

**Tabel 6. Uitgangsvraag 5 - Welke vorm van revalidatie kan klachten voorkomen/verminderen na afloop van de in opzet curatieve behandeling?,  
Overzicht RCT's**

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient Characteristics and group comparability	Interventions and compliance	Control/Comparator (including duration, dose)	Primary Outcome Measure(s), Secondary Outcome Measure(s)	Effect size - Primary outcome(s) Effect size - Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
Gielsen 2006	RCT	Public research funds	Out-patient clinics		Disease-free cancer patients with severe fatigue	987	6 months	By sequence of labeled cards in sealed numbered envelopes.	Mean age 45; no baseline differences reported	5-26 sessions of Cognitive behavioral therapy; compliance?	Waiting list	Fatigue severity by the Checklist Individual Strength (CIS) subscale and functional impairment by the Sickness Impact Profile (SIP)	CIS: MD 13.3; CI 8.6; 18.1 SIP: MD 383; CI 197,569 More clinically significant improvement in fatigue severity for CBT (54% vs. 4%) and functional impairment (50% vs. 18%) compared to controls	MD Psychological distress 21.6; CI 12.7, 30.4	Open label RCT: envelopes opened by researcher in presence of patients	B

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Milne 2008a	RCT	Public research funds	Hospital-based	Exercise training improves QOL, fatigue, anxiety and fitness	Women with stage I-III breast cancer ≥18 years, <2 years after diagnosis with no evidence of disease recurrence	58/2	24 weeks	Computer-generated program; concealed allocation	Mean Age 55; 70% received chemotherapy	Immediate exercise (IE) (week 1-12): 3 sessions/week of aerobic (+ resistance training (10-15 repetitions of 12 different exercises); 60% compliance	Delayed exercise (DE) (week 13-24): only telephone calls from week 1-12 thereafter intervention described; IE: reverse order; 62% compliance	QOL (FACT-B); fatigue (Schwartz cancer fatigue scale); anxiety (social physique anxiety scale-7); aerobic fitness	QOL: ↑ in IE (21 p) in 1-12 week period compared to ↑ 5.3 p in DE; in week 13-24 ↑ 6.5 in IE and ↑ 30 in DE. (ANOVA: p<0.001) Similar results for other outcomes		Blinding unclear	B
De Backer 2007b	Uncontrolled observational study	Public research funds	Hospital-based	Strength training is more effective than aerobic training	Patients treated with chemotherapy with curative intention.	57/9	18 weeks	Not stated		High intensity strength training; 6 dropped out due to cancer recurrence, 5 for others reasons.	No controls	Muscular strength, VO <sub>2max</sub> , QOL	VO <sub>2max</sub> increased by 10%; muscular strength increased. HRQOL improved		Lack of control group precludes conclusion about effects.	C

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De Backer 2008	Quasi-experimental study	Private funds	Hospital-based	High intensity resistance training improves quality of life	Cancer patients curatively treated with chemotherapy	49/4 and 22/5 controls	1 year	Not applicable	No significant differences in age, gender, cancer diagnosis or drop-outs	18 wks 2/wk training program comprising high intensity (6 exercises targeting large muscle groups at 65-80% of one-repetition maximum) and interval training	No exercise under supervision	Muscle strength, cardiopulmonary function, fatigue, HRQOL	Muscle strength and cardiopulmonary strength improved more in intervention group. No differences between groups in HRQOL or fatigue		Comparable groups; confounding by indication not likely	B

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May 2008	RCT	Public research funds	Referrals to rehabilitation		Patients ≥18 years; last cancer treatment > 3 months; ≥3 positive findings on physical complaints, reduced physical capacity, psychological problems, fatigue or sleep problems	147/144?	1 year	Randomisation list used by independent researcher at each center		Rehabilitation in groups of 8-12 cancer survivors; PT supervised by physical therapists; 84% adherence	CBT supervised by psychologist and social worker; 82% adherence	Physical activity (Physical Activity Scale for the elderly (PASE); VO <sub>2 peak</sub> ; muscle strength  Quality of life (EORTC QLQ-C30)	Changes in exercise capacity, muscle strength and physical activity not different between groups.  No difference between groups		Good quality; lack of blinding participants or staff not likely to effect the results	A2
Daley 2007a	RCT	Public research funds		Exercise therapy improves quality of life	Inactive women treated for localized breast cancer	108/12	8 weeks; follow-up 24 weeks	Telephone randomization using stratified random permuted blocks	Mean age 51; no smokers in intervention group compared to 14 and 11% in control groups	34 exercise therapy: 50 min. 1 to 1 aerobic exercise 77% compliance	36 exercise placebo: 24 1 to 150 min sessions with conditioning/ stretching exercises. 89% compliance. 38 usual care	1: Quality of life (FACT-G) 2nd: fatigue, depression	Exercise vs usual care: MD FACT-G 9.8; CI 2.2, 17. after 8 weeks. Exercise placebo vs usual care: MD 6.6; CI -0.9, 14. No differences after 24 weeks	After 24 weeks modest improvements in depression	Outcome assessors not blinded	B

