Bijlage 8 : Litertuursearches en evidencetabelle

Uitgangsvraag 1 Wanneer is er sprake van ondervoeding bij patiënten met kanker?

Study	Methods	Pa-tients	Inter-vention	Criteria	Results	Remarks	Level of evidence
Blum 2010	The ongoing development of a new classification system for cancer cachexia, which is based on literature reviews and Delphi processes within the European Palliative Care Research Collaborative.The purpose of this clinical assessment instrument is to really guide practice decisions in clinics.	See results	None	See results	- NCI Common Toxicity Criteria: weight loss with cut points of: 5% loss for Grade 1; 10% loss for Grade 2; 20% loss for Grade 3 and Grade 4 (life-threatening) not defined; - NCCTG-studies: Cancer cachexia was defined as weight loss (involuntary weight loss of 2% in 2 months or 5% in 6 months), anorexia (VAS >3/10; 0 no problem; 10 maximal problem) or impaired oral nutritional intake (<75% than normal or <20 kcal/kg body weight). These definitions are simple but might not depict the highly complex dimensions of cancer cachexia notably the composition of the weight loss, functional consequences of wasting, and underlying factors contributing to weight loss; - The Patient-Generated Subjective Global Assessment is a more extensive consideration of cachexia-related variables (weight history, amount and type of food intake, functional status score, symptoms related to food intake, physical examination focusing on body composition, comorbid conditions, age, cancer stage, the presence of fever, and corticosteroid use); - A generic definition for cachexia/wasting disease associated with any form of chronic illnesses including cancer was recently composed in a consensus meeting of international experts on this topic: weight loss with or without fat loss, and as additional criteria (three required for diagnosis) decreased muscle strength, reduced muscle mass, fatigue, anorexia, or biochemical alterations (anemia, inflammation, and low albumin) (Evans). - Based on a study in 170 weight-losing cancer patients	The development of a new classification system for cancer cachexia is still ongoing.	**D?**

					Fearon proposed a definition for cancer cachexia based on the simultaneous presence of three factors: (1) weight loss >10%, (2) low food intake <1,500 kcal/day, and (3) systemic inflammation, CRP >10 mg/l.; - Bozetti and the SCRINIO Working Group recently proposed a cancer cachexia classification after examining a database of 1,307 cancer outpatients. They defined a four different stages of severity based on weight loss of more than 10% or less than 10% and on the presence of the three symptoms: anorexia, early satiety, or fatigue. The stages range from asymptomatic pre-cachectic (or patients "at risk for cachexia") to symptomatic cachectic. The preceding attempts to define or clinically classify cancer cachexia have some evident limitations. They are notably heterogeneous in the number and type of included variables. Assessment of weight loss is a common point, but rather disparate cut points (2%, 5%, 10%, 20%, or other) are used without any statistical justification; some address bodycomposition and others do not. Symptoms, such as anorexia, anemia, early satiety, or fatigue may appear; however, these are not consistently included. For cancer cachexia, the value of fatigue to diagnose cachexia seems questionable and anemia has a high prevalence in cancer patients owing to antineoplastic therapy.		
van Bokhorst–de van der Schueren 1997	Transversal observational study	n= 64 (44 previously untreated tumour; 20 recurrence after previous radiothera	None	Percent weight loss during the past six months (PWL). For this purpose, actual weight was	<table><tr><td>Weight loss >10%, previous 6 months</td><td>20 (31%)</td></tr></table>	Aim: To define the usefulness of six different parameters in scoring malnutrition	**C**

		py) Mean age: 61 ± 10 years Inclusioncriteria: T2–T4 histologically proven squamous cell carcinomas of the oral cavity, larynx, oropharynx, or hypopharynx who were eligible for surgery. Recruitment: patients admitted to the department of Otolaryngology/Head and Neck Surgery of the Free		measured, and usual body weight, defined as the body weight of 6 months prior, was requested; Percent ideal body weight (PIW) (length and wrist circumference were used to work out frame size). PIW computed as the midpoint of the weight range for a given height and frame size from the 1983 Metropolitan Life Insurance Tables. The PIWs 80% to 90%, 70% to 79%, and <69% can be interpreted as mild malnutrition,	<table><tr><td>PIW ≥ 90% PIW 80% - 89% PIW 70% - 79% PIW <80%</td><td>49 (77%) 11 (17%) 2 (3%) 2 (3%)</td></tr><tr><td>Alb ≥35 Alb 27–34 Alb 21–26 Alb <21</td><td>51 (80%) 12 (19%) 1 (2%) -</td></tr><tr><td>NI ≥1.31 NI <1.31</td><td>21 (33%) 43 (67%)</td></tr><tr><td>TLC ≥1800 TLC 1500–1799 TLC 900–1499 TLC <900</td><td>28 (44%) 16 (25%) 17 (27%) 10 (2 %)</td></tr></table> Conclusion: The different nutritional parameters used in the literature do not accurately reflect the nutritional status of the head and neck cancer patient, because malnutrition can vary between 20% and 67%, depending on the parameter used.		

		University Hospital, The Netherlands		moderate malnutrition, and severe malnutrition, respectively. Nutritional index (NI). NI=(0.14 × Alb (g/L)) + (0.03 × PIW (%)) + (0.73 × TLC (109/mm3)) – 8.90. An outcome less than 1.31 was considered to be deviating from a normal nutritional status. Serum albumin (Alb). Albumin levels between 27 and 35 g/L reflect mild depletion; between 21 and 27 g/L, moderate depletion; and <21 g/L, severe			

				depletion. Total lymphocyte count (TLC). TLC of 1500–1800 mm3 is considered to reflect mild depletion; 900–1500 mm3, moderate depletion; and <900 mm3, severe depletion. Body fat (BF) and lean body mass (LBM).			
Bosaeus 2001	Cross-sectional study	n= 297 M: 160, F: 137 Mean age: 67 years (range: 30–90 years) Tumour localization: Colorectal (n= 82), Pancreatic (n=71), Upper	None	Dietary intake of energy and protein from a 4-day food record Height, weight and weight loss	BMI: < 18,5 kg/m^2 10% 18,5-25 kg/m^2 62% > 25 kg/m^2 28% - Weight-stable (actual weight within 5% of habitual weight before the onset of disease) 29% - Weight gain (actual weight > 5% above habitual weight) 5% - Moderate weight loss (5-10% of pre-illness weight) 24% - Severe weight loss (> 10% of of pre-illness weight) 43% Energy intake: kcal/day 248 - 4,650 Mean (SD) 1,716 (627) (no sign. differences between weight-losing or in underweight patients)	Aim: To investigate whether changes in dietary intake could explain reported weight loss in unselected patients with generalized malignant disease of solid tumour type.	**C**

		gastrointestinal (n=66), Biliary (n=48), Other (n=32) Inclusioncriteria: generalized malignant disease (tumour spread to local or distant lymph nodes), with a solid tumour type; no other efficient or established tumour treatment; and expected survival of 6 months or more. Recruitment: Department of			kcal/kg.day Mean (SD) (underweight cancer patients (n=29) had a higher energy intake compared to cancer patients of normal weight (n=184) and patients with >10% weight loss (n=127) had a higher energy intake per unit weight compared with weight-stable cancer patients (n=85) Protein intake: g/day Mean (SD) (no sign. differences between weight-losing or in underweight patients) g/kg.day mean (SD) (no sign. differences in protein intake per unit body weight in weightlosing cancer patients compared to weight-stable cancer patients; protein intake per unit body weight in underweight cancer patients was higher compared to normal-weight cancer patients)	4 – 77 26 (10) 17 - 197 66 (24) 0.2 – 3.1 0.99 (0.39)		

<table>
<tr><td></td><td></td><td>Surgery, University Hospital Go¨teborg, Sweden</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Bovio 2008</td><td>Case serie</td><td>n= 144
Male: 92, Female: 52
Mean age: 67 years (range 29-90 years)
Data about weight loss:
Male: 83, Female: 45

Inclusion criteria: advanced cancer without treatment options, admitted to the Palliative Care Unit of the Maugeri foundation in Pavia (Italy)</td><td>None</td><td>Criteria for malnutrition:
BMI<18,5 kg/m^2
Weight loss > 10% in the last 6 months

ArmFatArea (ARA) < 5^e percentile compared to the reference value
ArmMuscleArea (AMA) < 5^e percentile compared to the reference value</td><td>
<table>
<tr><th></th><th>Female</th><th>Male</th></tr>
<tr><td>BMI<18,5 kg/m^2</td><td>23%</td><td>13%</td></tr>
<tr><td>Weight loss > 10% in the last 6 months</td><td>44%</td><td>63%</td></tr>
<tr><td>Triceps Skinfold Thickness < 5^e percentile compared to the reference value</td><td>35%</td><td>14%</td></tr>
<tr><td>Arm circumference < 5^e percentile compared to the reference value</td><td>37%</td><td>65%</td></tr>
<tr><td>ARA < 5^e percentile compared to the reference value</td><td>38%</td><td>23%</td></tr>
<tr><td>AMA < 5^e percentile compared to the reference value</td><td>19%</td><td>63%</td></tr>
</table>
</td><td>Aim: to compare different methods of measurement for malnutrition. Percentages depend on the used criteria. In this study be aware of referral bias and exclusion.</td><td>C</td></tr>
</table>

<table>
<tr>
<td></td>
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<td>Exclusion criteria: patients receiving artificial nutrition, non-cooperative patients and patients not able to undergo anthropometric measurements</td>
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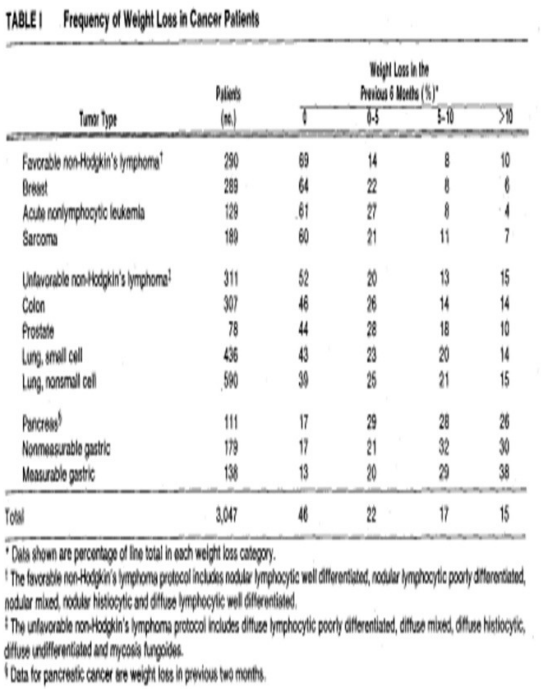
<tr>
<td>Bozetti 2009</td>
<td>Multicentre case serie</td>
<td>1000 patients from January 2004 till July 2007 Italy
Mean age: 64 years (range 18-92 years)
Gender ratio → M:F = 1:8</td>
<td>None</td>
<td></td>
<td>See Table: Mean weight loss per tumour type and tumour stage
<table>
<tr><td>Primary tumor</td><td>% weight loss</td><td>nutritional score</td></tr>
<tr><td>esophagus</td><td>15.9/16.3(-16.2 to 40.l)</td><td>3.0/3.6 (0.0-6.0)</td></tr>
<tr><td>pancreas</td><td>15.1/16.4(-3.8 to 36.9)</td><td>3.0/2.9 (0.0-6.0)</td></tr>
<tr><td>stomach</td><td>11.7/15.0(-9.6 to 43.0)</td><td>2.0/2.5 (0.0-6.0)</td></tr>
<tr><td>smallbowel</td><td>4.1/5.0 (-8.9 to 22.0)</td><td>1.0 (0.0-4.0)</td></tr>
<tr><td>Colon-rectum</td><td>5.2/8.0 (-20.0 to 43.0)</td><td>1.0 (0.0-6.0)</td></tr>
<tr><td>lung</td><td>6.6/9.5(-22.5 to 42.9)</td><td>2.0/2.3(0.0-5.0)</td></tr>
<tr><td>Head-neck tumorstage</td><td>7.7/9.0 (-22.7 to 32.2)</td><td>2.0/2.1 (0.0-5.0)</td></tr>
<tr><td>0</td><td>2.1/2.1 (-5.9 to 5.0)</td><td>0.0/0.0 (0.0-0.3)</td></tr>
<tr><td>1</td><td>6.0\6.4 (-8.9 to 32.5)</td><td>1.0/1.0(0.0- 5.0)</td></tr>
<tr><td>2</td><td>7.4/9.4 (-8.4 to 37.3)</td><td>2.0/2.0 (0.0-5.0)</td></tr>
<tr><td>3</td><td>8.3/8.5 (-16.2 to 43.0)</td><td>2.0/2.0 (0.0-5.0</td></tr>
<tr><td>4</td><td>6.9/9.4 (-22.7 to 40.1)</td><td>1.0/1.0 (0.0-5.0)</td></tr>
<tr><td>ECOG perf. score</td><td></td><td></td></tr>
<tr><td>0</td><td>3/1/3.3 (-22.7-32.5)</td><td>1.0/1.0 (0.0-5.0)</td></tr>
<tr><td>I</td><td>8.3/8.6 (-20.0 to 43.0)</td><td>2.0/2.0 (0.0- 5.0</td></tr>
</table></td>
<td>Aim: to assess the prevalence of malnutrition in patients with different types of cancer. Differences in weight are reported, not differences in prevalence.</td>
<td>C</td>
</tr>
</table>

					II	14.3/14.4 (-11.6 to 43.0)	3.0/3.0 (0.0-6.0)
					III	15.9/16.2 (-2.9 to 42.9)	4.0/4.0 (0.0-6.0)
					IV	21.4/22.3 (17.8 to 35.0)	4.5/4.5 (4.0-5.0)
					therapy		
					Never done/completed	7.9/10.1 (-20.0 to 43.0)	2.0/1.1(0.0-6.0)
					One ongoing	7.3/7.3 (-22.7 to 43.0)	1.0/1.1 (0.0-5.0)
					Two/three ongoing	8.6/11.3 (-8.2 to 27.5)	2.0/1.7(0.0-5.0)
Correia 2007	Case serie	44 patients with gastric cancer December 2003 - November 2004 Inclusion criteria: recent (<4 weeks) diagnose gastric cancer Exclusion criteria: patients receiving artificial nutrition or	None		**Criteria voor cachexia:** weight loss > 5% in the past months OR weight loss >10% in the past 6 months PG-SGA (well-nourished, mild malnutrition and severe malnutrition) Prevalence of malnutrition dependent of the method of measurement, in gastric cancer patients between 30 and 70% TNF-α and IL-1 can be used as proxy for PG-SGA TN-α correlates with all Quality of Life dimensions	Aim: : to evaluate whether TNF-α could be used as early prognostic indicator for increased risk of malnutrition. Small number of patients. Only one type of cancer.	**B/C** (comparing different measures of weight loss related to TNF-α)

		submitted to major surgery, radiotherapy or chemotherapy in the year prior to assessment, as well as with chronic and cachetizing conditions other than gastric cancer					

Dewys 1980	Reanalysis of the data derived from case records of patients who participated in 12 prospective chemotherapy trials of the Eastern Cooperative Oncology Group	N=3047 Exclusion: no information about weight loss available	None		 TABLE I Frequency of Weight Loss in Cancer Patients * Data shown are percentage of line total in each weight loss category. † The favorable non-Hodgkin's lymphoma protocol includes nodular lymphocytic well differentiated, nodular lymphocytic poorly differentiated, nodular mixed, nodular histiocytic and diffuse lymphocytic well differentiated. ‡ The unfavorable non-Hodgkin's lymphoma protocol includes diffuse lymphocytic poorly differentiated, diffuse mixed, diffuse histiocytic, diffuse undifferentiated and mycosis fungoides. § Data for pancreatic cancer are weight loss in previous two months.	Aim: to assess the prevalence of malnutrition in patients with different types of cancer. Differences in weight are reported, not differences in prevalence.	**C**

Tumor Type	Patients (no.)	Weight Loss in the Previous 6 Months (%)* 0	0-5	5-10	>10
Favorable non-Hodgkin's lymphoma†	290	69	14	8	10
Breast	289	64	22	8	6
Acute nonlymphocytic leukemia	129	61	27	8	4
Sarcoma	189	60	21	11	7
Unfavorable non-Hodgkin's lymphoma‡	311	52	20	13	15
Colon	307	46	26	14	14
Prostate	78	44	28	18	10
Lung, small cell	436	43	23	20	14
Lung, nonsmall cell	590	39	25	21	15
Pancreas§	111	17	29	28	26
Nonmeasurable gastric	179	17	21	32	30
Measurable gastric	138	13	20	29	38
Total	3,047	46	22	17	15

Correia 2007	Case serie	44 patients with gastric cancer December 2003 - November 2004 Inclusion criteria:	None		**Criteria voor cachexia:** weight loss > 5% in the past months OR weight loss >10% in the past 6 months PG-SGA (well-nourished, mild malnutrition and severe malnutrition) Prevalence of malnutrition dependent of the method of measurement, in gastric cancer patients between 30 and 70% TNF-α and IL-1 can be used as proxy for PG-SGA	Aim: : to evaluate whether TNF-α could be used as early prognostic indicator for increased risk of malnutrition. Small number of patients. Only one type of cancer.	**B/C** (comparing different measures of weight loss related to TNF-α)

		recent (<4 weeks) diagnose gastric cancer Exclusion criteria: patients receiving artificial nutrition or submitted to major surgery, radiotherapy or chemotherapy in the year prior to assessment, as well as with chronic and cachetizing conditions other than gastric cancer			TN-α correlates with all Quality of Life dimensions		
Evans 2008	Consensus conference	Conference with 25 participants	None		Table 1. Diagnostic criteria for wasting disease (cachexia in adult Weight loss of at leat 5%* in 12 months or less in presence of underlying illness**, plus THREE of the following criteria: - Fatigue***	Aim: to formulate criteria for cachexia	D

					- Anorexia****
					- Low fat-free mass index
					- abnormal biochemistry
					  o increased finflammatory markers CRP(>5.0mg/l) Il-6 >4.0pg/,;)
					  o aneamia (<12g/dl)
					  o low serum albumin (,3.2g/dl)
					* edema-free
					** in cases where weight loss cnnot be documents a BMI < 20.0 kg/m2 sufficient
					***fatigue is defined as pshysical and/or mental weariness resulting from exertion;inablitity to continue exercise at the same intensity with a resultant deterioration in performance
					****limited food intake(i.e total caloric intake <20 kcal/kg body weight/d: 70% of usual food intake) or poor appetite Lean tissue depletion(i.e mid upeer arm muscle circumference,10th percentile for age and gender; appendicle skeletal muscle index bij DEXA (kg/m2) bij DXA , 5.45 in females and,7.25 in males		

Gudny 2008	Case serie	30 patients from 79 invited patients Mean age: 55 years (range 29-72) M=9; F=21 Inclusion criteria: patients receiving chemothe rapy for cancer of	None		The following outcome measurements have been compared: BMI, triceps skinfold thickness, mid-arm muscle circumference, serum albumin, serum prealbumin, total lymphocyte count and unintentional weight loss of more than 5% within the preceding month or 10% or more within the previous 6 months According to the full nutritional assessment, six of the 30 (20%) cancer patients in chemotherapy were diagnosed as malnourished. The SSM identified seven of 30 patients (23%) as malnourished. The SSM had a sensitivity of 0.83 and the specificity was 0.96.	Aim: To develop and test a screening tool voor cachexia. Be careful with the interpretation of the sensitivity and specificity and take the study population into account. Low number of patients.	C

<table>
<tr><td></td><td></td><td>the lungs, colon or breast</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Gupta 2008</td><td>Case serie retrospective</td><td>132 ovarian cancer patients treated at Cancer Treatment Centres of America at Midwestern Regional Medical Centre (MRMC) between January 2001 and May 2006. None of these patients had received any treatment at MRMC when enrolled in this investigation.</td><td>None</td><td></td><td>SGA A: 50% (well nourished)
SGA B: 26,5% (moderately malnourished)
SGA C: 23,5% (severely malnourished)

Multivariate Cox Proportional Hazard Model
<table>
<tr><th>Independent Variable</th><th>Unit of increase</th><th>RR</th><th>95% CI</th><th>P-value</th></tr>
<tr><td>Moderately malnourished</td><td>Well-nourished as referent</td><td>2.1</td><td>1.2-3.6</td><td>0.008</td></tr>
<tr><td>Severely malnourished</td><td>Well-nourished as referent</td><td>3.4</td><td>1.9-5.8</td><td><0.001</td></tr>
<tr><td>Stage at Diagnosis</td><td>Stage I and II as referent</td><td>2.1</td><td>1.1-4.0</td><td>0.02</td></tr>
</table></td><td>Aim: to investigate the prognostic role of the Subjective Global Assessment
Limitation: just one type of cancer</td><td>C</td></tr>
</table>

		median age: 54.4 years (range 25.5 – 82.5 years)			<table><tr><td>Treatment History</td><td>Newly Diagnosed as referent</td><td>4.8</td><td>2.4-9.7</td><td><0.001</td></tr></table> Univariate and multivariate survival analyses found that low SGA scores (i.e. wellnourished status) are associated with better survival outcomes.		
Jager 2007	Case serie	447 patients screened; data of 40 patients not complete n= 407 (head and neck cancer) M: 302 F: 105 Mean age: 63.3±13.8 Inclusioncriteria: newly diagnosed tumour in the head and neck region, either a (second)	None	Critical weight loss defined as ≥5% in 1 month or ≥10% in 6 months	Prevalence critical weight loss: 19% Highest prevalence: cancer in the hypopharynx, oropharynx/oral cavity and supraglottic larynx. Loss of appetite, dysphagia/passage difficulties and loss of taste/aversion were significantly associated with critical weight loss.	Aim: to assess the prevalence of critical weight loss and to analyze the risk factors for critical weight loss before treatment in head and neck cancer patients	**C**

		primary or a recurrent tumour. Recruitment: referred to the ear, nose and throat department of the University Medical Centre Groningen (UMCG) between November 2001 and August 2004,					
Jensen 2010	An International Guideline Committee was constituted to develop a consensus approach to defining malnutrition syndromes for adults in the clinical setting. Consensus was achieved through a series of meetings held at the A.S.P.E.N. and	-	None	-	Definitions: Starvation-related malnutrition: When there is chronic starvation without inflammation. Examples of this syndrome include medical conditions like anorexia nervosa. Chronic disease-related malnutrition: When inflammation is chronic and of mild to moderate degree. Examples of this syndrome include organ failure, pancreatic cancer, rheumatoid arthritis or sarcopenic obesity. Acute disease or injury-related malnutrition When inflammation is acute and of severe degree. Examples of this syndrome include major infection, burns,	Definition not specified for cancer.	**D**

	ESPEN Congresses.				trauma or closed head injury.		
Laky 2007	Case serie	n= 145 Benign conditions : n=44 (30%) Ovarian tumours of LMP: n=8 (6%) Histologically proven gynaecological malignancy: n=93 (64%) Mean age: 59.1 ± 14.7 years (range 20-91 years) Inclusioncriteria: suspected or proven gynaecological cancer Exclusion criteria: recurrent cancer,	None	Scored patient-generated subjective global assessment (PG-SGA) and serum albumin	128 patients recalled their weight 1 month ago: - weight loss n=51 (40%) - no weight change n=41 (32%) - weight gain n=36 (28%) 126 patients remembered their weight 6 months ago: - weight loss n=50 (40%) - no weight change n=42 (33%) - weight gain n=34 (27%) PG-SGA class A (well nourished) : 116 (80%) PG-SGA class B (moderately malnourished) : 29 (20%) PG-SGA class C (severely malnourished) : 0 Patients with endometrial cancer higher weight and BMI than patients with ovarian cancer (P=0.05). Ovarian cancer patients had significantly lower serum albumin levels (P=0.003) and higher PG-SGA scores (P<0.001) than patients with other types of cancer.	Aim: To assess the nutritional status of patients with gynaecological cancer	**C**

		treatment for another cancer less than 5 years ago, cognitive impairments (e.g. schizophrenic, dementia) and non-English-speaking patients. Recruitment: Queensland Centre for Gynaecological Cancer, Brisbane, Australia; a tertiary referral centre for gynaecological cancer					
Lees 1999	Case serie	n= 100 M: 71, F: 29 Mean age: 64	None	Weight, BMI	Prior to starting RT: Weight loss : 57% Stable weight : 31% Weight gain : 12%	Aim: to investigate the incidence of weight loss in head and neck cancer patients prior to	**C**

		years (range: 32-89) Tumour localization: Larynx (n=33) Inclusioncriteria: patients with head and neck cancer undergoing commencing radical or palliative radiotherapy Recruitment: Clatterbridge Centre for Oncology			Mean weight loss: -6.5 kg in a mean period of 5.8 months	radiotherapy treatment	
Lisboa 2008	Cross-sectionele studie met controles	Groep 1: 29 vrouwen Inclusie: nog onbehandelde cervixkan	geen		<table><tr><th>Test</th><th>Onbehandelde cervix ca</th><th>Controles</th><th>P</th></tr></table>	Doel: nagaan of veranderde vetstofwisseling een rol speelt bij cachexie (risico) Geen info over matchingsprocedure. Kleine serie. Op zoek	**B/C**

		ker bij eerste diagnose Gem leeftijd 46 (29-60) jaar. Gem aantal kinderen: 4 (1-12) Stagering: IIa: 4; IIb: 10; IIIb: 15; Groep 2: 25 gezonde vrouwen. Gem leeftijd 44 (28-63) jaar Gem aantal kinderen 2 (0-12)				Gewichtsafname t.o.v. 6 maanden geleden	3,6 (sd 5,6) kg	0,2 (sd 2,2) kg	<0.01 (te verwachten)	naar aanknopingspunten op het gebied van vetzuren.	
						Calorie intake volgens 24 uurs recall methode	1087 (sd 496) kcal/dag	1493 (sd 471) kcal/dag	<0,01 (te verwachten)		
						Ratio verzadigd 18.0 en mono onverzadigd 18.1 vetzuur	1,84 (sd 0.39)	2,27 (sd 0,36)	<0.001		
					Symptomen in groep 1: 58,6% constipatie 44,8% anorexia 34,5% misselijkheid of braken 3,4% diarree					
Martin 2007	Prospective population-based cohort study	430 patients eligible: - 89	None	Before and six months after surgery: weight,	Six months after operation: 14.6% of patients had a stable or increased BMI 63.7% had lost more than 10 per cent of their preoperative BMI				Aim: to estimate weight change after surgery in a population-based	C

