hospitals (Urban) n=112 Inclusion dates: July 2009 to October 2014	Eligibility criteria: Histological diagnosis of cancer; an ECOG performance status (PS) 2; life expectancy>6 months; sufficient English to complete questionnaires; and assessed medically fit by treating physician and Physical Activity Readiness Questionnaire (PAR-Q). Excluded: NR Median age: 64 (34-80) M:F: 61:50 Tumor types: Non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) Tumor stages: III/IV Palliative stage: Mixed Group comparability not reported	Intervention: Cancer-specific individualized, 8-week supervised Physical Activity (PA) intervention exercise (Move Your Body, behaviour change sessions) and nutrition (Eat for Health) education materials plus General health education materials. Individualized to baseline fitness and interests. It included a behaviour change program based on Theory of Planned Behaviour. week. Sessions lasted 1h: 45-min PA; 15-min behaviour support. PA was predominantly aerobe, and home-based PA was encouraged. EX participants received a pedometer, PA diary, and workbook. 8 weeks Control: Usual care (UC) (nutrition and PA education materials)	EORTC-QLQ-C30 physical functioning (6 months): EX: 76.67, C: 73.07 (diff 3.6; 95%CI -5.8 to 12.99; p=0.45) FACT Fatigue (6 months, adjusted): EX: 37.07, C: 35.76 (diff 1.31; 95%CI -3.51 to 6.12; p=0.59) EORTC-QLQ-C30 Global QOL (6 months) EX: 61.21, C: 54.42 (diff 6.79; 95%CI -4.39 to 17.97; p=0.23)	No differences at any other EORTC-QLQ-C30 QOL domains (Role functioning, Social functioning); GHQ, Pittsburg Sleep inventory; San Diego shortness of breath Questionnaire; (independent) Activities of daily living. Social cognitive determinants of exercise: EX: 26.64, C: 22.07 (diff 4.57, 95%CI 1.34 to 7.80, p=0.006) No SAE; Other AE: EX: 4 musculoskeletal events likely related to exercise (back or muscle soreness) resolving without treatment, 4 minor adverse events, which resolved without intervention.	RCT Dropouts: Missing's/too unwell/deceased: Intervention (n=56): 2/6/12, control (n=55): 6/12/8 Cochrane score 4/7 (downgraded due to lack of blinding and incomplete outcome assessment)

Galvao Journal of Clinical Oncology 2010	Design: RCT ACTRN12607000263493 Funding: Government Cancer Council of Western Australia. Number of centers: 1 Country: Australia Setting: Urban n=57 Inclusion dates: July 2007 to September 2008	Eligibility criteria: Histologically documented prostate cancer; minimum prior exposure to AST longer than 2 months; without PSA evidence of disease activity; anticipated to remain hypogonadal for the subsequent 6 months. Excluded: Bone metastatic disease; musculoskeletal, cardiovascular, or neurological disorders that could inhibit them from exercising; inability to walk 400 meters or undertake upper and lower limb exercise; and resistance training in the previous 3 months Mean age: Ex: 69.5 (7.3); C: 70.1 (7.3) M:F: 57:0 Tumor types: Prostate cancer Tumor stages: localized and nodal metastases Palliative stage: NR There were no significant differences between groups at baseline.	Intervention: Combined progressive resistance (chest press, seated row, shoulder press, triceps extension, leg press, leg extension and leg curl, with abdominal crunches) and aerobe training (15 to 20 minutes of cardiovascular exercises (cycling and walking/ jogging) at 65% to 80% maximum heart rate and perceived exertion at 11 to 13 (6 to 20 point, Borg scale) twice a week for 12 weeks; one to five participants under direct supervision of an exercise physiologist. 12 weeks Control: Usual care	No difference in SF36 Physical functioning from 0-12 weeks: Ex: 81.7 (14.8) to 82.9 (17.3); C: 74.0 (28.9) to 77.5 (18.7); p=0.441 QLQ-C30-fatigue favored exercise from 0-12 weeks, p=0.021 SF-36 general health favored exercise from 0-12 weeks: Ex from 66.0 (23.1) to 71.4 (17.5); C: from 67.3 (23.1) to 60.2 (26.7), p=0.022 No differences for whole body fat, trunk fat, %fat mass, whole body weight	Soft tissue composition and dynamic muscle strength favored the exercise group. Quality of life assessed by the SF-36 (Table 6) showed better change scores for vitality (P .019), and the physical health composite scores (P .020) for the EX group. Assessments using the QLQ-C30 identified better change scores for EX in role (P .001), cognitive (P .007), nausea (P .025), and dyspnea (P .017), and a borderline difference for physical (P .062), emotional (P .098), pain (P .092), and insomnia (P .055). There were no adverse events during testing or the exercise intervention.	RCT Dropouts: 4 patients in each group had missing data Cochrane score 5/7 downgraded for blinding
Hojan Polish Archives of Internal Medicine 2017	Design: RCT ISRCTN80765858 Funding: NR No conflict of interest (stated) Number of centers: 1 Country: Poland	Eligibility criteria: Histologically confirmed diagnosis of high-risk or intermediate-risk PCa; ADT scheduled for a total period of 36 months; patients before RT (a total	Intervention: 5 exercise sessions/wk for 8 weeks (during RT—between assessments I and II), and 3 d/wk for the next 10 months; either individually (strength training performed with the	QLQ-C30 physical functioning at baseline ex: 79.7 (18.9) C: 81.9 (15.4); 12 months Ex: 78.4 (17.8) C: 65.1 (19.5), p<0.01	Significant advantage of exercise for weight, BMI, waist-to-hip ratio (p<0.001) NR	RCT Dropouts: Ex: 1, C: 5 Cochrane score 5/7 downgraded for blinding

	Setting: Regional cancer center n=72 Inclusion dates: December 2012 to December 2014	dose of 76 Gy in 38 fractions); ECOG 0–1; >= 18 years Excluded: Distant metastases and/or disease progression resulting in RT or the introduction of chemotherapy; with insufficiently controlled arterial hypertension or cardiac diseases resulting in circulation failure (heart failure above class II according to the New York Heart Association classification) or uncontrolled asthma; with insufficiently controlled metabolic diseases or endocrine, rheumatic, and absorption disorders, as well as other tumors; with preexisting bone metastases at high risk for fracture; or with a psychiatric illness or dementia or organic brain disease. Mean age: 66.2 (4.94) M:F: 72:0 Tumor types: Prostate cancer Tumor stages: NR Palliative stage: NR There were no significant differences between groups at baseline.	assistance of a physiotherapist) or in groups (exercises on treadmills or cycle ergometers, supervised by a therapist); brisk walking, running indoors or on a treadmill, various cycling activities (30 min); 25-minute resistance exercises; 65 to 70 minutes total; workout of 60 minutes 12 months Control: Usual care	FACT-F at baseline ex 113.4 (3.5) C:112.9 (3.9); 12 months Ex: 105.8 (7.7) C: 75.5 (8.1), p<0.001 QLQ-C30 global health at baseline ex: 53.7 (18.2) C: 54.1 (23.0); 12 months Ex: 57.4 (19.7) C: 52.3 (17.8), p=0.11 Significant advantage of exercise for distance 6min walk test (p<0.001), significant differences in blood markers only for total Psa, Il-6		
Jensen Support Care Cancer 2014	Design: RCT NR Funding: Non-governmental organization foundation “Stiftung Leben mit Krebs” Number of centers: 1 Country: Germany	Eligibility criteria: Advanced gastrointestinal cancer, including gastric, colorectal, pancreatic, and biliary tract cancer; ≥18 years; life expectancy ≥6 months; beginning of a new palliative treatment line Excluded: Symptomatic brain metastases; uncontrolled	Intervention: RET: resistance exercise training: supervised training sessions over 45 min; twice a week until a total of 24 sessions; 12 weeks; Resistance training of large muscle groups, including the legs, arms, back, and knees, was performed; Strength exercises were	QLQ-C30-physical functioning (change from baseline) RET: -2.4 (95%CI -8.5 to 3.7), AET: -3.3 (95%CI -9.8 to 3.3) QLQ-C30-fatigue (change from baseline)	NR NR	RCT Dropouts: RET: 2 AET: 3 Cochrane score 2/7 (downgraded due to unclear randomization, lack of blinding and incomplete outcome assessment)