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Cadmus 2009	RCT (YES study)	Public research funds	Home-based	Exercise improves QOL ans psychosocial and physical functioning	Inactive post-menopausal breast cancer survivors 34-79 years who completed adjuvant therapy ≥1 yr	75/1	6 months	Computer generated; concealed allocation	Mean age 55; groups comparable	Supervised training program at local health club/67%	Usual care + exercise program materials	Happiness, depression (CES-D), anxiety	Overall no significant changes in QOL	In subset of patients with low QOL at baseline intervention better on FACT-B social/family well being (p<0.001) and SF-36 social funct. (p<0.05)		B

**Tabel 7. Uitgangsvraag 6 – Welke vorm van revalidatie kan klachten voorkomen/verminderen tijdens de ziekte- en symptoomgerichte palliatieve fase?**

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size – Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
Brown 2006	Stratified RCT	Linse Bock Foundation and Saint Mary's Hospital Sponsorship Board. No indication of conflicts of interest	Division of Radiation Oncology Mayo Clinic Rochester	To examine the effect of participation in a structured, multidisciplinary intervention on fatigue for advanced cancer patients	Inclusion criteria: adult advanced cancer patients planned to undergo radiation therapy – cancer diagnosis within the last 12 months, expected survival of at least 6 months, but 5-year survival probability $\leq$ 50%, treatment recommendation of radiation therapy for at	Randomized: Intervention: 57; control: 58 Completed week 4 assessment: Intervention: 46; control: 54	4 weeks intervention. Completion of questionnaires at week 4, 8, and 27	Stratification for tumor type, age, gender, and ECOG score, using a minimization procedure that balances the marginal distributions	Comparable groups. 35% women, 80% over 50 years, 60% on current chemotherapy, mean radiation therapy dose 5322 cGy in 29 fractions, 80% married, 55% employed, median hemoglobin 12,3, mean MMSE 28,7, mean POMS 68, mean SDS 66, mean LASA 54, mean STAI 55	Participants attended 8 90-minute sessions over 4 weeks. Manual about the sessions. Each sessions had a theme focusing on quality of life. Begin: 20 minutes exercise, followed by educational information, cognitive-behavioral strategies, discussion, and support. Motion,	No intervention, standard care	Primary: single-item Linear Analogue Self Assessment (LASA) fatigue questionnaire. Secondary: Profile of Mood States (POMS), Fatigue-Inertia Subscale and Vigor-Activity Subscale, Spielberger's State-Trait Anxiety Inventory (STAI), Symptom Distress Scale (SDS)	No significant differences in mean fatigue scores between arms at any week. There were trends not reported favoring the standard treatment (less fatigue when no intervention)	Overall quality of life improved in the intervention arm (i.e. primary endpoint of the initial study, but not reported in detail in this article)	Randomized study, but not blinded (full blinding is not possible because of the intervention, but the investigators could have been blinded). Total number of participants is not that high	B

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					least 2 weeks. Exclusion criteria: MMSE < 20, ECOG ≥ 3, active alcohol or substance dependence (except nicotine), active thought disorder, suicidal plans, participation in psychosocial research trial					stretching, functional exercises. Individualized home program. End of session: relaxation exercise						
Cristopher 2004	Pilot, pre-post study in one group	No information	Oncology Community Outreach Program, University of Massachusetts	To evaluate the impact of a community-based 12-week exercise program on physical and psychosocial well-being in	Participants of fall and winter exercise programs. Women that survived cancer. No criteria about life expect-	21 patients (12 fall exercise, 9 winter exercise)	12 week exercise program, pre- en post-test questionnaires	No randomization	All women, all-most all breast cancer patients, mean age 60 years, almost all white patients, 80%	12 week exercise program, twice a week, low-impact aerobics, toning, flexibility exercises,	No control group	Psychosocial Adjustment to Illness Scale (PAIS-SR), Profile of Mood States-short form (POMS-SF), Symp-	Almost no statistically significant differences were found. In the group that attended the fall exercise statistically	No other outcomes	No comparative design, weak description of important parameters, e.g. exercise program, patient recruitment,	C