		(20,7%) died - 38 (8,8%) no radical resection - 43 (14,2%) no response to the questionnaire - 27 (8,9%) questionnaire not in time for the follow-up 233 patients left for analyses (7 missing values for weight or height) Mean age: 65 years Male: 180; Female: 53 Inclusioncriteria:		height, BMI Six months after surgery: questionnaire about health-related quality of life (QLQ-C30 en QLQ-OES18)	20.4% had lost more than 20 per cent of their preoperative BMI Weight loss was more pronounced among patients with higher preoperative BMI. Appetite loss, eating difficulties and odynophagia were significantly linked to postoperative weight loss, whereas dysphagia or reflux did not correlate with malnutrition.	setting and to identify nutritional problems that might correlate with weight loss	

		Patients with oesophageal or cardia cancer who underwent radical tumour resection between April 2001 and October 2004 Recruitment: Data were collected through the Swedish Esophageal and Cardia Cancer Register, a nationwide registry of oesophageal cancer surgery					
Meijers 2010	Delphi study with three phases: phase 1 - literature	Twenty-two experts	None	See results	No full agreement among experts on the elements defining and operationalism of malnutrition.	-	**D**

	review; phase 2 - questions for semistructured interviews; phase 3 - final list of elements for defining and operationalism of malnutrition (developed from the results of the semistructured interviews) was sent to 30 nutritional experts. These experts were asked to provide feedback by ranking the elements.	from nine different countries (response 73.3%); of the 22 participating experts, 14 respondents were working as physicians or scientists and 8 were nutritionists or research dietitians in the malnutrition field.			In phase 2, three elements (deficiency of energy, deficiency of protein, decreased fat-free mass) were selected for the definition of malnutrition. Respondents ranked all three elements (deficiency of energy, deficiency of protein, decreased fat-free mass) as relevant but they disagreed on the level of importance of the elements. Experts remarked that they missed function, lack of other nutrients (e.g., micronutrients), and inflammatory activity in the presented list. In addition, eight elements (involuntary weight loss, body mass index (BMI), no nutritional intake, acute disease effect, less nutritional intake than normal, normal intake but increased demands, normal intake but increased losses, and age) were selected in phase 2 for the operationalism of malnutrition. Elements mentioned to be important in operationalism of malnutrition were involuntary weight loss, BMI, and no nutritional intake. Opinions on cutoff points regarding these elements differed strongly among experts (weight loss varied from >10% overall , >10% in 6 mo, 5% in 1 mo, 5% in 3 mo, 10% loss over 3/12 mo, 5 kg or 10% in 4 wks, 3 kg in previous month or 6 kg in 6 mo, any weight loss; BMI cutoff point ranged from <18 to 21 kg/m2; the time span for no nutritional intake ranged from 3 to >10 d). Another important element mentioned in the operationalism of the definition of malnutrition was the acute disease effect but the experts' views varied greatly as to how this disease effect should be defined (inflammatory activity such as elevated C-reactive protein, hypoalbuminic status, physical immobilization, and disease categories according to the Nutritional Risk Scale). Experts missed loss of body mass and physical activity/function in the presented list. Conclusion A definition of malnutrition should include at least the elements deficiency of energy, deficiency of protein, and decrease in fat-free mass. Also, function and inflammation		

					are suggested to be important for defining malnutrition. The operationalism of the definition should at least include the elements involuntary weight loss, BMI, and nutritional intake. However, no consensus was reached on the cutoff points for these measurements.		
Muscaritoli 2010	The Special Interest Group (SIG) on cachexia-anorexia in chronic wasting diseases was created within ESPEN and developed a consensus paper about the definition of cachexia, pre-cachexia and sarcopenia as well as the criteria for the differentiation between cachexia and other conditions associated with sarcopenia.	-	None	-	**Malnutrition** is a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function, and clinical outcome. **Sarcopenia** is a condition characterized by loss of muscle mass and muscle strength. Diagnosis of sarcopenia: ▪ A low muscle mass: percentage of muscle mass ≥ 2 standard deviations below the mean measured in young adults of the same sex and ethnic background; ▪ Low gait speed: walking speed <0.8 m/s in the 4-m walking test. **Cachexia** may be defined as a multifactorial syndrome characterized by severe body weight, fat and muscle loss and increased protein catabolism due to underlying disease(s). Cachexia is to be considered the result of the complex interplay between underlying disease, disease-related metabolic alterations (i.e. increased inflammatory status, increased muscle proteolysis, impaired carbohydrate, protein and lipid metabolism) and, in some cases, the reduced availability of nutrients (because of reduced intake, impaired absorption and/or increased losses, or a combination of these). Remark: not all malnourished patients are cachectic, all cachectic patients are invariably malnourished. Diagnosis of cachexia: see article Evans et al 2008. **Pre-cachexia** is defined based on the presence of all the following criteria: ▪ underlying chronic disease; ▪ unintentional weight loss ≤5% of usual body weight	Article not specified for cancer.	**D**

					during the last 6 months; ▪ chronic or recurrent systemic inflammatory response (indicated by elevated serum levels of inflammatory markers like C-reactive protein); ▪ anorexia (revealed by visual analogue scales; specific questionnaires (a score ≤24 on the FAACT questionnaire); reduced nutrient intake below <70% estimated needs). **Anorexia** is defined as the reduction/loss of appetite. The pathogenesis of secondary anorexia (due to chronic disease) is complex and multifactorial: ▪ inflammation-driven resistance of the hypothalamus to appropriately respond to orexigenic (i.e. appetite stimulating) and anorexigenic (i.e. satiety stimulating) signals; ▪ symptoms which are related to changes in the physiological mechanisms controlling eating behavior, depression and psychological discomfort; ▪ pain, difficulty in swallowing, nausea/vomiting, meat aversion, early satiety, changes in taste and smell. Diagnosis of anorexia: ▪ visual analogue scale; ▪ Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire; ▪ North Central Cancer Treatment Group (NCCTG) Anorexia/Cachexia questionnaire. **Sarcopenic obesity** is defined by increased body mass index associated with depleted lean body mass and function. It may be the consequence of insulin resistance, physical inactivity, overfeeding and aging.		
Nourissat 2008	Transversal observational study	n= 907 M: 441, F: 459 Mean age: 62.3 years (range: 18	None	Criteria for malnutrition: - weight loss since the start of illness or onset	<table><tr><td>BMI<18,5 kg/m^2</td><td>8.6%</td></tr><tr><td>Weight loss last 2 wks</td><td>21.9%</td></tr></table>	Aim: To investigate the association between weight loss and impaired QoL. Very heterogeneous patient population (tumour location and	**C**

		to 90 years) Tumour localization: Breast (n=197), colorectal (n=164), lung (n=138), prostate (n=67), ovary (n=33) Tumour stage at diagnosis (n = 888): Local (n=327), locoregional (n=314), metastatic (n=247) Inclusioncriteria: > 18 years old, with an evolving cancer at different management stages.		of initial symptoms (primary outcome) - weight loss over the last two weeks - weight loss over the last month - weight loss over the last 6 months - body mass index - Nutrition Risk Index (NRI) Subjective classification using Worksheet 5 of the Patient-Generated Subjective Global Assessment (PG-SGA)	Weight loss >5% last months or >10% last 6 months: 23.7% Weight loss >10% of pre-illness weight: 29.7% Moderate or severe malnutrition using Worksheet 5 of PG-SGA: 43.4% NRI: not analysed because only a few patients had albuminaemia		stage of disease) → prevalence of malnutrition not described per tumour or per stage of disease.	

		Exclusion criteria: primary skin, ocular, or CNS tumour, malignant haemopathy, patients not been treated in the last 2 years or not informed about their diagnosis or unable to answer the questionnaire. Recruitment: 23 departments in six university-hospitals in Clermont Ferrand and Saint Etienne, France					
Pacell	Retrospective	Eligible:	None	Preoperative	Preoperative percentage weight loss: 0-5 113	Aim: evaluating the	**C**

i 2008	cohort study	223 patients Excluded: • 11 received preoperative neoadjuvant chemo or radio-chemotherapy • 9 were treated with hyperthermic intraoperative intraperitoneal chemotherapy • 7 received both procedures. Included: n= 196 M: 120, F:		percentage weight loss, serum albumin levels and body mass index.	(57.6%) 5.1-10 52 (26.5%) >10 31 (15.8%) Serum albumin: <3.0 37 (18.9%) 3.0-3.4 45 (23%) ≥3.5 114 (58.1) BMI: < 18.5 17 (8.7%) 18.5-24.9 85 (43.3%) 25-29.9 65 (33.2%) ≥30 29 (14.8%)	incidence of mortality and major and minor postoperative complications in patients who underwent surgery for gastric cancer stratified according to the preoperative percentage weight loss, serum albumin levels and BMI	

		76 Mean age: 65.5 ± 11.6 (range 32-91) Inclusioncriteria: patients with gastric cancer who underwent surgery (all stages). Exclusion criteria: Preoperative neoadjuvant chemo or radio-chemotherapy and/or hyperthermic intraoperative intraperitoneal chemotherapy. Recruitme					

		nt: Division of Digestive Surgery of the Catholic University of Rome between January 2000 and December 2006					
Ravasco 2003	Case serie (prospective, cross-sectional study) Patients with tumour stage I and II have been compared to patients with tumour stage III and IV.	205 consecutive cancer patients from Portugal M=133;V=72 Mean age: 53 ± 12 years (range 33-86 years) Inclusion criteria: patients with head and neck, gastro-oesophageal, colon and rectum cancer, referred	None		By using a general linear model, with nutritional status as the dependent variable, the patients' nutritional deterioration was related to the following variables: ▪ cancer stage (*P*=0.0001) ▪ location of the primary tumour (*P*=0.001) ▪ duration of the disease (*P*=0.002) ▪ energy intake (*P*=0.003) ▪ protein intake (*P*=0.003) ▪ surgery (*P*=0.01) ▪ chemotherapy (*P*=0.02) The PG-SGA had a very high sensitivity and specificity, and a strong capacity for detecting patients at nutritional risk compared with body mass index.	Aim: to evaluate the relative contributions of cancer staging, duration and diet on patients' nutritional deterioration. No data about Odds-ratios. Nutritional depletion is multifactorial, dependent mainly on the stage of disease and the location of the primary tumour.	**C**

<table>
<tr><td></td><td></td><td>for radiotherapy (primary, adjunctive to surgery, combined with chemotherapy or with palliative intent)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Read 2006</td><td>Case serie
Comparing three groups of patients on the basis of the filled-in PG-SGA.

The PG-SGA classifies patients into three distinct categories:
A = well nourished
B = suspected of malnutrition
C = malnourished</td><td>141 consecutive patients attending the medical oncology day centres in Sidney between April 2002 and November 2004.

Exclusion criteria: earlier treatment with radiotherapy or chemothe</td><td>None</td><td></td><td>
<table>
<tr><th>1. umour type</th><th>Number</th><th>A (well nourished)</th><th>B (suspected of malnutrition)</th><th>C (malnourished)</th></tr>
<tr><td>Colorectal</td><td>47</td><td>43%</td><td>55%</td><td>2%</td></tr>
<tr><td>Lung</td><td>32</td><td>31%</td><td>59%</td><td>10%</td></tr>
<tr><td>Stomach</td><td>10</td><td>0%</td><td>70%</td><td>30%</td></tr>
<tr><td>Pancreas</td><td>15</td><td>0%</td><td>73%</td><td>27%</td></tr>
<tr><td>Esofagus</td><td>4</td><td>0</td><td>75%</td><td>25%</td></tr>
</table>
</td><td>Aim: Using the PG-SGA to calculate the prevalence of malnutrition in patients with different tumour types. Malnutrition seems to depend on the tumour type. However, the prevalence of malnutrition strongly depends on the stage of disease of which no information is available.</td><td>C</td></tr>
</table>

		rapy M= 87; F= 54 Mean age: 66 years (SD 12.4; Range: 22-91 years) A = well nourished (n=48) B = suspected of malnutrition (n=79) C = malnourished (n=14)			<table><tr><td>***Head and neck***</td><td>33</td><td>55%</td><td>39%</td><td>6%</td></tr></table>		
Ross 2004	Longitudinal observational study (prospectively)	n= 780 Tumour localization: Small cell lung cancer (SCLC; n=290), stages III and IV non-small-cell lung	None	Patients with weight loss greater than 10% of preillness weight at the time of presentation were compared to those with weight loss less than 10% of	- No difference in the incidence of weight loss among men (62%) compared to women (57%; P=0.2). - Weight loss more frequently in patients with mesothelioma (76%) than with SCLC (59%; P=0.01) or NSCLC (58%; P=0.005) NSCLC; weight loss is associated with: - fewer patients completing at least three cycles of chemotherapy - more treatment delays - increased incidence of anaemia as a toxicity (No differences in other toxicities from chemotherapy) - more symptoms at presentation - fewer symptomatic responses	Aim: To examine whether weight loss at presentation influences outcome in patients who received chemotherapy for lung cancer or mesothelioma	**C**

		cancer (NSCLC; n=418), and mesotheli oma (n=72) Median age: 63 years (range 27–85 years) Male: 64%; Female: 36% Inclusionc riteria: patients with SCLC, stage III or IV NSCLC, or mesotheli oma treated with chemothe rapy. Exclusion criteria: weight loss status at		preillness weight	- no significant difference in response rate Mesothelioma; weight loss was associated with: - fewer patients completing at least three cycles of chemotherapy - fewer symptomatic response - lower response rate SCLC: Weight loss neither affected the number of patients completing at least three cycles of chemotherapy, the incidence of toxicity nor the response rate. Weight loss: - independent predictor of shorter overall survival for patients with SCLC (P=0.003, relative risk (RR)=1.5), NSCLC (P=0.009, RR=1.33) and mesothelioma (P=0.03, RR=1.92) independent predictor of progression-free survival in patients with SCLC (P=0.01, RR=1.43).		

		presentation unknown; not receiving a standard chemotherapy regimen within 2 months of presentation; prior radiotherapy, prior adjuvant or palliative chemotherapy. Recruitment: Patients at the Lung Unit of the Royal Marsden between 1994 and March 2001					
Sarhill 2003	Case serie	451 consecutive patients screened	None	Weight; weight loss, BMI; triceps skinfold (TSF)	- 87% lost weight in the 6 months before assessment - 71.6% lost more than 10% of pre-illness weight - The most common factor identified which contributed to weight loss was hypophagia (*n*=275/307) - Men had lost weight more often and to a greater extent	Aim: Evaluation nutritional status	**C**

		→ 99 ineligible (confusion and altered mental status (*n*=35), actively dying (*n*=28), patient refusal (*n*=20), language barrier (*n*=11), and hearing or communication impairment (*n*=5). n= 352 Median age: 61 years (range 22–94 years) Male: 180; Female: 172 Tumour localization: Lung		thickness, mid-arm circumference, arm muscle area (AMA), bioelectrical impedance; biochemical data (Hb, albumin, CRP)	than women - BMI normal or high: 87% (from this group: 11% had AMA values consistent with severe muscle mass reduction). - AMA (measured in 349 pts): Severe muscle mass reduction was seen in 30%, and in 78% of these BMI was either normal or increased - TSF thickness (measured in 337 pts): evidence of severe fat storage deficiency in 51%, and amongst these BMI was usually (86%) either normal or increased - anemic (hemoglobin <12 g/dl in females and <13.5 g/dl in males; (measured in 106 pts):): 72% - hypoalbuminemic (albumin measured in 103 pts): 66% - CRP (measured in 50 pts): 74% high CRP - Most common gastrointestinal symptoms: weight loss (*n*=307), anorexia (*n*=285), and early satiety (*n*=243) - 47% received corticosteroids; 7% megestrol acetate - 3% received enteral nutrition; 2% pareneteral nutrition; 1% other supplements		

		(n=18); Colorectal (n=11); Breast (n=8); Prostate (n=6); Kidney (n=6); Multiple myeloma (n=4); Unknown primary (n=4); Head and neck (n=4); Esophagus (n=4); Pancreas (n=3); Others (n=32) Inclusioncriteria: patients with advanced (metastatic) cancer Recruitment: Patients presenting to the Palliative					

		Medicine Program of the Cleveland Clinic Foundation between November 1998 and August 1999.					
Segura 2005	Observational cross-sectional multi-centred study (the sample is representative from the whole of Spain)	n= 781; M: 490, F: 268 (drop-out: 23?) Median age: 62 years (range: 19 to 92 years) Tumour localization: Most common diagnosis was lung cancer (22.9%), colo-rectal cancer (13.2%), breast cancer (13%). Metastatic phase: 56% of patients	None	Scored Patient-Generated Subjectice Global Assessment (PG-SGA)	<table><tr><td>BMI<18,5 kg/m^2</td><td>6.5%</td></tr><tr><td>Weight: increase no change weight loss <5%, weight loss 5–10%, weight loss >10% current weight less than usual weight weight loss in the previous 2 weeks</td><td>21.2% 30.6% 26.1 % 15.5% 6.5% 70.4% 37%</td></tr><tr><td>food intake lower-than-usual over the previous month moderate decrease in intake practically no intake</td><td>48% 56.3% 14%</td></tr></table>	Aim: To determine the prevalence of malnutrition in cancer patients with advanced disease. Serious diseased population selected. Information about the stage of disease is lacking.	**C**

		Inclusioncriteria: Patients >18 years of age with tumours staged as locally advanced, metastatic and/or loco-regional relapse, receiving hospitalised attention or attending outpatient clinics or receiving home-based care. Exclusion criteria: Patients with concomitant diseases such as AIDS or other cachexia-			<table><tr><td>Factors impeding intake: loss of appetite pain lack of taste in food sensation of early satiation dryness of the mouth constipated nausea problems of swallowing vomiting mouth ulcers food smells are disagreeable diarrhoea other factors</td><td>42.2% 22.3% 21.6% 21.5% 20.2% 19.2% 17.9% 16.3% 9.6% 9% 9% 6.7% 9.6%</td></tr><tr><td>PG-SGA indicating moderately or severely malnourishment</td><td>52%</td></tr></table> Tumours with the greater percentageof weight loss in the previous 2 weeks were those of the oesophagus (57.7%), stomach (50%) and larynx (47.1%) and the least were those of the prostate (17.6%). Tumours with locoregional relapse where those with the greater frequency of weight loss (40%). The higher numbers of symptoms related to foodintake-difficulties were in patients with tumours of the pancreas, stomach and prostate.		

		inducing diseases and those who were unable to respond to the self-evaluation questionnaire, or those who chose not to provide consent to participation in the study. <u>Recruitment</u>: recruited in medical oncology, radiation oncology, palliative care and home-based healthcare departments in Spain between October 2001 and April 2002.					

Wie 2010	Cross-sectional study	n= 14972 admitted; screening examinations in 12112 pts; nutritional status assessed in 8895 pts. M: 4947, F: 3948 Mean age: 55.3 years Tumour localization: Stomach (n=2069), Liver (n=1497), Lung (n=1747), Colorectum	None	Nutritional status was defined on the basis of body mass index (BMI), serum albumin (S-alb), total lymphocyte count (TLC), and type of diet. High risk of malnutrition: BMI <18.5 kg/m2; S-alb <2.8 g/dL; TLC <1200 cells/mm3 or no oral intake requiring enteral or parenteral nutrition. Moderate risk of	BMI: <18,5 kg/m^2 18,5 - 20 kg/m^2 BMI: ≥ 20 kg/m^2	22.4% 8.3% 69.3%	Aim: To investigate the prevalence and risk factors of malnutrition in hospitalized cancer patients in Korea according to tumour location and stage.	**C**
					High risk of malnutrition Moderate risk of malnutrition	36.5% 24.8%		
					The prevalence of malnutrition was higher in male patients with longer hospital stays and readmitted patients. Patients with liver and lung cancer (86.6% and 60.5%, respectively) and patients with advanced cancer stage (60.5%, III or IV) had a higher prevalence of malnutrition than other patients.			

		(n=1778), Breast (n=877), Uterus (n=927) Cancer stage: I (n=1096), II (n=913), III (n=1530), IV (n=2087) Inclusionc riteria: hospitaliz ed cancer patients admitted to the National Cancer Centre of Korea		malnutrition: BMI 18.5 - 20 kg/m2, S-alb 2.8 - 3.3 g/dL, TLC 1200 - 1500 cells/mm3 or diet tolerated. Low risk of malnutrition: other subjects			

Uitgangsvraag 2 Wat zijn de gevolgen van ondervoeding bij patiënten met kanker?

Author + year Prospective (P) or Retro-spective (R) Categories: 1:nutritional parameter as primary endpoint 2:unspecified analysis of prognostic factors 3:primary endpoint not nutritional	**N**	**Diagnosis and treatment**	**Curative (C)** **Adjuvant** **(A)** **Palliative (P)**	**Multi-variate analysis (MV) or uni-variate analysis (UV)**	**Influence of nutritional parameters on survival, quality of life, response or other outcomes** **WL = weight loss** **MN = malnutrition** **NuS = nutritional status** **C = cachexia** **SA = serum albumin** **OS = overall survival** **DFS = disease-free survival** **QoL = quality of life** **UV = univariate analysis** **MV = multivariate analysis** **S = significant** **NS = not significant** **PD = progressive disease**				**Remarks PS=performance status**
					Survival	QoL	Response	Other	
LUNG CANCER									
Alifano, 2003 R 2	67	Superior sulcus tumor (lung) Surgery	C	MV	WL in MV NS for OS				Radical resection and comorbidity in MV S for OS
Ando 1999 R 2	158	St. IV NSCL (lung) Chemotherapy	P	MV	WL in UV S for OS (at 8 and 12 wk), in MV NS				PS en number of organs with metastases in MV S for OS
Borges 1996 P 2	945	Unresectable NSCLC (lung cancer) Chemotherapy	P	MV			WL in MV NS for response		Age and platelet count in MV S for response
Bremnes 2003 P 2	436	SCLC (lung cancer) Chemotherapy	P	MV	WL: in UV S for OS, in MV only S for OS in pat. with extensive disease				Gender, extent of disease, PS, hemoglobin, WBC and platelet count en NSE in MV S for OS

Buccheri 2001 P 1	388	NSCLC (lung cancer) Treatment not specified	?	MV	WL: in MV S for OS				WL defined in several ways Stage of disease and PS in MV S for OS
Buccheri 1995 P 2	128	Lung cancer	Mixed C and P	MV	WL: in MV S for OS				Difficulty doing work or housework and stage of disease in MV S for OS
Casas 2003 P 3	51	Lung cancer (NSLC and SCLC) Concurrent radio- and chemotherapy erythropoietin	Mixed C and P	MV	WL: in MV S for OS				Nadir Hb, final Hb improvement and pathologic findings in MV S for OS
Christodolou 2002 P/R? 2	516	SCLC (lung cancer)	P	MV	WL in MV NS for OS?		WL in MV S for response		Stage, PS, superior caval vene syndrome, site of metastases, serum-AP and –LDH and thoracic irradiation in MV S for OS Stage, PS, gender, age, site of metastases and serum-AF in MV S for response
Colinet 2005 R in 735 pat P in 136 pat 3	735/ 136	NSCLC (lung cancer)	C/P	MV	In retrospectieve analysis WL in MV S for ‘poor prognosis’ (OS?), in prospective MV NS?				Nieuw comorbiditeit score, stadium, PS, histologie, leuco- en lymfocyten, LDH en CYFRA21-1 in prospectieve MV S for ‘poor prognosis’
De Cos 2008 P 2	102 7	Lung cancer	?	MV?	WL: S for OS				Early TNM stage, surgical treatment, asymptomatic status at diagnosis and cardiovasculair disease were S for OS
Espinosa 1995 R	292	Advanced NSCLC (lung	P	MV	WL en SA: in MV S voor OS				PS, lymfocyte count, number of metastases and presence of bone

2		cancer) Chemotherapy							metastasen in MV S for OS
Ferrigno 1995 R 2	388	Lung cancer Treatment?	?	MV	WL in MV S for OS				Stage, PS, gender, alpha-1-acid glycoprotein and histology in MV S for OS
Florescu 2008 P 2	?	NSCLC (lung cancer) Erlotinib	P	MV	WL in MV S for OS				Smoking history, PS, anemia. Serum-LDH, response to previous chemotherapy, time from diagnosis, number of prior regimens, EGFR-receptor copy and ethnicity were in MV S for OS
Herndon 2008 P 3	157 7	NSCLC st. III/IV and SCLC (lung cancer)	P	MV	WL in MV S for OS				Gender, PS, dyspnea, liver, adrenal or bone metastases, marital status and serum-Ap IN mv s FOR os
Hespanhol 1995 R 2	411	Advanced NSCLC (lung cancer) Radiotherapy and/or chemotherapy	P	MV	WL and SA in MV S for OS				PS, stage, serum=LDH lymphocytes and hoarseness in MV S for OS
Jeremic 2006 P? 2	116	NSCLC (lung vancer) stage I and II Radiotherapy	C	MV	WL in MV S for OS and distant metastasis-free S				PS, site, histology and reason for not undergoing surgery in MV S for OS PS in MV S for distant metastases-free S
Jeremic 2003 P 2	285	NSCLC (lung cancer) stage IV Chemotherapy	P	MV	WL in MV S for OS				Gender, PS, number of metastatic sites, liver and brain metastases in MV S for OS
Julien 1999 P/R? 3	120	NSCLC (lung cancer) Chemotherapy	P	MV	WL in MV S for OS in metastatic patients				Response to chemotherapy in MV S for OS

