Bijlage Evidence tabellen

Voedingsinterventies

Vraag 1: Wat is het effect van voedingsinterventies (dieetadviezen, drinkvoeding, sondevoeding, parenterale voeding) op gewichtsverlies en kwaliteit van leven bij patiënten met kanker, hartfalen, COPD en ALS?

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Bouleuc 2020	• Design: RCT • Funding: public grants from the French Ministry of Health and National Cancer Institute (PHRC 20110728); CoI: no financial relationships • Setting: 13 centres, France • Sample size: N=148 • Duration: recruitment June 2012 – Mar 2017, median follow-up 33.8 months	• Eligibility criteria: patients with advanced cancer and with malnutrition defined as a BMI <18.5 for patients aged <70 years and BMI <21 for those aged > 70 years or as weight loss of 2% in 1 week, 5% in 1 month, or 10% in 6 months; life expectancy less than 12 months and more than 2 months; functional gastrointestinal tract without symptomatic peritoneal carcinomatosis or intestinal obstruction; and patients with a central venous catheter • Exclusion criteria: patients with head and neck and esophageal-gastric cancer and any contraindication for parenteral nutrition (such as poorly controlled diabetes, severe heart failure, or severe ascites and edema) • *A priori* patient characteristics: ○ Mean age: 66.3y ○ M/F: 50/61 ○ Mean BMI: 20.58 kg:m²	Parenteral nutrition: by central venous route, 30–35 kcal/kg/day with 1.2–1.5 g/kg/day of protein, without exceeding 1.25 times the resting state energy expenditure (N=70) vs. Oral feeding: a minimum intake of 1000 kcal/day and 6 g of nitrogen was prescribed 5 days a week (N=78)	CRITICAL OUTCOMES • Weight: mean change from baseline at 2 months 0.33kg for all patients, no statistically significant difference observed between treatment arms • Anorexia / appetite: EORTC QLQ-C15-PAL, dimension “appetite loss”, deterioration-free survival: HR 1.27; 95%CI 0.86-1.88, p=0.233 IMPORTANT OUTCOMES • Adverse events: severe adverse events 7 vs. 1, p=0.0105 • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: EORTC QLQ-C15-PAL ○ QOL deterioration-free survival: ▪ Global QOL: HR 1.31; 95%CI 0.88-1.94; p=0.18 ▪ Physical functioning: HR 1.58; 95%CI 1.06-2.35; p= 0.024 ▪ Fatigue: HR 1.19; 95%CI 0.80-1.77; p=0.393 ▪ Pain: HR 1.79; 95%CI 1.20-2.66; p=0.004 • Performance status: median time to performance status deterioration 1.6 vs. 5.7 months, HR 2.24, 95%CI 1.21-4.15, p=0.008 • Survival: median overall survival 2 vs. 3 months, p=0.14	Level of evidence: high risk of bias • Patients were randomized following Zelen’s single-consent design, which allows physicians to randomize patients before consent and then obtain informed consent on the intervention only from those patients randomized to the experimental arm • Randomization method and allocation concealment unclear • Unclear blinding, but unlikely • 111/148 patients finally included with consent; 107/148 randomized patients included in analysis
Capozzi 2016	• Design: RCT • Funding: Alberta Cancer Foundation’s Joe’s Team Donor-Directed Funds; CoI: none	• Eligibility criteria: aged>18 years; newly diagnosed with nasopharyngeal, oropharyngeal, or hypopharyngeal cancer; scheduled to receive radiation	Immediate 12-week lifestyle intervention: (N=…) vs.	CRITICAL OUTCOMES Weight/BMI: • …: ○ …	Level of evidence: … risk of bias • Randomized using a computer-based, random-number generation program

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Setting: single university centre, Canada • Sample size: N=60 • Duration: follow-up of 24 weeks	or concurrent chemoradiation treatment; able to walk without assistance; received clearance for exercise from their treating oncologist • Exclusion criteria: … • *A priori* patient characteristics: ○ …	Delayed 12-week lifestyle intervention (N=…)	Quality of life:	• …
Cereda 2019	• Design: RCT • Funding: Fondazione IRCCS Policlinico San Matteo, partially by the Italian Ministry of Health (project code RF - 2011 - 02351315) and Ricerca Corrente grant no. 08067617, and by Difass International srl. (provision of WPI).; CoI: none • Setting: single centre, Italy • Sample size: N=166 • Duration: follow-up of 3 months • Study ID: NCT02065726	• Eligibility criteria: adult (age ≥ 18 years), malnourished (6 - month unintentional weight loss ≥10%) advanced cancer patients (lung, stomach, esophagus, pancreas, colon, blood, breast, and head - neck) candidate to or undergoing chemotherapy, ECOG performance status ≤2 and were not receiving any type of artificial nutrition (enteral or parenteral) • *A priori* patient characteristics: ○ Mean age: 65.1 vs. 65.7y ○ M/F: 100/66 ○ Stage IV: 75.6% vs. 86.9% ○ BMI: 22.0 vs. 22.3 kg/m²	Nutritional counselling with whey protein isolate supplementation, 20 g/day for 3 months (N=82) vs. Nutritional counselling without whey protein isolate supplementation (N=84)	CRITICAL OUTCOMES • Weight: ○ Treatment effect at 1 month: 0.4 (95%CI -0.3 to 1.2), p=0.22 ○ Treatment effect at 3 months: 1.7 (0.2-3.1), p=0.023 • Anorexia / appetite: not reported IMPORTANT OUTCOMES • Adverse events: ○ No apparent gastrointestinal intolerance event ○ No death was related to the study intervention ○ No other intervention-related adverse events • Change of calorie intake: adjusted MD +0.40 kcal/kg/d (95%CI -1.76 to 2.55; p=0.72) • Lean body mass: fat-free mass index (kg/m^2) ○ Treatment effect at 1 month: 0.12 (-0.27 to 0.51), p=0.53 ○ Treatment effect at 3 months: 0.46 (0.02-0.90), p=0.041 • Quality of life: EORTC QLQ - C30 ○ Global score, treatment effect at 3 months: 2.40 (95%CI -2.71 to 7.51), p=0.35 • Performance status: not reported • Survival: not reported	Level of evidence: high risk of bias • Computer - generated random blocks randomization list (varying block sizes) • Randomization list was prepared by a local statistician, who was not involved in the selection and enrollment of patients • Concealment was achieved using sealed envelopes • Patients not blinded • Study statistician was blinded to treatment assignment • 135/166 randomized patients included in analysis
Chewaskulyong 2024	• Design: RCT • Funding: Faculty of Medicine at Chiang Mai University, in Thailand, grant numbers 077/2563; CoI: none	• Eligibility criteria: adult patients with newly diagnosed lung cancer (any stage) undergoing definitive treatment (chemotherapy, radiotherapy, targeted therapy, and immunotherapy), ECOG	Nutrition counselling: counselling by dietitian; focus on energy requirement of 25-30 kcal/kg per day and a protein requirement of 1-1.5 g/kg per day; oral	CRITICAL OUTCOMES • Weight/BMI: ○ Mean body weight: ▪ At 3-4 weeks: 54.91 vs. 53.38 kg, p=0.504	Level of evidence: high risk of bias • All randomization allocations were performed externally using computer-generated random number

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Setting: single university centre, Thailand • Sample size: N=80 • Duration: follow-up 12 weeks	performance status of 2 or lower • Exclusion criteria: patients with two primary tumors, heart failure, edema or ascites, dysphagia, bowel obstruction, a history of gastrointestinal tract surgery, a life expectancy of less than 1 month, or on total parenteral nutrition • *A priori* patient characteristics: ○ Mean age: 62.99y ○ M/F: 49/31 ○ Stage IV: 73.25% ○ BMI 18.5-22.9 kg:m²: 46.25%	nutritional supplements if needed (N=43) vs. Routine care: general dietary recommendations from a physician (N=37)	▪ At 12 weeks: 55.28 vs. 53.62 kg, p=0.506 ○ % weight change: ▪ At 3-4 weeks: -0.76 vs. -2.55, p=0.0499 ▪ At 12 weeks: -1.08 vs. -4.33, p=0.053 ○ Mean BMI: ▪ At 3-4 weeks: 21.53 vs. 20.73 kg/m², p=0.343 ▪ At 12 weeks: 21.60 vs. 20.80 kg/m², p=0.359 ○ % BMI change: ▪ At 3-4 weeks: -0.84 vs. -2.49, p=0.061 ▪ At 12 weeks: -1.48 vs. -4.47, p=0.093 • Anorexia / appetite: ○ Nutrition score: ▪ At 3-4 weeks: 6.46 vs. 7.09, p=0.308 ▪ At 12 weeks: 5.03 vs. 6.13, p=0.067 ○ % nutrition score change: ▪ At 3-4 weeks: -11.28 vs. -7.26, p=0.564 ▪ At 12 weeks: -26.01 vs. -14.54, p=0.099 IMPORTANT OUTCOMES • Adverse events: not reported • Calorie/food intake: ○ Energy intake: ▪ At 3-4 weeks: 1508.34 vs. 1368.10, p=0.03 ▪ At 12 weeks: 1594.19 vs. 1395.02, p=0.006 ○ % energy intake change: ▪ At 3-4 weeks: 5.67 vs. 2.27, p=0.197 ▪ At 12 weeks: 13.37 vs. 4.91, p=0.065 • Lean body mass: not reported • Quality of life: T-FLIC 2 ○ Mean score: ▪ At 3-4 weeks: 49.98 vs. 45.58, p=0.06 ▪ At 12 weeks: 52.31 vs. 49.67, p=0.255 ○ % change: ▪ At 3-4 weeks: 2.49 vs. 6.89, p=0.344 ▪ At 12 weeks: 9.98 vs. 18.03, p=0.108 • Performance status: not reported • Survival: ○ Median PFS: 9.54 vs. 9.90 months, p=0.473	codes via blocked randomization (with a block size of four); the sequence was not concealed and not blinded until the interventions were assigned • Open-label study • ITT analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				○ Median OS: 18.82 vs. 17.18 months, p=0.516	
Conway 2024	• Design: RCT • Funding: Queensland Health, Health Practitioner Research Scheme; CoI: none • Setting: single centre, Australia • Sample size: N=33 • Duration: follow-up of 12 weeks	• Eligibility criteria: patients with confirmed diagnosis of COPD, free from an exacerbation of COPD for at least 4 weeks prior to enrollment (stable COPD), and identified as at risk of malnutrition using the Malnutrition Screening Tool and/or had a BMI ≤ 21 kg/m^2 • Exclusion criteria: patients unable to provide informed consent, who were already receiving nutritional support, or who had an underlying condition that would likely impact future nutritional status and/or response to nutritional support • *A priori* patient characteristics: ○ Mean age: 66.8 vs. 66.6y ○ M/F: 18/15 ○ BMI: 18.7 vs. 17.7 kg/m^2 ○ COPD severity: moderate N=5, severe N=13, very severe N=15	Oral nutritional supplements in addition to routine care: one tin (840g) per week, enough to make two serves of Sustagen® per day (group B: N=16) vs. Routine care: dietary counselling with recommendation to purchase a powdered oral nutritional supplement (Sustagen®) (group A: N=24) Sustagen®: per day 450kcal, 27.6g protein; prepared with 200ml of full-fat milk (per day 264 kcal, 13g protein)	CRITICAL OUTCOMES • Weight: at the end of the nutritional intervention, both groups had increased body weight above baseline, with no differences between the groups (Group A: +0.95, SD 2.2 kg versus Group B: +1.3, SD 3.2 kg; p=0.203) • Anorexia / appetite: no statistical comparison IMPORTANT OUTCOMES • Adverse events: not reported • Calorie/food intake: no statistical comparison • Lean body mass: not reported • Quality of life: no statistical comparison ○ Significantly improved for the cohort (Group A and Group B: SGRQ total score -4.4, 95%CI −0.2 to −8.7; p=0.040), and this crossed the threshold (≤4) for minimally important clinical difference • Performance status: not reported • Survival: not reported	Level of evidence: high risk of bias • Randomization method and allocation concealment unclear • Unclear blinding of patients • Partly blinding of outcome assessment • 33/40 patients included in analysis
Degirmenci 2018	• Design: RCT • Funding: unclear; CoI: unclear • Setting: 2 centres, Turkey • Sample size: N=40 • Duration: follow-up of 12 weeks	• Eligibility criteria: diagnosis of COPD by specialist doctors, having BMI below 18.5 kg/m², being over 18 years old, cognitively intact, not pregnant and lactating • *A priori* patient characteristics: ○ Mean age: 74.7y ○ M/F: 39/1 ○ Mean BMI: 17.18 kg/m²	Enteral nutrition support (18 g protein, 11 g fat, 39 g carbohydrates, 1.2 g HMB, 1.7 g fructooligosaccharides, 352 mg calcium and 12 µg vitamin D in 220 ml volume), 2 packs/day for 12 weeks (N=20) vs. No nutritional support (N=20)	CRITICAL OUTCOMES • Weight/BMI: ○ … ▪ … • Anorexia / appetite IMPORTANT OUTCOMES • Adverse events: • Calorie/food intake: • Lean body mass: • Quality of life: ○ …: ▪ … • Performance status: • Survival:	Level of evidence: high risk of bias • Unclear how many patients were randomized, 63 or 40? • Unclear randomization method and allocation concealment • Unclear blinding, but probably not
Dorst 2013	• Design: RCT	• Eligibility criteria: patients with definite, probable, or laboratory	High-caloric food supplement with high fat	CRITICAL OUTCOMES	Level of evidence: high risk of bias