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				women cancer survivors	any				married, mean time since diagnosis 44 months, mean time since treatment ended 22 months	relaxation techniques		Tom Distress Scale (SDS), Piper Fatigue Scale (PFS), Quality of Life-Cancer Survivors Scale (QOL-CS)	significant improvement was measured on subscales (domestic environment, psychosocial distress, and social well-being)		poor article, very few patients, no distinction in cancer stage and life expectancy	
Cramp 2008	Cochrane systematic review	No external sources of support, internal source: faculty health social care, University West England, no indications of conflict of interest	-	To evaluate the effect of exercise on cancer-related fatigue during and after cancer treatment	Only RCTs were included. Adults of any age, regardless of gender, tumour type, tumour stage, type of cancer treatment. Patients could be in active treatment, in long-term follow-up or receiving	28 RCTs included, total 2083 patients	-	-	Most patients had breast cancer, stages of cancer varied, stages of treatment varied, most patients were women, mean age 39-69 years	Any exercise intervention aimed to reduce fatigue associated with cancer	No exercise, usual care, alternative treatment	Patient-reported fatigue (multiple scales), exercise maintenance on follow-up, attrition, time spent exercising, aerobic capacity, quality of life measures, anxiety, depression, self-efficacy	Less fatigue in patients that were in the intervention group (SMD -0.23; 95% BI -0.33 - 0.13). Post test changes: intervention more effective (SMD -0.23; 95% BI -0.36 - -0.09) In breast	Only meta-analyses reported in this evidence table. To report valid results of single studies (that are mentioned in the review), one should have more information of those single trials are collected	Good Cochrane systematic review. Value for this guideline however limited, because of no distinction in analyses in subgroups of cancer stage (although these data are collected)	A1



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London 2005	Prospective observational study	Robert Wood Johnson Foundation Promoting Excellence National Program Office, Supportive Care of the Dying	CALL Care sites, facilities of supportive care for the dying: a coalition for compassionate care	To evaluate the CALL-intervention in patient with life-threatening cancer, cardiac illness, respiratory conditions or dementia	palliative care  Cancer stage IV, Car-diac illness stage III or IV or ejection fraction $\leq$ 25%, Dementia stage 6 or 7 of FAST, Respiratory illness Karnofsky score $<$ 50 or required oxygen for activities of daily living	295 patients at enrollment, no completed questionnaires at 18 months (94 patients died during the study)	18 months	No randomization	Mean age 72 years, 62% female, 88% whites, 41% lived at home with family, 21% alone at home, and 26% in a nursing home	CALL Care Approach: a variety of services (e.g. coordinate physician visits, connect with spiritual care provider, educate patient and family, plan for universal activities, pro-active bereavement follow-up), coordinated by a specific multidisciplinary CALL Care team	No control group	Scores on Modified City of Hope Patient Questionnaire (55 items on physical, emotional/relationship, spiritual, health-care experience, and health care providers communication) at enrollment, 1, 3, 6, 9, 12, 15, and 18 months	Comparing the enrollment score and the last data alive there were better, but insignificant scores on fatigue and nausea, and better significant scores on sleep, mouth/ food symptoms (e.g. dry mouth, appetite changes), intestinal problems, breathing	No other outcomes	No comparative design, no information on patient recruitment, large amount of patients lost-to-follow-up, probably selective	C

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Lowe 2009	Systematic review	National Cancer Institute of Canada Canadian Cancer Society, Sociobehavioral Cancer Research Network	-	To review the evidence of physical activity as supportive care intervention in palliative cancer patients	A study had to examine a physical activity intervention in palliative cancer patients, aged 18 years or older, regardless of gender, tumor type, or type of cancer treatment. Palliative cancer was defined as progressive, incurable locally recurrent or metastatic cancer, with a life expect-	6 studies, total 84 patients. All pilot studies, some case-reports	-	-	Mean age 58 years, 64/84 women, most patients having breast cancer, followed by gastrointestinal cancer	Supervised group exercise programs and unsupervised home-based physical activity program (Duke Energizing Exercise Plan for 9 patients, Arm-chair Fitness and gentle exercise video for 38 breast cancer patients, group exercise program focused on muscle strength,	Most studies had no comparison	Primary outcomes: Patient-reported quality of life, patient-reported physical functioning, patient-reported fatigue. Secondary outcomes: objective measures of physical fitness and physical functioning, patient-reported palliative symptoms	In one of the studies significant lower decline in total well-being scores in intervention group. The only RCT showed no significant differences	No other outcomes	Systematic review of poor studies, only one RCT, rest of the studies non-comparative and even case reports. No meta-analysis. Classification on the validity is not possible due to the poor quality of the underlying studies	No level