	Setting: Outpatient oncology clinic, University hospital n=26 Inclusion dates: NR	cardiovascular diseases; higher grades of osteoporosis; peripheral arterial insufficiency; insufficiently controlled coronary heart disease; arterial hypertension; metabolic diseases Mean age: 55 (13.1) M:F: 11:10 Tumor types: gastric, colorectal, pancreatic, and biliary tract cancer Tumor stages: advanced stage Palliative stage: Disease directed treatment There were no significant differences between groups at baseline.	performed at 60–80 % of the one repetition maximum (1-RM) and consisted of two to three sets of 15–25 repetitions each. Intervention: AET: aerobe exercise training; supervised sessions lasting 45 min on a bicycle ergometer twice a week for 12 weeks. Starting with 60 % of their predetermined pulse rate in week 1–4, the working load was intensified to 70–80 % in week 5–12. The exercise duration started with 10 min in week one and was increased up to 30 min in week 12. 12 weeks	RET: 24.2 (95%CI 0.2 to 48.3), AET: 21.1 (2.5 to 39.6) QLQ-C30-global health status (change from baseline) RET: -14.4 (95%CI -31.6 to 2.8), AET: -13.3 (-26.2 to -0.3)		
Ligibel Cancer 2016	Design: RCT NCT00405782 Funding: Non-governmental organization McMackin Foundation. Number of centers: 2 Country: US Setting: Cancer centers (Urban) n=101 Inclusion dates: September 2006 to March 2011	Eligibility criteria: Metastatic breast cancer or locally advanced disease not amenable to surgical resection, a life expectancy of 12 months, baseline performance of 150 minutes of recreational physical activity per week, and an Eastern Cooperative Oncology Group performance status of 0 to 1 Excluded: Untreated brain metastases, uncontrolled cardiac disease, or other contraindications to moderate-intensity exercise. Mean age: 49 M:F: 0:101	Intervention: 16-week, moderate-intensity aerobe exercise program, delivered through a series of in-person (4 weeks monthly) and telephone contacts (weekly) by an exercise physiologist. Sessions focused on building exercise self-efficacy, overcoming barriers to exercise, documenting any injuries, and reviewing safe exercise practices. Heart rate monitor, a pedometer, and an exercise journal; 6-week membership to a gym in their local area. 16 weeks	EORTC-QLQ-C30 physical functioning (16 weeks, change from baseline): EX: 4.79 (SD 2.4), C: 0.93 (SD 2.1), p=0.23 FACIT-fatigue (16 weeks, change from baseline): EX: 2.7 (SD 8.4), C: 2.7 (SD 9.3) p=0.63 EORTC-QLQ-C30 Global QOL (16 weeks, change from baseline) EX: 6.0 (SD	No differences at any other EORTC-QLQ-C30 QOL domains (Role functioning, Emotional functioning, Cognitive functioning, Social functioning); Nausea/vomiting; Pain; Insomnia; Appetite loss; constipation; Diarrhea. Dyspnea (16 weeks, change from baseline): EX: -6.3 (SD 23.1), C: 4.0 (SD 19.8), p=0.04	RCT Dropouts: Missings/discontinued/never started: Intervention (n=48): 10/10/1, control (n=53): 7/3/2 Cochrane score 2/7 (downgraded due to unclear randomization, lack of blinding and incomplete outcome assessment)

		Tumor types: Metastatic breast cancer or locally advanced disease not amenable to surgical resection Tumor stages: NR Palliative stage: Disease directed treatment "Baseline characteristics were distributed similarly"	Control: Usual care for 16 weeks and was then offered participation in the exercise intervention	17.5), C: -1.0 (SD 21.5), p=0.17 Treadmill test (16 weeks, min. change from baseline): EX: 0.61 (SD 0.2), C: 0.37 (SD 0.2), p=0.35	No injuries or other adverse events were reported	
Litterini Archives of Physical Medicine and Rehabilitation 2013	Design: RCT NR Funding: Non-governmental organization Northern New England Clinical Oncology Society and Exeter Hospital Number of centers: 1 Country: US Setting: Cancer center, palliative care service, rehabilitation department, and a local hospice. n=66 Inclusion dates: February 2010-March 2012	Eligibility criteria; >=18 years; advanced cancer Excluded: debilitating psychiatric illness; mental confusion; decreased mental capacity; difficulty communicating in English; lacked medical clearance. Mean age: 62.35 (12.49) M: F: 30:36 Tumor types: All: most with breast, lung, or colorectal cancer Tumor stages: advanced stage Palliative stage: Terminal phase There were no significant differences in age or seks between groups.	Intervention: Resistance exercises on circuit weight training equipment; Amount of resistance, repetitions, and sets were as tolerated. Intervention: Intervention: Cardiovascular exercises; >1 machine; duration and intensity were progressed as tolerated. 10 weeks	VAS Fatigue (mean difference in change from baseline): 9.03 (95%CI -0.02 to 18.08), p=0.050 SPPB total score (mean difference in change from baseline): 0.75 (95%CI 0.44 to 1.06, p<0.001	VAS pain (Mean difference in change from baseline): 1.71 (95%CI -3.39 to 6.81), p=0.50 No adverse events were reported	RCT Dropouts: Resistance: 11, Cardio: 3 Cochrane score 3/5 downgraded for allocation concealment, blinding and incomplete outcome data
Lopez-Sendin Journal of Alternative & Complementary Medicine 2012	Design: RCT NR Funding: NR No conflict of interest (stated) Number of centers: 1 Country: Spain Setting: Oncology department, university hospital (Urban) n=24	Eligibility criteria: >18 years old; any type of tumor in stage III-IV; intensity of pain > 4 on a numerical pain rate scale Excluded: fragile tissue (skin, hair, or bone); systemic status (e.g., neutropenia, hypercalcemia, hypothyroidism, or anemia); unconscious; unable to complete the	Intervention: physiotherapy: several different therapeutic massage techniques: effleurage, petrissage, and strain/counter strain techniques over the tender points; passive mobilization; active-assisted or active-resisted exercises, and local- and global-resisted exercises, as well as proprioceptive	BPI (2 weeks, difference in change from baseline) worst pain: -1.5 (95%CI -3.08 to -0.08); BPI index: -	NR NR	RCT Dropouts: Ex: 4 (2 sedation, 1 refused, 1 died), C: 5 (1 sedated, 1 chemotherapy, 2 refused, 1 died) Cochrane score 3/5 downgraded for allocation concealment, blinding and incomplete outcome data