Komaki 2000 R 2	143	Superior sulcus tumors (lung cancer) Multidisciplinary approach	C	MV	WL in MV S for OS				Supraclavicular fossa or vertebral body involvement, stage and surgical treatment in MV S for OS
Kong 2005 P/R? 3	106	Inoperable NSCLL (lung cancer) Radiotherapy	C/P	MV	WL in MV S for OS				Radiation dose in MV S for OS
Kramer 2006 P? 3	266	NSCLC (lung cancer) Treatment?	?	MV	WL in UV S for OS, in MV NS				Stage (defined by PET) and PS in MV S for OS
Langendijk 2000 P 3	198	Inoperable NSCLC (lung cancer) Radiotherapy	C/P	MV	WL in MV S for OS				N-stage, PS and global QoL in MV S for OS
Lord 2002 P 3	56	NSCLC stage II and IV Chemotherapy	P	MV	WL in MV S for OS				ERCC1 expression and PS in MV S for OS
Martin-Ucar 2003 R 2	41	NSCLC En-bloc chest wal land lung resection	C	UV	Preoperative low BMI in UV S for 60-day mortality				Age >75 yrs and low preoperative FEV1 in UV S for 60-day mortality
Martins 1999 R? 2	163 5	NSCLC st I-IV (lung cancer) Surgery, RT and chemotherapy	C/P	MV	WL in MV S for OS in stage III and IV				Superior caval vene syndrome, PS, type, dyspnoea, N-status in stage III/IV and treat-ment in MV S for OS
Palomares 1996 P 1	152	NSCLC (lung cancer)	C/P	MV	WL in MV S for OS				Stage and gender in MV S for OS
Rosenfeld 1997 P 3	170	SCLC (lung cancer) Chemotherapy	C/P	MV			WL in MV S for response		Serum-LDH and stage in MV S for response
Ross	418/	Lung cancer	P	MV	WL in MV S for OS		WL in		

2004 P 1	290/ 72	(NSCLC/SCLC) and mesothelioma Chemotherapy					NSCLC and meso-thelioma S for response to CT		
Schea 1995 R 3	81	SCLC limited disease (lung cancer) Chemoradiation	C	MV	WL in UV NS for OS				
Scott 2003 P 1	106	Inoperable NSCLC (lung cancer)	P	MV		WL related to PS, QoL and symptom scores			G?
Sculier 1994 R 2	105 2	Advanced NSCLC (lung cancer)	P	MV	WL in UV S for long term S, in MV NS				Limited disease and response to chemo-therapy in MV S for OS
Socinsky 2004 P 2	694	Unresectable NSCLC (lung cancer Radiotherapy	P	MV	WL in MV NS for OS			WL in MV S for gr. 3 oesophagitis	
Songur 2004 P 1	71	Advanced NSCLC Treatment?	P?	MV	MN, SA and serum-IL6 in MV S for OS				Serum-LDH in MV S for OS
Svobodnik 2004 P 2	650	Lung cancer survivors	C	UV		WL related to QoL			Gender, PS, stage and histology related to QoL
Tammemagi 2004 R 2	115 4	Lung cancer	?	MV	WL in MV S for OS				Hoarseness, hemoptysis, dyspnea, chest pain, neurological symptoms and weakness/fatigue in MV S for OS
Tamura 1998 P	253	SCLC (lung cancer)	C/P	MV	WL and SA in MV S for OS limited desease with				Stage, number of metastatic sites and serum-LDH in MV S for

2					WL: S= 13,5 month				OS
Tas 1999 R 2	207	SCLC, extensive disease (lung cancer)	P	UV/MV?	WL and SA S for OS				PS, gender, stage and serum-LDH S for OS
Werner 1999 P 2	682	NSCLC (lung Cancer) Chemotherapy and/or radiotherapy	P	MV	WL in MV S for OS				PS, N-stage and use of chemotherapy in MV S for OS
MALIGNANT MESOTHELIOMA									
Borasio 2008 R 2	394	Malignant pleural mesothelioma 27 pat. resection + chemotherapy	P	MV	WL: in UV S for OS, in MV NS				PS, platelet count, histology and degree of pleural involvement in MV s for OS
Edwards 2000 R 2	142	Malignant mesothelioma	P	MV	WL in UV S for OS, in MV NS				Cell type, Hb, WBC, PS and gender in MV S for OS
Herndon 1998 P 2	337	Malignant mesothelioma	P	MV	WL in UV S for OS, in MV NS				Pleural involvement, serum-LDH, PS chest pain, platelt count, histology and age in MV S for OS
Martin-Ucar 2001 P 2	51	Malignant mesothelioma Palliative resection	P	UV	WL in UV S for OS				Type in UV S for OS
HEAD AND NECK CANCER									
Argiris 2004 P 2	399	Recurrent or metastatic carcinoma of head and neck Chemotherapy	P	MV	WL in MV S for OS		WL in MV S for response		PS, differentiation, site and priot RT in MV S for OS PS, residual disease, site and differentiation in MV S for response

Van den Berg 2008 P 1	47	Head and neck ca Surgery and/or radiotherapy	C	UV		WL related to QOL			
Capuano 2008 P 1	40	Head and neck ca Chemoradio-therapy	C	UV	WL in UV S for OS			WL related to treatment interruption, infections, hospital readmissions and early mortality	
Capuano 2009 P 1	61	Head and neck ca	C	UV		WL related to QOL			
Dequanter 2004 R 2	135	Advanced laryngopharyngeal cancer 60: primary surgical treatment 75: surgical salvage following RT	C	MV	Nutritional score: in MV S for OS				Involved lymph nodes, positive resectionmargins, loco-regional relapse and metastases inMV S for OS
Dubray 1996 P 3	217	Squamous cell ca of the head and neck Radiotherapy	C	MV	WL: in MV S for OS and locoregional failure				Stage, site, gender and anemia in MV S for OS
Isenring 2003 P 1	60	Head and neck ca, rectal ca and abdominal ca Radiotherapy	C/A	UV		SGA related to QoL during treatment			
Liu 2006 R 1	1010	Oral ca Treatment?	C?	MV	BMI and SA in MV S for OS				
Nguyen 2002	97	Oral cavity and oropharyngeal	C/P	MV	WL in MV S for OS				Stage en previous radiotherapy in MV S for

R 1		carcinomas (recurrent, persistent and secondary)							OS
Pedruzzi 2008 R 2	361	oropharyngeal Oropharyngeal carcinoma RT/RT + chemo	C	MV	WL in MV S for OS				Age, PS, comorbidity, symptoms and dose of RT in MV S for OS
Petruson 2005 P 1	49	Head and neck ca	?	UV		WL associated with poor QoL			
Ravasco 2004 P 1	271	Head and neck, oesophagus, stomac and colorectal ca	?	MV		WL related to QoL			Site, nutritional intake and chemotherapy related to QoL
Salas 2008 P 1	72	Unresectable head and neck ca Chemoradio-therapy	C	MV	SA in UV S for OS, in MV NS		SA, WL and BMI in UV S for response, in MV NS		Response to chemo-radiation in MV S for OS CRP in MV S for OS
Van Bokhorst 1999 P 1	64	Head and neck ca st T2-4	C	MV	Nutritional parameters in MV only for men S for OS				N-stage, radicality of resection and post-operative complications in MV S for OS
Yueh 1998 R 2	308	Recurrent, persistent and secondary ca of the oral cavity and oropharynx	C/P	MV	WL in MV S for OS				Constrictor invasion and stage in MV S for OS
GASTROINTESTINAL CANCER									
Andreyev 1998 R 1	1555	Locally advanced and metastatic esophagus, stomach, pancreas, colon and rectum ca Chemotherapy	P	MV	WL in MV S for OS	WL related to QoL	WL in UV S for response	WL related to toxicity of chemotherapy	PS, site and presence of liver metastases in MV S for OS

Bakaeen 2000 R 2	101	Duodenal adenoca	C/P	MV	WL in MV S for OS				Stage and resection margins in MV S for OS
Christein 2002 R 2	222	Eesophagus ca Resection	C	MV	WL: in UV S for OS, in MV NS				Positive lymph nodes, tumor location, intra-operative blood transfusion and adjuvant treatment in MV S for OS
Conion 1995 R 2	38	Primary gastrointesti-nale sarcomas	C	UV?	WL: in UV S for OS				Pain at presentation, grade, completeness of resection and site in UV S for OS
Costa 2006 R 2	230	Gastric ca Surgery	C	MV	WL; in MV S for OS				Sex, lymfocyte count, nodal metastases lymphadenectomy and lymph node ratio in MV S for OS
Deans 2007 P? 2	220	Oesophageal or gastric ca Surgery	C	MV	WL in MV S for OS				Stage, PS and CRP in MV S for OS
Di FF 2007 R 1	105	Locally advanced esophageal ca Chemoradiation	C	MV	BMI in MV S for OS, WL and SA NS		SA in MV S for response, WL and BMI NS		Retrospective WL not defined (gedefinieerd) NG?
Di FF 200*6* R 2	116	Locally advanced squamous cell esophageal ca Chemoradiation	C	MV	WL in MV S for OS				Clinical CR and WHO in MV S for OS

Uitgangsvraag 3 Leidt kanker tot een normale, verhoogde of verlaagde behoefte aan macro- en/of micronutriënten?

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcomes	VII Critical appraisal of study quality
Amaral Journal of Human Nutrition and dietetics 2008	Prospective validation study Aim of the study: (1) MUST and MST to predict NRS-2002 (reference) (2) MUST, MST and NRS-2002 to predict length of stay A probalistic sample of 50% inpatients of an oncology hospital, between March and June 2005 Portugal N=130 The first of every 2 admitted patients who met the inclusion criteria was consecutively included in the study, until half the departments' available beds were allocated. All measurements were performed on the second day of	Men: n=73 (30.9%) Women: n=57 (69.1%) Mean age 57.1±13.5 years (range 22–97) Tumor localizations: Head and neck: n=27 Peritoneal and gastro-intestinal: n=25 Breast: n=23 Genital-urinary system: n=17 Lymph ganglia: n=10 Divers: n=28	MUST MST Reference method: NRS-2002	Validity MUST and MST: MUST Sensitivity: 97.3 % Specificity:77.4 % Positive predictive value: 63.2 % Negative predictive value: 98.6 % Agreement with NRS-2002: 83.1%, kappa: 0.64 MST Sensitivity: 48.7 % Specificity: 94.6 % Positive predictive value: 78.3 % Negative predictive value: 82.3 %	*Predictive validity:* The odds of having a longer length of stay (≥7 days) were higher for MUST estimates (odds ratio corrected for sex and age = 3.24, 95% CI = 1.5-7.00; p=0.038) than for NRS-2002 (corrected odds ratio=2.47, 95% CI=1.05-5.8; p=0.003) Agreement: 81.5% Kappa: 0.49	Level of evidence: B NRS-2002 is a screening tool instead of an assessment tool and NRS-2002 is no gold standard. Confounding factors: not completely controlled co-morbidities. Due to the numerous non-nutritional factors that influence length of stay, its use as a screening outcome can be criticized. Interobserver reliability was not assessed.

	hospital admission excluding surgical patients who were evaluated on the first day because they were operated on the second day of hospital stay. Eligibility criteria: Age ≥18 years, not pregnant, able to provide informed consent and a planned LOS in hospital longer than 24 h Excluded: paediatric, intensive care and intermediate care units, bone marrow transplant unit and brachytherapy departments All data were collected by one interviewer, who was not involved in the patients' care.					
Bauer European Journal of Clinical Nutrition 2002	Cross-sectional validation study Aim of the study: PG-SGA to predict SGA (reference).	Men: n=40 (56%) Women: 31 (44%). Mean age: 57.6±15.4 years. Types of cancer: 49 % lymphoma,	Scored PG-SGA Reference method: SGA Compared with weight loss in the previous 6 months	PG-SGA: Sensitivity: 98% Specificity: 82% False positive: 4% False negative: 1%	*Predictive validity:* Median length of stay of SGA A patients was significantly lower (7 days, range 1-24 days) than that of	Level of evidence: B Interobserver reliability was not assessed.

	Eligibility criteria: All patients ≥18 y admitted to an oncology ward of a tertiary private hospital over a period of 3 months Australia N=71 A dietitian experienced in performing SGA and PG-SGA assessed all patients.	13% breast cancer 4% cancer of the prostate, oesophagus, lung, sarcoma and myeloma,	and BMI		SGA B+C (13 days, range 1-40 days); p=0.024. The median length of stay of well-nourished patients (SGA A) was 7.0 (range 1 – 24) days which was significantly lower than that of malnourished (SGA B+C) patients (13.0 days, range 1 – 40 days; p=0.024). Significant correlation between PG-SGA and length of stay (r=0.3, p=0.034). No significant differences in mortality within 30 days after discharge between the SGA groups was found. Regression analysis determined that PG-SGA, % weight loss, BMI and were no significant predictors of length of stay or mortality within 30 days of	

					discharge.	
Bauer Asia Pacific J Clin Nutr 2003	Cross-sectional validation study. Aim of the study: To assess sensitivity and specificity of MAG nutrition screening tool against SGA. All patients admitted to an oncology ward of a tertiary private hospital over a period of three months N=65 Australia Eligibility criteria: all patients ≥18 years admitted to an oncology ward A dietitian experienced in performing SGA performed SGA assessments. An independent experienced dietitian performed assessments with the MAG nutrition screening tool.	Men: n=39 (60%) Women: n=26 (40%) Mean age 56.4±15.2 years. The major diagnoses were 49% lymphoma and 13% breast cancer.	MAG NST Reference method: SGA	MAG nutrition screening tool: Sensitivity: 59% Specificity: 75% False positive: 31% False negative: 6% Positive predictive value: 88% Negative predictive value: 38%		Level of evidence: B Interobserver reliability was not assessed.
Detsky J Parenteral Enteral	Validation study	Mean age of patients at Toronto	SGA (classes A, B or C)	Correlation between SGA and albumin	*Predictive validity:* Predictive value of	Level of evidence: B

Nutrition 1987	2 teaching hospitals Toronto Canada: Toronto General Hospital: n=106 Toronto Western Hospital: n=96 Period: 2 years Inclusion criteria: planned major gastrointestinal surgery Exclusion criteria: patient being senile or comateuse, having been under study before, not speaking English, being on continuos ambulatory peritoneal dialysi, being psychiatric patient, fulfillment of 'study quota' (the research staff could handle only a limited number of patients at one time) Each patient had a nutritional assessment on admission or prior to the surgical procedure. In 109 patients,	General Hospital = 47.75 years Mean age of patients at Toronto Western Hospital = 56.0 years ($p<0.05$)	Reference methods: anthropometry: % ideal weight, % ideal lean body weight, % body fat, creatinine-height index, prognostic nutritional index score (PNI, based upon albumin, transferrin, triceps skinfold and delayed cutaneous hypersensitivity)	(mean albumin of SGA class C = 32.1 ±1.6 g/l): kendall's tau = -0.33 Correlation between SGA and transferrin (mean transferrin of SGA class C 150±15.9 mg/dl): kendall's tau = -0.22 Correlation between SGA and creatinine-height index (mean of SGA class C 65.0±9.0 %): kendall's tau =-0.20 All comparisons: $p< 0.005$ Transferrin, creatinine-height index, % ideal weight, % body fat and total lymphocyte count were not useful in predicting complications.	SGA to predict major postoperative complications: area under curve ROC 0.64 (SE: 0.074); likelihood ratio of SGA class C: 4.44 High degree of interobserver agreement (n=109): Kappa=0.784 (SE=0.08;95% confidence interval 0.624 to 0.944)	Study problems: - the rate of major complications was unexpectedly much lower (8.9%) than expected (30% to 40%) - many patients refused the delayed cutaneous hypersensitivity test - 24-hr urine collection for creatinine-height index was difficult due to short preoperative hospitalization period

	SGA was scored by 2 observers (clinicians)					
Elia MUST report (BAPEN) 2003	Studies that investigated agreement with other tools: MUST vs SGA: medical wards, n=50 MUST vs nutritional risk score: medical wards, n=75 MUST vs dietitian's opinion: medical/surgical wards, n=100		MUST Reference methods: - SGA → only first 2 steps of MUST (BMI and weight loss) were compared with SGA in which SGA class B + and class C were combined to one category - nutritional risk score - dietitian's opinion	<u>Hospital:</u> MUST (BMI and weight loss) vs SGA (class A, class B+C): kappa = 0.783 MUST vs nutritional risk score: kappa = 0.775. MUST vs dietitian's opinion: kappa 0.771	*Predictive validity:* On orthopaedic wards (elective + trauma) (n=194) length of stay of patients with high risk of malnutrition (MUST≥2) was significantly higher than with low risk (MUST<1) (median 8 vs 5 days; Rank ANCOVA, controlled for age: p<0.006). In medical/elderly wards (n=100) length of stay of high risk patients was also significantly higher than of those with low risk (median 8 vs 4 days, Rank ANCOVA, controlled for age: p<0.014). In elderly wards (n=118) length of stay of high risk patients was significantly higher than of those with low risk (median 23 vs 13 days, Rank	Level of evidence: C The full version MUST (including BMI, weight loss and acute disease effect+intake) has not been validated against SGA, in neither the hospital setting nor the community. In the community, the unfamiliar methods 'MeReC tool' (Medical Resource Centre's) and the 'Hickson& Hill tool' were used.

					ANCOVA, controlled for age: p<0.008). Length of stay was calculated after excluding 28 patients who had died. In elderly wards (n=147) mortality was significantly higher for high risk patients than for low risk patients (32% vs 8%, logistic regression analysis, controlled for age: p<0.001).	
Ferguson Nutrition 1999	Validation study Wesley Hospital Brisbane Australian hospital All patients admitted to the hospital excluding pediatric, maternity, and psychiatric patients Period of 3 months N=408	Men: n=201 (49,3%) Women: n=207 (50,7%) Mean age 57.7 Average length of stay: 6.0 days	MST Reference method: SGA	MST: Sensitivity: 93% Specificity: 93% Positive predictive value: 98.4% Negative predictive value: 72.7%	*Predictive validity:* Patients classified as at risk of malnutrition according to MST had a significant longer length of stay (9.5 ±11.6 days) than patients not at risk of malnutrition (4.9±8.2 days); p<0.001 The interrater reliability of the malnutrition screening tool was high (93–97%). Agreement on MST	Level of evidence: B

					by two dieticians=96% (kappa=0.88, p<0.01)	
Ferguson Australasian Radiology 1999	Validation study Aim of the study: to validate the MST in oncology patients undergoing radiotherapy. Cancer center Non-consecutive 5-day study period Australia N=106 Eligibility criteria: All outpatients undergoing radiotherapy Each patient was interviewed by 2 dieticians: 1 dietician used the SGA and the other used the MST.	Men: 43% Women: 57% Mean age: 59.9±13.5 (range 15–89) years. Types of cancer: 31% breast cancer, 19% prostate cancer, 11% cancer of the gastrointestinal tract 9% cancers of the head and neck. Other sites included the back, arm, leg, eye, cervix, vagina, uterus and bladder. 14 patients declined to participate.	MST Reference method: SGA and nutritional status	MST: Sensitivity: 100% Specificity: 81% False positive: 17% False negative: 0% Positive predictive value: 40% Negative predictive value: 100%		Level of evidence: B Interobserver reliability was not assessed.
Isenring European Journal of Clinical Nutrition 2003	Prospective observational study. Aim of the study: to assess the relationship between PG-SGA and quality of life	Baseline: Men: n=51 (85%) Women: n=9 (15%) Mean age: 61.9±14.0 years Tumor localizations: Head and neck:	PG-SGA	*Predictive validity:* Correlation between PG-SGA and QoL (EORTC QLQ-C30): PG-SGA score at baseline significantly predicted 16% of	The PG-SGA score at baseline was significantly correlated with baseline BMI (r=-0.34, p=0.008) and with percentage weight loss	Level of evidence: B A potential limitation in the current study was the exclusion of subjects with physical, cognitive, language or

	(EORTC QLQ-C30). Two radiation oncology centres, Australia 4 week study: assessment at baseline (prior to RT) and after 4 weeks of RT treatment N= 60 Eligibility criteria: ambulatory patients ≥18 year commencing at least 20 fractions of RT to the head, neck, abdominal or rectal area A researcher experienced in using the scored PGSGA assessed all subjects.	88% (parotid: 15%, oesophagus: 13%, neck: 13%, mouth: 10%, vocal cords: 8%, other head and neck areas: 29%) Abdominall/rectal area: 12% Post-operative radiotherapy: 47% Pre-operative RT: 3% Primary radiotherapy: 50%		the variation in global QoL four weeks after commencing radiotherapy ($F_{(1,55)}$=4.9, p=0.032). A significant correlation between the change in PG-SGA score and change in global QoL after 4 weeks of radiotherapy (r=-0.55, p<0.001) was found. Regression analysis determined that 26% of the variation of change in QoL was explained by change in PG-SGA score ($F_{(1,55)}$=11.6, P¼0.001). Regression analysis showed that a change in PG-SGA score of 9 resulted in a change of 17 in the QoL score.	(transformed) in the previous 6 months (r=0.53, p<0.001).	emotional problems that prevented them from completing the PG-SGA. However, it was noted that no one was excluded on this basis.
Isenring Support Care Cancer 2006	Cross-sectional validation study. Aim of the study: (1) to determine the relative validity of	Men: n=18 (36%) Women: n=32 (64%) Mean age: 59.1± 3.8 years	MST Reference method: PG-SGA	MST: Sensitivity: 100 % Specificity: 92 % False positives: n=3 False negatives: n=0	Agreement: 90% (kappa=0.83; p<0.001).	Level of evidence: B A limitation of the study is the convenience sample used;

	the MST compared to PG-SGA (2) to assess inter-rater reliability. Chemotherapy unit at public hospital, Australia A convenience sample of consecutive outpatients over 8 weeks in May–June 2005. N=50 Eligibility criteria: age >18 years Exclusion criteria: acute medical concerns or cognitive impairment and non-English-speaking subjects. Each subject was interviewed by 2 researchers: the first one used the MST, the other used the PG-SGA.	Tumor localizations: Breast: n=19 Gastrointestinal: n=14 Lymphoma: n=7 Head and neck: n=3 Ovarian: n=2 Lung: n=2 Other (leukaemia, multiple myeloma, cervical): n=3		Positive predictive value: 80% Negative predictive value: 100%		however, the size of the error band for the 95% CI for sensitivity and specificity of the MST relative to the PG-SGA were clinically tolerable, indicating that the sample size was sufficient for this study. Inter-rater reliability was assessed in a subsample of 20 patients , comparing the MST-scores of the researcher with the MST scores completed by nursing staff/administration staf for the patients themselves.
Kondrup Clinical Nutrition 2003	Retrospective analysis of controlled trials	Hospitalized and out-patients studies	NRS 2002	Positive outcome >3 versus outcome <3	Only 45% of the studies were agreed by all 4 authors to	Level of evidence: C

	Development of NRS-2002: Degrees of severity of disease and undernutrition were defined as absent, mild, moderate or severe from data sets in a selected number of randomized controlled trials (RCTs) and converted to a numeric score. *Validation:* The NRS-2002 was validated against against 128 RCTs of nutritional support vs spontaneous intake to investigate whether the NRS-2002 could distinguish between trials with a positive outcome and trials with no effect on outcome. In each trial, the group of patients was classified with respect to nutritional status and severity of disease, and it was determined whether the effect	Studies excluded: duplicates, preliminary to later publication, non-English and inadequate nutritional preparation		Sensitivity: 75% specificity: 55% Among 75 studies of patients classified as being nutritionally at-risk, 43 showed positive effect of nutritional support on clinical outcome. Among 53 studies of patients not considered to be nutritionally at-risk, 14 showed a positive effect (P=0.0006).This corresponded to a likelihood ratio (true positive/false positive) of 1.7 (95% CI: 2.3-1.2). For 71studies of parenteral nutrition, the likelihood ratio was 1.4 (1.9-1.0), and for 56 studies of enteral or oral nutrition the likelihood ratio was 2.9 (5.9-1.4). The screening system appears to be able to distinguish between trials with a positive effect vs no effect, and it can therefore probably also	have a total score >3	

	of nutritional intervention on clinical outcome was positive or absent. Blind research by four authors 128 RCTs N= 8944			identify patients who are likely to benefit from nutritional support.		
Kruizenga Clin Nutr 2005	Validation study VU University medical centre, The Netherlands 291 patients (56/291 oncologic) on the mixed internal and surgery/oncology wards were screened on nutritional status (according to weight loss and BMI). All patients were asked 26 questions related to eating and drinking difficulties, defecation, condition and pain. Odds ratio, binary and multinomial logistic regression were used to determine the		SNAQ Reference method: severely malnourished: - BMI<18.5 or - unintentional weight loss >5% in 1 m or >10% in 6 m moderately malnourished = 5-10% unintentional weight loss in 6 m	Validity (cross-validation) of SNAQ ≥2 points Sensitivity: 79% Specificity: 83% Validity (cross-validation) of SNAQ ≥3 points Sensitivity: 76% specificity: 83% ROC area under curve SNAQ ≥2 points: 0.85 (95% CI 0.79-0.90, p<0.0001) ROC area under curve SNAQ ≥3 points: 0.85 (95% CI 0.79-0.90, p<0.0001)	Reproducibility for nurse-nurse: Kappa 0.69 (95% CI:0.45-0.94) Reproducibility for nurse-dietitian: Kappa 0.91 (95% CI:0.80-1.03)	Level of evidence: B

	set of questions that best predicts the nutritional status. Based on the regression coefficient a score was composed to detect moderately (≥2 points) and severely (≥3 points) malnourished patients. The validity, the nurse–nurse reproducibility and nurse–dietitian reproducibility was tested in another but similar population of 297 patients (67/297 oncologic). Excluded: patients who could not give informed consent, could not be weighted and patients aged <18 years					
Kruizenga Am J Clinc Nutr 2005	Controlled trial VU University medical centre, The Netherlands Intervention with historical control		Intervention group: screening with SNAQ at admission; patients with SNAQ score ≥2 received energy- and protein enriched meals and	In the intervention group, 76% of the malnourished patients were referred to a dietitian on the basis of their SNAQ	*Predictive validity:* In the total group (intervention + control group), nutritional intervention had no significant effect on	Level of evidence: B

	group. Intervention group: n=297, from mixed internal ward (general internal medicine, gastroenterology, dermatology, rheumatology, nephrology) and mixed surgical ward (general surgery, surgical oncology), admitted from Feb – June 2003 Oncologic patients in intervention group: 23% (67/297) Historical control group: n= 291 comparable patients admitted on same wards from April – October 2002 Oncologic patients in control group: 19% (56/291) Excluded: patients who could not give informed consent, could not be weighted and patients aged <18 years		2 in-between meals per day (in total: +600 kcal/+12 gram protein p/d) patients with SNAQ score ≥3 received energy- and protein enriched meals and 2 in-between meals per day (in total: +600 kcal/+12 gram protein p/d) plus treatment by dietitian Control group: usual hospital nutritional care, no routine screening for nutritional risk Nutritional status was assessed in all patients as well: severely malnourished - BMI<18.5 or - unintentional weight loss >5% in 1 m or >10% in 6 m moderately malnourished = 5-10% unintentional weight loss in 6 m	scores. In the control group, the nurse or physician referred 46% of the malnourished patients to a dietitian. Handgrip strength appeared to be an effect modifier for length of hospital stay in the malnourished group (interaction of intervention group x handgrip strength (lower than standard), *P*= 0.012). Analyses of the effect of screening and nutritional intervention on the length of hospital stay were, therefore, stratified by handgrip strength (lower or higher than the standard). No other interactions were present. Malnourished patients in the intervention group with low	length of hospital stay (p=0.13).	