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Funding: sponsored by Fresenius (Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany) and supported by the German ALS Network Group and the Helmholtz Virtual Institute Ulm; CoI: none • Setting: single university centre, Germany • Sample size: N=26 • Duration: follow-up of 12 weeks	supported ALS according to the revised El Escorial criteria; weight loss prior to inclusion in the study (mean 4.1 kg during the last six months) • Exclusion criteria: patients with arteriosclerosis, coronary heart disease, or severe liver or kidney diseases, patients on cholesterol-lowering drugs or with percutaneous endoscopic gastrostomy • *A priori* patient characteristics: ○ Mean age: 62.0y ○ M/F: 15/11 ○ Median BMI: 25.5 kg/m^2	content: 35% fat, 50% carbohydrates, and 15% protein (N=12) vs. High-caloric food supplement with high carbohydrate content: 0% fat, 89% carbohydrate, and 11% protein (N=14) Patients took the food supplement three times (3 x 200 ml) between their normal meals for 12 weeks; both food supplements had 150 kcal per 100 ml	• Body weight gain per month: 0.52 vs. 0.28 kg/month (p=0.37) • Anorexia / appetite: not reported IMPORTANT OUTCOMES • Adverse events: apart from one patient with diarrhoea (high-fat group), no adverse events have been observed in either group • Calorie/food intake: not reported • Lean body mass: ○ Median increase in body fat at 12 weeks, +2.8% vs. -1.2%, p=0.035 ○ Median decrease in muscle mass at 12 weeks, -0.5 vs. -0.1 kg, p=0.44 • Quality of life: not reported • Performance status: not reported • Survival: not reported	• Unclear randomization method and allocation concealment • "The study was conducted in an open, randomized manner" • Unclear ITT-analysis
Gurgun 2013	• Design: RCT • Funding: unclear; CoI: unclear • Setting: single university centre, Turkey • Sample size: N=46 • Duration: follow-up of 8 weeks	• Eligibility criteria: patients with advanced (severe or very severe) COPD and evidence of nutritional depletion (1. BMI ≤21 kg/m^2, fat-free mass index ≤15 kg/m^2 for women or 16 kg/m^2 for men; or 2. BMI ≤25 kg/m^2 plus weight loss of at least 5% in 1 month or at least 10% in 6 months before admission) • Exclusion criteria: patients with disabling conditions (neuromuscular, malignant disorders, unstable cardiovascular diseases, orthopaedic problems, severe pulmonary hypertension) and unwilling to complete the program; patients suffering from acute exacerbation over the previous 4 weeks and patients with lack of motivation or poor compliance • *A priori* patient characteristics:	Pulmonary rehabilitation and nutritional support: dietary advice, 3 packages of 250-ml nutritional drink (53.3% carbohydrates, 30% fat, 16.7% proteins) (N=15) vs. Pulmonary rehabilitation alone (N=15) vs. Usual care (N=16)	CRITICAL OUTCOMES • Weight, change from baseline at 12 weeks: +1.1 (p<0.05 vs. pulmonary rehabilitation alone or usual care) vs. +0.6 vs. -0.4 • BMI, change from baseline at 12 weeks: +0.2 (p<0.05 vs. pulmonary rehabilitation alone or usual care) vs. +0.08 vs. -1.1 • Anorexia / appetite: not reported IMPORTANT OUTCOMES • Adverse events: not reported • Calorie/food intake: not reported • Lean body mass: fat-free mass index (kg/m^2), change from baseline at 12 weeks, no statistical comparison: +0.6 vs. +0.1 vs. +0.1 • Quality of life: St. George's Respiratory Questionnaire, no statistical comparison ○ Symptom: -10.2 vs. -10.7 vs. +0.46 ○ Activity: -5.74 vs. -6.5 vs. -0.3 ○ Impact: -2.19 vs. -7.2 vs. +0.09 ○ Total: -6.2 vs. -6.7 vs. -0.18 • Performance status: not reported • Survival: not reported	Level of evidence: unclear risk of bias • Randomization with sealed envelopes, method unclear • Unclear allocation concealment • Unclear blinding • Unclear ITT analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		○ Mean age: 64.0 vs. 66.8 vs. 67.8y ○ M/F: 44/2 ○ BMI: 17.8 vs. 20.0 vs. 19.1 kg/m^2			
Ishiki 2015	• Design: RCT • Funding: University of Tokyo and Otsuka Pharmaceutical Factory Inc; CoI: none • Setting: 2 centres, Japan • Sample size: N=27 • Duration: follow-up until death • Study ID: UMIN000006936	• Eligibility criteria: age >20y; cancer diagnosis; incurable disease by any treatment, including surgery, radiotherapy, or chemotherapy; ability to eat orally when enrolled in the study; life expectancy >2 wk; ECOG performance status between 0 and 3; inpatient status, or being eligible for hospital admission • Exclusion criteria: 1) presence of dysphagia; 2) gastrointestinal obstruction or stricture; 3) cognitive problems; and 4) allergy to milk or soybean • *A priori* patient characteristics: ○ Median age: 69y ○ M/F: 10/11	Liquid enteral product, Ensure Liquid ® (N=9) vs. Amino Acid Jelly, Inner Power ® (N=9) vs. Both (N=9)	CRITICAL OUTCOMES • Weight/BMI: not reported • Anorexia / appetite: EORTC QLQ-C15-PAL ○ Appetite loss: EL 100, EL + IP 93.3, IP 75 IMPORTANT OUTCOMES • Adverse events: ○ Anorexia: grade 3/4 N=2 vs. N=3 vs. N=1 ○ Nausea: N=3 vs. N=1 vs. N=0 • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: EORTC QLQ-C15-PAL ○ Tendency toward better symptom scores in the IP arm with regard to fatigue and appetite loss: ▪ Fatigue: EL 94.5, EL + IP 75.5, IP 75 • Performance status: not reported • Median overall survival: EL 7 vs. EL + IP 8 vs. IP 9 days, no statistical comparison	Level of evidence: high risk of bias • Randomization was performed at the central data center using an allocation table • Open-label study • 21/27 randomized patients included in analysis
Kapoor 2017	• Design: RCT • Funding: none; CoI: none • Setting: palliative centre, India • Sample size: N=63 • Duration: follow-up of 6 months • Study ID: NCT02350855	• Eligibility criteria: female free-living cancer cachexic patients who were attending the palliative care clinic for symptom management; weight loss of more than 5% from pretreatment weight, body mass index less than 20 kg/m^2 along with hemoglobin level less than 12 g/dL, and energy intake of less than 1500 kcal/d • Exclusion criteria: patients with gastrointestinal tract disorders, on anabolic steroids, taking synthetic ONSs, and with life expectancy of less than 3 months • *A priori* patient characteristics: ○ Mean age: 44.0 vs. 47.8y	Nutritional counselling + 100 g of IAtta per day for 6 months: 400 kcal energy, 40 g carbohydrates, 26 g proteins, 16 g fat (N=30) vs. Nutritional counselling alone (N=33)	CRITICAL OUTCOMES • Weight: no p-value for inter-group comparison ○ At 3 months: +1.1 vs. -0.3 kg ○ At 6 months: +1.8 vs. -1.5 kg • Anorexia / appetite: EORTC-QLQ-C30, subdomain “appetite loss”: median ○ At 3 months: 0 vs. 100, p<0.001 ○ At 6 months: 0 vs. 100, p=0.001 IMPORTANT OUTCOMES • Adverse events: not reported • Calorie/food intake: energy intake (by dietary recall): ○ At 3 months: 1284.4 vs. 689.0, p=0.003 ○ At 6 months: 1485.3 vs. 803.0, p=0.001 • Lean body mass: not reported • Quality of life: EORTC-QLQ-C30	Level of evidence: high risk of bias • Randomization sheet generated by using nQuery software (7.0 version) • Patients in control group were unaware of the IAtta intervention in the other group • 32/63 randomized patients included in final analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		○ Cancer type: genitourinary tract N=22, breast N=14, lung N=6, ano-rectum N=5		○ Global health status: median ▪ At 3 months: 66.6 vs.41.7, p=0.001 ▪ At 6 months: 66.7 vs. 16.7, p<0.001 ○ Social functioning: median ▪ At 3 months: 66.6 vs. 0, p=0.002 ▪ At 6 months: 66.7 vs. 0, p<0.001 ○ Fatigue: median ▪ At 3 months: 55.5 vs. 100, p<0.001 ▪ At 6 months: 66.7 vs. 100, p<0.001 ○ Pain: median ▪ At 3 months: 33.3 vs. 100, p<0.001 ▪ At 6 months: 16.7 vs. 33.3, p=0.129 • Performance status: not reported • Survival: not reported	
Kim 2019	• Design: RCT • Funding: Korea Medical Foods; CoI: none • Setting: single centre, South Korea • Sample size: N=58 • Duration: follow-up of 8 weeks	• Eligibility criteria: patients who were aged older than 20 years and who were diagnosed with progressive (metastatic) pancreatic and bile duct cancer, were scheduled to receive chemotherapy • Exclusion criteria: patients with liver failure (over a two-fold increase in aspartate transaminase/alanine transaminase), kidney failure (over a two-fold increase in blood urea nitrogen/creatinine), severe seroperitoneum or edema affecting weight evaluation, cancer that spread to the brain, BMI > 30 kg/m^2, patients incapable of oral intake, patients who had recently undergone pancreatic and bile duct cancer operation that could affect weight evaluation due to postsurgical digestive problems, and illiterate and foreign patients • *A priori* patient characteristics: ○ Mean age: 64.5 vs. 65.8y ○ M/F: 16/18 ○ Stage IV: 21/34 ○ Mean BMI: 22.9 vs. 23.5 kg/m^2	Oral nutritional supplement: Medifood Miniwell, two packs of 150 ml daily, 1.33 kcal/ml; 200 kcal energy, 9 g protein, 6 g fat, 29 g carbohydrate and 2.5 g fiber per pack (N=36) vs. No oral nutritional supplement (N=22)	CRITICAL OUTCOMES • Body weight, change from baseline at 8 weeks: +2.04 vs. -0.86, p=0.049 • Anorexia / appetite: ○ PG-SGA score at 8 weeks: 5.6 vs. 9.1, no statistical comparison ○ EORTC QLQ-C30, subdomain “anorexia”, change from baseline at 8 weeks: -15.6 vs. -5.26, p=0.248 IMPORTANT OUTCOMES • Adverse events: not reported • Calorie/food intake: energy intake at 8 weeks, 1946.4 vs. 1689.4, p>0.05 • Lean body mass: fat-free mass, change from baseline at 8 weeks: +1.01 vs. -1.04 kg, p=0.034 • Quality of life: EORTC QLQ-C30, change from baseline at 8 weeks ○ Global health status: 10 vs. 4.83, p=0.477 • Performance status: not reported • Survival: not reported	Level of evidence: high risk of bias • Simple randomization using the Statistical Analysis Software (SAS) 9.4 • Unclear allocation concealment • Not double-blinded • 34/58 randomized patients included in analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Kiss 2016	• Design: RCT • Funding: PhD scholarship from the Victorian Cancer Agency; CoI: not reported • Setting: two satellite radiotherapy centres, Australia • Sample size: N=24 • Duration: follow-up 3 months • Study ID: ACTRN12612000180819	• Eligibility criteria: patients over 18y of age planned for radical (chemo)RT for a primary diagnosis of NSCLC or SCLC • Exclusion criteria: planned for palliative intent RT, received induction chemotherapy (with the exception of SCLC patients in which this is standard care), had small peripheral tumors or no mediastinal disease, were planned for hyperfractionated RT, were non-English speaking, or had a cognitive impairment or psychiatric illness • *A priori* patient characteristics: ○ …	Care pathway to guide intensive dietary counseling (N=…) vs. Usual care (N=…)	CRITICAL OUTCOMES Weight/BMI: • …: ○ … Quality of life:	Level of evidence: high risk of bias • Randomized by the research dietitian using a purpose-built database; method itself and allocation concealment unclear • No blinding • Not all patients included in all analyses
Ludolph 2020	• Design: RCT • Funding: institutional support from the German Research Foundation (LU 336/16-1); CoI: the dietary supplement used in this study was provided at a cost reduction of 15% by Nutricia (Erlangen, Germany) • Setting: 12 sites of the clinical and scientific network of German motor neuron disease centers (ALS/MND-NET) • Sample size: N=207 • Duration: follow-up until 18 months after randomization • Study ID: NCT02306590	• Eligibility criteria: patients with possible, probable (clinically or laboratory-supported), or definite ALS according to the revised version of the El Escorial World Federation of Neurology criteria; disease duration of >6 months and <3 years, with disease onset defined as date of first muscle weakness, excluding fasciculation and cramps; best-sitting slow vital capacity of at least 50%; willing to complete a diet questionnaire throughout participation in the study; treated with 100mg riluzole daily for at least 4 weeks prior to inclusion • *A priori* patient characteristics: ○ Mean age: 62.4y ○ M/F: 121/80 ○ Mean CNAQ sum score: 29 ○ Mean BMI: 24.9 kg/m^2	High-caloric fatty diet: 30 ml 3x/day (additional fat 45 g/day and calorie 405 kcal/day) (N=102) vs. Placebo (N=99)	CRITICAL OUTCOMES • Change in BMI, median slope of BMI per month: ○ N=187: -0.06 vs. -0.09, p=0.09 • Anorexia / appetite: change in CNAQ sum score, median slope in points per month: ○ N=153: -0.16 vs. -0.08, p=0.39 IMPORTANT OUTCOMES • Adverse events: frequencies of adverse events and serious adverse events as well as laboratory safety variables were comparable between both groups • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: ○ Change in SEIQoL sum score, median slope in % per month: N=156: -0.10 vs. 0.00, p=0.55 • Performance status: not reported • Survival: ○ Overall survival: HR 0.97, 95%CI -∞ to 1.44, p=0.44	Level of evidence: high risk of bias • The randomization list was generated by an independent person; validated system, which involves a pseudorandom number generator to ensure that the resulting treatment sequence will be both reproducible and nonpredictable • Randomization was performed centrally by the Ulm University Hospital pharmacy (drug depot) • Double-blinded; patients and site personnel were masked to treatment allocation • Unclear if outcome assessment was blinded • 6/207 randomized persons not included in analysis
Mogelberg 2022	• Design: RCT • Funding: unclear; CoI: none	• Eligibility criteria: patients with severe COPD (stage III or IV) who were at nutritional risk and	Dietary counselling by experienced dieticians, aiming to reach a high	CRITICAL OUTCOMES • Weight/BMI: not reported	Level of evidence: high risk of bias