	Inclusion dates: NR	questionnaires used; projected to have less than 20 days to live; undergone manual therapy within the past 4 weeks Mean age: Ex: 55 (21), C: 54 (8) M:F: 18:6 Tumor types: all (lung, melanoma, sarcoma, pancreas, breast) Tumor stages: III/IV Palliative stage: Terminal phase No significant differences on baseline characteristics between both groups were found	neuromuscular facilitation (PNF) applied over joints and tight/painful muscles; six sessions of 30–35 minutes in duration over a 2-week period. 2 weeks Control: Sham: simple hand contact or ‘‘simple touch,’’ six sessions of 30–35 minutes in duration over a 2-week period	2.68 (95%CI -4.17 to -1.18); BPI least pain 1.1 (95%CI -1.64 to 3.64); BPI pain on the average -1.33 (95%CI -3.26 to 0.6); BPI pain right now -2.0 (95%CI -3.9 to -0.1)		
Mayo Clinical Rehabilitation 2014	Design: RCT NR Funding: Non-governmental organization MUHC and Research Institute of Pilot Project Competition. Number of centers: 1 Country: Canada Setting: University hospital (Urban) n=26 Inclusion dates: NR	Eligibility criteria: Adults, advanced cancer, undergoing interdisciplinary assessment and rehabilitation, moderate to severe rating of fatigue (VAS≥ 4/10, Cramp et al) Excluded: Unable to walk 100m unaided, waiting for a bone marrow transplant or surgery, uncontrolled pelvic or lower extremity metastatic disease. Mean age: Group 1: 59.6 (11.4) [44–78] Group 2: 57.1 (14.9) [34–88] Group 3: 54.4(12.2) [38–71] M:F: 14:12 Tumor types: all Tumor stages: 2-5 Palliative stage: NR Group comparability not reported	Intervention: During: Individualized 8 weeks walking program based on the participants’ current walking status and progressed according to fatigue level; pedometer; weekly standardized telephone call, during cancer rehabilitation program Intervention: After: Individualized 8 weeks walking program based on the participants’ current walking status and progressed according to fatigue level; pedometer; weekly standardized telephone call, after cancer rehabilitation program 8 weeks Control: Only the cancer rehabilitation program, daily fatigue diary, weekly standardized telephone call	Physical function (2min walktest,adapted CHAMPS, RAND-36) Response: During group: 39%, after group: 67%, Control: 50% Person Fatigue Measures (PFM): Response During Group: 43%, After Group: 68%, Control: 25% EQ-5D VAS response: During group: 64%, after group: 33%, Control: 28%	NR NR	RCT Dropouts: Loss n=12, ITT performed Cochrane score 2/7 (downgraded due to unclear randomization, lack of blinding and selective reporting)

Oldervoll The Oncologist 2011	Design: RCT NCT00397774 Funding: Non-governmental organization Norwegian Foundation for Health and Rehabilitation and the Norwegian Cancer Society Number of centers: 6 Country: Norway Setting: Palliative care units, local/regional hospitals (Mixed) n=231 Inclusion dates: October 2006 and May 2009.	Eligibility criteria: Incurable and metastatic cancer (either locoregional or distant metastases); a life expectancy of 3 months to 2 years; a Karnofsky performance status (KPS) score 60; adequate pain relief (pain intensity 3 on a 0–10 numerical rating scale); the ability to walk; and unimpaired cognitive function Excluded: NR Mean age: Ex: 62.6 (11.3), C: 62.2 (10.7) M:F: 87:143 Tumor types: Gastrointestinal, Lung, Breast, Urological, Gynecological, other Tumor stages: metastatic (100%) Palliative stage: Symptom oriented palliation At baseline, the groups were well balanced with respect to demographics, level of physical activity over the past year, and medical characteristics such as diagnosis, ongoing chemotherapy and radiation treatment, and comorbidities	Intervention: Six circuit stations: exercise for 2 minutes; continuing for 30 minutes in total; lower and upper limb muscle strength, standing balance, and aerobe endurance; Strengthening of the lower limb; Balance: stand on either a trampoline or a thick mat; Strengthening of the upper limb; General functioning: start in the standing position, descend to the floor, lie on back, then roll from side to side, and stand up again; Aerobe endurance: stationary bicycling or treadmill walking. 8 weeks Control: Usual care	Fatigue questionnaire (difference in change from baseline) total fatigue: -0.5 (95%CI -2.0 to 1.0), p=0.53; physical fatigue -0.3 (95%CI -1.6 to 1.0), p=0.62; mental fatigue -0.3 (95%CI -0.6 to 0.3), p=0.53	Other (difference in change from baseline) SWT 60 (95%CI 16 to 103.4), p=0.008; sit to stand 0.5 (95%CI -0.5 to 1.5), p=0.34; maximal stepping 3.0 (95%CI -1.9 to 7.7), p=0.22; handgrip strength 2.0 (95%CI 0.4 to 3.5), p=0.01 NR	RCT Dropouts: Ex: 43 (5 death, 27 disease progression, 11 other), C: 25 (5 death, 16 disease progression, 4 other) Cochrane score 3/5 downgraded for allocation concealment, blinding and incomplete outcome data
Pyszora Support Care Cancer 2017	Design: RCT NR Funding: Non-governmental organization	Eligibility criteria: Advanced cancer; intensity of fatigue ≥4 in a 10- point NRS (Numerical Rating Scale); survival expectancy of a month at the very least; functional status allowing	Intervention: Physiotherapy program. 2-weeks; six therapy sessions (three per week); 30 min per session; active exercises of the upper and lower limbs; selected techniques of myofascial release	ESS fatigue Ex: 4.6 (1.6), C: 6.3 (1.2), p<0.01	NR NR	RCT Dropouts: Ex: 1 death: C: 1 death Cochrane score 4/7 downgraded for blinding, unclear allocation concealment