				handgrip strength (*n*= 59) had a shorter length of hospital stay than did the malnourished patients in the control group with low handgrip strength (*n* =35) (no p-value shown). Weight change during hospital stay was not significantly different between the intervention (-0.1 ±7.9%) and control groups 0.3±5.9% (*P*= 0.6). The incremental costs of SNAQ treatment to reduce the length of hospital stay by 1 d were €76.10 (US$91.32).		
Kruizenga J Nutr Health Aging 2009	Multi-center, cross-sectional observational study Community-dwelling persons 65 years and older Netherlands	Development screening tool: N=308 Mean age; 83.9 Cross validation: nursing home N=476	SNAQrc Reference methods: - MNA - MNA-SF - MUST - SNAQ	MNA: Sensitivity: 95% specificity: 90% MNA-SF: Sensitivity: 98% specificity: 18%		Level of evidence: B

	N= 1128	mean age: 81.7 Residential home N=308 mean age: 85.3		MUST: Sensitivity: 53% specificity: 94% SNAQ: Sensitivity: 50% specificity: 85% SNAQrc: Sensitivity: 78% specificity: 56%		
Laky American Journal of Clinical Nutrition 2008	Validation study A tertiary referral centre for gynaecological cancer Australia Period: March 2004 until December 2006 Assessment before primary cancer treatment N = 194 Eligibility criteria: All women with suspected or proven primary gynecologic cancer Exclusion criteria: recurrent cancer, received treatment for other cancers	Mean age: 58.7 Types of cancer: Benign controls (*n* (%)) 60 (31) LMP (*n* (%)) 14 (7) Endometrial cancer (*n* (%)) 48 (25) Ovarian cancer (*n* (%)) 48 (25) Other gyn. cancer (*n* (%)) 24 (12)	PG-SGA Reference methods: - SGA - serum albumin - triceps skinfold thickness (TSF) - total body potassium - body density measurement	ROC area under the curve (SGA as reference): PG-SGA: 0.92 (95% CI: 0.83, 1.01; *P*< 0.001) Albumin: 0.92 (95% CI: 0.84, 1.01; *P*<0.001 - TSF: 0.70 (95% CI: 0.53, 0.88; *P*= 0.041) Total-body potassium: 0.77 (95% CI: 0.61, 0.94; *P* = 0.005		Level of evidence: B

	within the past 5 y, psychological or cognitive impairments (eg, schizophrenia or dementia), non-English-speaking					
Persson Clinical Nutrition 1999	Prospective study Outpatient unit of the department of oncology. Sweden February to December 1996 N = 87 Assessment by employed physician and dietitian	Male: 61 Female: 26 Mean age: 65 Tumor localization: Colectoral n=31 Gastric n=9 Pancreas n=8 Bile duct n=5 Anal n=1 Testis n=10 Prostate n=23 73 no treatment 11 chemotherapy 3 hormonal therapy	PG-SGA Reference methods: - biochemical measurement: serum albumin and prealbumin	Concordance between nutritional status assessed by the PG-SGA and levels of nutritional serum markers: serum albumin and prealbumin and weight loss correlated significantly with serum albumin and prealbumin. SGA class B and C had lower s-alb and prealb (SGA class B: s-alb 37.0, prealb 0.18; p<0.01) SGA class C: s-alb 37.2 and prealb: 0.22; p<0.01. Significant difference in survival between SGA class A and SGA class B+C, P < 0.01, with no difference between SGA class B and	90% agreement in classification into SGA class A,B or C between doctors and dietician. There was a statistically significant difference in survival between SGA class A and SGA class B+C, with no difference between SGA class B and SGA class C.	Level of evidence: C

				SGA class C		
Read Nutrition and cancer 2005	Comparison analysis Medical oncology day centres in two Sydney teaching hospitals 12 weeks N=157 Initial consultation with diagnoses Assessment and repeated: after 4-6 after 8-12 wk	All patients attending the hospital for initial consultation with diagnosis colorectal, lung, esophageal, gastric or pancreatic cancer. Male: 99 Female: 58 Mean age: 65 Tumor localization: Colectoral n= 78 Lung n= 44 Esophagus n=7 Gastric n=12 Pancreas n=16 Not treated: 52 (33%) Treatment intent/ % Adjuvant 45 (29) Palliative 112 (71)	MNA Reference method: PG-SGA	Baseline: Sensitivity: 97% Specificity: 69% PPV: 59% At 4-6 wk: Sensitivity: 79% Specificity: 69% PPV: 54% At 8-12 wk: Sensitivity: 93% Specificity: 82% PPV: 66%	The PG-SGA measures change more sensitively than the MNA. The PG-SGA takes more time to administer and requires a well trained person MNA is a simple tool and relatively easy	Level of evidence: B Difficulties interpreting MNA because points are deducted for 3 or more medications, full meals, no specify taking nutritional supplements by cancer patients
Rubenstein 2001	Development of MNA-SF, based upon reanalysis of data that were used from France, to develop the original MNA. These data were combined with data collected in	Overall, 73.8% were community dwelling, and mean age was 76.4 years.	MNA Items were chosen for the MNA-SF on the basis of item correlation with the total MNA score and with clinical nutritional status, internal consistency,	After testing multiple versions, identified are an optimal six-item MNA-SF total score ranging from 0 to 14. The cut-point score for MNA-SF was calculated using		Level of evidence: B

	Spain and New Mexico. Combined data: N = 881; 151 were from France, 400 were from Spain, and 330 were from New Mexico		reliability, completeness, and ease of administration.	clinical nutritional status as the gold standard (n = 142) and using the total MNA score (n = 881). The MNA-SF was strongly correlated with the total MNA score (r = .945). Using an MNA-SF score of > or = 11 as normal, sensitivity was 97.9%, specificity was 100%, and diagnostic accuracy was 98.7% for predicting undernutrition.		
Santoso Int J Gynecol cancr 2004	Prospective cohort study Parkland Memorial Hospital, Dallas,Texas N=67	Gynaecological cancer patients Cancer distribution: Cervical:39 Endometrial: 16 Ovarian: 11 Vulvar: 1 Mean age: 51.5 years Racial distribution: African Americans: 26 Hispanic: 20 Caucasians: 17 Asians: 4	SGA Reference method: standard objective nutritional assessment (PNI)	Agreement between the two methods of assessing nutritional status is fair to moderate (weighted kappa =0.435; 95%CI 0.28-0.59) Agreement is exact in 57%	In 21% the difference in ratings differed by two points on the ordinal scale; all had a normal SGA score except severe malnourishment on the PNI rating	Level of evidence: B
Thoresen	Palliative medicine	Patients with	SGA	SGA:	The SGA correlated	Level of evidence: B

Palliative Medicine 2002	unit university hospital Trondheim Norway 3 months N= 46	advanced cancer Male: 26 Female: 20 Mean age: 68	Reference method: objective nutritional assessment: - anthropometry: % weight loss, BMI, TSF, MAMC - serum albumin and serum prealbumin Malnutrition, according to the objective method, was defined as having two or more of six nutritional variables below the reference range.	Sensitivity: 96% Specificity:83%	highly to the objective nutritional criteria and the mean values of TSF, MAMC, BMI	

Uitgangsvraag 4 Wat is de meerwaarde van screening op tijdige herkenning en behandeling van ondervoeding bij patiënten met kanker op voedingstoestand, overleving, comorbiditeit, kwaliteit van leven en welke instrumenten kunnen bij patiënten met kanker het beste worden gebruikt?

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)
Barber 2000	Case-control study N=16	Patients with unresectable pancreatic adenocarcinoma with ongoing weight loss -no prior chemo/RT -no surgery in preceding 4 wks M/F: 10/6 Mean age: 63 (56–66)	-indirect calorimetry by ventilated hood Control group: Weight stable healthy controls (n=6)	<u>Cancer pts vs controls</u>: REE (kJ/day): 5690 vs 6170 (p>0.1) REE (kJ/day/kg body weight): 100.4 vs 78.7 (p<0.005) REE (kJ/day/kg lean body mass): 141.4 vs 120.1 (p<0.05) REE (kJ/day/kg body cell mass): 262.3 vs 229.3 (p<0.05)	-Baseline: No diff in overall REE between ca pts and C; REE per kg body weight, per kg LBM, per kg BCM sign. greater in cancer patients compared with controls
Bauer 2004	Cross-sectional study to investigate the difference between predicted and measured REE N=8	Patients with pancreatic cancer stage II (local spread) - IV (meta's) -palliative treatment ->5% weight loss last 6 mo M/F: 5/3 Mean age: 62	-Indirect calorimetry -Harris-Benedict with no injury factor; Harris-Benedict with 1.4 injury factor; Schofield; Owen; Mifflin; Cunningham; Wang equations; 20 kcal/kg ratio	No significant difference between mean measured and predicted REE from the Harris-Benedict (no injury factor), Schofield, Owen, Mifflin, Cunningham, and Wang equations and the 20 kcal/kg ratio method. The Harris-Benedict equations with an injury factor of 1.3 resulted in a significantly higher (P<0.001) mean predicted REE as compared to measured REE. The smallest bias was observed with the Wang equation (15 kJ) followed by the Harris-Benedict equations alone (22 kJ) and Owen equations (60 kJ). The 20 kcal/kg ratio method, Mifflin and Cunningham equations tended to underestimate REE values, while the Schofield equations and Harris-Benedict equations with an injury factor of 1.3 tended to	Individual data indicates that the limits of agreement for each of the prediction equations are wide, with the narrowest limit evident with the Cunningham and Wang equations (1,280 kJ for both) and the widest limits with the Schofield equations (2,134 kJ) and Harris-Benedict equations with an injury factor of 1.3 (2,105 kJ). Nine (60%) measurements of REE were within ±10% of REE predicted by the Harris-Benedict equations, three measurements (20%) were classified as hyper-metabolic (REE greater than

				overestimate REE values.	110% of the Harris-Benedict-predicted value) and three measurements (20%) were classified as hypometabolic (REE less than 90% of the Harris-Benedict-predicted value).
Bosaeus 2001	Cross-sectional study N=297	Solid tumor types spread to local or distant lymph nodes, mainly gastrointestinal tumors, undergoing a palliative care program (indomethacin, erythropoietin, dietary advice) M/F: 160/137 Mean age: 67 (30-90)	-indirect calorimetry by ventilated hood system -dietary intake by 4-day food record - body weight -BMI	-Mean REE=1533 kcal/day (930-2410) and 23 kcal/kg.day (13-36) -Severe weight loss (n=126): REE=24 kcal/kg.day -Weight stable (n=85):REE=22.5 kcal/kg.day -BMI<18.5 : REE=27.0 kcal/kg.day -BMI 18.5-25 : REE=23.6 kcal/kg.day -BMI>25 : REE=20.5 kcal/kg.day Mean energy intake: 1716 kcal (248-4650 kcal) 26 kcal/day/kg body weight (4-77) Underweight pts: 1739 kcal Normal weight pts: 1765 kcal Weight losing pts: 1689 kcal Weight-stable pts: 1732 kcal Hypermetabolic pts: 1723 kcal Normometabolic pts: 1712 kcal	-no sign diff. in energy intake between tumor types, in weight losing pts, or in underweight cancer pts - dietary intake not different between normo- and hypermetabolic pts -underweight cancer pts had a higher energy intake per kg body weight and overweight pts a lower energy intake/kg body weight compared to normal weight pts - pts with weight loss of more than 10% had a higher energy intake per kg body weight compared to weight-stable pts - Measured vs predicted: 48% elevated REE (>110% of predicted) n=143
Campbell 2007	Longitudinal study N=12 Evaluable: 10 Duration: pre-till end of treatment	Female with breast cancer with adjuvant chemotherapy, stage I-IIIA Mean age: 47	-REE by K4b^2 portable metabolic cart (Italy) -Baseline, end of treatment	Baseline: REE=1190 $\pm$ 80.3 kcal/day End of treatment: REE= 1206 $\pm$ 56.7 kcal/day (NS)	No change in REE from baseline to end of chemotherapy
Cao 2010	Cross-sectional study N=714 Esophageal (n=150)	Patients with newly detected cancer, no previous treatment with chemotherapy, radiotherapy or high doses of steroids	Indirect calorimetry with ventilated hood Controls (n=642): no malignant disease, no fever, organic dysfunction,	<u>Cancer vs controls</u> <u>REE: 1471 vs 1448 (ns)</u> <u>REE/FFM: 31.56 vs 30.31 (p<0.001)</u> Esophagus: 1480 kcal – 32.38 REE/FFM Gastric cancer: 1474 kcal – 31.57 REE/FFM	- Patients with esophageal, gastric, pancreatic, NSCLC showed higher REE/FFM whereas patients with colorectal cancer showed no sign diff. - Stage IV higher REE and REE/FFM

	Gastric (n=154) Colorectal (n=148) Pancreatic (n=128) NSCLC (n=134)	M/F: 477/237 Mean age: 56	treatment with steroids, diabetes, hyper/hypothyroidism, dialysis, fluid replacement	Colorectal: 1446 kcal – 30.31 REE/FFM Pancreatic: 1479 kcal – 31.66 REE/FFM NSCLC: 1478 kcal – 31.91REE/FFM Controls: 1448 kcal – 30.31 REE/FFM ***Stage I – II – III – IV*** REE: 1465 – 1446 – 1459 – 1515 REE/FFM: 30.97 – 31.23 – 31.44 – 32.40 ***WL vs WS*** REE: 1459 vs 1477 REE/FFM: 32.27 vs 31.28	than stage I, II, III - No diff in REE and REE/FFM in stage iV with and without livermeta's - WL cancer patients showed higher REE and REE/FFM than WS patients.
Del Rio 2002	Longitudinal study N=30 Evaluable: 23 Duration: 6 months	Women with breast cancer: -menopauzaal -stage I-II - 6 courses of adjuvant CMF Mean age: 55	-Indirect calorimetry -0, 3, 6 months - Placebo (n=7)	REE before chemo vs after chemo: decrease REE before placebo vs after placebo: decrease REE baseline vs 6 mo: increased progressively with weight gain; REE/FFM no change (T0: 35.2 ± 0.8 kcal/kg FFM.day; 6 months: 35.9 ± 0.7 kcal/kg FFM.day	
Demark-Wahnefried 1997	Longitudinal study N=20 Evaluable: 18 Duration: from start till end of chemotherapy	Female with breast cancer with adjuvant chemotherapy - premenopausal -stage I or II Mean age: 40 (27-52)	-Indirect calorimetry by ventilated hood -physical activity: Stanford Five-City Project Questionnaire -baseline (1-2 wks before chemo), midtreatment, treatment completion	<u>RMR (kJ/day) BL vs midtreatment vs study end</u>: 5665 ± 975 vs. 5343 ± 895 vs. 5544 ± 971 ($p<0.01$) <u>Physical activity (kJ/day)</u>: 2159 ± 490 vs. 1937 ± 347 during complete treatment ($p=0.04$)	RMR decreased sign. from baseline to midtreatment and rebounded to levels similar to those on baseline on completion of chemotherapy. Levels of physical activity decreased sign. during treatment

Demark-Wahnefried 2001	Longitudinal study N=60 Evaluable: 53 Duration: 1 year	Female with newly diagnosed operable breast cancer undergoing chemotherapy (n=36) or localized treatment (n=17) -premenopausal -stage I to III Mean age: 41.5	-indirect calorimetry (ventilated hood system) -physical activity: Stanford Five-City Project Questionnaire -baseline (within 3 wks of diagnosis), 2 mo, 6 mo, 1 year	No difference between groups in the linear across time. Significant difference in physical activity (p=0.01) (reduced in chemo group compared to localized treatment group.	
Dickerson 1995	Cross-sectional N=61	Female with ovarian cancer (N=31) and cervical cancer (N=30) Mean age: cervical 55; ovarian 58	Indirect calorimetry	REE (kcal/day): Cervical: REE 1179 Ovarian: REE 1332 (p=0.01)	Ovarian cancer more hypermetabolic than cervical cancer H& B formula unreliable estimate
Fredrix 1997	Longitudinal study N=53 Evaluable=39 for repeated measurement Duration: 12 months	Patients with newly detected untreated NSCLC and surgical resection M/F: 28/11 Mean age: 65.5	- indirect calorimetry by ventilated hood system - energy intake by diet history - body weight - body composition by BIA -before tumor resection (n=53) -3, 6, 12 mo after tumor resection (n=39)	BL: group no tumor recurrence vs tumor recurrence: REE (kcal/day): 1671 ± 277 vs 1731 ± 372 REE/FFM (kcal/kg): 32.6 ± 3.1 vs 32.4 ± 3.6 Change after one year no recurrence vs recurrence: REE (kcal/day): -71 ± 174 vs -132 ± 178 (NS) REE/FFM (kcal/kg): -1.1 ± 3.3 vs –1.1± 1.6 (NS) Before resection vs 6 mo vs 12 mo after resection in patients without tumor recurrence (n=30): REE (kcal/day): 1676 vs 1607 vs 1608 (p<0.05 compared to BL Before resection vs 3 mo vs 6 mo vs 12 mo after	- 68% of patients hypermetabolic - Mean REE/HB = 114% (n=53) - Hypermetabolic patients undergoing curative resection show a decrease in REE - REE in pts with tumor recurrence was unchanged - After curative tumor resection increase in body weight over 1 year (+3.5 kg; +0.5 kg FFM; +3.4 kg FM) - pts with tumor recurrence lost weight (-3.6 kg; -2.2 kg FFM; -1.4 kg FM) - In hypermetabolic patients energyintake increased after curative

				resection in hypermetabolic patients without recurrence (n=20): REE (kcal/day): 1764 vs 1653 vs 1660 vs 1650 (p<0.05 compared with T0) REE/FFM (kcal/kg): 34.3 vs 31.9* vs 32.5 vs 32.0 (*p<0.01 compared with T0) Before resection vs 3 mo vs 6 mo vs 12 mo after resection in normometabolic patients without recurrence (n=10): REE (kcal/day): 1484 vs 1564* vs 1502 vs 1502 (*p<0.01 compared with T0) REE/FFM (kcal/kg): 29.5 vs 30.9* vs 30.5 vs 29.6 (NS)	tumorresection
Garcia-Peris 2005	Longitudinal N=18 Evaluable: 18 Duration: start of treatment till 2 wks after treatment	Patients with head and neck cancer stage III and IV without distant metastasis undergoing - radiotherapy and concurrent chemotherapy (Cisplatinum) M/F: 15/3 Mean age: 57 (30-71)	-Indirect calorimetry (ventilated hood system) -before treatment, 2, 4, 6 wks during treatment, end of treatment, 2 wks after treatment -	Before vs 2 wk vs 4 wk vs end vs after treatment: REE (kcal/24h): 1563 vs 1437 vs 1380 vs 1430 vs 1480 REE (kcal/kg bw): 23.8 vs 22.3 vs 21.8 vs 24.2 vs 25.4 REE (kcal/kg FFM): 33.1 vs 31.3 vs 29.7 vs 33.3 vs 34.3	REE (kcal/24h) significantly changed during chemoradio-therapy. It was higher before treatment, at the end of treatment, and 2 wks after treatment (U-shaped curve)
Harvie 2004	\Longitudinal study N=21 Evaluable:17 Duration: pre-chemotherapy till 6 mo after commencing chemotherapy	Female with newly diagnosed breast cancer, 76% premenopausal, undergoing adjuvant RT +chemo (n=9) or chemo (n=8) Mean age: 46	- indirect calorimetry (ventilated hood system) - prior to chemo, prior 3rd cycle, 1 mo after final chemo, 9, 12 mo after start chemo Control group: Healthy age and weight matched women (n=21) recruited from hospital staff	Prechemo: REE= 5893 kJ/day; 134 kJ/kgFFM Change from prechemo: Midchemo: -391 kcal/day; -11.2 kJ/kgFFM Postchemo: -151 kcal/day (p<0.05); –1.8 kJ/kgFFM NS 3 mo postchemo: -183 kcal/day; -2.0 kJ/kgFFM 1 year postchemo: -8.3 kcal/day; 5 kJ/kgFFM (NS)	- Patients awaiting chemo sign. higher REE than controls
Harvie 2005	Longitudinal study N=83	Patients with: - Stage III or IV NSCLC (N=19)	- indirect calorimetry by ventilated hood system -before chemo, prior 2nd	Advanced NSCLC: Prechemo: 7250 kJ/day; 100 kJ/kg; 138 kJ/kg FFM	REE higher in NSCLC compared to controls REE melanoma/breast cancer

	Evaluable: 41 Duration: before till 1 month after treatment	- Metastatic melanoma (N=12) - Metastatic breast cancer (N=10) undergoing chemotherapy M/F: 24/17 Mean age: 56	cycle, 1 mo after end chemo (4-6 cycles) Control group: Healthy controls recruited from hospital staff matched for age and sex	Change from prechemo: -334 kJ/day; -5.9 kJ/kg; -3 kJ/kg FFM (NS) Melanoma: Prechemo: 7217 kJ/day; 89 kJ/kg; 129 kJ/kg FFM Change from prechemo: 66 kJ/day; 0 kJ/kg; -0.8 kJ/kg FFM (NS) Breast cancer: Prechemo: 5887 kJ/day; 78 kJ/kg; 129 kJ/kg FFM Change from prechemo: 15 kJ/day; 0.4 kJ/kg; 5 kJ/kg FFM (NS)	comparable to controls No sign. overall changes in REE over the course of chemotherapy
Harvie 2003	Longitudinal study N=50 Evaluable: 21 Duration: before and 1 month after chemotherapy	Patients with newly diagnosed advanced NSCLC (stage III and IV) undergoing chemotherapy (5 months) M/F: 15/6 Mean age: 59	-indirect calorimetry by ventilated hood -FM and FFM by skinfolds -energy intake: 4-day weighed food diaries -before and 1 month after chemotherapy	Baseline vs postchemo in men : REE (kcal) : 1934 vs 1806 REE % HB : 113 vs 105 Weight (kg) : 77.7 vs 78.2 FFM (kg) : 57.6 vs 55.6 FM (kg) : 20.0 vs 22.9 CRP (g/l) : 32 vs 9 Energy intake (kcal) : 2733 vs 2713 Baseline vs postchemo in women : REE (kcal) : 1289 vs 1311 REE % HB : 104 vs 105 Weight (kg) : 63.5 vs 62.8 FFM (kg) : 40.8 vs 41.4 FM (kg) : 22.2 vs 21.4 CRP (g/l) : 19 vs 24 Energy intake (kcal) : 2014 vs 1902	During chemo: - minimal weight change in both men and women - men sign increase in % body fat and a tendency for decrease in FFM, sign decrease REE -women FM, FFM and REE unchanged - no change in energy intake in both groups
Jager-Wittenaar 2010	Prospective cohort study N=35 Evaluable: 29 Duration: from 1 week before treatment till 4 months after treatment	Patients with primary or recurrent head and neck cancer with curative radiotherapy either alone, or in combination with chemotherapy or following surgery; receiving individual dietary counseling (with or without tube	- Body height, body weight, lean mass, fat mass, dietary intake - 1 week before, 1 month and 4 months after end of treatment	- During treatment, body weight significantly declined (-3.6±5.3 kg, p=0.019). - Sixty-two percent of weight loss was loss of lean mass (-2.4±2.8 kg, p=0.001). - Between first and second post-treatment assessment: no significant changes in body weight, BMI and lean mass. - Energy and protein intake did not change over time. - Patients with sufficient intake (≥35 kcal and	

		feeding or liquid dietary supplements) to meet nutritional objectives of 35 kcal/kg body weight and 1.5 gram protein/kg body weight. M/F: 23/6 Mean age: 61		≥1.5 gram protein/kg body weight) lost less body weight and lean mass than patients with insufficient intake (mean difference -4.0±1.9 kg, *p*=0.048 and -2.1±1.0 kg, *p*=0.054 respectively). - After treatment, only patients with sufficient intake gained body weight (2.3±2.3 kg) and lean mass (1.2±1.3 kg).	
Jatoi 2001	Case-control study N=24 Evaluable:18	Patients with NSCLC (stage I-IIIB) P-group: Age mean: 65 M/F: 10/8 BMI mean: 25 C-group: Age mean: 66 M/F: 10/8 BMI mean: 24	-indirect calorimetry with ventilated hood system Healthy controls matched for age, BMI and gender N=18 All subjects had undergone a history and physical examination and were found to be in good health with no clinical evidence of infection, fever, thyroid disease, or malignancy	<u>Cancer vs control</u>: Unadjusted: 1546 vs. 1476 kcal/day (70 higher; p=0.22) Adjusted LBM: 1581 vs 1441 kcal/day (140 higher; p=0.001) Adjusted BCM: 1621 vs 1449 kcal/day (173 higher; p=0.032) Adjusted TBW: 1550 vs 1468 kcal/day (82 higher; p=0.103)	LBM by DEXA BCM by potassium-40 TBW by tritiated water dilution Prior weight loss added as covariate → similar sign. differences in REE between cancer patients and controls
Johnson 2008	Cross-sectional N=36	Patients with lung (NSCLC) n=11, colon n=11, head and neck n=14 planned for surgery -stage II (local spread) -WL: >5% last 6 mo (n=18) -WS <2% last 6 mo (n=18) M/F: 28/8 Mean age:	-Indirect calorimetry - Harris-Benedict	<u>Weight stable vs weight loosing cancer patients</u>: Unadjusted: 1677 ± 273 vs 1521 ± 305 kcal/d (NS) Adjusted FFM: 1609 ± 53 vs 1589 ± 53 kcal/d (NS) <u>Weight loosing with high (CRP>10mg/L;n=9) vs low APR (CRP<10mg/L;n=9):</u> Unadjusted: 1624 ± 308 vs 1418 ± 283 kcal/d (p=0.11) Adjusted FFM: 1666 ± 64 vs 1376 ± 64 kcal/d (p=0.006)	No difference in REE between WL vs WS. In WL patients FFM-adjusted REE correlated with CRP (r=0.47, p=0.048) Harris-Benedict equation tend to underestimate REE in both groups