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Setting: single university centre, Denmark • Sample size: N=13 • Duration: follow-up of 12 weeks	had been referred for pulmonary rehabilitation by their general practitioner or outpatient clinic • Exclusion criteria: terminal or lung-transplanted patients, patients with severe comorbidities preventing the intervention • *A priori* patient characteristics: ○ Mean age: 68.3 vs. 71.7y ○ M/F: 3/7 ○ Mean BMI: 22.2 vs. 21.0 kg/m^2	protein diet as a supplementary component to pulmonary rehabilitation; an oral nutritional supplement (Atpro 200; 1570 kJ and 92 g protein per 100 g) was used to supplement the patients' diet to reach ≥ 25 E% /protein/day (N=7) vs. Standard pulmonary rehabilitation (N=6)	• Anorexia / appetite: not reported IMPORTANT OUTCOMES • Adverse events: not reported • Caloric intake at 12 weeks: 1755 kcal/day vs. 1644 kcal/day, no statistical comparison • Lean body mass: fat-free mass after 12 weeks: 45.9 (baseline 45.7) vs. 36.6 kg (baseline 36.6), ANCOVA 1.6, p=0.23 • Quality of life: not reported • Performance status: not reported • Survival: not reported	• Unclear randomization method and allocation concealment • Unclear blinding (but probably not) • Only 10/13 patients included in analysis
Obling 2019	• Design: RCT • Funding: Danish Cancer Society (R90-A6191), the Region of Southern Denmark, Odense University Hospital (12/26914), Baxter Healthcare Corporation "Broedrene Hartmanns fond", "Grosserer M. Brogaard and Hustru's fund", "Aase and Ejner Danielsen's fund", "Knud and Edith Eriksens memorial fund" "Inge and Joergen Larsen's memorial fund" and "Odense University Hospital; consultants council scholarship"; CoI: Baxter Healthcare Corporation • Setting: single university centre, Denmark • Sample size: N=47 • Duration: 24 weeks	• Eligibility criteria: histologically confirmed incurable gastrointestinal cancer (locally advanced or metastatic), age > 18 years, PS 0-2, nutritionally at risk according to NRS 2002 score of at least 2 • Exclusion criteria: functional or actual short bowel syndrome • *A priori* patient characteristics: ○ Median age: 66.9y ○ M/F: 30/17 ○ Median BMI: 21.3 kg/m^2 ○ >10% weight loss prior to inclusion: 61%	Best practice nutritional care, dietetic counselling and supplemental home parenteral nutrition for 24 weeks: all-in-one industrially prepared three chamber bags (Olimel N9E, Baxter International Corporation) containing 56.9 g protein, 1070 kcal/4477 kJ energy and 40 g fat per thousand ml (N=22) vs. Best practice nutritional care and dietetic counselling (N=25)	CRITICAL OUTCOMES • BMI: mean difference (95%CI) ○ 6 weeks: 0.43 (-0.7 to 1.6) ○ 12 weeks: 1.65 (0.4-2.9), p<0.05 ○ 18 weeks: -4.9 (-1.9 to 1.0) ○ 24 weeks: -0.66 (-2.1 to 0.8) • Anorexia / appetite: not reported IMPORTANT OUTCOMES • Adverse events: not reported • Calorie/food intake: ○ 24h recall energy (kJ/kg/d): mean difference (95%CI) ▪ 6 weeks: 29.7 (-14.0 to 73.3) ▪ 12 weeks: 2.9 (-4.6 to 51.5) ▪ 18 weeks: 12.9 (-39.4 to 65.2) ▪ 24 weeks: 35.2 (-21.2 to 91.6) • Lean body mass: ○ Fat-free mass/kg: mean difference (95%CI) ▪ 6 weeks: 1.73 (-1.4 to 4.9) ▪ 12 weeks: 6.44 (2.90-10.00), p<0.01 ▪ 18 weeks: 3.39 (-0.6 to 7.4) ▪ 24 weeks: 1.66 (-2.4 to 5.7) ○ Fat-free mass index (kg/m^2): mean difference (95%CI) ▪ 6 weeks: 0.51 (-0.6 to 1.6)	Level of evidence: high risk of bias • Restricted randomization method minimization; web-based open source program MinimPy was used for the minimization process by a specialist nurse who was not otherwise involved in the project • Open-label study • ITT analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				▪ 12 weeks: 2.03 (0.8-3.3), p<0.01 ▪ 18 weeks: 0.95 (-0.5 to 2.4) ▪ 24 weeks: 0.32 (-1.2 to 1.8) • Quality of life: ○ Overall score: mean difference (95%CI) ▪ 6 weeks: 2.44 (-11.0 to 15.9) ▪ 12 weeks: 16.00 (0.6-31.4), p<0.05 ▪ 18 weeks: 15.4 (-0.8 to 31.6) ▪ 24 weeks: 7.02 (-10.9 to 24.9) • Performance status: not reported • Survival: no significant differences ○ Median OS 168 vs. 169 days ○ 6-mo survival: 50% vs. 44% ○ 1-y survival: 14% vs. 20%	
Oh 2014	• Design: RCT • Funding: 2011 grant of Seoul Medical Center Research Institute; CoI: none • Setting: single centre, South Korea • Sample size: N=31 • Duration: until death	• Eligibility criteria: (1) a diagnosis of advanced cancer with no further plans for anticancer treatment; (2) inability to feed via an enteral route; (3) age18 years or older; (4) life expectancy 12 weeks or less; (5) ECOG performance status of 3 or 4; (6) the presence of a venous access device for administration of fluid or intravenous nutrients; (7) admission to the hospital for a minimum of 1 day for the initial period of this study; and (8) written informed consent • Exclusion criteria: (1) cardiac or renal disease that restricted the administration of fluid; (2) an electrolyte imbalance that required immediate correction; (3) poorly controlled diabetes (HbA1c greater than 8% despite therapy); or (4) an indication of unsuitability for participating in the clinical trial as determined by the attending physician • *A priori* patient characteristics: • Median age: 59y • M/F: 19/12 • Mean BMI: 21.1 vs. 23.2 kg/m^2	Parenteral nutrition (N=16) vs. IV fluid: maximum of 30mL/kg per day in addition to replacement of abnormal losses from the previous day to meet the physiologic fluid requirement of healthy adults (N=15)	CRITICAL OUTCOMES • Weight/BMI: not reported • Anorexia / appetite: not reported IMPORTANT OUTCOMES • Adverse events: not reported • Calorie/food intake: mean number of calories administered: 1286.8 vs. 374.7, p<0.001 • Lean body mass: not reported • Quality of life: not reported • Performance status: not reported • Survival: ○ Entire cohort: median survival 9 days ○ Comparison: 13 vs. 8 days, p=0.982	Level of evidence: high risk of bias • Block randomization method • Random allocation was made by research staff of Seoul Medical Center Research Institute • Unclear blinding, but unlikely • Unclear ITT analysis • The study ended early because many patients and families were extremely concerned about starvation

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Sukaraphat 2016	• Design: RCT • Funding: not reported; CoI: none • Setting: single university centre, Thailand • Sample size: N=50 • Duration: follow-up of 2 months	• Eligibility criteria: age at least 18 years, locally advanced unresectable or metastatic cancer patients undergoing first line chemotherapy, ECOG performance status of 2 or less, anorexia or eating less before being treated with chemotherapy, oral intake more than 50% compared to usual eating • Exclusion criteria: patients who had dysphagia, bowel obstruction, and diabetes • *A priori* patient characteristics: ○ Mean age: 61.3 vs. 62.7y ○ M/F: 33/17 ○ Stage IV cancer: 94% ○ BMI 18.5-24.9 kg/m^2: 52%	Dietary counselling: counselling by dietitian; focus on energy requirement of 30-35 kcal/kg per day and a protein requirement of 0.8-1.2 g/kg per day; supplemental diet if needed (N=25) vs. Routine care: general dietary recommendations from a physician and nurse (N=25)	CRITICAL OUTCOMES • Weight: mean % change from baseline ○ At end of chemotherapy: +2.29 vs. -1.70, p=0.03 ○ 2 months after chemotherapy: +2.56 vs. -0.27, p=0.19 • BMI: mean % change from baseline ○ At end of chemotherapy: +2.27 vs. -1.53, p=0.03 ○ 2 months after chemotherapy: +2.55 vs. -0.09, p=0.25 • Anorexia / appetite: PG-SGA score ○ At end of chemotherapy: 6.67 vs. 10.04, p<0.001 ○ 2 months after chemotherapy: 5.65 vs. 7.75, p<0.01 IMPORTANT OUTCOMES • Adverse events: not reported • Calorie/food intake: mean energy intake change ○ At end of chemotherapy: 1832 vs.1640.92, p=0.21 ○ 2 months after chemotherapy: 1847.19 vs. 1615.45, p=0.06 • Lean body mass: not reported • Quality of life: T-FLIC 2 score ○ At end of chemotherapy: 46.16 vs. 39.4, p=0.01 ○ 2 months after chemotherapy: 46.45 vs. 41.1, p=0.08 • Performance status: not reported • Survival: not reported	Level of evidence: high risk of bias • Unclear randomization method and allocation concealment • Unclear blinding (but probably not) • 40/50 randomized patients included in analysis
van der Werf 2020	• Design: RCT • Funding: Alpe d'HuZes/Dutch Cancer Society Fund (project number 2011e5262); CoI: none • Setting: 5 hospitals, the Netherlands • Sample size: N=107 • Duration: 9-12 weeks	• Eligibility criteria: adult patients diagnosed with metastatic colorectal cancer, WHO performance score 0-2 and scheduled for first-line chemotherapy with capecitabine and oxaliplatin, infusional 5-fluorouracil and oxaliplatin or capecitabine alone, with or without bevacizumab	Nutritional counselling by dietitian: energy- and protein enriched diet with regular foods was recommended (N=51) vs. Usual care (N=54)	CRITICAL OUTCOMES • Body weight: ○ Intervention effect from T0 till T1: 1.7 (95%CI 0.0-3.3; p=0.045) • Anorexia / appetite: EORTC QLQ-C30, subdomain "appetite loss" ○ Intervention effect from T0 till T1: 3.4 (95%CI -10.3 to 17.2 ; p=0.621) IMPORTANT OUTCOMES	Level of evidence: hoog risk of bias • Central randomization by data manager; randomization lists generated by statistician • Study measurements were performed by a research assistant, blinded for the group allocation

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		• *A priori* patient characteristics: ○ Mean age: 65y ○ M/F: 66/39 ○ Mean BMI: 25.6 vs. 25.7 kg/m^2 ○ Weight loss >5% in last 6 months: 39% vs. 43%		• Adverse events: any grade 3/4 toxicity, OR 0.697 (95%CI 0.277-1.750; p=0.443) • Calorie/food intake: ○ Energy goal completely achieved at T1: 61% vs. 40%, p=0.043 • Lean body mass: not reported • Quality of life: EORTC QLQ-C30 ○ Global health, intervention effect from T0 till T1: 2.2 (95%CI -6.4 to 10.7; p=0.617) ○ Physical functioning, intervention effect from T0 till T1: 0.7 (-7.2 to 8.6; p=0.86) • Performance status: not reported • Survival: ○ Median PFS: 9.6 vs. 7.6 months, p=0.039 ○ Median OS: 21.7 vs. 16.0 months, p=0.046	• Unclear blinding • 102/107 randomized patients included in analysis at 9-12 weeks
Wang 2022	• Design: RCT • Funding: Project of Shanghai Xuhui District Health Committee in 2019 (Grant No. SHXH201940), the Appropriate Technology Promotion Project of the Shanghai Health Commission (Grant No. 2019SY005), the Shanghai Health Commission and the Shanghai Key Medical Specialty (Grant No. ZK2019B10), and the Shanghai Municipal Health and Wellness Commission (Grant No. 201940421); CoI: none • Setting: single centre, China • Sample size: N=40 • Duration: follow-up of 12 months	• Eligibility criteria: ALS patients who received gastrostomy; normal digestive function; ability and willingness to comply with doctor's instructions and to complete treatment; normal routine test results, such as blood, liver and kidney function, and electrocardiogram • Exclusion criteria: loss of follow-up after gastrostomy, history of gastrectomy, portal hypertension caused by esophageal and gastric varices • *A priori* patient characteristics: ○ Mean age: 57.5 vs. 56.8y ○ M/F: 28/12 ○ Weight loss before the intervention: 0.72 vs. 0.74 kg ○ BMI: 23.9 vs.23.6 kg/m^2	Complete high-caloric nutrition in addition to conventional diet: Ensure®, 2x/day, 53.8g in 195 ml of warm water; energy 1801 kj, 15.9 g protein, 14 g fat, 57.4 g carbohydrate (N=20) vs. Routine conventional diet alone (N=20)	CRITICAL OUTCOMES • Weight: slight increase in body weight in the Ensure group compared with the control group (F=3.763, p=0.06), after adjustment for baseline body weight • BMI: increase was higher in the Ensure than in the control group, however, this difference was not significant (F=1.45, p=0.24) • Anorexia / appetite: not reported IMPORTANT OUTCOMES • Adverse events: no serious adverse events occurred in either group • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: not reported • Performance status: not reported • Survival: ○ Overall survival: significantly better in intervention group (p=0.049) ○ 3-month survival: 100% vs. 80% ○ 6-month survival: 100% vs. 70% ○ 1-year survival: 80% vs. 55%	Level of evidence: unclear risk of bias • Computer-generated random number sequence • Unclear allocation concealment • Unclear blinding • ITT-analysis

Abbreviations: 95%CI: 95% confidence interval; ALS: amyotrophic lateral sclerosis; BMI: body mass index; CNAQ: Council of Nutrition Appetite Questionnaire; CoI: conflict of interest; IV: intravenous; RCT: randomised controlled trial; RR: relative risk; SC: subcutaneous; SEIQoL: Schedule for the Evaluation of Individual Quality of Life.