	Nicolaus Copernicus University CollegiumMedicum, Bydgoszcz, Poland Number of centers: 1 Country: Poland Setting: Palliative care department, University hospital n=60 Inclusion dates: January 2010 - May 2011	the patient to participate in the proposed therapy; ≥18 years old Excluded: anaemia (haemoglobin ≤8 g/dl); the existence of comorbidities causing fatigue (e.g. multiple sclerosis, Parkinson's disease, heart failure); infection requiring antibiotics; age <18; inability to understand written and spoken Polish. Mean age: Ex: 72.4 (9.5), C: 69.3 (13.7) M:F: 21:39 Tumor types: alimentary system, urogenital system, lung, CNS, mammary gland, hematological, indefinite Tumor stages: advanced stage Palliative stage: Symptom oriented palliation Study groups did not differ significantly with respect to age, tumor location and the study site. However, a significant gender difference was observed (p=0.03).	(MFR); selected techniques of proprioceptive neuromuscular facilitation (PNF); dedicated therapist, licensed in PNF method and trained in the application of myofascial release techniques. 2 weeks Control: no exercise	ESAS (12 days): Pain Ex: 1.2 (1.5), C: 1.7 (2.0), p=0.2; nausea Ex: 0.3 (0.8), C: 0.9 (2.0), p=0.1; depression Ex: 2.7 (2.1), C: 2.8 (2.6), p=0.8; anxiety Ex: 2.5 (2.1), C: 2.5 (2.5), p=0.9; drowsiness Ex: 2.3 (2.5), C: 3.8 (2.7), p=<0.05; appetite 3.1 (2.5), C: 3.8 (2.8), p=0.4; well-being Ex: 3.0 (1.2), C: 5.0 (1.3),p=<0.01; breathlessness Ex 0.8 (1.5), 0.9 (1.6), p=0.7		
Rief Radiation Oncology 2014	Design: RCT NCT01409720 Funding: NR NR Number of centers: 1 Country: Germany Setting: Radio oncology department, university hospital (Urban)	Eligibility criteria: Histologically confirmed cancer of any primary and bone metastases of the thoracic or lumbar segments of the vertebral column, or of the os sacrum; age of 18 to 80 years; a Karnofsky performance score ≥ 70; already initiated bisphosphonate therapy	Intervention: RT: resistance training; 2 weeks; 30 min. under the guidance of a physiotherapist; practice at homes three times a week and continued the resistance training themselves until the last investigation after six months. 2 weeks	EORTC QLQ-FA 13: Physical fatigue: Treatment effect (t0-t2) after 3 month p= 0.637, (t0-t3) after 6 month p=0.013; Effect size (t0-t2) after 3 month -0.04, (t0-t3)	NR During the trial there were no adverse events.	RCT Dropouts: 3 months Ex: 5, C: 8; 6 months Ex: 12, C: 12 Cochrane score 4/7 (downgraded due to lack of blinding and incomplete outcome assessment)

	n=60 Inclusion dates: September 2011-March 2013	Excluded: NR Mean age: Ex: 61.3 (10.1), C: 64.1 (10.9) M:F: 33:27 Tumor types: spinal metastases of any origin Tumor stages: metastatic Palliative stage: Disease directed treatment No information about group comparability	Control: Sham-like PT: physical therapy; 2 weeks; 15 min. passive physical therapy in form of breathing exercises for a period of two weeks.	after 6 month -0.71; Emotional fatigue: Treatment effect (t0-t2) after 3 month p= 0.796, (t0-t3) after 6 month p=0.156; Effect size (t0-t2) after 3 month -0.14, (t0-t3) after 6 month -0.35; Cognitive fatigue: Treatment effect (t0-t2) after 3 month p=0.248, (t0-t3) after 6 month p=0.433; Effect size (t0-t2) after 3 month -0.24, (t0-t3) after 6 month -0.19; Interference with daily life: Treatment effect (t0-t2) after 3 month p=0.093, (t0-t3) after 6 month p=0.006; Effect size (t0-t2) after 3 month -0.48, (t0-t3) after 6 month -0.91; Social sequelae: Treatment effect (t0-t2) after 3 month p=0.129, (t0-t3) after 6 month p=0.363; Effect size (t0-t2) after 3 month -0.40, (t0-t3) after 6 month -0.37		

				EORTC QLQ-BM 22: Painful sites: Treatment effect (t0-t2) after 3 month p=0.399, (t0-t3) after 6 month p=0.445; Effect size (t0-t2) after 3 month -0.24, (t0-t3) after 6 month -0.43; Pain characteristics: Treatment effect (t0-t2) after 3 month p=0.905, (t0-t3) after 6 month p= 0.761; Effect size (t0-t2) after 3 month -0.09, (t0-t3) after 6 month -0.24; Functional interference: Treatment effect (t0-t2) after 3 month p=0.285, (t0-t3) after 6 month p=0.081; Effect size (t0-t2) after 3 month -0.21, (t0-t3) after 6 month -0.56; Psychosocial aspects: Treatment effect (t0-t2) after 3 month p=0.001, (t0-t3) after 6 month p=0.010; Effect size (t0-t2) after 3 month -0.79, (t0-t3) after 6 month -0.77		

Taaffe European Urology 2017	Design: RCT ACTRN12609000200280 Funding: Public research funds, government National Health and Medical Research Council 534409, Prostate Cancer Foundation of Australia, Cancer Council of Western Australia, and Cancer Council of Queensland. Number of centers: NR Country: Australia Setting: Urban n=163 Inclusion dates: 2009 to September 2012	Eligibility criteria: Histologically documented PCa; minimum exposure to ADT of 2 mo; without prostate-specific antigen (PSA) evidence of disease activity; anticipated to receive ADT for the subsequent 12 mo Excluded: Bone metastatic disease; musculoskeletal, cardiovascular, or neurological conditions that could inhibit them from exercising; inability to walk 400m or undertake exercise; structured resistance and aerobe training in the previous 3 mo. Mean age: ILRT 68.9 (9.1); ART 69.0 (9.3); 68.4 (9.1) M:F: 163:0 Tumor types: Prostate cancer Tumor stages: localized and nodal metastases Palliative stage: Disease directed treatment There were no significant differences among groups at baseline	Intervention: ILRT month 1-12 (impact loading (bounding, skipping, drop jumping, hopping, and leaping activities) + resistance training (chest press, seated row, shoulder press, leg press, leg extension, and leg curl)): twice weekly in University-affiliated exercise clinics; supervised (up to 10 participants); home training twice weekly that consisted of two to four rotations of skipping/hopping/ leaping/drop jumping. Intervention: ART month 1-6: (aerobe (20–30 min of exercise at 60–75% of estimated maximal heart rate using various modes which included walking/jogging and cycling or rowing) + resistance training (as in ILRT)): supervised exercise in the clinic twice weekly; home-based aerobe activity such as walking or cycling with the goal to accumulate 150 min/wk of aerobe activity; month 7-12: home-based maintenance program 12 months Control: DEL month 1-6: (usual care/delayed exercise) were provided with a printed booklet with information about exercise; month 7-12: twice weekly supervised	From 0 to 12 months: ILRT 27.9 (20.7) to 22.5 (16.6), ART: 23.4 (18.1) to 17.7 (15.0), DEL: 25.8 (20.2) to 20.3 (15.3) Vitality: With training, there was no significant interaction (p=0.525); from 0-12 months: ILRT 50.0 (10.8) to 22.5 (16.6), ART: 51.5 (10.7) to 17.7 (15.0), DEL: 50.3 (10.0) to 20.3 (15.3)	No other differences for cardiorespiratory fitness. For muscle strength there was a significant interaction with treatment No withdrawals due to adverse effects from exercise; ILRT compressed spinal discs (n=1); ILRT shoulder issues (n=1); ART cardiovascular problems (n=2), with one requiring heart bypass surgery; ART back pain (n=1); DEL difficulty walking (n=1); DEL back surgery (n=1).	RCT Dropouts: Three men had missing data for fatigue and one participant had missing data for vitality Cochrane score 3/7 downgraded for blinding, unclear allocation concealment, selective reporting