		WL: 61 WS: 59			
Kutynec 1999	Longitudinal study N=18 Evaluable: 13 Duration: 12 weeks	Female with early stage breast cancer, premenopausal undergoing chemotherapy (n=8) or RT (n=10) Mean age: 43	-indirect calorimetrie	Before vs after chemotherapy: REE (kcal/day): 1196 vs 1244 REE(kcal/kg): 20 vs 21 REE (kcal/FFM): 37 vs 39 Before vs after radiotherapy: REE (kcal/day): 1294 vs 1344 REE(kcal/kg): 20 vs 20 REE (kcal/FFM): 35 vs 37	Total group: REE/FFM increased sign over time during therapy; a tendency for increase in REE (kcal/day) and REE/kg body weight during treatment
Ng 2004	Longitudinal N=38 Evaluable: 38 Duration: pre-RT till 6 months post-end-RT	Patients with nasopharynx cancer undergoing curative intent RT: -no distant meta's -without chemo or other oncological therapy M/F: 30/8 Mean age: 46 (33-71)	-Indirect calorimetry with ventilated hood -before RT, end-RT, 2 and 6 mo after RT	T0 vs T1 vs T2 vs T4: BMR : 1406 ± 204 vs 1230 ± 190* vs 1220 ± 195* vs 1199 ± 168* kcal (* p<0.001 vs T0) BMR/body weight : 22.5 ± 2.6 vs 22.1 ± 2.9 vs 22.3 ± 3.0 vs 22.0 ± 2.5 kcal/kg (all NS vs T0) BMR/lean body mass: 30.7 ± 3.0 vs 30.0 ± 3.4 vs 28.7 ± 3.6* vs 28.0 ± 2.4** kcal/kg(* p<0.01 vs T0; ** p<0.001 vs T0, p<0,01 vs T1)	-Sign. reduction in BMR at all post-RT time points. -BMR corecte for body weight did not change sign. among the 4 time points -BMR's corrected for lean body mass were at 2 and 6 mo after RT sign. lower than at T0 (p<0.01)
Pia de la Maza 2001	Longitudinal N=19 Evaluable: 15 Duration: pre/treatment till post/treatment	Female undergoing pelvic RT for gynecological malignancies -cervix 10 -endometrial 3 -rabdomiosarcoom1 -vaginal 1	-REE: canopy system -before and immediately after pelvic RT	Before vs after: REE (kcal/day): 1673 ± 488 vs 1585 ± 275 (p=0.05) REE/FFM (kcal/kg): 44.4 ± 12.0 vs 43.3 ± 4.1 (p=0.22)	REE was elevated prior to treatment (125% of predicted by H&B) and declined sign after 5 weeks, without changes in REE/LBM
Pia de la Maza 2004	Longitudinal study follow-up study Pia de la Maza 2001 (see above) Duration: 2 years after	Female with no tumor recurrence after pelvic RT: -cervix 10 -endometrial 3 -rabdomiosarcoom1 -vaginal 1 Mean age: 49	-REE: canopy system -TEE = REE x energy costs of activities (daily physical activity recalls)	2 years after pelvic radiation: REE (kcal/day): 1282 ± 174 (p<0.01) REE/FFM (kcal/kg): 33.2 ± 2.8 (p<0.01) TEE (kcal/day): 1680 ± 334 (p<0.01) TEE before pelvic RT: 2247 ± 344; TEE after pelvic RT: 2126 ± 352	REE and REE/FFM decreased sign. in this third evaluation compared with previous measurements. Physical activity classified as sedentary throughout the study and the calculated TEE declined progressively

	pelvic radiation				
Reeves 2006	Cross-sectional N=18	Patients with solid tumors: -lung n=8 -gastrointestinal n=7 bladder/cervical/testicular n=3 M/F: 11/7 Mean age: 65	Indirect calorimetry by breath-by-breath respiratory gas exchange 17 healthy subjects matched for gender,age, height, weight recruited from purposive volunteer sample of individuals from the affiliated institutions. Healthy subjects were in self-reported good health with no history of cancer or severe endocrine abnormalities, no surgery within 1 mo of the study, not treated with high-dose steroid medication.	<u>Cancer vs healthy controls</u>: Unadj. REE (kJ/d): 6660 ± 376 vs 5979 ± 303 (NS) FFM-adj REE (kJ/d): 6595 ± 276 vs 6024 ± 259 (NS) <u>FFM-adjusted REE</u>: Lung: 6825 ± 306 kJ Gastro: 6584 ± 331 kJ Other: 3774 ± 736 kJ With surgical removal of tumor > 1 mo (n=4): 7575 ± 514 kJ Tumor in situ: 6326 ± 310 kJ	-No sign difference in REE and FFM adj. REE between cancer and healthy C -FFM adj. REE differed sign. between tumor sites; adj. REE similar in patients with lungca and gastroint. cancer and lower in those with other cancers. - H&B, Owen, Mifflin, 20 kcal/kg method predicted within acceptable limits for just over 50% of the sample of cancer pts, remaining prediction methods failed to estimate REE within acceptable limits
Scott 2001	Case-control and longitudinal study N=12 Evaluable for case-control: 12 Evaluable for longitudinal study: 6 Duration: 8 weeks	Male with locally advanced NSCLC (stage III) without weight loss P-group: Mean age: 68 Weight:: 72 kg BMI: 24.6 C-group: Mean age: 30 Weight:: 83 kg BMI: 24.0 P and C-group not well comparable	-indirect calorimetry with ventilated hood system -baseline within 1 mo after diagnosis; 8 wks later Control group: Healthy male subjects not further described (N=7)	<u>Baseline healthy vs NSCLC</u>: REE (kcal/day): 1854 vs 1612 (p<0.05) REE (kcal/kg perday): 21.8 vs 21.0 (NS) REE (kcal/mol per K per day): 447 vs 540 (p<0.01) REE (% predicted): 103 vs 117 (p<0.01) <u>REE BL and after 8 weeks</u>: (n=6) Weight (kg): 74.9 → change -0.9 (p<0.05) REE (kcal/day): 1612 change 16 (NS) REE (kcal/mol per K per day): 517 change 38 (NS)	REE adj for metabolically active tissue was 15% higher in the NSCLC (P<0.01). REE correlated with CRP concentrations (r=0.753,p<0.01) Increase in REE maintained in pts with weight loss (healthy subjects → REE falls with weight loss) C- group: REE measured = REE predicted P-group: REE measured > REE predicted
Silver 2006	Longitudinal N=17 Evaluable: 17	Patients with head and neck cancer stage III and IVa with	- Indirect calorimetry with open-circuit system -Total physical activity	<u>Baseline vs 1-mo post CCR</u>: REE (kcal/day): 1667 ± 238 vs 1646 ± 210 (p=0.74)	-unadjusted REE:no sign. diff between pre- and posttreatment -measured REE did not differ from

	Duration: baseline till 1 months after chemoradiation	concurrent chemoradiation (CRR) after low dose induction chemotherapy M/F: 15/2 Mean age: 59 (51-69)	level (PAL) by Modified Baecke Questionnaire -baseline, 1 mo post CCR	REE/predicted: 0.98 ± 0.11 vs 1.12 ± 0.22 (p=0.10) REE/FFM (kcal/kg): 30.58 ± 3.22 vs 34.92 ± 6.6 (p=0.019) PAL: 5.33 ± 4.58 vs 1.64 ± 1.55 (p=0.003) Correlatie IL-10 and PAL: r=-0.63, p=0.01	predicted -REE was significantly increased when adj for FFM -total physical activity level declined significantly
Simons 1999	Cross-sectional study N=20	Males with lung cancer, newly diagnosed; ≥10% weight loss (n=10) compared to <10% weight loss (n=10) Mean age: 67	-indirect calorimetry by ventilated hood system -BCM by DEXA	<u>≥10% weight loss vs <10% weight loss</u>: REE/BCM (kJ/kg/day): 243 ± 33 vs 222 ± 26 (p=0.16)	-pts with weight loss ≥10% higher levels of sTNF-R55 and lower levels of albumin compared to pts with weight loss < 10% -sTNF-R55 correlated with REE/BCM (r=0.54, p=0.03)
Staal-van den Brekel 1995	Case-control study N=87	Patients with primary untreated NSCLC -stage I and II: 35 -stage III: 31 -stage IV: 21 Patients: M/F: 68/19 Mean age: 67 Controls: M/F: 13/13 Mean age: 59	-indirect calorimetry by ventilated hood system Control group: healthy age matched controls for control values inflammatory mediators (N=26)	<u>NSCLC:</u> Mean REE/HB = 118% ± 12%	-sign. increased levels of sTNF-Rs, sICAM-1, LBP and CRP in lung cancer pts compared to healthy controls -77% of pts increased REE - increased REE sign. related to increased levels of sTNF-R55, sE-selectin, LBP, CRP compared to normometabolic pts -all weight-losing pts were hypermetabolic (REE/HB = 124%)
Staal-van den Brekel 1997	Case-control study N=66	Patients with Lung cancer, untreated -33 SCLC -33 NSCLC SCLC: Mean age: 63 M/F: 24/9	-indirect calorimetry with ventilated hood system Control group: Healthy controls (by physical examination) with a stable weight > 1 year, BMI <30 matched for sex,	<u>Lungcancer vs healthy controls</u>: REE: 1691 ± 255 vs 1546 ± 248 kcal/day (p<0.01) REE/FFM: 1857 ± 213 vs 1643 ± 138 kcal/day (p<0.001) REE (%HB): 120 ± 14 vs 105 ± 9 (p<0.001) <u>SCLC vs NSCLC</u>:	-increased REE/FFM in lung cancer patients vs healthy controls -REE/FFM was sign higher in SCLC vs NSCLC -no diff in REE limited disease vs extensive disease -increased concentrations of sTNF-R75 and cortisol in SCLC compared to

		FFM: 48.6 NSCLC: Mean age: 65 M/F: 24/9 FFM: 48.7 C-group: Mean age: 66 M/F: 24/9 FFM: 51.0	age, FFM (N=33)	REE: 1758 ± 270 vs 1624 ± 224 kcal/day (p<0.025) REE/FFM: 1925 ± 238 vs 1789 ± 162 kcal/day (p<0.01) REE (%HB): 124 ± 14 vs 116 ± 14 (p<0.01)	NSCLC -no differences in sTNF-R55, LBP en CRP C- group: REE measured = REE predicted P-group: REE measured > REE predicted
Staal-van den Brekel (1997)	Longitudinal study N=12 Evaluable: 12 Duration: start treatment – 1 month after treatment	Patients with newly diagnosed small cell lung cancer undergoing 5 courses of chemotherapy Mean age: 62 M/F: 10/2 Mean weight loss: 4.0 kg	- indirect calorimetry by ventilated hood system - body composition by BIA - dietary intake by diet history method -before and 1 month after chemotherapy	<u>Before vs after chemotherapy:</u> REE (kcal/day): 1628 vs 1475 (p=0.01) REE / FFM (kcal/day): 1807 vs 1629 (p<0.005) Weight (kg): 63.7 vs 65.5 (NS) FFM (kg): 48.2 vs 49.1 (NS) FM (kg): 15.5 vs 16.4 (NS) Energy intake (kcal/day): 2156 vs 2154 (NS)	-all pts hypermetabolic before treatment -all pts showed tumor reduction after chemotherapy -sign reduction in REE - body weight and body composition remained stable -decrease in acute-phase proteins (CRP and LBP) -no correlation between decrease REE and decrease acute-phase proteins

<table>
<tr>
<td>Van den Berg 2006</td>
<td>Observational longitudinal study
N=68
Evaluable: 47
Duration: from diagnosis till 6 months after treatment</td>
<td>Patients with primary tumour stage II–IV in oral cavity, oropharynx, hypopharynx and primary curative treatment intentions

M/F: 28/19
Mean age: 60 (30–83)</td>
<td>- Weight
- Energy intake by a Food Frequency Questionnaire
- at the first visit, the end of
treatment and 6 months after treatment</td>
<td>
<table>
<tr><td colspan="6">Mean weight change during diagnosis, treatment and revalidation</td></tr>
<tr><td></td><td>Total (n=47)</td><td>Surgery (n=15)</td><td>Radiotherapy (n=19)</td><td>Surgery + radiotherapy (n=10)</td><td>Chemoradiation (n=3)</td></tr>
<tr><td>During diagnosis</td><td>-0.3</td><td>-1.5</td><td>-0.2</td><td>+0.4</td><td>+2.0</td></tr>
<tr><td>During treatment</td><td>-2.3</td><td>-0.5</td><td>-3.3</td><td>-0.6</td><td>-10.4</td></tr>
<tr><td>Early revalidation</td><td>-1.7</td><td>+1.6</td><td>-3.4</td><td>-3.9</td><td>-1.1</td></tr>
<tr><td>Late revalidation</td><td>-0.5</td><td>+3.2</td><td>-0.4</td><td>+0.7</td><td>-6.7</td></tr>
</table>

<table>
<tr><td colspan="6">Mean change in energy intake during treatment and revalidation</td></tr>
<tr><td></td><td>Total (n=47)</td><td>Surgery (n=15)</td><td>Radiotherapy (n=19)</td><td>Surgery + radiotherapy (n=10)</td><td>Chemoradiation (n=3)</td></tr>
<tr><td>During diagnosis and treatment</td><td>-122</td><td>-2</td><td>-267</td><td>+307</td><td>-1233</td></tr>
<tr><td>Early and late revalidation</td><td>+322</td><td>+171</td><td>+498</td><td>-31</td><td>+1141</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Weimann 1996</td>
<td>Longitudinal study
N=32
Duration: 10 days pre- and postoperatively</td>
<td>Patients with colorectal carcinoma undergoing surgery for the primairy tumor:
stage I-III: 18
stage IV: 14</td>
<td>-indirect calorimetry
- BIA
- 10 days pre- and postoperatively</td>
<td></td>
<td>No diff in REE between patients with and without liver metastases before and after surgery of the primary tumor</td>
</tr>
<tr>
<td>Wigmore 1995</td>
<td>Case-control study
N=16</td>
<td>Patients with irresectable pancreatic cancer with weight loss

M/F: 10/6
Mean age: 60</td>
<td>-indirect calorimetry by -ventilated hood system

Control group: Age-related subjects (n=17) comprising preoperative elective admissions for minor surgery with</td>
<td><u>Pancreatic cancer vs controls</u>:
REE (kcal/day): 1499 vs 1377 (p<0.02)
REE (kcal/kg BW): 25.58 vs 19.15 (p<0.001)
REE (kcal/kg FFM): 35.0 vs 26.2 (p<0.001)</td>
<td>-BL: REE sign. elevated in pancreatic pts vs controls</td>
</tr>
</table>

			nonmalignant disease		
Wigmore 1997	Crossectional study N=35	Newly diagnosed adenocarcinoma pancreas Mean age: 65.5 (54-72)	-indirect calorimetry by ventilated hood system -TEE: REE + reported physical activity level	<u>CRP<10 (n=16) mg/l vs CRP≥ 10 (n=19):</u> REE (kcal/kg.day): 23.3 vs 26.6 (p<0.002) Estimated TEE (kcal/day): 2272 vs 2265 (NS)	

Uitgangsvraag 5 Wat is het effect van medicamenteuze behandeling op ondervoeding bij patiënten met kanker?

PRIMARY STUDIES - MEGESTROL ACETATE (MA) VERSUS PLACEBO (P)						
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
Beller 1997	Randomised double-blind, P-controlled clinical trial N= 240 (174 evaluable) Duration: 12 weeks	Patients with endocrine resistent tumors and >5% weight loss, partly receiving chemotherapy 159 male, 81 female 12% <50 years, 63% 51-70 years, 25% >70 years	Intervention: MA 160 or 480 mg/day Control: P	Appetite: 480 mg MA significantly better than P, 160 mg MA NS Weight: NS for both doses	Mood and overall quality of life: 480 mg MA significantly better than P No significant differences in triceps skinfold, mid-arm circumference, fat area and muscle area Side-effects: 2 pulmonary embolism, 4 mild edema, all in the low-dose MA group; differences not significant	A2
Bruera 1990	Randomised double-blind, P-controlled crossover clinical trial N= 40 (31 evaluable) Duration: 2 weeks	Malnourished patients with advanced non-hormone responsive tumors with >10% weight loss Mean age 62 yrs	Intervention: MA 480 mg/day Control: P Crossover after 1 week	Appetite: significant change with MA vs P at 9 AM (15% vs -12%, p=.03) and at 4 PM (14% vs -5%,p=.015) Weight: significant change with MA vs (0,2 kg vs -0,8 kg, p=.0,8, p=.03) Preference for MA vs P by patients 66% vs 25% (p=.023) and by	Significant differences favouring MA for energy, triceps skinfold, calf circumference and caloric intake, no significant differences for nausea, wellbeing and arm circumference. Side-effects: mild edema in 3 patients	A2

				investigators 92% vs 6% (p <.001)	with MA and in 2 patients with P	
Bruera 1998	Randomised double-blind, P-controlled crossover clinical trial N= 84 (53 evaluable) Duration: 3 weeks	Patients with advanced non-hormone responsive tumors and anorexia 47 male, 37 female Mean age 62±11 yrs	Intervention: MA 480 mg/day Control: P Crossover after 10 days and 2-day washout	Appetite: significant difference in score with MA vs P (-1.07 vs .24, p=.0005) Weight: no significant difference. Patient preference for MA vs P 30 vs 15 patients (p=.001)	Significant differences favouring MA for activity, fatigue and well-being. No significant differences for nausea, overall QOL, mid-arm circumference, triceps skinfold, ECOG or Karnofsky performances tatus and energy intake. Side-effects: 1 edema with MA, 1 fatal acute pulmonary embolism with P	A2
Chen 1997	Randomised double-blind, P-controlled clinical trial N= 129 (128 evaluable) Duration: 8 weeks	Patients with head and neck cancer receiving radiotherapy 66 male, 22 female Mean age 51 years	Intervention: MA 160 mg/day or cisapride 15 mg/day Control: P	Appetite: less decrease for MA than for cisapride or P at 2 4, 6 and 8 weeks (all p-values.0001) Weight: less loss of body weight at 2, 4, 6 and 8 weeks with MA than with cisapride or P (p=.045, p=.024, p=.006 and p=.003); weight loss at 8 weeks 1.71 kg (MA), 5.41 kg (cisapride) and 3.99 kg (P)	No significant differences in serum albumine between groups Side-effects in two patinets with MA: mild peripheral edema and generalized pruritis with erythematous papules	B
De Conno 1998	Randomised double-blind, P-controlled clinical trial	Patients with far-advanced non-hormone responsive	Intervention: MA 320 mg/day Control: P	Appetite: significant difference in change of scores between MA	Differences in food intake NS at 7 days, significant at 14	A2

	N= 42 (33 evaluable) Duration: 2 weeks for randomized part, 76,5 weeks for open-label study	tumors and loss of appetite 31 male, 11 female Mean age 60 yrs	Double-blind phase during 2 weeks, open-label treatment with MA (titrated to response) for 76 days	and P at 7 days (2.0 vs 0, p=.0023) and 14 days (3.0 vs 0, p=.0064) Weight: no significant change in weight for MA and P after 7 days 0.59 vs -.06 kg, p=NS), signficant difference after 14 days (1.06 vs -.34 kg, p=.015) Patient preference for MA vs P at 7 days 70% vs 12% (p=.0009) and at 14 days 88% vs 25% (p=.0003)	days. No significant differences in performance status, mood and quality of life Side-effects: no differences between MA and P	
Erkurt 2000	Randomised double-blind, P-controlled clinical trial N= 100 Duration: 12 weeks	Patients with advanced cancer receiving radiotherapy 83 male, 17 female, Mean age 57 years	Intervention: MA 480 mg/day Control: P	Appetite: significant differences favouring MA (p=.000) Weight: More weight gain in MA group (3 to 5 kg vs -3,7 to -5,9 kg (p=.000)	Significant changes favouring MA for performance status, malnutrition, loss of taste and smell qualities No side-effects of MA observed.	B
Feliu 1992	Randomised double-blind, P-controlled clinical trial N= 150 (128 evaluable) Duration: 8 weeks	Patients with advanced non-hormone responsive tumors and >10% weight loss and/or anorexia Mean age 57,5 yrs	Intervention: MA 240 mg/day Control: P	Appetite: significant difference favouring MA (p <.01) Weight: more patients with weight gain >2 kg with MA (p <.001)	No differences in performance status Side-effects: no differences	A2
Fietkau 1997	Randomised double-blind, P-controlled clinical trial N= 64 (61 evaluable) Duration: 18 weeks	Patients with head and neck cancer receiving (chemo)radiotherapy with weight loss >5% in 6 weeks or >10% in 6 months	Intervention: MA 160 mg/day Control: P	Appetite: not reported Weight: increased weight in 45% of patients with MA and 20% of patients with P (p=.034)	No significant differences in quality of life, triceps skinfold thickness or upper arm circumference Side-effects:	A2

		Evaluable patients: 49 male, 12 female, median age 50 years			impotence in one patient with MA and diarrhoea in one patient with P	
Lai 1994	Randomised double-blind, P-controlled clinical trial N= 52 Duration: 3 weeks	Patients with cervical (n=41), endometrial or colorectal cancer receiving whole pelvis external rradiation 4 male, 48 female Median age 60 years	Intervention: MA 160 mg/day or prednisolone 30 mg/day Control: P	Appetite: 11 patients with improvement with MA, 6 with prednisolone and 4 with P (p=.024 for MA vs P, NS for prednisolone vs P) Weight: no significant differences between groups	No significant differences in well-being and Karnofsky performance status between groups. Side effects not reported.	B
Loprinzi 1990	Randomised double-blind, P-controlled clinical trial N= 133 (115 evaluable) Duration: 10 weeks	Patients with advanced hormone-insensitive tumors with >5 lb weight loss 88 male, 45 female Median age 68 yrs	Intervention: MA 800 mg/day Control: P	Appetite: improved in patients with MA (p=.003) Weight: gain of 15 lb in 16% of patients with MA and 2% of patients with P (p=.003)	Significant differences favouring MA for nausea, vomiting and food intake. No significant side-effects reported except mild edema	A2
McMillan 1994	Randomised double-blind, P-controlled clinical trial N= 38 (26 evaluable) Duration: 12 weeks	Patients with gastrointestinal cancer and >5% weight loss 17 males, 9 females Mean age 71 years	Intervention: MA 480 mg/day Control: P	Appetite: not reported Weight: no significant change in either group	Side-effects nausea in 1 patient with MA and 1 with P	B
McQuellon 2002	Randomised double-blind, P-controlled clinical trial N= 57 (56 evaluable) Duration: 12 weeks	Patients with head and neck and lung cancer receiving (chemo)radiotherapy 36 male, 20 female Mean age 62 years	Intervention: MA 800 mg/day Control: P	Appetite: Significant differences at 4 (p=.03) and 8 (p=.001) weeks for lung cancer patients Weight: weight loss 2.7 lb with MA and 10.6 lb with P (p=.02)	No differences in overall QOL Side-effects: less nausea and more dyspnoea and cough with MA	A2
Rowland 2006	Randomised double-blind, P-controlled clinical trial	Patients with Extensive small cell lung cancer receiving	Intervention: MA 800 mg/day Control: P	Appetite: better with MA (p=.03) Weight: increased	Significant differences in nausea and vomiting	A2