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Medicamenteuze interventies

Vraag 3: Wat is het effect van medicamenteuze interventies op gewichtsverlies en kwaliteit van leven bij patiënten met kanker?

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Ceolin 2024	• Design: systematic review • Funding: none; Col: none • Search date: unclear • Databases: Cochrane Library, Embase Ovid, PubMed, and Web of Science • Study designs: all • N included studies: N=5 RCTs • Protocol: ?	• Eligibility criteria: older adults (60+y) with cancer -related anorexia • Exclusion: case reports, abstracts, letters, and editorials	Cannabinoids: • Strasser 2006: cannabis extract vs. THC vs. placebo • Brisbois 2011: THC vs. placebo • Turcott 2018: nabilone vs. placebo	CRITICAL OUTCOMES • Weight: ○ Strasser 2006: “Active treatment demonstrated a significant improvement in … body weight compared to the placebo” ○ Turcott 2018: “At the 4 and 8-week evaluation, no statistically significant differences were found between the control and experimental groups concerning … anthropometric variables” • Anorexia / appetite: ○ Strasser 2006: “Active treatment demonstrated a significant improvement in appetite stimulation … compared to the placebo” ○ Brisbois 2011: “No THC-treated patients reported a decrease in appetite. In contrast, the majority of placebo-treated patients experienced a decrease in appetite (50%), or no change (20%)” ○ Turcott 2018: “At the 4 and 8-week evaluation, no statistically significant differences were found between the control and experimental groups concerning appetite … variables” IMPORTANT OUTCOMES • Adverse events: ○ Strasser 2006: “no significant differences were observed in adverse events between the groups” ○ Brisbois 2011: “no differences in side effects emerged between the two groups” • Calorie/food intake: ○ Brisbois 2011: “Caloric intake remained unchanged between the THC and placebo groups”	• Selection process by two independent reviewers; unclear for data extraction • Restricted to English articles • Quality appraisal: Jadad, individual items reported • Included relevant RCTs: Brisbois 2011, Strasser 2006, Turcott 2018, Jatoi 2002

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				○ Turcott 2018: "The control group … recorded a statistically significant decrease in energy consumption" • Lean body mass: not reported • Quality of life: ○ Strasser 2006: "Active treatment demonstrated a significant improvement in … quality of life domains … compared to the placebo" ○ Turcott 2018: "The functional, emotional, social, pain, and insomnia scales of the quality of life were better in the group treated with nabilone at the eighth week of administration" • Performance status: not reported • Survival: not reported	
Khatib 2018	• Design: systematic review • Funding: none; CoI: none • Search date: Jul 2017 • Databases: CENTRAL, Medline, Embase • Study designs: RCTs • N included studies: N=3 RCTs • Protocol: Cochrane	• Eligibility criteria: cachectic patients of 18 years and over with a histological or clinical diagnosis of cancer, or meeting any of the international criteria for cancer cachexia	Ghrelin	CRITICAL OUTCOMES • Weight: not reported • Anorexia / appetite: ○ Lundholm 2010: Ghrelin 10 vs. 0.5 μg/kg; appetite score (VAS) at 8 weeks 6.8 vs. 4.0, p<0.02 IMPORTANT OUTCOMES • Adverse events: ○ Neary 2004: Ghrelin vs. placebo; no adverse events were observed in either of the intervention groups ○ Lundholm 2010: Ghrelin 10 vs. 0.5 μg/kg; no adverse events ○ Strasser 2008: Ghrelin 8 vs. 2 μg/kg; high-dose vs. placebo 17 vs. 6; low-dose vs. placebo 7 vs. 12 • Calorie/food intake: ○ Neary 2004: Ghrelin vs. placebo; mean energy intake 9270 vs. 6854 kJ, p=0.09 ○ Lundholm 2010: Ghrelin 10 vs. 0.5 μg/kg; food intake at 8 weeks 28.2 vs. 25.5 kcal/kg/day ○ Strasser 2008: Ghrelin 8 vs. 2 μg/kg; nutritrional intake at lunch compared to baseline, high-dose vs. placebo 251 vs. 230 kcal, low-dose vs. placebo -105 vs. -17 kcal; nutritrional intake at lunch and rest of the day	• Review process by independent researchers • No language restrictions • Quality appraisal: RoB tool • Relevant included RCTs: Neary 2004, Lundholm 2010, Strasser 2008

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				compared to baseline, high-dose vs. placebo 244 vs. 156 kcal, low-dose vs. placebo 145 vs. 228 kcal; all NS • Lean body mass: ○ Lundholm 2010: Ghrelin 10 vs. 0.5 μg/kg; at 8 weeks 47.8 vs. 45.1 kg • Quality of life: ○ Lundholm 2010: Ghrelin 10 vs. 0.5 μg/kg; SF-36 physical component at 8 weeks 27 vs. 30; SF-36 mental component at 8 weeks 41 vs. 34 • Performance status: not reported • Survival: not reported	
Maltoni 2001	• Design: systematic review + meta-analysis • Funding: not reported; CoI: not reported • Search date: June 1999 • Databases: Medline, Cancerlit, Embase, Cinahl • Study designs: RCTs • N included studies: N=15 RCTs • Protocol: ?	• Eligibility criteria: patients with a proven diagnosis of advanced hormone-independent tumor, with decrease in appetite and/or weight loss	Progestins	CRITICAL OUTCOMES • Weight: ○ MPA: ▪ Downer 1993: MD change from baseline at 6 weeks, p<0.05 ▪ Kornek 1996: % with at least 10% weight gain, 20% vs. 0%, p=0.06 ▪ Neri 1997: MD, p=0.001 ▪ Simons 1996: MD at 6 weeks, p=0.15; MD at 12 weeks, p=0.04 ○ MA: ▪ Bruera 1998: MD from baseline p=0.4 ▪ Rowland 1996: weight gain at least 10% 21% vs. 7%, p=0.004 • Anorexia / appetite: ○ MPA: ▪ Downer 1993: VAS (0-100), change from baseline, at 3 weeks p<0.01, at 6 weeks p<0.05 ▪ Kornek 1996: improvement on 5-point scale, 60% vs. 43% ▪ Simons 1996: VAS (0-10), MD after 6 weeks p=0.08, after 12 weeks p=0.01 ○ MA: ▪ Bruera 1998: MD from baseline p=0.005 IMPORTANT OUTCOMES • Adverse events: ○ MPA: ▪ Simons 1996: edema 17% vs. 4% ▪ Downer 1993: no differences	• Review process by independent researchers • No language restrictions • Unclear quality appraisal • Included relevant RCTs: Beller 1997, Bruera 1990, Bruera 1998, De Conno 1998, Downer 1993, Feliu 1992, Kornek 1996, Loprinzi 1990, Neri 1997, Rowland 1996, Schmoll 1992, Simons 1996, Tchekmedyian 1992, Vadell 1998, Westman 1999

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				▪ Kornek 1996: mild and infrequent adverse events ▪ Neri 1997: hypertension (20 episodes), water retention (20 episodes), fine tremors (15 episodes), cramps (11 episodes), perspiration (11 episodes), vaginal spotting (6 episodes), thrombosis (1 episode), cushing syndrome (1 episode) ○ MA: ▪ Bruera 1998: 1 edema (MA), 1 acute pulmonary embolism (placebo) ▪ Rowland 1996: edema p=0.002, flebitis p=0.01 • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: not reported • Performance status: not reported • Survival: not reported	
Ruiz-Garcia 2018	• Design: systematic review + meta-analysis • Funding: not reported; CoI: none • Search date: Nov 2016 • Databases: Medline, Embase, CENTRAL • Study designs: RCTs • N included studies: N=38 RCTs, of which 25 on cancer • Protocol: unclear	• Eligibility criteria: patients with a clinical diagnosis of anorexia–cachexia related to cancer, AIDS, or another underlying pathology (independent of sex, age, or ethnicity); previous weight loss • Exclusion of cross-over studies	Megestrol acetate	CRITICAL OUTCOMES • Weight: ○ MA vs. placebo: 4 studies, N=250, MD 2.36 kg, 95%CI 1.00-3.71, p=0.0007, I^2 68% ○ MA vs. no treatment: 2 studies, N=101, MD 1.45 kg, 95%CI 0.15-2.75 • Anorexia / appetite: not reported IMPORTANT OUTCOMES • Adverse events: ○ MA vs. placebo: 8 studies, N=638, RR 1.46, 95%CI 1.05-2.04 ○ MA vs. no treatment: 2 studies, N=101, RR 0.90, 95%CI 0.39-2.08 • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: ○ MA vs. placebo: 1 study, N=33, SMD 0.18, 95%CI -0.51 to 0.86, p=0.61 ○ MA vs. no treatment: 2 studies, N=99, SMD -3.89, 95%CI -14.07 to 6.28 • Performance status: not reported • Survival: deaths ○ MA vs. placebo: 6 studies, N=877, RR 1.26, 95%CI 0.70-2.27	• Unclear if review process was done by independent researchers • Unclear language restriction • Included relevant RCTs: Beller 1997, De Conno 1998, Feliu 1992, Loprinzi 1990, Schmoll 1992, Tchekmedyian 1992, Vadell 1998, Casado 2008, Fietkau 1996, Gambardella 1998, Gebbia 1996, Giacosa 1997, Heckmayr 1992, Jatoi 2002, Jatoi 2004, Kanat 2013, Loprinzi 1994, Macbeth 1994, Madeddu 2012, McMillan 1994, NCT00503516, Sancho-Cuesta 1993, Schmoll 1991, Tomiska 2003, Ulutin 2002

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				○ MA vs. no treatment: 2 studies, N=90, RR 1.01, 95%CI 0.42-2.45	
Talebi 2024	• Design: systematic review + meta-analysis • Funding: Haematology-Oncology and Stem Cell Transplantation Research Center of Tehran University of Medical Sciences (code: 62676 and IR. TUMS.HORCSCT.REC. 1401.038); CoI: none • Search date: June 2023 • Databases: PubMed, Scopus, ISI Web of Science, clinical trial registries • Study designs: RCTs • N included studies: N=13 RCTs • Protocol: CRD42022358849	• Eligibility criteria: cancer patients > 18y • Exclusion: studies were omitted if they lacked a suitable control, and MA was administrated as a complex with other drugs or active substances	Megestrol acetate	CRITICAL OUTCOMES • Weight: ○ 12 studies, N=1369, MD 0.64 kg, 95%CI -0.11 to 1.39, p=0.093, I^2 69.1 ○ Each 200 mg/day increment in MA consumption had a significant increase in weight gain (MD 0.44; 95%CI 0.13-0.74, p=0.005, I^2 97.1%) • Anorexia / appetite: 3 studies, N=163, MD 0.29, 95%CI -0.05 to 0.64, p=0.096, I^2 18.3% IMPORTANT OUTCOMES • Adverse events: not reported • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: 2 studies, N=176, MD 1.15, 95%CI 0.76-1.54, p<0.001, I^2 0.0% • Performance status: not reported • Survival: not reported	• Review process by independent researchers • Unclear language restriction • Included relevant studies: Beller 1997, Bruera 1990, De Conno 1998, Fietkau 1996, Kanat 2013, Loprinzi 1999, Ma 2022, Madeddu 2012, McMillan 1994, McQuellon 2002, Tchekmedyian 1992, Vadell 1998, Westman 1999
Taniguchi 2023	• Design: systematic review + meta-analysis • Funding: unclear; CoI: none • Search date: Jul 2022 • Databases: PubMed, CENTRAL, Embase, ICHUSHI • Study designs: RCTs • N included studies: N=7 RCTs • Protocol: CRD42022340705	• Eligibility criteria: adult patients with any type and stage of cancer; placebo-controlled trials • Exclusion: animal, in vitro, observational studies, and narrative and systematic reviews	Anamorelin	CRITICAL OUTCOMES • Total body weight: ○ All studies: 5 studies, N=1190, MD 1.73 kg, 95%CI 1.34-2.13, p<0.00001, I^2 0% ○ Anamorelin 50 mg: 2 studies, N=137, MD 1.89 kg, 95%CI 0.71-3.08, p=0.002, I^2 0% ○ Anamorelin 100 mg: 3 studies, N=1053, MD 1.71 kg, 95%CI 1.29-2.14, p<0.00001, I^2 0% • Appetite: ○ All studies: 3 studies, N=361, SMD 0.23, 95%CI -0.09 to 0.55, p=0.16, I^2 52% ○ Anamorelin 50 mg: 2 studies, N=137, SMD -0.03, 95%CI -0.51 to 0.45, p=0.90, I^2 48% ○ Anamorelin 100 mg: 2 studies, N=224, SMD 0.44, 95%CI 0.18-0.71, p=0.001, I^2 0% IMPORTANT OUTCOMES • Adverse events: ○ All adverse events:	• Review process by independent researchers; for data extraction, first researcher extracted, second reviewer checked • No language restrictions • Quality appraisal: RoB2 tool • Included relevant RCTs: Garcia 2013, Garcia 2015, Takayama 2016, Temel 2016, Currow 2017, Katakami 2018