			exercise on a cycle ergometer at an intensity of 70% maximal heart rate and flexibility exercises in the clinic.			
Uster Clinical Nutrition 2017	Design: RCT NCT01540968 Funding: Non-governmental organization Krebsliga Schweiz (Swiss Cancer Foundation, Switzerland), Number: KFS-2833-08-2011; Werner und Hedy Berger-Janser Stiftung Number of centers: 1 Country: Switzerland Setting: Cancer center n=58 Inclusion dates: March 2012-October 2014	Eligibility criteria: Metastatic or locally advanced tumors; gastrointestinal or lung tract cancer; ECOG <= 2; Life expectancy >6 months Excluded: enteral tube feeding or parenteral nutrition; brain metastases or symptomatic bone metastases; ileus within the last month Mean age: 63.0 (10.1) M:F: 40:18 Tumor types: Metastatic after Colorectal; Oesophago-gastric; NSCLC; SCLC; Pancreas; Others Tumor stages: III/IV Palliative stage: NR At baseline, the groups were well-balanced with regard to demographics, diagnoses, medical characteristics and primary endpoint (p > 0.05).	Intervention: Physical exercise (alongside nutritional intervention): twice a week; groups of two to six patients; supervised by an experienced physiotherapist; 60 min/session; strength and balance training exercises; large muscle groups (arms, pectoral and abdominal muscles, lower back, thighs, and gluteal region); leg press, leg flexion, pull down, abdominal trainer and bench press; Balance training included (i) single leg stance, (ii) tandem stance, (iii) marching in place and (iii) heel raises 3 months Control: Usual care	Physical functioning (change from baseline): 3 months: Ex: 0 (3.3), C: -8.7 (3.8); 6 months: Ex: -1.2 (3.6), C: -2.0 (4.0); p=0.34 Fatigue (change from baseline): 3 months: Ex: -1.5 (4.4), C: 2.2 (5.2); 6 months: Ex -1.3 (4.7), C: -4.9 (5.3); p=0.75 Global health (QoL) (change from baseline): 3 months: Ex: 4.5 (3.4), C: 2.7 (4.0); 6 months: Ex 5.7 (3.7), C: 2.7 (4.1); p=0.72	All other function and symptom scales were not significantly different between groups, except for nausea and vomiting (p<0.01) NR	RCT Dropouts: Ex: 4 death, 1 withdrawal, 4 death; C: 6 death, 3 withdrawal Cochrane score 4/7 (downgraded due to lack of blinding and incomplete outcome assessment)
Vanderbyl Support Care Cancer 2017	Design: RCT NCT01374100 Funding: Non-governmental organization Peter Brojde Lung Cancer Centre; Backler Foundation; Jewish General Hospital Foundation; Angel Ball, Stephen and Lillian Vineberg	Eligibility criteria: Scheduled or eligible for anti-cancer treatment; ECOG 0–2; life expectancy estimated at >4 months. Excluded: exercise contraindicated; active psychiatric conditions; simultaneous participation in interventions to address anxiety or depressive symptoms; history of	Intervention: Qigong: 12 group sessions; 45 mins; 6-weeks; Dedicated physiotherapist; walking exercise program; Dedicated physiotherapist; coordinated arm movements while in a state of deep relaxation or meditation; breathing pattern	6MWT: 6 weeks: change from baseline: QG: -4.0 (45.7), SET: 73.3 (60.1), p=0.002; further physical tests not significant (speed walk, Sit-to-stand, reach forward, reach up)	All other HADS sub scores not significantly different except for poor sleep p=0.03, impaired wellbeing p=0.03, weakness p=0.01) NR	RCT Dropouts: QG: 8, SET: 4 Cochrane score 4/7 (downgraded due to lack of blinding and incomplete outcome assessment)

	and the Lila Sigal Hockey Marathon. Number of centers: 1 Country: Canada Setting: Cancer center, general hospital (Urban) n=36 Inclusion dates: 2009 to 2011	severe cardiac, neuromuscular or skeletal disease or brain metastases. Mean age: QG 66.1 (11.7), SET: 63.7 (7.7) M:F: 14:10 Tumor types: Gastrointestinal, Lung Tumor stages: III/IV Palliative stage: Disease directed treatment	Intervention: SET: Standard endurance and strength training intervention: either individually or in a group; Dedicated physiotherapist 6 weeks	FACT-G: 6 weeks: change from baseline: QG: 3.6 (6.6), SET: 3.5 (14.1), p=0.98 HADS anxiety: 6 weeks: change from baseline: QG: -0.6 (2.1), SET: -0.4 (3.3), p=0.82		

Uitgangsvraag 6: Psychosociale interventies

Wat zijn de effecten van psychosociale interventies in vergelijking met zorg zonder psychosociale interventie op vermoeidheid, kwaliteit van leven en (fysiek) functioneren bij patiënten met vermoeidheid bij kanker in de palliatieve fase?

Patiënten Patiënten met vermoeidheid en kanker in de palliatieve fase
Interventie psychosociale interventies
Comparator Geen psychosociale interventies
Outcome Vermoeidheid, kwaliteit van leven, (fysiek) functioneren

Systematic reviews

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and all other outcomes	VII Critical appraisal of study quality
Poort Cochrane Database of Systematic Reviews 2017	Design: Cochrane review Funding: public research funds, government NIH via PaPaS and Dutch Cancer Society Databases: CENTRAL, MEDLINE, Embase, CINAHL, PsycINFO, and seven clinical trial registries Study designs: RCT N included studies: 14 (qualitative); 12 (quantitative) Search date:	Eligibility criteria: Adult patients (>=18y); incurable (advanced or metastatic) cancer; receiving some form of disease-focused treatment, such as chemotherapy, hormonal therapy, targeted therapy, immunotherapy, surgery, and/or radiation therapy. (subgroup information or >80% of total population). Excluded: Patients received terminal care (i.e. hospice or end-of-life care). Mean age: between 50 and 64 years Tumor types: all Tumor stages: Incurable cancer Palliative stage: Disease directed treatment	Intervention: Cognitive behavioural therapies (n=5); supportive-expressive group therapies (n=3); energy conservation approaches with activity management or sleep modification techniques (n=2); psychosocial support and education with methylphenidate or placebo (n=1); antidepressant medication with problem-solving therapy and behavioural activation (n=2); psychoeducational intervention consisting of education and relaxation with personal feedback (n=1). Control interventions: Usual care, no intervention (n=8); usual care, wait list condition (n=1); attentional control	Very low quality evidence for post-intervention outcome benefit on fatigue of psychosocial interventions (SMD -0.25, 95%CI) -0.50 to 0.00; p=0.05; n = 535, studies = 12; I2 = 43%)	Very low quality evidence for first FU benefit on fatigue of psychosocial interventions (SMD -0.66, 95%CI -1.00 to -0.32; p= 0.0001; n = 147, studies= 4; I2 = 0%). ; Very low quality evidence for no second FU benefit on fatigue of psychosocial interventions (SMD -0.41, 95%CI -1.12 to 0.30; p= 0.26; n = 91, studies = 2,I2 = 29%); Very low-quality evidence for post-intervention benefit of psychosocial interventions for physical functioning (SMD 0.32, 95%CI 0.01 to 0.63; P = 0.04; n = 307, studies = 7; I2 =35%). Very low quality evidence for no first FU benefit of psychosocial interventions in physical functioning (SMD 0.37, 95%CI -0.20 to 0.94; p=0.21; n = 122, studies = 2; I2 = 36%). Very low quality evidence for	Amstar score: 10/11; Risk of bias included studies: Randomization 8/14, Allocation concealment 6/14, blinding 5/14, Incomplete outcome data 8/14, selective reporting 13/14, size 1/14