	N= 243 Duration: 104 weeks	chemotherapy Mean age not reported		nonfluid weight gain with MA (p=.004)	with MA No differences in overall QOL Side-effects: more thromboembolic events in MA-group	
Schmoll 1991	Randomised double-blind, P-controlled clinical trial N= 55 (34 evaluable) Duration: 8 weeks	Patients with advanced cancer and cachexia	Intervention: MA 480 or 960 mg/day Control: P	Appetite: no significant difference between groups Weight: trend for less weight loss with MA than with placebo	Increase of fat and lean body mass in high-dose MA group, decrease in low-dose MA and P-group	B
Schmoll 1992	Randomised double-blind, P-controlled clinical trial N= 91 (65 evaluable) Duration: 8 weeks	Patients with advanced cancer and >5% weight loss Mean age 59 yrs	Intervention: MA 480 or 960 mg/day Control: P	Appetite: improvement in 71% of high-dose MA group, 82% of low-dose MA group and 35% of P-group Weight: 43% weight gain with high-dose MA, 30% weight gain with low-dose MA and 24% with P (non-significant trend for increased weight with high-dose MA)	Side-effects mild in both dose groups	B
Tchekmedyan 1992	Randomised double-blind, P-controlled clinical trial N= 89 (67 evaluable) Duration: 24 weeks	Patients with advanced hormone-insensitive tumors with anorexia and weight loss >5% receiving radio- and/or chemotherapy Evaluable patients: 46 males, 19 females, Median age 63.5 yrs	Intervention: MA 1600 mg/day Control: P	Appetite: significant difference between MA and P (p=.02) Weight: weight gain in 56% of patients with MA and 40% of patients with P (p=.06)	Side-effects: edema, dyspnoea and thrombosis in both arms	A2
Vadell 1998	Randomised double-blind, P-controlled clinical trial N= 150 (107	Patients with progressive, symptomatic ,untreatable cancer	Intervention: MA 160 or 480 mg/day Control: P	Appetite: no significant differences Weight: weight gain in 68% of patients with	Significant increase in triceps skinfold thickness with high-dose MA	A2

	evaluable) Duration: 12 weeks	111 male, 39 female Mean age 65 yrs		high-dose MA, 38% of patients with low-dose MA and 37% of patients with P (p <.03). Mean weight change with high dose MA 5.41 kg, with low-dose MA -2.60 kg and with P 1.34 kg	Non significant differences in mid-arm circumference, performance status, QOL and serum albumine Side-effects: minimal and reversible	
Westman 1999	Randomised double-blind, P-controlled clinical trial N= 255 (190 evaluable) Duration: 12 weeks	Patients with advanced hormone-insensitive tumors with anorexia and/or weight loss, partly receiving radio- and/or chemotherapy 141 male, 114 female Median age 70 yrs	Intervention: MA 320 mg/day Control: P	Appetite: significant difference at 4 weeks favouring MA(p<.0001), no significant differences at 8 and 12 weeks Weight: no significant weight change with MA, significant weight loss with P (p=.0048)	Significant differences favouring MA in mean global QOL at 12 weeks (p=.028) Side-effects mild	A2
PRIMARY STUDIES - MEDROXYPROGESTERONE ACETATE (MPA) VERSUS PLACEBO (P) OR NO TREATMENT (NT)						
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
Downer 1993	Randomised double-blind, P-controlled clinical trial N= 60 (43 evaluable) Duration: 6 weeks	Patients with advanced malignant disease and anorexia, partly receiving chemotherapy Mean age 61 yrs	Intervention: MPA 300 mg/day Control: P	Anorexia: significant improvement with MPA at 3 weeks (p=.0002) and 6 weeks (p=.015) Weight: no significant changes in either group	Significant improvement of serum-prealbumine with MPA No significant changes in anthropometric measurements, performance status, energy, mood or pain in either group No differences in side-effects	A2

Kornek 1996	Randomised double-blind, P-controlled clinical trial N= 31 (24 evaluable) Duration: 12 weeks	Patients with advanced gastrointestinal cancer and weight loss >5% Median age 64 yrs	Intervention: MPA 500 mg/day Control: P	Appetite: no signifcant differences Weight: median weight change at 3 months with MPA 3 kg and with P -2,5 kg ; weight gain >10% with MPA 20% and with P 0% (p=.06)	'Partial responses in quality of life' in 40% of patients with MPA and in 14% with P No significant differences in performance status	B
Neri 1997	Randomised comparative clinical trial N=279 (246 evaluable) Duration:12 weeks	Cancer patients receiving radiotherapy and/or chemotherapy Median age 61 yrs	Intervention: MPA 1000 mg/day Control: NT	Appetite: not reported Weight:significant difference between MPA and P (p=.001)	Improvement of performance status with MPA Side-effects: water retention (20 episodes), hypertension (20), tremor 15, perspiration (11), vaginal spotting (6), thrombosis (1), Cushing syndrome (1)	A2
Simons 1996	Randomised double-blind, P-controlled clinical trial N= 206 (134 evaluable) Duration: 12 weeks	Patients with incurable, non-hormone sensitive tumors 150 males, 56 females Median age 64 years	Intervention: MPA 1000 mg/day Control: P	Appetite: significant difference at 6 weeks (p=.008) and 12 weeks (p=.01) Weight: weight change at 12 weeks 0,6 kg with MPA and -1.4 with P (p=.04)	No benificial effects of MPA on QOL Side-effects: trend towards peripheral edema (17% of patients with MPA, 4% with P)	A2
Simons 1998 Subgroup of study of Simons 1996	Randomised double-blind, P-controlled clinical trial N= 54 (33 evaluable) Duration:12 weeks	Patients with non-hormone sensitive tumors 45 males, 9 females Median age 65 years	Intervention: MPA 1000 mg/day Control: P	Appetite: not reported Weight: less weight loss with MPA (p <.001)	Significant increase with MPA in energy intake (p=..01), fat mass (p=.009) and REEat 6 weeks (p=.009) No significant changes in fat-free mass and REE at 12	A2

					weeks	
Tominaga 1994	Randomised double-blind, P-controlled clinical trial N= 199 Duration: 12 weeks	Patients with advanced or recurrent breast cancer receiving chemotherapy	Intervention: MPA 1200 mg/day Control: NT	Appetite: improvement with MPA (p=.04) Weight: less weight loss with MPA (p<.001)	Less nausea with MPA Higher response rate with MPA (p=.04) Side-effects: moon face, edema and vaginal bleeding	B
PRIMARY STUDIES - MEGESTROL ACETATE (MA) IN DIFFERENT DOSAGES						
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
Beller 1997	Randomised double-blind, P-controlled clinical trial N= 240 (174 evaluable) Duration: 12 weeks	Patients with endocrine resistent tumors and >5% weight loss, partly receiving chemotherapy 159 male, 81 female 12% <50 years, 63% 51-70 years, 25% >70 years	Intervention: MA 160 or 480 mg/day Control: P	Appetite: 480 mg MA significantly better than P, 160 mg MA NS Weight: NS for both doses	Mood and overall quality of life: 480 mg MA significantly better than P No significant differences in triceps skinfold, mid-arm circumference, fat area and muscle area Side-effects: 2 pulmonary embolism, 4 mild edema, all in the low-dose MA group; differences not significant	A2
Gebbia 1996	Randomised clinical trial N=122 Duration: 30 days	Patients with advanced cancer, resistant to chemotherapy 84 males, 38 females Mean age 64 years	Interventions: MA 160 and 320 mg/day	Appetite; not-significant trend (p=.305) for better appetite with higher dose Weight loss: not-significant trend (p=.242) for more weight gain (45% vs 31%) with higher dose	Side-effects: peripheral edema in 18% with low dose and 15% with high dose; venous thrombosis in 6% with low dose and 5% with high dose	A2

Heckmayr 1992	Randomised clinical trial N=66 Duration: 16 weeks	Patients with therapy-resistent lung cancer with weight loss >10% 51 male, 15 female Mean age 67 years	Interventions: MA 160 and 320 mg/day	Appetite:improvement in both groups (difference NS) Weight: mean weight gain 3 kg with high dose and 2 kg with low dose MA		B
Loprinzi 1994	Randomised clinical trial N=342 (334 evaluable) Duration: 18 weeks	Advanced incurable cancer (no breast or endometrial cancer) with weight loss >2 lb in 2 months 226 male, 116 female Median age 67 years	Interventions: MA 160, 480, 800 and 1280 mg/day	Appetite: Greatest improvement with 800 mg MA/day (p<.02) Weight: percentages of patients with >10 weight gain: 8% (160 mg/day), 8% (480), 15% (800) and 13% (1280), p=.31	No significant differences in nausea, vomiting, edema, impotence or irregular menses	A2
Schmoll 1991	Randomised double-blind, P-controlled clinical trial N= 55 (34 evaluable) Duration: 8 weeks	Patients with advanced cancer and cachexia	Interventions: MA 480 or 960 mg/day Control: P	Appetite: no significant difference between groups Weight: trend for less weight loss with MA than with placebo	Increase of fat and lean body mass in high-dose MA group, decrease in low-dose MA and P-group	B
Schmoll 1992	Randomised double-blind, P-controlled clinical trial N= 91 (65 evaluable) Duration: 8 weeks	Patients with advanced cancer and >5% weight loss Mean age 59 yrs	Interventions: MA 480 or 960 mg/day Control: P	Appetite: improvement in 71% of high-dose MA group, 82% of low-dose MA group and 35% of P-group Weight: 43% weight gain with high-dose MA, 30% weight gain with low-dose MA and 24% with P (non-significant trend for increased weight with high-dose MA)	Side-effects mild in both dose groups	B

Ulutin 2002	Randomised clinical trial N=119 Duration: 12 weeks	Patients with advanced non-small cell lung cancer 95 male, 24 female Mean age 57 years	Interventions: MA 160 or 320 mg/day	Appetite: no differences Weight: weight gain at 3 months higher with high-dose MA (p=.038)		B
Vadell 1998	Randomised double-blind, P-controlled clinical trial N= 150 (107 evaluable) Duration: 12 weeks	Patients with untreatable cancer with weight loss >5% 111 male, 39 female Mean age 65 yrs	Interventions: MA 160 or 480 mg/day Control: P	Appetite: no significant differences Weight: weight gain in 68% of patients with high-dose MA, 38% of patients with low-dose MA and 37% of patients with P (p <.03). Mean weight change with high dose MA 5.41 kg, with low-dose MA -2.60 kg and with P 1.34 kg	Significant increase in triceps skinfold thickness with high-dose MA Non significant differences in mid-arm circumference, performance status, QOL and serum albumine Side-effects: minimal and reversible	A2
PRIMARY STUDIES - MEGESTROL ACETATE (MA) VERSUS OTHER DRUGS						
Chen 1997	Randomised double-blind, placebo-controlled clinical trial N= 129 (128 evaluable) Duration: 8 weeks	Patients with head and neck cancer receiving radiotherapy 66 male, 22 female Mean age 51 years	Interventions: MA 160 mg/day or cisapride 15 mg/day Control: P	Appetite: less decrease for MA than for cisapride or P at 2 4, 6 and 8 weeks (all p-values.0001) Weight: less loss of body weight at 2, 4, 6 and 8 weeks with MA than with cisapride or P (p=.045, p=.024, p=.006 and p=.003); weight loss at 8 weeks 1.71 kg (MA), 5.41 kg (cisapride) and 3.99 kg (P)	No significant differences in serum albumine between groups Side-effects in two patinets with MA: mild peripheral edema and generalized pruritis with erythematous papules	B
Jatoi 2002	Randomised clinical trial N=485 (469	Patients with advanced, non-hormone sensitive	Interventions: MA 800 mg or dronabinol 5	Appetite:improvement with MA in 75% of patients, with	No differences in QOL between arms Side-effects: 18% with	A2

	evaluable) Duration: >4 weeks	incurable cancer and weight loss >5 lb in 2 months and/or estimated caloric intake <20 kcal/kg/day 312 male, 157 female Mean age 67 years	mg/day or MA + dronabinol	dronabinol in 49% (p=.0001, compared to MA) and with combination in 66% (p=.17, compared to MA) Weight: >10% physician-reported weight gain with MA in 14% of patients, with dronabinol in 5% (p=.009) and with combination in 11% (NS, compared to MA)	MA and 4% with dronabinol (p=.02); no significant differences for other side-effects	
Jatoi (2004)	Randomised double-blind trial N=429 (421 evaluable) Duration: treatment as long as patient and oncologist considered it beneficial	Patients with incurable cancer and self-reported 2-month weight loss ≥2.3 kg and/or caloric intake <20 kcal/kg.day and/or appetite problem 293 male, 128 female Mean age 66 years	Interventions: 2 cansof EPA supplement (600 kcal, 32 g protein, 2.2 g EPA, 0.9 g DHA) + placebo, megestrol acetate (MA) : 600 mg/d + isocaloric, isonitrogenous placebo cans or combination	Appetite:improvement by NCCTG: EPA: 63%, MA: 69% (p=0.004), EPA+MA: 66% (NS) Appetite by FAACT: EPA: 40, MA: 55 EPA+MA: 55 (p=0 .004). (higher score = better appetite) Weight gain ≥ 10% of baseline weight: EPA: 6%, MA: 18% (p=0.004) EPA+MA: 11% (NS)	No differences in overall QOL Side-effects: with the exception of increased impotence in MA-treated patients, toxicity was comparable	A2
Lai 1994	Randomised double-blind, placebo-controlled clinical trial N= 52 Duration: 3 weeks	Patients with cervical (n=41), endometrial or colorectal cancer receiving whole pelvis external irradiation 4 male, 48 female Median age 60 years	Interventions: MA 160 mg/day or prednisolone 30 mg/day Control: P	Appetite: 11 patients with improvement with MA, 6 with prednisolone and 4 with P (p=.024 for MA vs P, NS for prednisolone vs P) Weight: no significant	No significant differences in well-being and Karnofsky performance status between groups. Side effects not reported.	B

				differences between groups		
Loprinzi 1999	Randomised double-blind, placebo-controlled clinical trial N= 475 (455 evaluable) Duration: 4 weeks	Patients with advanced, non-hormone sensitive, incurable cancer and weight loss >5 lb in 2 months and/or estimated caloric intake <20 kcal/kg/day 310 male, 165 female Median age 68 years	Interventions: MA 800 mg/day or dexamethasone 3 mg/day or fluoxymesterone 20 mg/day	Appetite: improved with MA in 66% of patients, with dexamethasone in 70% and with fluoxymesterone in 44% (p=.001) Weight: weight gain>10% with MA 10%, with dexametha-sone 7% (p=.42, compared to MA) and with fluoxymesterone 4% (p=.08, compared to MA); median weight gain 0.46 kg, 0.15 kg and 0.39 kg, resp.	Side-effects: more venous thrombosis with MA (5%) than with dexamethasone (1%); higher rate of drug discontinuation because of toxicity and/or patinet refusal with dexamethasone (36%) than with MA (25%)	A2
Mantovani 2010	Randomized open-label clinical trial N=332 Evaluable: 290 Duration:16 weeks	Patients with cancer, treated with curative or palliative intent with weight loss >5% in the previous 3 months and/or abnormal values of proinflammatory cytokines 170 male, 120 female Mean age: 62	Interventions: 1. Medroxyproges-terone acetate 500 mg/day or megestrol acetate 320 mg/day 2. EPA 2-2.2 g/day as addition to protein / energy dense supplement 3. L-carnitine 4 g/day 4. Thalidomide 200 mg/day 5 All of the above	Significant difference between arms. Post-hoc analysis: Appetite: significantly improved in arm 5 Weight: significant increase in lean body mass in arm 5	Significant improvement of performance status in arm 3, 4 and 5 Significant decrease of REE and fatigue in arm 5 Toxicity negligible and comparable between arms	B
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**

Bruera 1985	Randomized, double-blind crossover trial N=40 Evaluable: 31 Study period: 14 days	Terminally ill cancer patients Male: 18 Female: 22 Mean age: 54	Methylprednisolone 32 mg (MP) or placebo for 5 days; days 5-7 treatment free; day 8-12 crossover	Appetite increased in 24 of 31 patients (77%) with MP (baseline VAS 26.5; placebo VAS 29.5; MP VAS 40.1; $p<0.05$) Food intake increased in MP patients (baseline 43% of each meal; placebo 50%; MP 65%; $p<0.01$) No change in nutritional status	No serious toxicity was found at the dose of MP used	A2
Della Cuna 1989	Double-blind, placebo-controlled, multicenter study N=403 (150 completed 8-week study period)	Patients with advanced, preterminal carcinoma no longer candidate for aggressive anticancer therapy Male/Female: 196/207 Mean age: 62.7 (16-91)	125 mg/day intravenous methylprednisolone sodium succinate (MPSS) versus placebo	No statistically significant differences between groups in body weight	QoL: MPSS significant more effective than placebo Side-effects: significantly more in MPSS-treated (38.2%) than placebo-treated (28.1%) patients ($P < 0.05$).	A2
Inoue 2003	Randomized placebo controlled trial N=70 Evaluable: 68 Study period: 6 days	Patients with advanced gastric or colorectal cancer scheduled to receive chemotherapy (irinotecan) Male/female: 44/24 Median age: Dex: 60 (31-78); placebo: 58 (28-76)	Dexamethasone (Dex: 8 mg/day i.v. on days 2–4), or placebo (normal saline i.v. on days 2–4).	No significant differences in acute emesis or fatigue between the two groups, significant improvements in delayed emesis (P=0.004) and anorexia (P=0.028) for the Dex patients.	Side effects: Mild or moderate adverse effects in four (11.4%) patients receiving Dex and eight (24.2%) receiving placebo.	B
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**

Moertel 1974	Randomized controlled double blind study N= 116 Evaluable: ? Study period: 4 weeks	Far-advanced gastrointestinal cancer; unresectable and unsuitable for chemotherapy Male/female: ? Mean age: ?	Dexamethasone (0.75 and 1.5 mg four times daily) versus placebo	Improved appetite and sense of well-being in dexa-group compared to placebo no weight gain or improved performance status	Survival of the steroid treated patients identical to placebo treated patients Side effects: one placebo patient gastrointestinal hemorrhage; 36% dexamethasone-group experienced edema or increase in pre-existent edema compared to 30% in the placebogroup.	B
Popiela 1989	Randomized, prospective, double-blind, placebo-controlled, multicenter trial N= 173 Evaluable: ? Study period: 8 weeks	Terminal cancer patients with no further anticancer therapy Male/female: 0 / 173 Mean age: MPSS: 64.9; placebo: 65.8	Daily 125 mg infusions of methylprednisolone sodium succinate (MPSS) or placebo	Significant improvement in quality of life , feeling of weakness, appetite, nausea, anxiety, sense of well-being, and alertness in the steriod group compared to placebo No significant differences across time with regard to weight	Overall mortality rates or time to death: no significant differences between treatment groups Side effects: - infectious complications comparable between treatment groups - 145 medical events reported by 63.5% MPSS patients and 53.4% placebo patients. - significantly more gastrointestinal and cardiovascular side-effects reported in the steroid group.	A2

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
Willox 1984	Double blind crossover trial; order of treatment was randomised N=61 Evaluable: 41 Study period: 5 wks	Patients with solid tumors (gastro-intestinal tumors being most common) with or without chemotherapy 16 Male; 25 female Mean age: 60 years	Prednisolone: 5 mg thrice daily for two weeks; third week reduced dosage placebo: one tablet thrice daily for two weeks ; third week when the dosage was reduced	Prednisolone was significantly better than placebo ($p < 0.001$) in improving appetite Weight did not change in either group	When taking prednisolone the patients showed a trend towards increased intake and a significant increase in wellbeing ($p < 0-001$). No side effects reported	A2
PRIMARY STUDIES - EICOSAPENTANOIC ACID (EPA) VERSUS PLACEBO (P) OR NO TREATMENT (NT)						
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
Gogos 1998	Prospective randomized controlled trial N=64 (60 evalauble) Duration: 40 days	Patients with generalized solid tumors, no tumor treatment available anymore 36 male, 24 female Mean age 58 years	Intervention: 18 g fish oil/day (3.1 g EPA; 2.1 g DHA) Control: P (sugar tablets)	Appetite: not reported Weight: no differences	Fish oil group increase in survival compared to P ($p=0.025$) No effect serum albumin and serum transferrin In malnourished group increase in Karnofsky performance score with EPA No serious toxicity except for mild abdominal discomfort and transient diarrhea	A2
Fearon 2006	Randomised double-blind, P-controlled randomized trial N=518 Duration: 8 weeks	Patients with advanced gastrointestinal or lung cancer, age 18-80 years, ≥5% loss of	Intervention: EPA diethyl ester 2 g (n=175) or 4 g daily Control : P	Appetite, weight and lean body mass: no significant differences	Sign. improvement in physical function with EPA No differences between groups for	A2

		preillness stable weight 355 male, 163 female Median age 67 years			CRP, albumin or Karnofsky performance status, EPA and P well tolerated; no difference in adverse events between the groups	
Fearon 2003	Multicentre, randomised, P-controlled double-blind trial N= 200 Duration: 8 weeks	Patients with advanced pancreatic cancer who lost >5% of their pre-illness stable weight over the previous six Months 110 male, 90 female Neab age 67 years	Intervention: protein / energy dense supplement enriched with n-3 fatty acids (480 ml, 620 kcal, 32 g protein, 2.2 g EPA) N=95 Control: isocaloric isonitrogenous supplement without EPA N=105	Appetite: Weight: no significant differences Post hoc: if taken insufficient quantity, only the EPA enriched supplement results in net gain of weight, lean tissue, and improved QoL	No differences in QOL Both supplements well tolerated. The mean consumption was 1.4 cans in both groups (EPA-arm: 1.5 g EPA/day	A2
Bruera 2003	Randomised P-controlled double-blind trial N=91 (60 evaluable) Duration: 2 weeks	Patients with advanced, locally recurrent and/or metastatic cancer with anorexia, loss of >5% preillness body weight, ability to maintain oral food intake 17 male, 43 female Mean age 64 years	Intervention: 18 fish-oil capsules (3.2 g EPA, 2.2 g DHA Control: P (olive oil)	Appetite and weight: no significant differences	No differences in tiredness, nausea, well-being, caloric intake, nutritional status, or function. Majority of patients were not able to swallow >10 fish oil capsules per day (burping and aftertaste).	A2
Guarcello 2007	Randomised double-blind trial N=46 Duration: 60 days	Patients with lung cancer eligible for chemotherapy, weight loss >10% vs usual weight previous 6 mo. 43 male, 3 female	Intervention: 2 cans EPA-enriched energy dense oral supplement (590 kcal, 32 g protein) N=26	Appetite: not reported Weight: significant increase with EPA at 60 days	Significant increase of energy/protein intake and QOL with EPOA, significant decrease of CRP Both supplements	B

		Mean age 67 years	Control: 2 cans isocaloric isonitrogenous supplement without EPA (550 kcal, 30 g protein) N=20		well tolerated.	
Jatoi 2004	Randomised double-blind trial N=429 (421 evaluable) Duration: treatment as long as patient and oncologist considered it beneficial	Patients with incurable cancer and self-reported 2-month weight loss ≥2.3 kg and/or caloric intake <20 kcal/kg.day and/or appetite problem 293 male, 128 female Mean age 66 years	Interventions: 2 cansof EPA supplement (600 kcal, 32 g protein, 2.2 g EPA, 0.9 g DHA) + P, megestrol acetate (MA) : 600 mg/d + isocaloric, isonitrogenous P cans or combination	Appetite:improvement by NCCTG: EPA: 63%, MA: 69% (p=0.004), EPA+MA: 66% (NS) Appetite by FAACT: EPA: 40, MA: 55 EPA+MA: 55 (p=0 .004). higher score = better appetite Weight gain ≥ 10% of baseline weight: EPA: 6% MA: 18% (p=0.004) EPA+MA: 11% (NS)	No differences in overall QOL Side-effects: with the exception of increased impotence in MA-treated patients, toxicity was comparable	A2
Bruera 2003	Randomised P-controlled double-blind trial N=91 (60 evaluable) Duration: 2 weeks	Patients with advanced, locally recurrent and/or metastatic cancer with anorexia, loss of >5% preillness body weight, ability to maintain oral food intake 17 male, 43 female Mean age 64 years	Intervention: 18 fish-oil capsules (3.2 g EPA, 2.2 g DHA Control: P (olive oil)	Appetite and weight: no significant differences	No differences in tiredness, nausea, well-being, caloric intake, nutritional status, or function. Majority of patients were not able to swallow >10 fish oil capsules per day (burping and aftertaste).	A2
Guarcello 2007	Randomised double-blind trial N=46 Duration: 60 days	Patients with lung cancer eligible for chemotherapy, weight loss >10% vs usual	Intervention: 2 cans EPA-enriched energy dense oral supplement (590	Appetite: not reported Weight: significant increase with EPA at 60 days	Significant increase of energy/protein intake and QOL with EPOA, significant decrease of	B

		weight previous 6 mo. 43 male, 3 female Mean age 67 years	kcal, 32 g protein) N=26 Control: 2 cans isocaloric isonitrogenous supplement without EPA (550 kcal, 30 g protein) N=20		CRP Both supplements well tolerated.	
Jatoi 2004	Randomised double-blind trial N=429 (421 evaluable) Duration: treatment as long as patient and oncologist considered it beneficial	Patients with incurable cancer and self-reported 2-month weight loss ≥2.3 kg and/or caloric intake <20 kcal/kg.day and/or appetite problem 293 male, 128 female Mean age 66 years	Interventions: 2 cansof EPA supplement (600 kcal, 32 g protein, 2.2 g EPA, 0.9 g DHA) + P, megestrol acetate (MA) : 600 mg/d + isocaloric, isonitrogenous P cans or combination	Appetite:improvement by NCCTG: EPA: 63%, MA: 69% (p=0.004), EPA+MA: 66% (NS) Appetite by FAACT: EPA: 40, MA: 55 EPA+MA: 55 (p=0 .004). higher score = better appetite Weight gain ≥ 10% of baseline weight: EPA: 6% MA: 18% (p=0.004) EPA+MA: 11% (NS)	No differences in overall QOL Side-effects: with the exception of increased impotence in MA-treated patients, toxicity was comparable	A2
PRIMARY STUDIES - HYDRAZINE VERSUS PLACEBO						
Chlebowski 1987	61 consecutive patients (including all 30 patients given placebo and 3 1 given hydrazine) were randomly assigned treatment in a double-blind fashion 40 patients received hydrazine sulfate and represented a consecutive series of	Patients with advanced cancer; weight loss > 10% from usual body weight, prior to chemotherapy Male: I :61% P:65% Median age: I :56 P:59	Hydrazine (60 mg, 3 times/d) oral administration versus placebo	83% of hydrazine and 53% of placebo patients maintained or increased their weight *(P* < 0.05). Appetite improvement was more frequent in the hydrazine group (63% *versus* 25%, *P* < 0.05).	71% of patients reported no toxic effects	B