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				▪ All studies: 5 studies, N=1405, RR 1.03, 95%CI 0.96-1.10, p=0.48, I^2 63% ▪ Anamorelin 50 mg: 2 studies, N=176, RR 1.01, 95%CI 0.86-1.19, p=0.89, I^2 76% ▪ Anamorelin 100 mg: 3 studies, N=1229, RR 1.03, 95%CI 0.96-1.12, p=0.40, I^2 59% ○ Severe adverse events: ▪ All studies: 5 studies, N=1405, RR 1.01, 95%CI 0.72-1.41, p=0.95, I^2 55% ▪ Anamorelin 50 mg: 2 studies, N=176, RR 0.95, 95%CI 0.56-1.62, p=0.86, I^2 40% ▪ Anamorelin 100 mg: 3 studies, N=1229, RR 1.05, 95%CI 0.65-1.69, p=0.84, I^2 68% ○ Drug-related adverse events: ▪ All studies: 4 studies, N=433, RR 1.84, 95%CI 1.34-2.53, p=0.0002, I^2 0% ▪ Anamorelin 50 mg: 2 studies, N=176, RR 1.53, 95%CI 0.90-2.60, p=0.12, I^2 0% ▪ Anamorelin 100 mg: 3 studies, N=257, RR 2.05, 95%CI 1.38-3.05, p=0.0004, I^2 0% • Calorie/food intake: not reported • Lean body mass: ○ All studies: 3 studies, N=360, MD 1.06, 95%CI 0.30-1.81, p=0.006, I^2 72% ○ Anamorelin 50 mg: 2 studies, N=137, MD 1.08, 95%CI -0.66 to 2.82, p=0.22, I^2 78% ○ Anamorelin 100 mg: 2 studies, N=223, MD 1.14, 95%CI 0.21-2.06, p=0.02, I^2 73% • Quality of life: 4 different instruments ○ All studies: 5 studies, N=1340, SMD 0.16, 95%CI 0.04-0.27, p=0.006, I^2 0% ○ Anamorelin 50 mg: 2 studies, N=137, SMD 0.38, 95%CI 0.03-0.73, p=0.03, I^2 0% ○ Anamorelin 100 mg: 3 studies, N=1203, SMD 0.13, 95%CI 0.01-0.25, p=0.03, I^2 0% • Performance status: not reported • Overall survival: 2 studies, HR 0.99, 95%CI 0.85-1.14, p=0.84, I^2 31%	

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Almeida 2023	• Design: RCT • Funding: The São Paulo Research Foundation (FAPESP Grant:	• Eligibility criteria: age ≥50 years; confirmed diagnosis of malignant neoplasm by histopathology; progression of	Mirtazapine 15-30 mg/day for 8 weeks (N=26)	CRITICAL OUTCOMES • Weight: gain of at least 1 kg	Level of evidence: unclear risk of bias

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	2018/04526-0) and from the Foundation for Support to Teaching, Research and Assistance of the Clinics Hospital, Ribeirão Preto Medical School, University of São Paulo (FAEPA Grant: 198/2019); the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil (CAPES)—Financing Code 001; CoI: none • Setting: single university centre, Brazil • Sample size: N=52 • Duration: 8 weeks • Study ID: unclear	disease both locally and metastatic; complaint of anorexia graded by the patient as ≥2 by the Edmonton Symptom Assessment Scale (ESAS); weight loss > 5% in the last six months or >2% in the last two months associated with a BMI < 20 kg/m^2 or reduced muscle mass; life expectancy ≥30 days by the Palliative Prognostic Score; performance status ≥60% according to the Karnofsky Performance Status scale • Exclusion criteria: diagnosis of depression or use of antidepressant therapy within the last four weeks with a score ≥12 in the items related to depression on the Hospital Anxiety and Depression scale; use of unstable doses of corticosteroids; moderate renal and/or hepatic dysfunction; decompensated hypothyroidism; uncorrected electrolyte disturbances; central nervous system (CNS) metastases; mechanical obstruction of the gastrointestinal tract; clinically voluminous ascites and generalized edema; persistent and uncontrolled nausea and/or vomiting; inability to ingest medications orally; use of nasoenteral tube; polycythemia; previous thromboembolic event; acute myocardial infarction or cerebrovascular event within less than six months; decompensated heart failure; use of pacemaker; poorly controlled type 2 diabetes	vs. Megestrol acetate 160-320 mg/day (N=26)	○ At 4 weeks: raw RR 1.37, 95%CI 0.70-2.65, p=0.36; adjusted RR 2.69, 95%CI 1.09-2.44, p=0.0032 ○ At 8 weeks: raw RR 0.84, 95%CI 0.41-1.75, p=0.65; adjusted RR 1.41, 95%CI 0.41-4.88, p=0.585 • Appetite: ESAS (0-10), decrease of at least 2 points ○ At 4 weeks: raw RR 1.08, 95%CI 0.73-1.59, p=0.70; adjusted RR 1.21, 95%CI 0.82-1.79, p=0.345 ○ At 8 weeks: raw RR 1.65, 95%CI 1.07-2.54, p=0.02; adjusted RR 1.85, 95%CI 1.17-2.92, p=0.008 IMPORTANT OUTCOMES • Adverse events: ○ % with at least one potentially adverse event: RR 0.92, 95%CI 0.83-1.3, p=0.145 ○ Vomiting: RR 0.27, 95%CI 0.07-0.99, p=0.04 ○ Constipation: RR 0.41, 95%CI 0.21-0.80, p=0.009 ○ Most frequent potentially adverse effects in mirtazapine group: drowsiness (69.2%), fatigue (65.4%), nausea (53.8%), constipation (38.5%), dyspnea (34.6%), edema (34.6%), leg weakness (30.8%), vomiting (34.6%), and dizziness (23.1%) ○ Most frequent potentially adverse effects in megestrol group: fatigue (57.7%), nausea (34.6%), constipation (30.8%), edema (26.9%), dyspnea (26.9%), and leg weakness (23.1%) • Calorie/food intake: not reported • Lean body mass: not reported by randomized groups • Quality of life: not reported • Performance status: not reported • Survival: not reported	• Electronic randomization was performed on the “sealed envelope” website (https://www.sealedenvelope.com/simple-randomiser/v1/lists, accessed on 5 March 2019) in six blocks with eight patients and one block with four • Unclear allocation concealment • Only one person responsible for the randomization and preparation of the vials • Double-blinded • Blinded outcome assessment and analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		mellitus or systemic arterial hypertension; HIV infection; moderate to severe cognitive deficit; institutionalization; hospital admission at the time of the initial assessment; current use of megestrol or mirtazapine; allergy to the studied medications; refusal to participate • *A priori* patient characteristics: ○ Mean age: 64.5 vs. 67.0y ○ M/F: 27/25 ○ Cancer type: upper GI N=26, colon N=12, lung N=9 ○ Stage IV: N=39			
Arrieta 2024	• Design: RCT • Funding: scholarship grant for Women in Science from L' Oreal-UNESCO, Conalmex, in collaboration with the Mexican Academy of Sciences, 2021; CoI: Astra Zeneca • Setting: tertiary care centre, Mexico • Sample size: N=86 • Duration: 8 weeks • Study ID: NCT04748523	• Eligibility criteria: patients with advanced (stage IIIB to IV) NSCLC who were receiving active oncologic treatment and had an Anorexia Cachexia Scale (ACS) score ≤32, ECOG ≤2, life expectancy >8 weeks • Exclusion criteria: known allergy to mirtazapine, undergoing treatment with antidepressants (minimum washout period of 4 weeks), being treated with megestrol acetate, moderate hepatic and/or renal dysfunction (bilirubin level ≥ 1.5 x above normal limits (UNL), AST and ALT ≥ 5 x UNL, or creatinine ≥5 x UNL), unable to take oral medications, mechanical obstruction of the gastrointestinal tract, ascites or generalized edema, history of phenylketonuria (preparation contains phenylalanine), delirium • *A priori* patient characteristics: ○ Mean age: 63.5y ○ M/F: 30/41 ○ Stage IV: 87.9 vs. 92.1%	Mirtazapine 15 mg/day for 15 days, increased to 30 mg/day until completion of 8 weeks (N=43) vs. Placebo (N=43)	CRITICAL OUTCOMES • Weight: median change after 8 weeks, -0.1 vs. -0.1 kg, p=0.90 • BMI: mean change after 8 weeks, +0.0 vs. +0.3 kg/m², p=0.55 • Anorexia / appetite: ○ Anorexia cachexia scale, median change after 8 weeks, +12.0 vs. +11.0, p=0.34 ○ EORTC-QLQ-C30, appetite loss subscale: ▪ At 4 weeks: median change from baseline, -33.3 vs. -33.3, p=0.093 ▪ At 8 weeks: median change from baseline, -33.3 vs. -33.3, p=0.539 IMPORTANT OUTCOMES • Adverse events: prevalence of hematologic and nonhematologic adverse events (CTCAE v5.0) was similar between groups; no differences in gastrointestinal and nonhematologic adverse effects between both arms • Calorie/food intake: ○ Energy intake: mean change from baseline ▪ At 4 weeks: 379.3 vs. 138.6 kcal/day, p=0.06 ▪ At 8 weeks: 357.7 vs. 226.5 kcal/day, p=0.38 ○ % of requirement achieved: mean change from baseline	Level of evidence: high risk of bias • Randomization according to a list pre-established by random numbers • Central allocation • Double-blinded • Unclear if assessor was blinded • 58/86 patients included in analysis at 8 weeks (71 at 4 weeks)

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				▪ At 4 weeks: 26.1 vs. 8.8% p=0.001 ▪ At 8 weeks: 31.5 vs. 17.2%, p=0.19 • Fat-free mass: median change after 8 weeks, +0.7 vs. +1.2 kg, p=0.82 • Quality of life: EORTC-QLQ-C30, global health status ○ At 4 weeks: median change from baseline, +12.4 vs. +8.3, p=0.699 ○ At 8 weeks: median change from baseline, +16.7 vs. 0.0, p=0.172 • Performance status: not reported • Survival: not reported	
Bruera 1985	• Design: cross-over RCT • Funding: not reported; CoI: not reported • Setting: single centre, Argentina • Sample size: N=40 • Duration: 20 days • Study ID: unclear	• Eligibility criteria: terminally ill patients (in whom multiple therapeutic techniques had previously failed), not receiving chemotherapy, radiotherapy or hormonal treatment during the month preceding the trial; no major contraindication for corticosteroids (history of infection, peptic ulcer, diabetes or severe psychiatric disturbances); no neurological deficits or altered levels of consciousness • *A priori* patient characteristics: ○ Mean age: 54y ○ M/F: 18/22 ○ Cancer type: colon N=9, breast N=8, lung N=6	Oral methylprednisolone 2x16 mg/day for 5 days (N=40) vs. Placebo (N=40)	CRITICAL OUTCOMES • Weight: not reported • Appetite: ○ VAS 0-100, mean 40.1 vs. 29.1, p>0.05 ○ Better with methylprednisolone: 77% ○ Better with placebo: 10% ○ "No change in nutritional status was observed after either phase of the study" IMPORTANT OUTCOMES • Adverse events: cushingoid facies N=2, anxiety N=2, mild fluid retention N=1 • Calorie/food intake: food consumption, % of each meal, 65% vs. 50%, p<0.01 • Lean body mass: not reported • Quality of life: not reported • Performance status: ECOG, 3.0 vs. 3.2, p>0.05 • Survival: not reported	Level of evidence: high risk of bias • Unclear randomization method and allocation concealment • Double-blinded • Unclear if assessor was blinded • Days 5-7 were treatment-free; cross-over at day 8 • From day 13-20 all patients received methylprednisolone 32 mg/day • 31/40 patients included in analysis
Bruera 2003a Bruera 2003b	• Design: RCT • Funding: Tobacco Settlement Foundation, Houston, TX; CoI: not reported • Setting: 2 centres, Canada • Sample size: N=91 • Duration: 14 days • Study ID: unclear	• Eligibility criteria: patients with locally recurrent or metastatic cancer, presence of anorexia plus weight loss, ability to maintain oral food intake over the course of the study (2 weeks), normal cognition • *A priori* patient characteristics: ○ Mean age: 63.0 vs. 64.6y ○ M/F: 17/43 ○ Cancer type: gastrointestinal N=21, genitourinary N=11, lung N=11, breast N=6	18 x 1000 mg of fish oil in capsules (N=46): 3240 mg EPA/day, 2160 mg DHA/day, 18 mg vitamin E/day vs. 18 x 1000 mg olive oil in capsules (N=45)	CRITICAL OUTCOMES • Weight: mean change from baseline at 14 day, +0.03 vs. -0.89 kg, NS • Appetite: VAS 0-100 mm, mean change from baseline at 14 day, -9.8 vs. -9.0, NS IMPORTANT OUTCOMES • Adverse events: total, 18 vs. 8 • Calorie/food intake: mean change from baseline at 14 day, +51 vs. -57 kcal, NS	Level of evidence: high risk of bias • Patients were randomly assigned using sealed envelopes produced by a computer-generated random sequence • The pharmacist did not disclose the type of medication given to the investigators or patients until the termination of the