			(n=3); self-directed educational intervention (n=1); educational materials about breast cancer and its treatment, relaxation, and nutrition (n=1).		no post-intervention effect of psychosocial interventions for social functioning (EORTC QLQ-C30; MD 4.16, 95%CI -11.20 to 19.53; p=0.60; n = 141, studies = 4; I2 = 55%). Very low quality evidence for no post-intervention effect of psychosocial interventions for role functioning (EORTC QLQ-C30; MD 3.49, 95%CI -12.78 to 19.76; p=0.67; n = 143, studies = 4; I2 = 52%). Very low quality evidence for no post-intervention effect of psychosocial interventions for emotional functioning (SMD -0.11, 95%CI -0.56 to 0.35; p=0.65; n = 115, studies = 3; I2 = 23%). Very low quality evidence for no post-intervention effect of psychosocial interventions for cognitive functioning (EORTC QLQ-C30 MD -2.23, 95%CI -12.52 to 8.06, p=0.67; n = 86, studies = 2; I2 = 23%). No apparent differences in adverse events in 3 studies (qualitative analysis)	

Bijlage 10 Methode ontwikkeling

De richtlijnteksten die gebaseerd zijn op uitgangsvragen, zijn opgebouwd volgens het volgende vaste stramien: uitgangsvraag en aanbevelingen, literatuur, conclusies, overwegingen en referenties. De evidence tabellen staan in bijlage 9. De antwoorden op de uitgangsvragen (derhalve de aanbevelingen in deze richtlijn) zijn voor zover mogelijk gebaseerd op gepubliceerd wetenschappelijk onderzoek.
De uitgangsvragen zijn óf evidence-based (via de GRADE-methodiek) óf consensus-based (zonder systematisch literatuuronderzoek) uitgewerkt.

De GRADE-methodiek

Selectie
Naast de selectie van studies op relevantie werd tevens geselecteerd op bewijskracht. Hiervoor werd gebruik gemaakt van de volgende hiërarchische indeling van studiedesigns gebaseerd op bewijskracht:
1. Gerandomiseerde gecontroleerde studies (RCT's)
2. Niet gerandomiseerde gecontroleerde studies (CCT's)

Waar deze niet voorhanden waren werd verder gezocht naar vergelijkend cohortonderzoek.

Critical appraisal
De kwaliteit van bewijs wordt weergegeven in vier categorieën: hoog, matig, laag en zeer laag. RCT's starten hoog en observationele studies starten laag. Vijf factoren verlagen de kwaliteit van de evidentie (beperkingen in onderzoeksopzet, inconsistentie, indirectheid, imprecisie, publicatie bias) en drie factoren kunnen de kwaliteit van de evidentie verhogen (sterke associatie, dosis-respons relatie, plausibele (residuele) confounding) (zie tabel 1).

Tabel 1. GRADE-methodiek voor het graderen van bewijs

Quality of evidence	**Study design**	**Lower if ***	**Higher if ***
High (4)	**Randomized trial**	**Study limitations** -1 Serious -2 Very serious **Inconsistency** -1 Serious -2 Very serious **Indirectness** -1 Serious -2 Very serious **Imprecision** -1 Serious -2 Very serious **Publication bias** -1 Likely -2 Very likely	**Large effect** + 1 Large + 2 Very large **Dose response** + 1 Evidence of a gradient **All plausible confounding** + 1 Would reduce a demonstrated effect, or + 1 Would suggest a spurious effect when results show no effect
Moderate (3)			
Low (2)	**Observational study**		
Very low (1)			

Algehele kwaliteit van bewijs
Omdat het beoordelen van de kwaliteit van bewijs in de GRADE-benadering per uitkomstmaat geschiedt, is er behoefte aan het bepalen van de algehele kwaliteit van bewijs. Zowel voor als na het literatuuronderzoek wordt door de richtlijnwerkgroep bepaald welke uitkomstmaten cruciaal, belangrijk en niet belangrijk zijn.
Het niveau van de algehele kwaliteit van bewijs wordt in principe bepaald door de cruciale

uitkomstmaat met de laagste kwaliteit van bewijs. Als echter de kwaliteit van het bewijs verschilt tussen de verschillende cruciale uitkomstmaten zijn er twee opties:

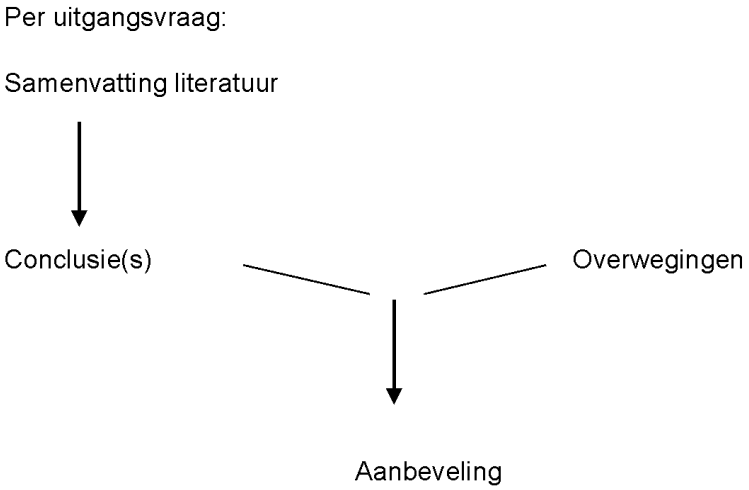
- De uitkomstmaten wijzen in verschillende richtingen (zowel gewenst als ongewenste effecten) of de balans tussen gewenste en ongewenste effecten is onduidelijk, dan bepaalt de laagste kwaliteit van bewijs van de cruciale uitkomstmaten de algehele kwaliteit van bewijs;
- De uitkomstmaten in dezelfde richting wijzen (richting gewenst of richting ongewenst effecten), dan bepaalt de hoogste kwaliteit van bewijs van de cruciale uitkomstmaat dat op zichzelf voldoende is om de interventie aan te bevelen de algehele kwaliteit van bewijs.