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					Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size – Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					tancy of less than 12 months				standing balance and aerobic endurance for 34 patients)							
Mustian 2006					Newly diagnosed cancer patients undergoing curative treatment → therefore this study is excluded for further analysis											
Oldervoll 2006	Pilot study, Phase II	Norwegian Foundation for Health and Rehabilitation and the Norwegian Cancer Society. No indication of conflict of interest	Oncological outpatient clinic at St. Olav Hospital in Trondheim and Hos-pice Lovenberg	To evaluate the effect of a 6-week structured exercise program on HRQOL, fatigue, and physical performance in cancer patient with	Cancer patients with a life expectancy between 3 and 12 months, Karnofsky performance score ≥ 60, adequate pain relief, and lived	63 patients at enrollment, 29 patients dropped out due to sudden death, or medical or social reasons. There seems to be	6 weeks	No randomization	15 males, 19 females, mean age 65 years, 88% not employed, median KPS 80, different types of cancer (16 gastro-intestinal cancer),	Exercises in groups (3-8 patients per group), twice a week, 50 minutes per session, 6 weeks long. Warm-up circuit training with 6	No control group	EORTC-Quality of Life Questionnaire-C 30 (EORTC QLQ-C30), Fatigue Questionnaire (FQ), 6 minute walk, timed sit-to-stand, functi-	Significant improvement in emotional functioning (69 → 78, p=0,002). Fatigue score decreased: 51 → 43 (p=0,06; less fatigue).	Increase in walking distance by 29 meter (p=0,007), decrease in time sit-to-stand of 1 second (p=0,001)	Well-documented study, but non-comparative design. Only a few patients in the study	C

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				short life expectancy	less than 30 minutes from the hospital. Consecutive patients	selective follow-up → 34 patients in analysis			80% metastases	stations, relaxation/ stretching session. Focus on muscle strength, standing balance, and aerobic endurance		onal reach	Same trends on other scales. Physical functioning and global quality of life remained stable. Dyspnea reduced (42 → 60, p=0.006), role + social functioning improved (50 → 63, p=0.02 and 55 → 65, p=0.008).			
Porock 2000	Pre-test post-test design, pilot study	Silver Chain Nursing Foundation and Edith Cowan University	Home Hospice Care Service in Perth, Western Australia	To determine the effects of an individualized exercise program (Duke Energizing Exercise Programme)	Patients with advanced cancer, ECOG classification of 1 and more, estimated life expectancy of at least 1	11, 2 dropped out for selective reasons (feeling unwell, finishing it all too much), 6 completed	4 weeks	No randomization	9 patients, mean age 60 years, 6 female, 4 bowel cancer, 2 pancreas cancer, 7 patients with	Physiotherapist specialized in oncology and palliative care conducted home visit and educated the	No control group	Multidimensional Fatigue Inventory (MFI), Symptom Distress Scale (SDS), Hospital Anxiety and	Minimal fluctuation in the mean MFI subscale scores, quality of life scores improved from day 0 to	No other outcomes	Very few patients in the study, lack of complete data, non-comparative study	C



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Strasser 2004	Retrospective descriptive comparative study	Swiss Cancer Research	Multidisciplinary Clinic and traditional pain and symptom management clinic at the University of Texas MD Anderson Cancer Center	To characterize symptoms, recommendations, and effect of multidisciplinary team on symptom expression and overall satisfaction of patient and families. Comparison with traditional pain and symptom management	First 138 consecutive patients at the MD clinic and a consecutive sample of 77 patients seen at the PSM clinic	138 patients in MD clinic, 77 patients in PSM clinic. No lost-to-follow-up due to retrospective design	Retrospective chart analysis, + follow-up (mean 9 days) at MD Center	No randomization	Adults with primary tumors of various types. Referral to the clinics for pain control, end-of-life issues (only MD), and management of multiple symptoms (only MD), 54% female, mean age 54 years, median survival 10 weeks in MD, and 51 weeks in PSM clinic	MD Clinic has no waiting area, patients have private room with bed and bathroom. In 5 hours the patient is assessed by a physician, nurse, social worker, physical, occupational, speech therapist, pharmacist, nurse practitioner, and pastoral care worker. On-site counseling, specific education, and simple interventions	Traditional pain and symptom management given by a physician and a nurse	In MD Clinic: ad-hoc questionnaire with 7 items, to be answered on a 5-point scale, focused on satisfaction. Retrospective chart review on symptoms, results of standardized assessments, and recommendations	In the MD group patients received median 4 non-physician recommendations, in the PSM group none. In MD group significant improvement in pain, nausea, depression, anxiety, sleep, shortness of breath, and well-being, but not in fatigue, anorexia, or drowsiness. No comparative data, patients in	No other outcomes	Both groups are not comparable at baseline due to differences in the severity of the disease. Almost no comparisons have been made between the groups, so this study is best worth given a non-comparative retrospective study, however with useful information	C