	patients N=101 Evaluable: 58 Study period: 30 days					
Chlebowski 1990	Randomised prospective placebo-controlled clinical trial N=65 Evaluable: ? Study period: follow up for intake, albumin and weight: 28 days	Patients with advanced unresectable NSCLC Male: I :56% P:69% Median age: I :59 P:58	Chemotherapy (cisplatin, vinblas-tine) with three times daily oral hydrazine sulfate (60 mg) or placebo capsules	Hydrazine compared to placebo resulted in sign. greater caloric intake and albumin maintenance ($p<0.05$) Change in kcal/day: +223 in I-group vs -152 in P-group.	Hematologic and gastrointestinal toxicity comparable between the groups (nausea somewhat higher in placebo group)	A2
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
Kosty 1994	Randomised placebo-controlled double blind clinical trial N=291 Evaluable: 266 Study period: measurements at 2-month intervals	Patients with stage IIIB or IV NSCLC Intervention group: Male: 67% Female: 33% Mean age: 61 Placebo: Male: 77% Female: 23% Mean age: 61	Chemotherapy (cisplatin, vinblas-tine, bleomycin) with three times daily oral hydrazine sulfate (60 mg) or placebo capsules	No differences between the two groups for degree of anorexia, weight gain of loss, overall nutritional status.	QoL significantly worse in hydrazine group Sensory neuropathy or motor neuropathy was sign. higher in the hydrazine group; other toxicity no differences between the groups	A2
Loprinzi 1994	Randomised placebo-controlled double blind study N=128 Evaluable: 127 Study period: hydrazine sulfate/placebo continued	Patients with advanced colorectal cancer resistant to chemotherapy Intervention group: Male: 57% Female: 43% Placebo: Male: 59%	60 mg hydrazine sulfate capsules, one capsule per day for 4 days, 4-9 days: two capsules per day; thereafter 3 capsules per day or placebo capsules	Slightly faster weight loss in hydrazine group (not sign.) Trend for more anorexia in hydrazine arm	Poorer survival and poorer QoL in hydrazine group	A2

	indefinitely; measurements at 1-month intervals	Female: 41%				
Loprinzi 1994	Randomised placebo-controlled double blind study N=243 Evaluable: 237 Study period: monthly evaluated (3 months)	Patients with newly diagnosed, unresectable non-small-cell lung cancer treated with cisplatin and etoposide	Hydrazine sulfate 60 mg/day or placebo	Response rates were similar in the two treatment arms; trends for worse time to progression and survival in the hydrazine sulfate arm.	No significant differences in the two study arms with regard to toxicity or quality of life	A2
PRIMARY STUDIES - CYPROHEPTADINE VERSUS PLACEBO						
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
Pawlowski 1975	Randomised placebo-controlled study Evaluable: 51 Study period: 2 months		Cyproheptadine (12 mg/day) versus placebo	Mean appetite rating scores after 2 months higher in I-group than in placebogroup ($P<0.05$) Weight gain after 2 months in I-group versus placebo ($P<0.05$)		B
Kardinal 1990	Randomized, placebo-controlled, double-blind clinical trial N=293 Evaluable: 251 Study period: 3 months	Patients with advanced malignant disease Intervention group: Male: 51% Female: 49% Placebo: Male: 61% Female: 39% Mean age: 65	Cyproheptadine, *8* mg orally three times a day versus placebo	Appetite mildly enhanced by cyproheptadine No significantly progressive weight loss in cyprohepta-dine patients; patients assigned to cyprohep-tadine lost an average of 4.5 pounds per	Patients assigned to cyproheptadine had less nausea ($P = 0.02$), less emesis ($P = 0.11$), more sedation ($P = 0.07$), and more dizziness ($P = 0.01$) than placebo patients	A2

				month compared to 4.9 pounds per month for placebo patients (P = 0.72).		
PRIMARY STUDIES - PENTOXIFYLLINE VERSUS PLACEBO						
Goldberg 1995	Randomized, placebo-controlled, double-blind trial N=70 Evaluable: 70 for weight gain; 43 for appetite Study period: 2 months	Patients with advanced malignancy with weight loss or intake less than 20 kcal/kg/day Intervention group: Male: 66% Female: 34% Mean age: 65 Placebo: Male: 63% Female: 37% Mean age: 67	Pentoxifylline 400 mg or placebo tablets three times daily	No appetite improvement by pentoxifylline % weight gain not different in both groups	Similar frequencies of nausea, vomiting, fluid retention, abdominal pain and heartburn in both groups; no other toxicity reported	A2
PRIMARY STUDIES - THALIDOMIDE VERSUS PLACEBO						
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
Gordon 2005	Single centre double blind randomised controlled trial N=50 Evaluable: 33 patients at four weeks; 20 patients at eight weeks Study period: 24 weeks	Patients with advanced pancreatic cancer with at least 10% weight loss Intervention group: Male: 12 Female: 11 Mean age: 69 Placebogroup: Male: 13 Female: 11 Mean age: 71	Thalidomide 200 mg daily or placebo	4 wks: thalidomide patients gained 0.37 kg in weight and 1.0 cm3 in arm muscle mass (AMA) compared with a loss of 2.21 kg (absolute difference -2.59 kg (p = 0.005) and 4.46 cm3 (absolute difference -5.6 cm3 (p = 0.002) in the placebo group 8 wks: thalidomide patients lost 0.06 kg in weight and 0.5 cm3 in AMA	No significant difference in global health score or physical functioning between the two groups Survival 148 days in the thalidomide group (95% CI 67–171) compared with 110 days in the placebo group (95% CI 75–136) (p=0.45) Thalidomide well tolerated	B

				compared with a loss of 3.62 kg (absolute difference -3.57 kg (p = 0.034) and 8.4 cm3 (absolute difference -7.9 cm3 (p = 0.014) in the placebo group		
PRIMARY STUDIES – MELATONINE VS UNTREATED CONTROLGROUP						
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
Lissoni 1996	Randomised controlled trial N=100 Evaluable: 86 Study period: 3 months	Patients with metastatic solid tumours for whom no other effective treatment was available Intervention group: Male: 29 Female: 16 Mean age: 66 Control group: Male: 27 Female: 14 Mean age: 64	Supportive care alone, or supportive care plus melatonine (MLT) (20 mg per day orally in the evening)	Weight loss > 10% in 13 of 41 (32%) pts treated by supportive care alone, and in 2 of 45 (4%) patients concomitantly treated by MLT (P < 0.01). Mean weight loss was significantly higher in patients treated by supportive care alone than in patients who received MLT (16 vs 3, P < 0.001) No difference in food intake	Mean serum levels of TNF progressively increased in the supportive care group (NS); TNF mean concentrations significantly decreased (P < 0.05) in patients concomitantly treated by MLT No MLT-related toxicity observed	B
Lissoni 2003	Randomised controlled trial N=100 Evaluable: 100 Study period: 60-72 months	untreated metastatic non-small cell lung cancer patients Intervention group: Male: 28 Female: 21 Mean age: 61 Control group: Male: 31 Female: 20 Mean age: 59	Chemotherapy alone or chemotherapy and melatonin - four cycles of cisplatin (20 mg/m/day, i.v.) and etoposide (100 mg/m/day, i.v.) for three consecutive days repeated at 21-day	Melatonin significantly reduced the percentage of weight loss greater than 10% (3 of 49 versus 21 of 51, P < 0.001)	Overall tumor regression rate and 5-year survival were significantly higher in patients concomitantly treated with melatonin Chemotherapy was better tolerated in patients treated with melatonin	B

			intervals. - melatonin – orally everyday without interruption 7 days prior to chemotherapy – at 20 mg/day in the evening			
PRIMARY STUDIES – MEGESTROL ACETATE + IBUPROFEN VERSUS MEGESTROL ACETATE + PLACEBO						
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
McMillan 1999	Randomised controlled trial N=73 Evaluable: 41 Study period: 12 weeks	Patients with locally advanced or metastatic gastro-intestinal cancer with >5% weight loss, receiving supportive care only and expected survival >2 months Intervention group: Male: 13 Female: 22 Median age 69 years Control group: Male 17 Female: 21 Median age: 72	Megestrol acetaat 480 mg/day in combination with ibuprofen 1200 mg/day or placebo	Weight gain at 4-6 wks (n= 41) and at 12 weeks (n=27) 1,0 (ibuprofen) versus -1.5 (placebo) (p<.01) and 2.3 vs -2.8 kg,(p<.001), respectively. Change in appetite score at 4-6 and 12 wks 2.0 vs 3.0 (NS) and 1.0 vs 1.0 (NS)	Change in mid-upper arm circumference at 4-6 and 12 weeks 0,1 (ibuprofen) versus -0,6 (placebo) (p<.01) and 0 and -1.0 (p<.05), respectively. No significant differences in change in biceps and triceps skinfold thickness or in serum albumine. Significant change in EuroQol-EQ-5D score in ibuprofen group.	B
PRIMARY STUDIES – COX-2 INHIBITOR VS COX-2 INHIBITOR WITH ERYTROPOIETINE						
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
Daneryd 1998	Randomised controlled trial N=108	Patients with solid, mainly gastrointestinal tumors with	Oral indomethacin alone (50 mg twice a day) or the	Body weight and resting energy expenditure	No statistical difference in survival between study and	B

	Evaluable: ? Study period: 30 months	progressive cachexia with an expected patient survival time of >6 months Intervention group: Male: 26 Female: 24 Mean age: 65 Control group: Male: 27 Female: 31 Mean age: 67	combination of indomethacin (50 mg twice a day) and s.c. injections of rhEPO; range, 12.000-30,000 units per week) injected three times a week until blood hemoglobin concentration was normalized within reference values for healthy individuals	significantly lower among control patients; food intake, body fat, and lean body mass not different between the two groups	control patients	
PRIMARY STUDIES – GHRELINE VS PLACEBO						
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
Neary 2004	Randomised, placebo-controlled, double blind, cross-over clinical trial N=7 Evaluable: 7 Study period: 3 hours	Patients with metastatic cancer who reported loss of appetite Male: 1 Female:6 Mean age: 54	Ghrelin (5 pmol/ kg.min) or saline infusion over a 90-min period before lunch-buffet. Subjects were randomized to receive ghrelin then saline (four patients) or saline then ghrelin (three patients).	Energy intake from the buffet increased by 31% (P = 0.005) during ghrelin infusion compared to saline. Total energy intake (24-h period) 9,270 KJ after ghrelin treatment *vs.* 6,854 KJ after saline (P = 0.09). Significant increase of 23% in perceived pleasantness of the meal after ghrelin compared to saline (P = 0.02).	No side effects were observed	B
Strasser 2008	Randomised, placebo-controlled, double-blind, double-	Patients with advanced incurable cancer who had loss	Ghrelin on days 1 and 8 and placebo on days 4 and 11	Nutritional intake and eating-related symptoms did not	Drug-related adverse events did not differ between ghrelin and	B

	crossover study N=21 (1 immediately dropped out) Evaluable:18 Study period: 17/18 days	of appetite and weight Male:17 Female: 3 Range age: 45-80	or vice versa, given intravenously over a 60-min period before lunch: 10 pts received 2 ug kg^{-1} (lower-dose) ghrelin; 11 received 8 ug kg^{-1} (upper-dose) ghrelin	differ between ghrelin and placebo	placebo. No grade 3/4 toxicity or stimulation of tumour growth was observed.	
PRIMARY STUDIES – NANDROLON						
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
Chlebowski 1986	Randomized controlled trial N=37 Study period: 4 weeks	Patients with inoperable, non-small cell lung cancer who received no prior chemotherapy Intervention group: Male: 8 Female: 9 Mean age: 56 Control group: Male: 13 Female: 7 Mean age: 59	The defined chemotherapy regimen alone or in conjunction with a 4-week course of nandrolone decanoate given as a weekly intramuscular 200-mg injection	Less severe weight loss in nandrolone decanoate arm (average weight loss 0.8 kg *versus* 0.21 kg, respectively, niet significant), with half as many patients experiencing weight loss on nandrolone decanoate (25% *versus* 12%).	Nandrolone decanoate group, longer median survival (8.2 months *versus 5.5* months; NS) Virilizing effects of nandrolone decanoate were not seen	B
PRIMARY STUDIES – CANNABIS VS PLACEBO						
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
Strasser 2006	Multicenter randomized double-blind placebo-controlled clinical trial N=243 Evaluable:164	Patients with advanced incurable cancer with ≥5% weight loss in 6 months Male: 54% Female: 46%	Cannabis extract (CE) or delta-9-tetrahydrocannabinol (THC) 2.5 mg or placebo orally, twice daily for 2 weeks	No significant difference between the three arms for appetite, body weight, weight loss and QoL. Increased appetite: CE: 75%	No differences in toxicity between the 3 arms	A2

	Study period: 6 weeks	Mean age: 61		THC: 60% PL: 72% (p=0.068)		
PRIMARY STUDIES – ATP VS USUAL CARE						
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
Agteresch 2000	Randomised controlled trial N=58 Evaluable: 50 for body weight Study period: 28 weeks	Patients with NSCLC stage IIIB or IV and a Karnofsky index of 60% or higher Intervention group: Male:20; Female:8 Mean age:64 Control group: Male:18; Female:12 Mean age:61	10 intravenous 30-hour ATP infusions, at 2- to 4-week intervals, vs no ATP	Mean weight changes per 4-week period were −1.0 kg in the control group and 0.2 kg in the ATP group (*P* =.002). Muscle strength declined in the control group but remained stable in the ATP group (*P* = .01).	QOL score changes per 4-week period in the ATP group showed overall less deterioration than in the control group 64% of ATP courses without side effects, Most common side effects: chest discomfort, urge to take a deep breath	B
Agteresch 2002	Randomised controlled trial N=58 Evaluable: 50 for antropometry Study period: 28 weeks	Patients with NSCLC stage IIIB or IV and a Karnofsky index of 60% or higher Intervention group: Male:20 Female:8 Mean age:64 Control group: Male:18 Female:12 Mean age:61	10 intravenous 30-hour ATP infusions, at 2- to 4-week intervals, vs no ATP	No change in body composition in the ATP group, whereas, per 4 weeks, the control group lost 0.6 kg FM (*P* =.004), 0.5 kg FFM (*P* = .02) and decreased 568 KJ/d in energy intake (*P*= .0001). Appetite also remained stable in the ATP group but decreased sign. in the control group (*P* = .0004).	64% of ATP courses without side effects, Most common side effects: chest discomfort, urge to take a deep breath; side effects were transient and resolved within minutes after lowering the ATP dose	B
Beijer 2009	Randomised controlled trial N=99 Evaluable: 83 Study period: 8 weeks	Preterminal cancer patients with mixed tumour types Male: 66% Female: 34% Mean age: 66	8 weekly 8-10 hour ATP infusions vs no ATP	Triceps skinfold thickness: between group difference per 8 weeks: 1.76 mm; p=0.009. No differences	63% of ATP courses without side effects, Most common side effects: dyspnoea, chest discomfort, urge to take a deep breath;	B

				between groups for appetite, body weight, mid-upper arm circumference and nutritional intake	side effects were transient and resolved within minutes after lowering the ATP dose	
PRIMARY STUDIES – ETANERCEPT VS PLACEBO						
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
Jatoi 2007	Randomized Placebo-Controlled Double Blind Trial N=66 Evaluable: 63 Study period: 24 weeks	Patients with incurable malignancy with a history of weight loss of ≥2.27 kg over the preceding 2 months and/or an estimated caloric intake of <20 kcal/kg/day Intervention group: Male:17 Female:16 Mean age:64 Control group: Male:14 Female:16 Mean age:68	Etanercept at a dose of 25 mg subcutaneously twice weekly versus a comparably administered placebo. Etanercept at a dose of 25 mg subcutaneously twice weekly for a possible total of 24 weeks or identical placebo administered subcutaneously twice weekly for a possible total of 24 weeks	No patient gained ≥10% of their baseline weight; 27% of the etanercept-treated patients and 3% of the placebo-exposed patients gained 0–4% of their baseline weight, and 17% and 9%, respectively, gained 5% to 9% of their baseline weight (NS) The NCCTG Anorexia/Weight Loss Questionnaire and the FAACT questionnaire found no significant diff. in appetite over time in the 2 treatment groups	Patients treated with etanercept had higher rates of neurotoxicity (29% vs 0%) but lower rates of anemia (0% vs 19%) and thrombocytopenia (0% vs 14%). Infection rates were negligible in both groups	A2
PRIMARY STUDIES – INFLIXIMAB VS PLACEBO						
Study ID	**Method**	**Patient characteristics**	**Intervention(s)**	**Results primary outcome**	**Results secondary and other outcome(s)**	**Critical appraisal of study quality**
Wiedenmann 2008	Multicenter randomized, double-	Patients with stage II–IV pancreatic cancer	Placebo or 3 mg/kg or 5 mg/kg of	Mean change LBM at 8 weeks: +0.4 kg for	No difference in change Karnofsky	A2

	blinded, placebo-controlled study N=89 Evaluable: 51 Study period: 8 weeks for LBM	and weight loss ≥10% compared with premorbid weight or ≥5% within 90 days before randomization Male: 48 Female: 41	infliximab at weeks 0, 2, and 4 and then every 4 weeks to week 24; patients also received 1,000 mg/m2 of gemcitabine weekly from weeks 0–6 and then for 3 of every 4 weeks until their disease progressed	placebo, +0.3 kg for 3 mg/kg of infliximab, and +1.7 kg for 5 mg/kg of infliximab Mean total weight and BMI of patients in all groups were comparable at 8 weeks	performance between placebo and 5 mg/kg of infliximab, with no patients improving in either group Overall QOL less favorable in patients receiving 3 mg/kg of infliximab compared with placebo Safety findings were similar in all groups	
Jatoi 2010	Randomized, double-blinded, placebo-controlled study N=61 Study period: assessment at 1-month intervals	NSCLC with no curative options Intervention group: Male:84% Female:16% Median age:71 Control group: Male:69% Female:31% Median age:75	Infliximab/docetaxel *versus* placebo/docetaxel (infliximab 5mg/(kg day) intravenously on day 1 and weeks 1, 3, and 5 during the first 8-week cycle followed by day 1 on weeks 1 and 5 of every 8-week cycle thereafter)	No patient in either arm achieved 10% or greater weight gain; a 5% or greater weight decline was observed in 5 (21%) infliximab/ docetaxel patients and in 10 (38%) placebo/docetaxel patients ($p = 0.17$). No significant differences in appetite over time between Groups	More fatigue and lower levels of functional and physical well-being in infliximab/docetaxel group Adverse events were not statistically different between groups	A2

Uitgangsvraag 6 Wat is effect van sondevoeding en/of parenterale voeding op ondervoeding bij kanker?

Study	Study design	Sources of funding	Search			Number of included studies	Eligibility criteria	A priori patients characteristics	Interventions	Control / Comparators	Effect size primary outcome parameters Effect size secondary parameters	Effect size all other parameters	Results critical appraisal	Level of evidence
			period	databases	included study designs									
August, 2009[1]	Clinical guideline in accordance with Institute of Medicine reccomenations as systematically developed statements	NS	NS	M,C and other	SR, RCT's and other	Perioperative nutrition support (26 RCT's, 1 Syst Rev) Periop nutr support in severely malnourished patients (8 RCT's) Nutr support as adjunct to chemotherapy (14 RCT's, 13 of	PN vs control (n=11), PN vs EN (n=12), EN vs control (n=5) PN vs control (n=7), PN vs EN (n=1) PN vs control (n=11),	Mostly GI cancer patients, malnourished and well-nourished Mostly GI cancer patients Different types of cancer	See eligibility criteria	See eligibility criteria	Conflicting outcomes on morbidity or mortality No differences in mortality: 3 studies, Lower mortality: 2 studies No differences in morbidity: 1 study Fewer complications; 6 studies Mostly no differences in toxicity, response rate	-	No meta-analyses performed	No improved outcomes with routine use of EN/PN in all patients undergoing major cancer surgery: A1 Periop nutrition may be beneficial in malnourished patients if given 7-14 preop, however benefits must be weighed against risks: A1 Nutr support should not be used routinely as

						moderate quality) Nutr support as adjunct of RT (1 RCT, 2 non RCT's) Nutr support in malnourished patients receiving anti-cancer treatment (7 RCT's of moderate quality, 1 RCT of good quality, 3 non-RCT's) Nutr support in palliative care (6 non-randomized trials, 1 RCT)	EN vs control (n=3) EN (n=2) or EN/PN (n=1) prior/during RT PN vs control (n=6), EN vs control (n=6) Home PN	GI cancer (n=1), H&N cancer (n=2) Different types of cancer, 1 RCT of good quality on > 1000 H&N cancer patients Advanced cancer			or survival GI cancer: less weight loss, fewer treatment interruptions. H&N cancer: no reduced weight loss; worse survival for PN patients No survival benefit of nutr support. Improvements in weight and N-balance Home PN improves survival (n=2), QOL in selected patients/responders (n=3). Responders have a good performance	Less diarrhea, less hypergly	Best and largest RCT limited to H&N cancer patients Mostly studies with historical controls	an adjunct to CT: B Nutr support should not be used routinely in patients undergoing H&N, abdominal or pelvic irradiation: C Nutr support is appropriate in patients receiving active anticancer treatment who are malnourished and who are expected not to be able to eat for a polonged period of time: B The palliative use of nutrition support therapy in terminally ill cancer patients is hardly indicated: C

								Hematologic and solid malignancies			status, minimal disease symptoms or indolent disease progression	cemia in EN group		
						Parenteral Nutrition in Hematopoietic Cell Transplantation (1 RCT of good quality, 6 RCT's of moderate quality, 5 non-RCT's)	PN vs oral (n=4), PN vs EN (n=3) or vs intravenous fluids (n=4)				PN vs EN: increased morbidity, but less weight loss, no differences in severity of GVHD			PN is appropriate in patients undergoing HCT who are malnourished and expected not to be able to eat for a prolonged period of time: B
								Hematologic and solid malignancies			PN vs intravenous fluids: no differences in morbidity, no difference in GVHD		Small number of patients included, different study designs,	
						EN peri-transplant HCT (2 RCT's of moderate quality, 3 historical cohorts)	EN vs PN							EN should be used in pts with a functioning GI tract in whom oral intake is inadequate: B
								Pts with GVHD after HCT			Possible decreased risk of GVHD in EN group			
						Nutr support in patients with GVHD after HCT (2 RCT's, 2 non-RCT's)	PN vs oral or intravenous fluids, PN vs EN							Nutrition support is appropriate for patients with GVHD after HCT accompanied by
											PN does not decrease the incidence of			

											GVHC. No data of impact of nutritional support on the resolution of GVHD			poor oral intake and/or malabsorption: C
Braunschweig, 2001[2]	Meta-analysis	NS	1966 - 1999	M	Prospective RCT's	27 Studies: 20 studies PN vs EN and 7 studies PN vs standard care. 13 Studies included cancer patients	Prospective RCT's comparing PN with EN or standard care with outcomes on morbidity or mortality	4 Sources for heterogeneity defined a priori: 1. study-quality, 2. year of publication, 3. nutritional status, 4. percentage patients with cancer (<50%, ≥ 50%)	PN PN	EN Standard care	<u>PN vs EN</u>: EN sign lower risk of infections (RR 0.66); this remained significant in subgroup analysis for cancer patients: No favourable outcomes of EN vs PN on mortality or other complications <u>PN vs standard care:</u> lower risk of infection (RR 0.77) and trend towards fewer other complications (RR 0.87) to standard care vs PN. No significant	-	Only half of the studies were on cancer patients. These could not be seperated from other studies. Meta-analysis and test for heterogeneity performed.	Tube feeding and standard care are associated with a lower risk than is parenteral nutrition: A1 Mortality is higher and the risk of infection tends to be higher with standard care than with parenteral nutrition in patients with malnutrition: A1

											differences in mortality. In studies with high % of PEM standard care was associated with higher risk of mortality (RR 3.0) and trend toward higher risk of infection (RR 1.117). After removing events of removing catheter sepsis risk of infection remained lower in EN (RR 0.7) and standard care (RR 0.79) compared with PN			
Braunschweig, 2004[3]	Review of 4 meta-analyses	NS	-	-	4 Meta-analyses	4 Meta-analyses 1. Heyland, 2. Heyland, 3. Braun schweig, 4. Koretz including 113 prospective		1. Critically ill, 2. surgical, 3. pts with marginal GI function, 4. any prospectiv	PN		PN does not affect mortality; PN does not reduce complications in normally nourished patients; PN is associated		Most of the RCT's included poor quality	For outcome parameters as described the level of evidence is: A

						RCT's		e RCT			with reduced mortality and a trend for reduced infections and complication rates in malnourished patients; PN reduces postop complications in patients having surgery for cancer of the esophagus or stomach			
Corry, 2008[4]	RCT	NS	-	-			Adult pts with squamous cell carcinoma of the Head & Neck, planned for curative RT of chemoradiation who were anticipated to require EN		PEG tube (n=15)	Nasagastric tube (n=18)	No sign differences in nutritional status, overall complication rates, chest infection rates, unscheduled treatment breaks	Costs for PEG 10 times as high as costs for NG feeding tube. PEGs were used signifantly longer than were NG tubes	Planning: inclusion of 150 patients. Due to poor accrual, the study was closed after 3 yrs with only 42 pts included, 33 pts eligible for analysis. Bias through missing data. Distribution of tumour sites was different in	No superiority of PEG tubes over NG tubes; balance of benefit towards NG tube: B

													each of the two groups.	
CBO Richtlijn perioperatief voedingsbeleid, 2007[5]	Evidence based guideline	NS	1999 - 2005	C, M, E, guidelines from countries outside the Netherlands	All kinds of studies were included. Quality of studies was assessed before drawing conclusions	Preoperative nutrition (1 review, 1 meta-analysis, 2 RCT's) Perioperative nutrition (pre- op and postop) (4 RCTS, 1 review) Postoperative enteral nutrition, 15 studies, quality of studies not rated. Postop EN or PN, 5 studies and 2 meta-analyses	PN or EN	Surgical patients, not exclusively cancer patients Both malnourished and well nourished patients included	PN or EN PN or EN EN EN	Standard care Standard care PN PN or control	Preop PN in malnourished patients reduces complications. Preop EN no effects on complications Most complications in malnourished pts not receiving nutritional support. Periop EN or PN reduces compl ications with 20-36% Early postop EN reduces weight loss, improves immune response, reduces infections, reduces LOS. EN shorter LOS than PN	More abdominal side effects in EN patients	Preop nutrition: only 2 studies on EN, making drawing of conclusions impossible	In malnourished patients, optimalisation of nutritional status with PN is useful: A. This should take 7-10days: D Perioperative EN or PN is useful for malnourished cancer patients requiring surgery: A This may include delay of operation with 10-15 days: B Early postop nutrition reduces postop morbidity, also in well-nourished patients: A. EN favours PN: A