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				• Lean body mass: mean change from baseline at 14 day, +0.49 vs. -0.55 kg • Quality of life: overall well-being VAS 0-100 mm, mean change from baseline at 14 day, -4.6 vs. -9.8, NS • Performance status: KPS 0-100, mean change from baseline at 14 day, 0.0 vs. -6.9, NS • Survival: not reported	study unless clinically required to do so • Unclear if assessor was blinded • 60/91 patients included in analysis
Currow 2021	• Design: RCT • Funding: The Commonwealth of Australia; CoI: none • Setting: 12 centres, Australia • Sample size: N=190 • Duration: 5 weeks • Study ID: ACTRN12608000405314	• Eligibility criteria: patients aged ≥ 18 years; diagnosed with advanced cancer and known to a palliative care team; mentally competent; able to take oral medications; baseline appetite score of ≤ 4 on a 0–10 numeric rating scale (NRS; where 0 is no appetite and 10 is best possible appetite); and an Eastern Cooperative Oncology Group (ECOG) score of 0–3 or Australia-modified Karnofsky performance status (AKPS) score of 30–100 • Exclusion criteria: history of documented thromboembolic disease or an implanted vascular access device without adequate anticoagulation using local protocols; severe or uncontrolled ischemic heart disease, congestive cardiac failure or severe hypertension (systolic blood pressure > 180 mmHg); taking corticosteroids (excluding inhaled corticosteroids) or progestogens; tube fed; clinically significant ascites (given theoretical concerns of worsening fluid retention with the active interventions); unmonitored diabetes; uncontrolled nausea and vomiting; pregnant or breastfeeding; active infection;	Megestrol acetate 480 mg per day up to 4 weeks (N=61) vs. Dexamethasone 4 mg per day up to 4 weeks (N=67) vs. Placebo (N=62)	CRITICAL OUTCOMES • Weight: no differences in weight stability between groups (p=0.2417), and therefore pairwise comparisons were not conducted ○ Responders at week 1: 87% vs. 74% vs. 85% • Appetite: ○ NRS at week 1: ▪ Responders: 79.3% vs. 65.5% vs. 58.5%, p=0.067 ▪ Megestrol vs. placebo: OR 2.68, 95%CI 1.15-6.23 ▪ Dexamethasone vs. placebo: OR 1.34 (95%CI 0.62-2.90) ○ MSAS appetite score at week 1: ▪ Responders: 68.2% (p=0.0697) vs. 38.3% (p=0.3114) vs. 48.9% ○ "There was no difference in the proportion of responders on the FAACT anorexia sub-scale" IMPORTANT OUTCOMES • Adverse events: participants with at least one grade 3, 4 or 5 treatment emergent adverse event: 16.4% vs. 29.7% vs. 20.0% • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: FACT-G total score, mean change from baseline: -2.1 vs. -4.8 vs. -0.8, p=0.576 • Performance status: AKPS at week 1 ○ Responders: 98% vs. 95% vs. 92%, p=0.3367 • Survival: not reported	Level of evidence: high risk of bias • Randomisation schedules were developed for each site using random number tables generated at an independent site using block sizes of four • Capsules were prepared in a central manufacturing pharmacy, where tablets were encased in an opaque capsule to have all study drugs and placebo appearing identical • All study staff, along with participants were blinded to the treatment allocation for the entire duration of the study • Participants were considered to be responders if they had a 25% improvement over the baseline score or a one-point improvement if the baseline score was zero on the NRS appetite score • No ITT analysis

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		or diarrhea within the last 7 days • *A priori* patient characteristics: ○ Mean age: 71.4 vs. 71.2 vs. 74.7y ○ M/F: 114/76 ○ BMI: 22.36 vs. 21.97 vs. 22.22 kg/m²			
Della Cuna 1989	• Design: RCT • Funding: not reported; CoI: not reported • Setting: multicenter study, Belgium; the Netherlands, Italy, Poland, Spain, Yugoslavia • Sample size: N=403 • Duration: 8 weeks • Study ID: unclear	• Eligibility criteria: patients of either sex and of any age with advanced, preterminal carcinoma; with pain, debility, cachexia, anorexia, or other signs of advanced disseminated disease; no longer candidates for aggressive anticancer therapy; expected to survive for at least 2 months • Exclusion criteria: patients who were suffering from acute febrile illness, who were psychotic, who had an active peptic ulcer, and who were pregnant; those who had had major surgery within 2 weeks prior to consideration for the study; those who were receiving corticosteroid therapy or who had finished corticosteroid therapy within 1 month prior to consideration for the study; and those who were mentally deficient or disturbed • *A priori* patient characteristics: ○ Mean age: 62.4 vs. 63.0y ○ M/F: 196/207	Methylprednisolone 125 mg IV per day for max 8 weeks(N=207) vs. Placebo (N=196)	CRITICAL OUTCOMES • Weight: no significant differences • Anorexia / appetite: LASA: at each weekly follow-up evaluation, methylprednisolone produced significantly more improvement than placebo in the LASA appetite score ($p<0.05$); only presented in graph IMPORTANT OUTCOMES • Adverse events: 38.2% vs. 28.1%, $p<0.05$ • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: ○ NOSIE: methylprednisolone was significantly more effective than placebo in improving the NOSIE total score at all but week 6 of treatment; only presented in graph ○ LASA: at each weekly follow-up evaluation, methylprednisolone produced significantly more improvement than placebo in the LASA total score and in the pain, appetite, vomiting, and well-being scores ($p<0.05$); only presented in graph • Performance status: not reported • Survival: mortality rate was similar between methylprednisolone-treated males (40.2%), placebo-treated males (35.5%), and methylprednisolone-treated females (40.0%); however, the mortality rate of 27.7% for female placebo-treated females was significantly lower than for their methylprednisolone-treated counterparts	Level of evidence: high risk of bias • Computer-generated randomization scheme • Unclear allocation concealment • Double-blinded • Unclear if assessor was blinded • No ITT analysis: at 8 weeks only 150/403 patients included in analysis
Fearon 2003 Bauer 2005	• Design: RCT • Funding: Abbott Laboratories, Chicago,	• Eligibility criteria: patients with histologically proven or a firm radiological or operative	Oral nutritional supplement, 2 cans/day, protein	CRITICAL OUTCOMES	Level of evidence: high risk of bias

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Moses 2004 (substudy)	IL, USA; CoI: not reported • Setting: multicentre study (N=12), international • Sample size: N=200 • Duration: 8 weeks • Study ID: unclear	diagnosis of pancreatic cancer, weight loss >5% in the previous 6 months, life expectancy > 2 months and Karnofsky performance score of 60 or more • Exclusion criteria: patients were excluded if they had undergone surgery, endoscopic stenting, radiotherapy, or chemotherapy during the previous four weeks; had other active medical conditions (major gastrointestinal disease, chronic renal failure, uncontrolled diabetes, and human immunodeficiency virus); a BMI >30 kg/m²; or received medication which could profoundly modulate metabolism or weight, in particular, the use of fish oil or n-3 fatty acid preparations exceeding 200 mg/day EPA, or one capsule of fish oil/day within the previous 90 days; no gross ascites or oedema, jaundice, pyrexia, severe anaemia, or clinical or radiological evidence of infection • *A priori* patient characteristics (N=185): ○ Mean age: 67 vs. 68y ○ M/F: 110/90 ○ Stage IV: 52% vs. 41%	(16g) and energy (310 kcal) dense, with 1.1 g EPA (N=95) vs. Isocaloric, isonitrogenous control supplement without n-3 fatty acids (N=105)	• Weight: change from baseline at 8 weeks, -0.25 vs. -0.37 kg/month, p=0.74 • Anorexia / appetite: not reported IMPORTANT OUTCOMES • Adverse events: ○ No significant differences in the number of patients who experienced adverse events or serious adverse events between the experimental and control groups ○ None of the serious adverse events were considered to be due to the oral supplements • Calorie/food intake: ○ Total intake/day: change from baseline at 8 weeks, +15 vs. +6, NS • Lean body mass: change from baseline at 8 weeks, +0.27 vs. +0.12 kg/month, p=0.88 • Quality of life: no significant differences in quality of life measures between the two groups • Performance status: not reported • Survival: median, 142 vs. 128 days, NS	• Patients were randomised at enrolment in permutation blocks of two using a sequential series of numbered sealed envelopes containing computer generated random assignments • A copy of the randomisation sequence was kept in a locked cabinet apart from the study personnel; randomisation envelopes were opened by a third party who shipped the product directly to the patients' homes • Patients, investigators, and study personnel were blinded to the treatment group allocation • Not all patients were included in analysis • Industry-sponsored
Fearon 2006	• Design: RCT • Funding: Scotia Pharmaceuticals, United Kingdom; CoI: reported in detail • Setting: multicentre study (N=61), international • Sample size: N=518	• Eligibility criteria: patients with a clinical diagnosis of gastrointestinal and lung cancer (radiological / histological / cytological confirmation) between the ages of 18-80 years with 5% or more loss of preillness stable weight; life expectancy of 2	2 g EPA 95% diester per day (N=175) vs. 4 g EPA 95% diester per day (N=172) vs.	CRITICAL OUTCOMES • Weight: MD in weight change vs. placebo ○ 4 weeks: 2g EPA 0.1 (95%CI -0.6 to 0.8), 4g EPA 0.2 (95%CI -0.6 to 0.9), global p=0.88 ○ 8 weeks: 2g EPA 1.2 (95%CI 0.0 to 2.3), 4g EPA 0.3 (95%CI -0.9 to 1.5), global p=0.066	Level of evidence: high risk of bias • Random assignment was performed via random number tables by a third party with minimization based on trial center, type of cancer (lung or

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Duration: 24 weeks • Study ID: unclear	months or longer; Karnofsky performance status of 70 or higher • Exclusion criteria: patients receiving ongoing antineoplastic therapy (including chemotherapy); if they had undergone major surgery, chemotherapy, or radiotherapy in the previous 4 weeks, had current or incipient dysphagia/obstruction to the GI tract, concomitant treatment with fish oil supplementation, systemic steroid therapy, nystatin, or metronidazole • *A priori* patient characteristics: ○ Median age: 67y ○ M/F: 355/163 ○ Cancer type: lung N=231, upper GI N=198, lower GI N=83	Placebo (N=171)	• Appetite: VAS (0-100), MD in change vs. placebo ○ 4 weeks: 2g EPA -3.4 (95%CI -12.5 to 5.7), 4g EPA -3.3 (95%CI -12.4 to 5.9), global p=0.65 ○ 8 weeks: 2g EPA -6.6 (95%CI -17.6 to 4.5), 4g EPA -1.2 (95%CI -12.3 to 9.9), global p=0.38 IMPORTANT OUTCOMES • Adverse events: ○ No significant differences between the groups in the numbers of patients who experienced any adverse events (placebo, 704 AEs affecting 131 patients; 2 g EPA, 806 AEs affecting 143 patients; 4 g EPA, 687 AEs affecting 137 patients) or serious AEs (placebo, 100 serious AEs affecting 64 patients; 2 g EPA, 134 serious AEs affecting 67 patients; 4 g EPA, 99 serious AEs affecting 64 patients) ○ None of the serious AEs were considered to be due to the EPA or placebo medication • Calorie/food intake: not reported • Lean body mass: MD in change vs. placebo ○ 4 weeks: 2g EPA -0.4 (95%CI -1.6 to 0.8), 4g EPA -0.3 (95%CI -1.6 to 0.9), global p=0.75 ○ 8 weeks: 2g EPA 0.9 (95%CI -0.3 to 2.0), 4g EPA -0.1 (95%CI -1.3 to 1.1), global p=0.14 • Quality of life: measured, but not reported • Performance status: KPS, MD in change vs. placebo ○ 4 weeks: 2g EPA 1.1 (95%CI -2.1 to 4.4), 4g EPA 1.4 (95%CI -1.9 to 4.7), global p=0.60 ○ 8 weeks: 2g EPA 0.4 (95%CI -3.6 to 4.5), 4g EPA 1.3 (95%CI -2.7 to 5.4), global p=0.76 • Survival: median, 155 vs. 142 vs. 140 days, p=0.75	gastrointestinal), NSAID use (beyond 75 mg aspirin dose), and method of diagnosis (clinical or histological) • Double-blinded • Unclear if assessor was blinded • Not all patients were included in analysis • Industry-sponsored
Finocchiaro 2012	• Design: RCT • Funding: supported by grants from Piedmont	• Eligibility criteria: patients with a clinical diagnosis of advanced inoperable non-small	Four capsules containing 510 mg of EPA and 340 mg of	CRITICAL OUTCOMES • Weight:	Level of evidence: high risk of bias