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Sola 2004	Cochrane systematic review			To determine the effectiveness of non-invasive interventions delivered by health-care professionals in improving symptoms, psychosocial functioning and quality of life	Only RCT's and CCT's were included. Studies on patients of either sex and any age diagnosed with lung cancer (also with some patients with other thoracic cancer) at any stage of their illness	9 studies	-	-	No aggregate data on patient characteristics, no specific data for those patients in the palliative phase of their disease, all patients had lung cancer	Various interventions have been studied in the RCT's and CCT's, divided in 6 groups: Nursing interventions to manage breathlessness, nursing programs, nutrit-	-	Well-being (subjective or objective perception of improvement in physical health, or of symptoms related to cancer, metastases or side effects of treatment; or improvement of psycho-	Nurse led breathing programs may produce beneficial effects. Nurse follow-up can be as effective and leads to greater patients satisfaction than physician follow-up, coun-	No other outcomes	Well designed Cochrane systematic review with extensive description of the methods, no metaanalysis	A1
										are provided. Multidisciplinary team discussion on assessment and recommendation, given to the patient. Follow-up in 1-2 weeks is provided.			the MD clinic were overall as on subscores very satisfied			

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Temel 2009	Uncontrolled feasibility study	Public funds	Hospital-based	To assess feasibility of exercise program for patients with advanced NSCLC	Patients <12 weeks of diagnosis of non-small cell lung cancer (NSCLC)	25/14	12 weeks	None	Patients aged 48-81 with advanced NSCLC, mostly (70%) treated with chemotherapy	A Structured exercise program consisting of 16 twice weekly sessions over 12 weeks. The program took place in groups (8-10 patients) lasting 90-120 minutes. After warming up a 30 minutes aerobic	No control	Feasibility (adherence to the intervention); secondary: functional capacity (6 m walking test), quality of life (QOL), symptoms and fatigue (FACT-L)	Of 25 accrued patients, 20 completed baseline assessment and 11 attended all sessions (44% adherence); No changes in QOL, fatigue or mood. Lung cancer symptoms improved.	-	It is unclear what selection of eligible patients participated. It is unclear whether observed effect is related to the intervention	C



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Yoshioka 1994	Uncontrolled study		Hospice-based		Terminal cancer patients (<6 months to death) admitted to a hospice and provided with a rehabilitation program.	355/?	6 months		Patients aged 17-88 with terminal cancer	robic exercise. A strength component consisted of 3 sets of 10 repetitions of 6 different exercises over 30-40 minutes	No control	ADL (Barthel index). Questionnaires mailed to relatives 3 months after death.	No adherence data. Most patients experienced some relief		26% of eligible patients accrued in the study	C

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Marciniak 1996	Retrospective case series		Hospital-based		Adult cancer patients admitted for comprehensive inpatient rehabilitation	159			Patients aged 17-88, 38% of which had metastatic disease	sed bed exercises, endurance training, chesty physiotherapy, + some specific treatments	No control	Functional status	Functional gains between admission and discharge (mean 42.9- >56.0) (p< 0.001) Presence of metastatic disease did not influence functional outcome.			C
Headley 2004	Quasi-experimental study				Women ≥17 years with stage IV breast cancer	38/32		No randomization		30min. seated exercise program (armchair fitness) 3	No exercise program	Fatigue and QOL (FACIT-F); pain	Less increase in fatigue and less decline in QOL for		Unclear how patients were assigned to treatment group.	B

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					scheduled to receive chemotherapy and able to sit.					times a week. 84% adherence			experimental group		Subjects in the control group more educated and more frequently unmarried.	