Tabel 2. Formulering conclusies op basis van kwaliteit van bewijs per uitkomstmaat

Kwaliteit van bewijs	**Interpretatie**	Formulering conclusie
Hoog	Er is **veel vertrouwen** dat het werkelijk effect dicht in de buurt ligt van de schatting van het effect.	Er is bewijs van hoge kwaliteit dat... *(Referenties)*
Matig	Er is **matig vertrouwen** in de schatting van het effect: het werkelijk effect ligt waarschijnlijk dicht bij de schatting van het effect, maar er is een mogelijkheid dat het hier substantieel van afwijkt.	Er is bewijs van matige kwaliteit dat... *(Referenties)*
Laag	Er is **beperkt vertrouwen** in de schatting van het effect: het werkelijke effect kan substantieel verschillend zijn van de schatting van het effect.	Er is bewijs van lage kwaliteit dat.... *(Referenties)*
Zeer laag	Er is **weinig vertrouwen** in de schatting van het effect: het werkelijke effect wijkt waarschijnlijk substantieel af van de schatting van het effect.	Er is bewijs van zeer lage kwaliteit dat.... *(Referenties)*
Formulering algehele kwaliteit van bewijs: hoog/matig/laag/zeer laag		

Methode voor het formuleren van 'Overwegingen'

Naast de evidence uit de literatuur (conclusies) zijn er andere overwegingen die meespelen bij het formuleren van de aanbeveling. Deze aspecten worden besproken onder het kopje 'Overwegingen' in de richtlijntekst. Hierin worden de conclusies (op basis van de literatuur) geplaatst in de context van de dagelijkse praktijk en vindt een afweging plaats van de voor- en nadelen van de verschillende beleidsopties. De uiteindelijk geformuleerde aanbeveling is het resultaat van de conclusie(s) in combinatie met deze overwegingen.



Figuur 1. Van bewijs naar aanbeveling

Bij het schrijven van de overwegingen zijn onderstaande zaken in acht genomen.

1. Kwaliteit van het bewijs
   Hoe hoger de algehele kwaliteit van het bewijs, des te waarschijnlijker wordt het formuleren van een sterke (positieve of negatieve) aanbeveling.
2. Balans van gewenste en ongewenste effecten
   Hoe groter het verschil is tussen de gewenste en ongewenste effecten, des te waarschijnlijker wordt het formuleren van een sterke (positieve of negatieve) aanbeveling. Hoe kleiner dit verschil of hoe meer onzekerheid over de grootte van het verschil, des te waarschijnlijker wordt het formuleren van een conditionele aanbeveling.
   Toelichting:
   - Bespreken effectiviteit in relatie tot bijwerkingen en complicaties in het licht van de kwaliteit van bewijs, de precisie van de effectgrootte en minimaal klinisch relevant geacht voordeel.
   - Sterkte van het effect vergeleken met geen interventie.
   - Aanwezigheid van comorbiditeit.
   - Klinisch niet relevantie van het effect.
3. Patiëntenperspectief
   Hoe groter de uniformiteit in waarden en voorkeuren van patiënten bij het afwegen van de voor- en nadelen van een interventie, des te waarschijnlijker wordt het formuleren van een sterke (positieve of negatieve) aanbeveling.
4. Professioneel perspectief
   Hoe groter de uniformiteit in waarden en voorkeuren van professionals ten aanzien van de toepasbaarheid van een interventie, des te waarschijnlijker wordt het formuleren van een sterke (positieve of negatieve) aanbeveling.
   Toelichting:
   - Kennis en ervaring met technieken/therapieën.
   - Risico’s die professional loopt bij het toepassen van de interventie.
   - Verwachte tijdbesparing.
   - Verlies aan tijd door het invoeren van de interventie.

N.B.: de hierna volgende factoren (5, 6 en 7) alleen evalueren als een positief geformuleerde aanbeveling wordt overwogen! Een positief geformuleerde aanbeveling is een aanbeveling waarbij een bepaalde interventie wel 'dient' plaats te vinden (sterk) of wel 'kan worden overwogen' (zwak/conditioneel). Als dat daarentegen juist niet het geval is, is sprake van een negatief geformuleerde aanbeveling

5. .Middelenbeslag
   Hoe minder middelen er worden gebruikt (m.a.w. hoe lager de kosten van een interventie zijn vergeleken met de beschouwde alternatieven en andere kosten gerelateerd aan de interventie), des te waarschijnlijker wordt het formuleren van een sterke aanbeveling. Hoe meer onzekerheid over het middelenbeslag, des te waarschijnlijker wordt een conditionele aanbeveling.
6. Organisatie van zorg
   Hoe meer onzekerheid of de geëvalueerde interventie daadwerkelijk op landelijke schaal toepasbaar is, des te waarschijnlijker wordt het formuleren van een conditionele aanbeveling.
   Toelichting:
   - De beschikbaarheid/aanwezigheid van faciliteiten & medicijnen.
   - De wijze waarop de organisatie van de zorg aangeboden dient te worden/grootte van de verandering in de organisatie-zorgproces/infrastructuur voor implementatie.
   - Voorbeeld: een bepaalde diagnostiek of behandeling kan alleen in bepaalde centra worden uitgevoerd in verband met de aanwezigheid van faciliteiten zoals een PET scan.
7. Maatschappelijk perspectief
   (Juridische overwegingen/ethische overwegingen/industriële belangen/vergoeding door verzekeraars/politieke en strategische consequenties)
   Hoe groter de onzekerheid hierover is, des te waarschijnlijker wordt het formuleren van een conditionele aanbeveling.
   Toelichting:
   - Indien twee behandelingen even effectief zijn waarvan één behandeling wordt vergoed, zal deze laatste behandeling mogelijk de voorkeur hebben.

Methode voor het formuleren van aanbevelingen

GRADE kent twee soorten aanbevelingen: sterke aanbevelingen of conditionele (zwakke) aanbevelingen. De sterkte van aanbevelingen reflecteert de mate van vertrouwen waarin – voor de groep patiënten waarvoor de aanbevelingen zijn bedoeld - de gewenste effecten opwegen tegen de ongewenste effecten.

Formulering:

- Sterke aanbevelingen: Doe/geef etc. (of er dient…. te worden gegeven/gedaan)
- Zwakke/conditionele aanbevelingen: Overweeg….. te geven/te doen.

Consensus-based methodiek

Naast de evidence-based uitwerking (GRADE) zijn er ook uitgangsvragen via de consensus-based methodiek uitgewerkt. Hierbij zijn de richtlijnteksten ook gebaseerd op evidence, maar is er geen systematisch literatuuronderzoek gedaan en zijn de gevonden studies niet methodologisch beoordeeld.

Bijlage 11 Implementatie

Bevorderen van het toepassen van de richtlijn in de praktijk begint met een brede bekendmaking en verspreiding van de richtlijn.
Bij verdere implementatie gaat het om gerichte interventies om te bevorderen dat professionals de nieuwe kennis en kunde opnemen in hun routines van de palliatieve zorgpraktijk, inclusief borging daarvan.
Als onderdeel van elke richtlijn stelt IKNL samen met de richtlijnwerkgroep een implementatieplan op. Activiteiten en interventies voor verspreiding en implementatie vinden zowel op landelijk als regionaal niveau plaats. Deze kunnen eventueel ook op maat gemaakt worden per instelling of specialisme. Informatie hierover is te vinden op http://www.iknl.nl/.
Het implementatieplan bij deze richtlijn is een belangrijk hulpmiddel om effectief de aanbevelingen uit deze richtlijn te implementeren voor de verschillende disciplines.