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Region and University of Turin, Italy; CoI: none • Setting: multicentre study • Sample size: N=33 • Duration: 66 days • Study ID: Eudra-CT 2006-002978-21	cell lung cancer, 18-70y, 10% or less weight loss over the last three months, before the start the study; patients received 3 courses of chemotherapy with Cisplatin and Gemcitabine; life expectancy was two months or longer; Karnofsky Performance Status was 80 or higher • Exclusion criteria: patients were excluded if they had undergone chemotherapy failure, if metastases were present, if they were diabetic, had cardiovascular or infectious diseases, previous cancer (less than 5 years before or with relapse signs) or inflammatory disease; patients with neurological deficiency or psychiatric diseases were also excluded • *A priori* patient characteristics: ○ Mean age: 58.1 vs. 60.57y ○ M/F: 19/8	DHA per day for 66 days (N=19) vs. Four capsules containing 850 mg of placebo per day (olive oil) (N=14)	○ Change from baseline at 66 days, +3.4 vs. +0.92 kg, NS ○ BMI at day 66: 27.65 vs. 25.58 kg/m², NS • Anorexia / appetite: not reported IMPORTANT OUTCOMES • Adverse events: not reported • Calorie intake at day 66: 2160 vs. 1730.29 kcal/day, NS • Lean body mass: not reported • Quality of life: not reported • Performance status: not reported • Survival: not reported	• Patients were randomised at enrolment using a sequential series of numbered sealed envelopes containing computer-generated random assignments • A copy of the randomisation sequence was kept in a locked cabinet apart from the study personnel • Study products were packaged identically and were not distinguishable from one another; double-blinded • Unclear if assessor was blinded • 6/19 patients in the active treatment group dropped out, and were not included in the analysis
Gogos 1998	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single university centre, Greec • Sample size: N=64 • Duration: 40 days • Study ID: unclear	• Eligibility criteria: patients with generalized solid tumors, not under chemotherapeutic or immunomodulating treatment during the previous 4 months, no other efficient or established tumor treatment when the trial began • *A priori* patient characteristics: ○ Mean age: 57.75y ○ M/F: 36/24 ○ Cancer type: gastrointestinal N=21, breast N=13, lung N=11, liver N=7, pancreas N=8	18 x 1000 mg of fish oil in capsules (N=32): 3060 mg EPA/day, 2070 mg DHA/day, 200 mg vitamin E/day vs. Placebo sugar tablets (N=32)	CRITICAL OUTCOMES • Weight: no effect in either group, no data reported • Anorexia / appetite: not reported IMPORTANT OUTCOMES • Adverse events: no serious toxicity, except for mild abdominal discomfort and transient diarrhea • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: not reported • Performance status: KPS, significant increase from 51 to 72 in the group of malnourished patients 40 days during omega-3 supplementation (p=0.01); no comparison reported • Survival: significant increase in survival compared with placebo, p<0.025	Level of evidence: unclear risk of bias • Unclear randomization method and allocation concealment • Unclear blinding • 60/64 patients included in analysis • Each group was divided into a subgroup with a good nutritional state and a subgroup with malnutrition • A group of 15 healthy individuals served as controls

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Hunter 2021	• Design: RCT • Funding: partially supported by the Cairo University Research Support Program and the Friends of Patients of Kasr Al-Ainy Oncology Center Association; CoI: none • Setting: single university centre, Egypt • Sample size: N=120 • Duration: 28 days • Study ID: unclear	• Eligibility criteria: adult patients with locally advanced or metastatic disease receiving palliative anti-cancer treatment or best supportive care only, cachexia, loss of appetite, ECOG 0-2, life expectancy >3 months, normal organ functions, ability to take pills orally and not dependent on tube feeding, and ability to understand and communicate in Arabic • Exclusion criteria: weight gain for a known cause (e.g. ascites), score ≥4 on a single-item 7-point Likert scale assessing depression (where 0 indicates no depression and 6 extreme feelings of depression), cognitive impairment (dementia or delirium); uncontrolled symptoms that may affect appetite (e.g. nausea and pain) until their control for at least 2 weeks, comorbidities that may affect appetite (e.g. thyroid dysfunction and hypoadrenalism), treatment with antipsychotic agents for 30 days prior to or during protocol therapy, intake of supplements or medications that may stimulate appetite (e.g. megestrol acetate and corticosteroids), and positive pregnancy test in premenopausal women • *A priori* patient characteristics: ○ Mean age: 55.4 vs. 53.5y ○ M/F: 64/56 ○ Cancer type: pancreas N=21, breast N=18, pleura N=17, colorectal N=15, lung N=13	Mirtazapine 15 mg/day for 28 days (N=60) vs. Placebo (N=60)	CRITICAL OUTCOMES • Weight: median change from baseline at day 28, -0.25 vs. -0.5 kg, p=0.72 • Appetite score (0-10): median change from baseline at day 28, 2 vs. 2, p=0.462 IMPORTANT OUTCOMES • Adverse events: ○ No significant difference in adverse events prevalence between the two arms except for any grade sleepiness and grade 3−4 sleepiness which were significantly more prevalent in the mirtazapine arm ○ Other adverse events encountered in the mirtazapine arm but not the placebo: hand tremors (3/48, 6.2%), visual hallucinations (3/48, 6.2%), abnormal dreams (1/48, 2.1%) • Calorie/food intake: not reported • Lean body mass: median change from baseline at day 28, +0.3 vs. -0.1 kg, p=0.192 • Quality of life: FAACT total score, mean change from baseline at day 28, 2.49 vs. 0.73, p=0.181 • Performance status: not reported • Survival: median, 174 vs. 184 days, p=0.84	Level of evidence: unclear risk of bias • Random allocation sequence was generated using the online random sequence generator available from Random.Org • Mirtazapine/placebo tablets were placed in sequentially numbered similar containers by investigator who was the only investigator aware of the content of the containers; he did not participate in enrolment, care provision or outcome assessment throughout the trial • Treatment allocation was concealed from participating patients, recruiter, care providers and outcome assessor • 100/120 patients included in per-protocol analysis, 113/120 patients in “ITT”-analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Jatoi 2004	• Design: RCT • Funding: supported in part by Public Health Service grants CA-25224, CA-37404, CA-15083, CA-63826, CA-63849, CA-35269, CA-35448, CA-35195, CA-35113, CA-60276, CA-52352, CA-35101, CA-35103, CA-63848, CA-35272, and CA-37417; CoI: none • Setting: multicentre, 26 sites, North-America • Sample size: N=421 • Duration: +/- 3 months • Study ID: unclear	• Eligibility criteria: patients (≥18 years of age) with incurable malignancies, other than brain, breast, ovarian, prostate, or endometrial cancer; estimated life expectancy of ≥3 months; Eastern Cooperative Oncology Group performance status of 2 or better; self-reported, 2-month weight loss of at least 5 lb (2.3 kg) and/or a physician-estimated caloric intake of less than 20 calories/kg of body weight/d; all patients had to perceive loss of weight and/or appetite as a problem, and physicians had to view weight gain as beneficial • Exclusion criteria: ongoing tube feedings or parenteral nutrition; edema or ascites; use of adrenal steroids (except short-term dexamethasone with chemotherapy), androgens, progestational agents, or other appetite stimulants within the past month; brain metastases; insulin-requiring diabetes; pregnant, nursing, or unwillingness to use contraceptives, if of child-bearing capacity; poorly controlled hypertension or congestive heart failure; history of thromboembolism; and obstruction of the alimentary tract, malabsorption, or intractable vomiting • *A priori* patient characteristics: ○ Mean age: 66 vs. 65 vs. 66y ○ M/F: 293/128 ○ Cancer type: lung N=166, gastrointestinal N=141, other N=114	EPA (2.18g + 0.92g DHA), 2 cans/day + placebo liquid suspension (N=141) vs. Megestrol acetate 600 mg/day + isocaloric, isonitrogenous placebo cans (N=140) vs. EPA, 2 cans/day + Megestrol acetate 600 mg/day (N=140)	CRITICAL OUTCOMES • Weight: ○ 10% weight gain: 6% vs. 18% vs. 11%, p=0.01 ○ Mean weight change from baseline: -1.0 vs. +1.3 vs. +0.1 kg (EPA vs. MA p=0.008; p=0.03 across 3 arms) • Appetite: ○ NCCTG: improvement 64% vs. 68% vs. 66%, p=0.69 ○ FAACT at 4w: 40% vs. 55% vs. 55% (p=0.004) IMPORTANT OUTCOMES • Adverse events: ○ Impotence (males): 3% vs. 9% vs. 19%, p=0.0006 ○ Thromboembolic events : 6% vs. 8% vs. 2% ○ Nausea : 23% vs. 14% vs. 16%, p=0.11 ○ Vomiting : 7% vs. 6% vs. 9%, p=0.52 • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: Uniscale, median change from baseline at maximum score 0 vs. 0 vs. 1, p=0.93 • Performance status: not reported • Survival: no statistically significant differences in median survival, p=0.82	Level of evidence: unclear risk of bias • Unclear randomization method and allocation concealment • Double-blinded • Unclear if assessor was blinded • ITT analysis
Kanat 2013	• Design: RCT	• Eligibility criteria: adult cancer patients (aged ≥18 years) with	Megestrol acetate 320 mg/day + meloxicam	CRITICAL OUTCOMES	Level of evidence: unclear risk of bias