Elia, 2006[6]	SR	NS	- 2004	P, C, T, CE, NEL, NSF	47 RCT's en 16 CCT's	Chemotherapy or radiotherapy and BMT Surgery	Enteral nutrition, oral nutritional support (EPA supplementention, not further summarized)	Adults, well nourished or malnourished, all kinds of cancer, all kinds of treatment, any therapy, hospital or community setting	EN/ ONS EN/ ONS EN	Routine care Routine care PN	2 CCT's reported improved intake 4CCT's reported significant benefits with regard to reducing weight loss 4 RCT's and 1 CCT: no sign effect on mortality (OR 1,0 (0.62, 1.11) Complications: no effect 4 RCT's: perop nutrition no effects on mortality (OR 2.44 (0.75, 7.95)). 5 RCT's: periop nutrition no effects in LOS (0.40 days,(-0.9, 1.82)) 3 RCT's: no differences in		Most studies of methodologically poor quality. Enteral nutrional support studies and oral nutritional support studies were not separated in the meta-analyses	In patients undergoing cancer surgery EN, compared to PN, reduces complication rate and length of stay: A Enteral nurition has no benefit over parenteral nutrition or routine care with regard to mortality, neither for surgical, chemotherapy or radiotherapy patients: A

											infectious complications (OR 1.36 (0.86,2.13)) Improved QOL in 2 RCT's using preop EN vs routine care 8 RCT's: shorter LOS (1.72 fewer days (0.9, 254)) 4 RCT's: lower incidence any complications (OR 0.62 (1.5. 0.77)) 11 RCT's: lower incidence infectious complications (OR 0.67 (0.55, 0.82)) 2 RCT's: lower sepsis scores (2.21 points (1.49, 2.92)) Mortality: no differences EN vs PN (OR 0.72 (0.4, 1.29))			
Good, Cochr	System atic		C, M, E,	Medlin e	RCT's or	4 Prospective	Advanced cancer	Palliative care	PN or	-	Survival: Cochrane		No RCT's or	Decision making based on

ane Review w2008 [7]	Review		Cinahl, Cancerlit, Caresearch, Dissertation abstracts, Science citation index, reference lists	1966-2008, Embase 1980-2008	prospective controlled trials	non-controlled trials (Bozzetti 2002, Meier 2001, Orrevall 2005 – qualitative study - and Pirone 1997) and 1 Cochrane review (Langmore 2006). The studies by Bozzetti, Orrevall and Prironi included only participants with advanced cancer	(Results of the study by Meier and Langmore not further described because they didn't address cancer patients)	participants who received medically assisted nutrition, palliative care, incurable cancer or dementia or neurodegenerative diseases, HIV, chron heart failure, chronic airway limitations, > 18 y of age	EN		review: conflicting results. Bozzetti mean survival time on HPN 4 months. Pironi 12.2 wks (HPN) resp 17.2 wks (HEN) QOL: no improvement (Bozzetti, Langmore). Perceived benefit in qualitative study (Langmore). Performance score stable until progressive decline of disease (Bozzetti)		prospective controlled trials were identified. No studies were suitable for statistical analyses. Only prospective non-controlled studies included Insufficient good quality studies to make any recommendations.	perceived benefits and harm: D
Goonetilleke, 2006 [8]	SR	NS	M, E	1994-2004	RCT's and other, (n=10)	Perioperative (7 RCT's, 2 non-RCT's, 1 study was not on EN or PN),	Pancreatic resection (n=4), gastrointestinal cancer incl pancreatic cancer				Routine TPN has no clinical benefit and may be associated with greater risk of morbidity. Enteral		Pooled analysis unfeasible because of wide disparity in study protocols	Routine PN is not beneficial; EN reduces infective complications: A

							(n=5)				nutrition associated with lower incidence of infective complications			
Koretz, 2001 [9]	SR	NS	IM, C, E, manual search	1974 - ?	RCT's	82 RCT's. 9 RCT's involved PN in patients with upper GI cancer. 26 RCT's involved PN in patients undergoing oncologic therapy. (Other not summarized)		Esophageal or stomach cancer Patients receiving CT (19 RCT's), Radiotherapy (3 RCT's) or BMT (4RCT's)	PN PN	Standard care Standard care	Decrease of major postop complications (absolute risk difference -18% (-34%, -2%). Other outcomes (complications, LOS), trends in favour of PN Increase of total complication rate (+40%) and infectious complication rate (+16%) with PN. Decrease in tumor-response rate (to chemotherapy in particular), -7% (-12%, -1%) No significant effects on mortality 0% (-5%, +5%) or	-	Meta-analyses were performed when data were available form at least 3 trials Most RCT's included well-nourished patients Inadequate data to assess efficacy of PN in patients who are severely malnourished	Periop PN is indicated in patients undergoing surgery for esophageal or stomach cancer: A PN does not influence survival in patients receiving chemotherapy or radiotherapy: A. Possible favorable effect of in-hospital PN during BMT: A In all other aspects PN in cancer patients receiving CT, PN causes net harm (increase in total

											treatment toxicity (bone marrow toxicity +22% (-10%, +54), GI toxicity (-9%, +11%). Trend for improved survival for PN during BMT (-9% (-22%,+4%)			and infectious complications, impaired tumor response to CT): A
Koretz, 2007[10]	SR	NS	1975-? (three decades)	NS	RCT's	Perioperative (not all cancer): 44 Non-surgical cancer treatment: 8	Perioperative patients Non-surgical cancer treatment	Hospitalised or non–hospitalised patients. Patients were not severely malnourished	EN EN PN (other not	No nutrition treatment PN	<u>Periop:</u> EN vs control (n=13): no differences in mortality or other complications, sign. less postop infections (-11%, 95% CI -20 to -1%) EN vs PN (N=16): less complications (all kinds), -8%, 95% CI -13 to -3% <u>Non-surgical cancer treatment:</u> EN	More diarrhoea -	Negative: search dates missing, searched databases missing. Not all periop trials included cancer patients Positive: Meta-analyses performed when 3 or more RCT's were available Non-surgical cancer	<u>Periop</u>: EN associated with less postop complications compared with standard care: A1 EN associated with less infectious complications than PN: A1 <u>Non-surgical cancer treatment</u>: No significant

						(other groups not summarized)	(other groups not summarized)		summarized)		vs control (n=2): No significant benefits nor harm		treatment: only 2 studies on EN included	benefits nor harm of EN vs standard care: B
Lewis, J 2009[11]	SR	NS	NS	C, P, M, L	13 RCT's	8 RCT's lower GI surgery, 3 RCT's predominantly lower GI surgery, 1 RCT uppert GI surgery, 1 trial surgery site not reported	Patients undergoing elective GI surgery for a wide variety of GI conditions		EN started within 24 h after surgery	No postop EN or EN started > 24 h after surgery	Mortality: reduction in early EN group, RR 0.42 (0.18, 0.96) (6 RCT's) Length of hospital stay reduced in early EN group: -0.89 (-1.58,-020) (12 RCT's) No sign differences with regard to wound infections, intra-abdominal sepsis, pneumonia	Increased vomiting in early EN group (RR 1.23)	Quality of studies, adequacy of concealment and blinding assessed. Meta-analyses performed and heterogeneity tested. This review did not differentiate between cancer and non-cancer patients	Early pospoperative enteral nutrition, started within 24 h after GI surgery, decreases length of hospital stay and reduces mortality: A
Mc Gough, 2006[12]	SR	NS	1966 - 2003	M, E, C	14 RCT's, 12 prospective cohorts, 4 retrosp	36, of which 4 RCT's on enteral nutrition and 2 RCT's on parenteral nutrition		Patients with gynaecological, urological or rectal cancer undergoing radical	EN	No enteral nutrition	Improved energy and protein intake. No outcome measures as toxicity, survival, etc. reported	-	Different interventions and endpoints. Most studies weak in methodology.	No evidence base for EN or PN to prevent side-effects of RT: B

					ective studies, 2 qualitative studies, 1 validation study, 1 pilot study, 2 case reports	(other nutritional interventions not summarized)		pelvic radiotherapy	PN (other interventions not summarized)	Oral nutrition	Less side-effects of treatment, however strong bias towards severely malnourished patients in TPN arm		Overall no evidence base for nutritional intervention to prevent side-effects of RT	
Ryu, 2009[13]	RCT	NS	-	-	-	-	-	Pts with laryngeal or pharyngeal cancer undergoing surgery	EN, n=44, 3 drop outs	PN, n=40, no dropouts	No sign differences between group with regard to LOS, complications, nutritional status	EN group more subjective discomfort and diminished swallowing at 1 week . At two weeks or more no differences. PN much more		No differences in objective postoperative outcomes between EN and PN group: B

												expensive than EN		
Salas, 2009[14]	Randomized open multicenter trial	NS	-	-	-	-	-	Pts with H&N cancer stage III or IV with radio-chemotherapy, age ≥18 y, BMI ≥20, weight loss < 10%/6mo, Karnofski ≥70	Prophylactic gastrostomy (n=21)	No systematic gastrostomy (n=19)	No differences in mortality or BMI. QoL at 6 months was sign. higher in the gastrostomy group than in the control group (p=10 -3). Also higher Karnofsky index at baseline and higher initial BMI were related to a higher QoL at 6 mo		Results of improved QoL may have been influenced by other potential predictive factors, such as higher initial BMI or higher Karnofski score. Only well-nourished patients included	Prophylactic gastrostomy may improve post-chemoradiation QoL: B but does not affect nutritional status or mortality: B
Shang, 2006[15]	RCT	NS	-	-	-	-	Patients with advanced incurable cancer. Goals 95-100% of calorie and protein intake by either feeding strategy	All patients malnourished and receiving palliative chemotherapy or chemo-radiation therapy, n=152 (colorectal cancer n = 55,	intensified oral enteral nutrition + overnight PN n=72 (PN+)	Intensified oral enteral nutrition, no PN, n=80 (PN-) (intensified oral enteral = normal nutrition + oral	Survival 12.5 mo (PN+) vs 9 mo (PN-), p<0.001, cumulative survival rate p<0.0001 Statistically sign difference in mean BMI by week 48, in mean body cell mass by week 6, mean	Feeding goals reached in both groups, no sign differences in mean daily nuritional intake between groups		

								esophageal cancer n = 38 and gastric cancer n = 24, other (pancreas/ovarian/breast n=35))		sipfeeds)	albumin by week 6, and mean QOL by week 6 ,all in favour of PN+ group			
Wu, 2006[16]	RCT	-	-	-	-	-	Gastric or colorectal cancer	Moderately or severely malnourished (SGA)	7 days preop and postop EN or PN , 24.6 ± 5.2 kcal/kg/d and 0/23 ± 0.04 gN/kg/day (n=235)	Control group, no preop nutrition, postop 600 ± 100 kcal non-protein kcal and 62 ± 16 g aminoacids (n=233)	Sign reduction in complications (p=0.012) and mortality (p=0.003), length of hospital stay (p=0.014) and postoperative stay (p=0.000). No sign differences in septic complications between EN and PN patients		Large RCT in malnourished patients only	Periop nutritional support decreases the incidence of postop complications and is effective in reducing LOS and mortality: A2

NS = not stated
RCT= randomized controlled trial
CCT= controlled clinical trial
SR = systemic review
EN = Enteral nutrition
PN = Parenteral nutrition

PEM = protein energy malnutrition
HCT = hematologic cell transplantation
GVHD = graft versus host disease

Search Databases:
Pubmed = P
Medline = M
Cochrane = C
Embase = E
Index Medicus = IM
LILACS = L
Turning Research into practice = T
Clinical Evidence = CE
National Electronic Library of Health guidelines finder= NEL
National Service Framework = NSF

Uitgangsvraag 7 Wat is het effect van voorlichting en voedingsadviezen op ondervoeding bij patiënten met kanker?

I Study ID	II Method	III Patients characteristics	IV Internevention	V Results, primary outcome	VI Results secondary and other outcomes	VII Critical appraisal of study quality
van den Berg British Journal of Nutrition 2010	CCT Radboud University Medical Centre N = 38 (20 ICD, 18 SC) 20 weeks (diagnosis, treatment, early rehabilitation, rehabilitation)	Inclusion: patients with head and neck cancer stage II-IV, treated with radiotherapy, combined surgery or chemo radiation. Age 62	Individual dietetic counselling (IDC, optimal energy and protein requirement) compared with standard nutritional counselling (SC) on weight loss, BMI and malnutrition before, during and after treatment.	IDC showed a significant decrease in weight loss 2 months after treatment compared with SC IDC showed decrease of malnutrition. SC showed increase of malnutrition.	No difference in BMI between IDC and SC. No difference between de T stages.	Level of evidence B
Dintinjana Coll. Antropology 2008	CCT Clinical Hospital Centre Rijeka, Croatia N = 388 (215 Group I, 173 Group II) Baseline and 12 visits conform chemo schedule.	Inlcusion: patients with locally advanced or metastatic colorectal cancer during chemotherapy. Age: 67	Group I: data collected prospectively with nutritional support (nutritional counselling, enteral food supplement and 400 mg megasterol acetate dd) Group II: data collected retrospectively without nutritional support. At start compatible inf weightgain, appetite (NTS) and Karnofsky Perfomance Status	After chemotherapy completion: Group I vs Group II: BMI < 20: 33% vs 53% NTS ≥5: 34 vs 58% Loss of appetite: 37 vs 90% Decreasing in weight gain > 2kg/month: 26 vs 80%)	No implications and no changes in KPS	Level of evidence B Dropouts unknown Weakness in retrospective
Elia International journal	Systematic review with meta-analysis Pubmed, Cochrane, Turning research into	Eligibility criteria: neoplasm, cancer, tumor, nutrition, supplement, sip,	Oral supplement vs no supplement.	In patients undergoing radiotherapy, meta analysis showed that ONS significantly increase dietary intake (381	No effect shown on QoL, treatment respons or	Level of evidence B Weakness in RTC's

of oncology 2006	practice,Clinical Evidence, National Electronic Library for Health Guidelines, National Service Framework.	feed, formula, liquid, clinical trial. Adult persons, with any cancer, any nutritional status, any setting, nutritional support with liquid oral nutrition support (ONS) Excluded: only dietary counselling		kcal/day, 95% CI 193 tot 569 in 3 RCT's) compared to routine care.	mortality	
Halfdanarson Journal of Supportive Oncology 2008	Systematic review with meta analysis Medline, Embase, Central, Cinahl, We Science Only RCT's included focused on dietary counselling and standard QoL. 5 RCT's	Eligibility criteria: RCT, neoplasm, cancer, chemotherapy, radiotherapy, dietitian, dietary service, counsel, energy intake, body composition, body weight, weight loss, cachexia, malnutrition, nutritional status, nutritional assessment, nutritional support, nutrition physiology, QoL. 3 trials included patients with head and neck cancer undergoing radiotherapy, or colorectal cancer,, 1 trial with cancer of breast, lung and ovary treated with chemotherapy, 1 trail	Intervention: dietary counselling at the beginning of therapy or time of diagnosis, all reported QoL Comparator: No individual dietary counselling or standard care.	The stadaridized mean difference in QoL scores among patients who received dietary counselling was 0.56 (95% confidence interval, -0.01-1.14; P = 0.06.. In trials radiotherapy head and neck showed a positive effect on QoL. In the trail with chemotherapy and surgery was no effect shown.	There is a trend toward benefit for QoL.	Level of evidence A1

		stomac or colorectum cancer treated with surgery,				
Hytlander Clin.Gastroenterology and hepatology, 2005	RCT Funding: public research funds, non gouvernemental organisations Department of surgery Sahlgrenska University Hospital, Sweden N = 80 (26 EN + oral, 27 PN + oral, 26 oral) 12 months	Inclusion: patients with esophagus, stomach or pancreas cancer referred for resection Exclusion: impaired renal or hepatic function, disseminated disease, corticosteroid treatment Male: 82, female 44, age ± 63 P value: < .05	Intervention: EN or PN till preoperative weight was gained or patient wished to stop. 1) EN group: oral + 1000 Kcal by tubefeeding 2) PN group: oral + 1000 Kcal by PN Comparator 3) OR group: oral supportive care + enriched formulas	No difference in all groups concerning survival, hospital stay, body weight, whole body fat, lean body mass, recovery food intake.	PN was associated with more nutrition-related complications. EN reduced most extensively quality of life.	Level of evidence B Dropouts: 1 vs12 months EN-groep 3 vs 11 PN-group 7 vs 15 Oral-group 3 vs 12
Ireton-Jones Clinical Nutrition 1995	CCT 2 outpatient cancer clinics, Clinical Nutrition Network and Texas Oncology Center, Dallas. N = 103 (74 Group I, 29 Group II) Baseline and week 5	Inclusion: Outpatients with heterogeneous types of cancer. Exclusion unkown Male 55, Female 48 Age ±63	Group I: patients with nutritional risk referred to the registered dietitian for Nutritional Assessment (NA) and instruction. Group II: no nutritional instruction	Group I vs group II: NA improved or maintained: 54 – 29%. NA decreased: 46 vs 71 %.		Level of evidence B Dropout unknown Weakness by different groups
Isenring British Journal of Cancer, 2004	RCT Funding: non governmental organisation, Abbot Australia, Mead Johnson Queensland University, Wesley Hospital, radiation department N = 60 (29 Nutritional Intervention NI, 31 Usual Care UC)	Inclusion: outpatients with head and neck (88%) or GI (12%) treated with radiation (RT) at least 20 fractions Exclusion: < 18 y, hospitalstay > 5 days Male 51, female 9, Age 61.9	NI: intensive, individualised nutrition counselling by a dietitian using standard protocol and if required oral supplements UC: usual care: general advice and booklet	NI group had smaller deteriorations in weight ($p<0.001$) nutritional status ($p = 0.020$) and global QoL. ($p = 0.009$). NI: 24 % weight stable, 22% weight loss UC: 6% weight stable, 43% weight loss PG-SGA score: 0-4-8-12 weeks: NI: 6.4-8.0-6.8-4.8	No significant differences in fat-free mass and physical function	Level of evidence A2 Dropouts: 6 in follow up

	Baseline, 4, 8, 12 weeks			UC: 5.3-11.8-9.7-8.4		
Luis, de Ann Nutr Metab 2005	RCT N= 73 ambulant postsurgical patiens omega3 fatty acid-enhanced supplement (group 1) or an arginine-enhanced supplement (group 2) no controlle group 12-week period	ambulatory postsurgical patients with oral and laryngeal cancer were enrolled after discharge from hospital	patients were asked to consume two units per day of either a specially designed omega3 fatty acid-enhanced supplement (group 1) or an arginine-enhanced supplement (group 2) for a 12-week period no controle group	Differences were detected in weight with a significant increase in fat mass in group	The postoperative infectious compli-cations were similar in both groups (0 in group 1 and 8.57% in group 2; nonsignificant). No local compli-cations were detected in the surgical wound. Gastrointestinal tolerance (diarr-hea and vomiting episodes) of both formulas was good.	
Lundholm Cancer, 2004	RCT Funding: public research funds Department of surgery, Sahlgrenska University Hospital N = 309 (139 Nutritional Support NS, 170 Control Group CG) From start till death (0-24 months)	Inclusion: malignant disease solid tumours with progressive cachexia. No treatment useful. Expected survival < 6 months. Exclusion: brain metastases, survival > 6 months, impairment of kidney function, fever. Male 160, female 146	NS: idomethacin + EPO + nutrition focused patient care (counselling, oral support if intake was < 90% and home TPN if the intake was <70-80% of the estimate need) Comparator: CG: idomethacin + EPO without nutritional support	Intention-te-treat analysis: NS: improvement of weight gain and food intake. No statistically significant difference in survival, body composition, exercise tests.	As treated analysis: NS improvement of survival, improved intake and energy balance, greater maximum exercise capacity	Level of evidence B Dropouts: all by death A part of the CG received nutritional oral support or HPN
McCarthy Oncology Nursing	CCT Funding: public research fund University Hospital, Madison	Inclusion cancer outpatients (no head and neck) treated with first course of radiotherapy.	Experimental group: weekly dietary counselling plus a liquid nutritional supplement daily.	Experimental group increased their total caloric and protein intake above that of the control group	No reduce of the food-derived caloric or protein intake by the use of supplements	Level of evidence B Dropout 8

Forum, 1999	N = 40 (14 experimental group, 18 control group) Baseline and 4 x weekly	Exclusion: former radiation or other treatment, head and neck cancer Male 9, female 23, 57 y	Control Group: weekly dietary counselling only.			
Odelli Clinical oncology 2005	Case control Newcastle Mater Misericodiae Hospital, New South Wales, Australia N = 48 (24 after Nutrition Pathway (NP), 24 before implementation of the NP	Inclusion: patients with oesophageal cancer treated with chemo radiation. Exclusion - Male 33, female 15, 70 y	NP group: prospectively, nutritional support according the NP protocol after classification: low moderate or high risk. Control group: retrospectively, treated before the implementation of the NP protocol: referred for nutritional support if problems arose.	NP group vs Control group: Referred for dietitian: 96% vs 33% Weight loss: -4.2 vs – 8.9 kg	NP vs Control: Completing treatment: 92% vs 50% Unplanned hospital admission: 46% (3.2 d) vs 75% (13.5 d)	Level of evidence B Dropout unknown Weakness by retrospection
Person Nutrition and Cancer 2002	RCT Funding: public research fund Department of oncology, University Hospital, Uppsala N = 142: 45 Individual support (IS) 25 IS + Group rehabilitation (ISGR) 28 Group Rehabilitation (GR) 44 Standard Care (SC) Baseline, 1, 3, 6, 9, 12, 18, 24 months	Inclusion: Patients with colorectal (N=105) or gastric cancer (N=37) after diagnosis. Exclusion: KPS <40, earlier cancer diagnosis, no Swedish language.	IS: individual nutrition support, intensified primary health care, problem-focused individual psychological support. GR: eight-session group rehabilitation intervention ISGR: combination of IS and GR SC IS and ISGR contacted the dietitian and collected dietary intake, weight and QoL	IS and ISGR had significantly more rapidly and greater extent weight gain compared with GR and SC after 12 and 24 months. No difference in QoL but a positive correlation between weight development and QoL and a negative correlation between fatigue and weight development.	There was an indication, not statistically significant, of shorter survival in GR and SC	Level of evidence B Dropout by death Blinding not clear.

			GR and SC collected weight and QoL.			
Ravasco Head & Neck 2005	RCT Public research fund Center of Nutrition and Metabolism, Radiotherapy Department Santa Maria University Hospital N = 75 (25 group 1, 25 group 2, 25 group 3) Baseline, end of RT, 3 months after RT	Inclusion: Patients with head and neck cancer stage I/II and II/IV referred for RT 70 Gy in 35 fractions Exclusion: renal disease, diabetes mellitus Male 60, Female 15, Age 60 y.	Group 1: weekly dietary counselling with regular foods Group 2: usual diet plus daily 2 high protein energy-dens supplements Group 3: intake ad lib. Evaluation of nutritional intake, SGA and EORTC QlQ-C30 at baseline, end RT and 3 months after RT	During RT in groups 1 and 2 energy and protein intake increased. And decreased in group 3. After 3 months group 1 maintained intakes, whereas groups 2 and 3 returned to or below baseline levels. At 3 months reduction of RT symptoms was different: 90% in group 1, 67% in group 2, 51% in group 3.	During RT trend for less RT toxicity in group 1 After RT QoL function improved in group 1 and worsened in groups 2 and 3	Level of evidence A2 No dropouts
Ravasco Journal of Clinical Oncology 2005	RCT Public research fund Center of Nutrition and Metabolism, Radiotherapy Department Santa Maria University Hospital N = 111 (37 group 1, 37 group 2, 37 group 3) Baseline, end of RT, 3 months after RT	Inclusion: patients with colorectal cancer all stages referred for RT of 50 Gy in 28 fractions Exclusion: renal disease and diabetes mellitus. Male 66, female 45, Age 58 y	Group 1: weekly dietary counselling with regular foods Group 2: usual diet plus daily 2 high protein energy-dens supplements Group 3: intake ad lib. Evaluation of nutritional intake, SGA and EORTC QlQ-C30 at baseline, end RT and 3 months after RT	During RT in groups 1 and 2 energy and protein intake increased. And decreased in group 3. After 3 months group 1 maintained intakes, whereas groups 2 and 3 returned to or below baseline levels. After RT and at 3 months rates of symptoms were higher in group 3. Group 1 maintaines or improved function, symptoms and sigle-item scores, group 2 improved only a few functions and symptoms, group 3 remained poor.	QoL correlated in all groups with better or poorer intake or nutritional status.	Level of evidence A2 No dropouts
Wood Journal of Human	Case control. Nutrition & Dietetic department, Royal Free Hospital, London	Inclusion: patients with head and neck cancer treated with radiotherapy or	Prospective group: all patients were routinely referred to the dietitian for	In the prospective group after implementation of the guidelines fewer patients lost weight and there were no	Implementation is more likely if the dietitian is present in the	Level of evidence B Dropouts in follow up: 40%.

Nutrition and Dietetics 2005	N = 62 (32 prospective group, 30 retrospective group) Baseline till 4-6 weeks post-radiotherapy	chemo radiation. Exclusion: other cancers Male : female: 2:1, 63.6 years	weekly dietary advice. Retrospective group: nutritional data were collected from history.	admission for feeding. Weight loss: 19 vs 31% Weight gain 28 vs 0%.	head and neck clinic.	