Het plan wordt binnenkort toegevoegd aan de richtlijn.

Bijlage 12 Evaluatie

Momenteel worden methoden voor evaluatie van richtlijnen voor de palliatieve zorg onderzocht.

Bijlage 13 Kennishiaten

De richtlijnwerkgroep heeft tijdens het proces van richtlijnherziening kennishiaten verzameld voor de richtlijn Vermoeidheid bij kanker in de palliatieve fase.
Algemeen kan gesteld worden dat er nog weinig studies van goede kwaliteit beschikbaar zijn voor dit onderwerp en dat de algehele kwaliteit van bewijs voor de conclusies laag tot zeer laag is. Dit heeft tot gevolg dat op basis van literatuuronderzoek de effectiviteit veelal nog niet kan worden aangetoond. Veel zorgverzekeraars hebben als uitgangspunt alleen behandelingen te vergoeden (waaronder o.a. psychosociale interventies), wanneer het effect van de behandeling is aangetoond. Dit komt niet ten goede aan de kwaliteit van leven voor patiënten met kanker in de palliatieve fase met vermoeidheid die mogelijk baat hebben bij de behandeling, maar daarvoor niet in aanmerking komen.
Onderstaand staan de kennishiaten beschreven per uitgangsvraag, waarbij de volgorde de prioriteit aangeeft om nader onderzoek uit te voeren.
De kennishiaten zijn gepubliceerd als bijlage van de richtlijn en worden aangeboden bij de onderzoeksafdeling van IKNL. Daarnaast wordt geïnventariseerd bij welke andere onderzoeksagenda's de kennishiaten worden aangeboden.

Met vermoeidheid samenhangende factoren
Er is nog onvoldoende kennis beschikbaar factoren die samenhangen met de ernst van de vermoeidheid in de verschillende perioden van de palliatieve fase. Meer kennis over deze factoren, zowel somatisch, psychologisch als sociaal, kan aangrijpingspunten geven voor (nieuwe) interventies voor vermoeidheid.

Psycho-educatie
Er is zeer beperkt onderzoek beschikbaar over het effect van psycho-educatie op vermoeidheid in de palliatieve fase. Er werd slechts 1 studie gevonden met bewijs van lage kwaliteit voor een positief effect van psycho-educatie op vermoeidheid. Er is een gebrek aan bewijs voor het effect van psycho-educatie op kwaliteit van leven en (fysiek) functioneren. Onderzoek is gewenst naar de effectiviteit van psycho-educatie in de verschillende periode van de palliatieve fase. Ook is weinig bekend hoe de voorlichting het beste gegeven kunnen worden en welke adviezen gegeven moeten worden. Meer kennis kan helpen om patiënten in de palliatieve fase te coachen in het omgaan met vermoeidheid.

Psychosociale interventies
Voor het beantwoorden van de effectiviteit van psychosociale interventies zijn er een beperkt aantal studies beschikbaar. In deze studies zijn veelal een beperkt aantal patiënten met kanker in de palliatieve fase en met vermoeidheid geïncludeerd. Bij het merendeel van de studies is de aanwezigheid van vermoeidheid bij patiënten voorafgaand aan de interventie geen inclusiecriterium. Onderzoek is gewenst naar vormen van psychosociale interventies die gepast zijn binnen de verschillende perioden in de palliatieve fase.
Ook is er behoefte aan studies die de effectiviteit van specifieke interventies toetst voor patiënten in de palliatieve fase zoals mindfulness en cognitieve gedragstherapie. Daarbij is het ook van belang interventies te ontwikkelen die minder intensief en belastend zijn, denk bijvoorbeeld aan toepassing van e-health of minimale interventies die door specialistisch verpleegkundigen uitgevoerd kunnen worden.

Beweging en lichamelijke activiteit
Vanuit de beschreven literatuur is het niet mogelijk om een eenduidig antwoord te geven op de vraag of beweging/lichamelijke training een gunstig effect heeft op vermoeidheid, kwaliteit van leven en functioneren bij patiënten met kanker in de palliatieve fase. Belangrijke knelpunten zijn de grote heterogeniteit in de bestudeerde interventies, zowel wat betreft type als duur en intensiteit. Daarnaast hebben veel studies, mede door voortijdig uitval, onvoldoende power bereikt, dan wel zijn meerdere studies opgezet als pilotstudie. Ook hebben de meeste studies vermoeidheid niet als inclusiecriterium gebruikt, waardoor niet alle patiënten bij start matig-ernstig vermoeid waren. Onderzoek is gewenst

naar verschillende typen van bewegingsinterventies aangepast aan de conditie van de patiënt in de verschillende perioden van de palliatieve fase. Het is van belang de effectiviteit van interventies te onderzoeken in de groep ernstig vermoeide patiënten.

Medicatie
Omdat er onvoldoende kennis is over de onderliggende pathogenese van vermoeidheid bij kanker in de palliatieve fase, is het vaak niet mogelijk op de oorzaak gerichte, specifieke behandelingen te geven. Studies zijn verricht met corticosteroïden, psychostimulantia en antidepressiva. Belangrijke knelpunten hierbij zijn voortijdige uitval en lage power. Daarbij zijn slechts enkele studies specifiek uitgevoerd met vermoeidheid als inclusiecriterium. Goed-uitgevoerde multicenter studies zijn gewenst met innovatieve strategieën aangepast aan de vaak slechte conditie van patiënten.

Overige kennishiaten:
- Inzicht in de onderliggende pathogenese van vermoeidheid
- Beschermende en risicofactoren van vermoeidheid

Bijlage 14 Afkortingen

4DKL	Vier Dimensionale Klachten Lijst
BFI	Brief Fatigue Inventory
CIS	Checklist Individuele Spankracht
ESAS	Edmonton Symptom Assessment System
EORTC-QLQ-C30	European Organization for Research and Treatment for Cancer Quality of Life Questionnaire
EORTC-QLQ-BM-22	European Organization for Research and Treatment for Quality of Life Questionnaire -Bone Metastases Module
EORTC QLQ-C15-PAL	European Organization for Research and Treatment for Quality of Questionnaire - palliative cancer care patients.
FACT	Functional Assessment of Cancer Treatment
FACT-G	Functional Assessment of Cancer Therapy - General
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue scale
FCS	Fatigue Symptom Checklist
GFS	General Fatigue Scale
HADS	Hospital Anxiety and Depression Scale
MAF	Multi Assessment of Fatigue
MDASI	MD Anderson Symptom Inventory
MQOL	McGill Quality of Life Questionnaire
MVI	Multidimensionele Vermoeidheidsindex
NCCN	National Comprehensive Cancer Network
QoL–ACD	Quality of Life Questionnaire for Cancer Patients Treated with Anti-Cancer Drugs
POMS	Profiles of Mood States
PaTz-groep	Palliatieve thuiszorg
PFS	Revised Piper Fatigue Scale Intensity Subscale
PROMs	Patient Reported Outcome Measures
SQLI	Spitzer Quality of Life Index
USD	Utrecht Symptoom Dagboek
VAS	Visual Analogue Scale