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Funding: not reported; CoI: none • Setting: single university centre, Turkey • Sample size: N=69 • Duration: 3 months • Study ID: unclear	histological/radiological/clinical evidence of an advanced stage malignancy at any site, Karnosfky performance status ≥70%, loss of ≥5% of pre-illness body weight in the last 3 months, with or without abnormal values of plasma proinflammatory cytokines, and a life expectancy >3 months • Exclusion criteria: women of child-bearing age; patients with a mechanical obstruction of the alimentary tract, malabsorption, peripheral edema, ascites, diabetes mellitus, uncontrolled hypertension; history of myocardial infarction, unstable angina, arrhythmia, congestive heart failure, cerebrovascular accident, thromboembolic events, gastrointestinal inflammatory disease and peptic ulcer; if they had received adrenal steroids, androgens, progestational agents, or other appetite stimulants within the previous month • *A priori* patient characteristics: ○ Mean age: 60.76y ○ M/F: 48/14 ○ Cancer type: lung N=26, pancreas N=10, colorectal N=9, stomach N=8	15 mg/day during 3 months (N=23) vs. Megestrol acetate 320 mg/day + meloxicam 15 mg/day + EPA-enriched (2.2g) nutritional supplement (N=21) vs. Meloxicam 15 mg/day + EPA-enriched (2.2g) nutritional supplement (N=18)	• Weight after treatment: mean increase +4.7 vs. +2.06 vs. +1.75 kg, no significant differences in % change (p=0.61) • BMI: mean increase +2.4 vs. +2.5 vs. +2.6 kg/m², NS • Anorexia / appetite: ○ ACS-12: mean score after treatment -3.08 vs. -5.5 vs. -4.83, NS ○ VAS 0-100: mean score after treatment 72.18 vs. 53.8 vs. 72.8, NS IMPORTANT OUTCOMES • Adverse events: no significant differences • Calorie/food intake: not reported • Lean body mass: mean increase +1.9 vs. +1.4 vs. +1.1 kg, NS • Quality of life: not reported • Performance status: not reported • Survival: not reported	• Unclear randomization method and allocation concealment • Unclear blinding • 62/69 patients included in analysis
Kornblith 1993	• Design: RCT • Funding: grant from the National Cancer Institute, Bethesda, MD, to the Psycho-Oncology Committee of the Cancer and Leukemia Group B (CA31946); CoI: not reported • Setting: multicentre, US	• Eligibility criteria: accrual to the clinical trial (CALGB 8741); stage IV breast cancer; positive or unknown estrogen or progesterone receptors; 16 years of age or older; a CALGB performance status of 0 to 3 (< 50% time in bedrest); no prior chemotherapy for metastatic disease; no more	Megestrol acetate 160 mg/d (N=46) vs. Megestrol acetate 800 mg/d (N=44) vs.	CRITICAL OUTCOMES • Weight: ○ Gain (all): at 1 month: 10% vs. 16% vs. 24%; at 3 months: 5% vs. 30% vs. 47% ○ 20% gain: 4% vs. 14% vs. 17% • Appetite: VAS (0-7), increase at 1 month: 8% vs. 29% vs. 38%; at 3 months: 3% vs. 36% vs. 41%	Level of evidence: high risk of bias • Unclear methods • Substudy of RCT with 359 patients • 131/140 patients included in analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Sample size: N=140 • Duration: 3 months • Study ID: CALGB 8741	than one prior hormonal therapy, excluding progestins; no history of CNS metastases; no other serious medical or psychiatric illness • *A priori* patient characteristics: ○ Mean age: 61y	Megestrol acetate 1600 mg/d (N=41)	IMPORTANT OUTCOMES • Adverse events: ○ Fatigue: VAS (0-7), at 1 month 30% vs. 20% vs. 24%; at 3 months: 13% vs. 15% vs. 41% ○ Feeling bloated: VAS (0-7), at 1 month 3% vs. 12% vs. 27%; at 3 months: 0% vs. 27% vs. 34% • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: reported in graphs, only partially reported with quantitative data ○ Better physical functioning (FLS, p<0.0005), less psychologic distress (MHI, p=0.008), and an improvement in overall quality of life (FLIC, p=0.003) in group treated with 160 mg/day vs. 1600 mg/day ○ Patients who received the 800-mg/d dose responded similarly to those in the 160-mg/d group in terms of physical functioning, psychologic distress, and overall quality of life • Performance status: not reported • Survival: not reported	
Lundholm 1994	• Design: RCT • Funding: Supported in parts by Swedish Cancer Society Grants 93-B89-22XA, 2014-B92-O6XCD, and 2014-B93-O7XDD; Medical Research Council Grants B89-17X-00536-29B and B93-17X-08712-05B; Tore Nilson Foundation; the Assar Gabrielsson Foundation (AB Volvo); the Jubileumskliniken Foundation; the Inga-Britt and Ante Lundberg Research Foundation; the Axel and Margaret AxösonJohnson Foundation; the	• Eligibility criteria: patients with insidious or ongoing weight loss due to generalized malignant disease with a solid tumor type; no other efficient or established tumor treatment available to the patient; most recent tumor therapy completed beyond 6 months prior to starting treatment; expected survival estimated to be more than 6 months • Exclusion criteria: recent or present treatment with anti-inflammatory drugs, kidney function impairment with serum creatinine above 175 µmol/liter,body temperature or relapsing fever above 37.5°C,or cholestasis with	Prednisolone 2x10 mg/day orally (N=45) vs. Indomethacin 2x50 mg/day orally (N=45) vs. Placebo (N=45)	CRITICAL OUTCOMES • Weight: mean 69.7 vs. 62.5 vs. 64.6 kg, p=0.003 • Anorexia / appetite: not reported IMPORTANT OUTCOMES • Adverse events: not reported • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: not reported • Performance status: Karnofsky index, mean 73 vs. 75 vs. 66, p=0.03 • Survival: ○ Indomethacin-treated patients had a significantly prolonged survival compared to placebo-treated patients (p<0.05) ○ Pooled observations from patients on anti-inflammatory treatment revealed a significantly prolonged survival compared to	Level of evidence: … risk of bias • Stratified randomization using computer-based algorithm • Unclear allocation concealment • Patients were blinded for their treatment • Unclear if staff and assessors were blinded • Prematurely interrupted because of positive results • ITT analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Swedish and öteborg Medical Societies; and the Medical Faculty, University of Göteborg; CoI: not reported • Setting: single university centre, Sweden • Sample size: N=135 • Duration: unclear • Study ID: unclear	serum bilirubin levels above 60 µmol • *A priori* patient characteristics: ○ Mean age: 66 vs. 69 vs. 66y ○ M/F: 86/49 ○ Cancer type: liver/pancreas N=44, colon/rectum N=30, gastric N=18, oesophagus N=15		placebo-treated patients (p<0.03, 274 vs. 505 days)	
Mantovani 2008 Mantovani 2010a Mantovani 2010b Tanca 2009	• Design: RCT • Funding: MIUR National Research Project No. 2006067295; CoI: none • Setting: multicentre, Italy • Sample size: N=332 • Duration: 4 months • Study ID	• Eligibility criteria: patients (aged ≥18 years) with a histologically confirmed advanced stage tumor at any site, loss of ≥5% of ideal or pre-illness body weight in the previous 3 months with or without abnormal values of proinflammatory cytokines predictive of the onset of clinical cachexia, and a life expectancy ≥4 months • Exclusion criteria: women of child-bearing age, patients with a mechanical obstruction to feeding, medical treatments inducing significant changes in patient metabolism or body weight, and a history of thromboembolism • *A priori* patient characteristics: ○ Mean age: 61.5 vs. 60.6y ○ M/F: 40/29 ○ Cancer type: lung N=14, breast N=11, colorectal N=9	Medroxyprogesterone acetate 500 mg/day or megestrol acetate 320 mg/day (N=44) vs. EPA-enriched nutritional supplement (EPA 2.2g/day) (N=25)	CRITICAL OUTCOMES • Weight: not reported • Appetite: VAS, after treatment, 7.5 vs. 5.2 IMPORTANT OUTCOMES • Adverse events: no grade 3-4 events • Calorie/food intake: not reported • Lean body mass: after treatment, 43.3 vs. 41.2 kg • Quality of life: ○ EORTC-QLQ-C30: after treatment, 59.4 vs. 61.8 ○ EQ-5D: after treatment, 0.6 vs. 0.33 • Performance status: ECOG, after treatment, 1.7 vs. 1.2 • Survival: “roughly not different”	Level of evidence: high risk of bias • Unclear randomization method and allocation concealment • Unclear blinding • ITT analysis • Arm 3, 4 and 5 not considered here • Early stopping of recruitment for arm 1 and 2
McMillan 1999	• Design: RCT • Funding: Scottish Home and Health Department; CoI: not reported • Setting: two centres, UK • Sample size: N=73 • Duration: 12 weeks • Study ID: unclear	• Eligibility criteria: patients with histologically proven, locally advanced or metastatic gastrointestinal cancer, with more than 5% weight loss who were receiving supportive care only, and had a life expectancy of at least 2 months • Exclusion criteria: moderate or severe dysphagia; obvious functional obstruction to food	Megestrol acetate 480 mg/day + ibuprofen 1200 mg/day for 12 weeks (N=35) vs. Megestrol acetate 480 mg/day + placebo for 12 weeks (N=38)	CRITICAL OUTCOMES • Weight gain, median: ○ At 4-6 weeks: 1.0 vs. -1.5 kg, p<0.01 ○ At 12 weeks: 2.3 vs. -2.8 kg, p<0.001 • Change in appetite score (10-cm linear analogue scale), median: ○ At 4-6 weeks: 2.0 vs. 3.0, p>0.05 ○ At 12 weeks: 1.0 vs. 1.0, p>0.05 IMPORTANT OUTCOMES	Level of evidence: high risk of bias • Unclear randomization method and allocation concealment • Double-blinded • Unclear if assessor was blinded • 41/73 patients assessed at week 4-6

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		intake; grossly abnormal liver function tests; poorly controlled hypertension, congestive heart failure or a history of veno-occlusive disease • *A priori* patient characteristics: ○ Median age: 69 vs. 72y ○ M/F: 43/30 ○ Cancer type: pancreas N=49, gastric N=11, colrectal N=7, oesophageal N=4, cholangiocarcinoma N=1		• Adverse events: reported events were venous thrombosis, upper gastrointestinal bleeding and ascites; no statistical comparison reported • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: ○ EORTC QLQ-C30: "Comparing the two groups, there were no differences in any of the quality of life parameters measured" ○ EQ-5D: "Comparing the two groups at 12 weeks, there was a significant improvement in the EuroQol-EQ-5D quality of life score of the megesterol acetate/ibuprofen group ($p<0.05$)" • Performance status: measured, but not reported • Survival: not reported	
Sanchez-Lara 2014	• Design: RCT • Funding: supported in part by the National Council of Science and Technology of Mexico (CONACYT-Mexico 44395 and 71276); CoI: none • Setting: single center, Mexico • Sample size: N=112 • Duration: 6 weeks, median follow-up 5.8 months • Study ID: NCT01048970	• Eligibility criteria: patients aged 18-80 years with stage IIIb and IV histopathological confirmed NSCLC, ECOG status 0-2, no prior cytotoxic chemotherapy, and eligible to receive chemotherapy; required to have adequate laboratory results, measurable disease and life expectancy >12 weeks; all patients received paclitaxel (175 mg/m²) and cisplatin (75 mg/m²)/carboplatin (AUC 6) as first-line palliative chemotherapy every 3 weeks for at least two cycles and maximum of 6 cycles • *A priori* patient characteristics: ○ Mean age: 58.8 vs. 61y ○ M/F: 43/49 ○ Stage IV: 76.0 vs. 80.4%	Oral nutritional supplement, 2 cans/day, with 1.1 g EPA (N=54) vs. Individualized diet (N=58)	CRITICAL OUTCOMES • Weight: mean change after 2 cycles of chemotherapy, -0.33 vs. -2.2 kg, p=0.01 • Appetite loss subscale of EORTC-QLQ C30: mean change after 2 cycles of chemotherapy, -6.6 vs. -8.6, p=0.05 IMPORTANT OUTCOMES • Adverse events: ○ Nausea and vomiting, symptom scale, mean change after 2 cycles of chemotherapy: +8.4 vs. +11.4, p=0.83 ○ Neuropathy, symptom scale, mean change after 2 cycles of chemotherapy: +1.0 vs. +20.1, p=0.05 ○ Diarrhoea, symptom scale, mean change after 2 cycles of chemotherapy: -8.0 vs. +2.4, p=0.19 • Calorie intake: mean after 2 cycles of chemotherapy, 2195 vs. 1654 kcal, p<0.001 • Lean body mass: mean change after 2 cycles of chemotherapy, +1.6 vs. -2.0 kg, p=0.01 • Quality of life: EORTC-QLQ C30, global health, mean change after 2 cycles of chemotherapy, +11.1 vs. -6.0, p=0.136 • Performance status: not reported	Level of evidence: high risk of bias • Patients were randomly assigned (1:1) at enrolment in permutation blocks of two using a sequential series of numbered sealed envelopes containing computer generated random assignments • No blinding • 92/112 patients included in analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				• Survival: ○ Median overall survival 14.9 vs. 12.1 months, p=0.94 ○ Median PFS: 7.6 vs. 6.3 months	
Sandhya 2023	• Design: RCT • Funding: intramural grant of INR ₹ 46, 872 (Grant No. JIP/Res/Intramural/subcom/2020-21 dt. 11 Sep 2020; proposal no. 101); CoI: none • Setting: tertiary care center, India • Sample size: N=124 • Duration: 12 weeks • Study ID: CTRI/2020/08/027133	• Eligibility criteria: newly diagnosed patients ≥18 years of age planned for the first cycle of cytotoxic chemotherapy for locally advanced/metastatic gastric, hepatopancreaticobiliary, or lung cancer • Exclusion criteria: patients on long-term steroids or antipsychotics; patients who were treated with a low dose, oral (metronomic) chemotherapy, or tyrosine kinase inhibitors alone (without injectable cytotoxic chemotherapy) • *A priori* patient characteristics: ○ Median age: 55 vs. 55y ○ M/F: 79/45 ○ Cancer type: gastric N=68, lung N=43, hepatobiliary N=13	Olanzapine 2.5 mg/day for 12 weeks (N=63) vs. Placebo (N=61)	CRITICAL OUTCOMES • Weight: ○ Weight gain >5%: 56% vs. 8%, p<0.001 ○ End-of-study weight (median): 56 vs. 51.5 kg • Appetite: ○ VAS, improvement at 12 weeks: 40% vs. 12%, p<0.001 ○ FAACT ACS score >37 at 12 weeks: 21% vs. 3%, p=0.03 IMPORTANT OUTCOMES • Adverse events: ○ Proportion of grade 3-5 chemotherapy toxicities: 12% vs. 37%, p=0.002 ○ Toxicities attributable to trial drug: 23% vs. 15%, p=0.26 • Calorie/food intake: ○ Improvement in nutrition score (SGA) at 12 weeks: 43% vs. 9%, p<0.0001 ○ Number of patients who could achieve an adequate calorie intake of more than 75% of the required calories and protein: 52% vs. 18%, p<0.0001 • Lean body mass: not reported • Quality of life: improvement in CI-QOL score at 12 weeks: 70% vs. 50%, p=0.003 • Performance status: not reported • Survival: not reported	Level of evidence: low risk of bias • Computer-generated block random assignment schedule with variable block sizes • The sequence was created by a statistician uninvolved with patient enrollment and evaluation • Patients were evaluated by clinicians and nutritionists who were blinded to treatment allocation • 112/124 patients analyzed, but also ITT analysis reported for some outcomes
Tominaga 1994	• Design: RCT • Funding: not reported; CoI: not reported • Setting: multicentre study (N=56), Japan • Sample size: N=199 • Duration: median follow-up 172.9 weeks • Study ID: unclear	• Eligibility criteria: patients with advanced or recurrent breast cancer who had not received previous treatment or had failed to respond to previous treatment • *A priori* patient characteristics: ○ Mean age: 52.6 vs. 53.2y ○ Recurrent breast cancer: N=160	Induction chemotherapy + medroxyprogesterone acetate 1200 mg/day (arm II: N=96) vs. Induction chemotherapy (arm I: N=103)	CRITICAL OUTCOMES • Weight: incidence of weight gain 63.7% vs. 33.3%, p<0.001 • Anorexia / appetite: not reported IMPORTANT OUTCOMES • Adverse events: ○ Anorexia: 44.6% vs. 60.4%, p=0.04	Level of evidence: high risk of bias • Randomisation using “envelope method” • Unclear allocation concealment • Unclear blinding • No ITT analysis • Induction chemotherapy: combination of

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				○ Nausea/vomiting: 39.6% vs. 60.4%, p=0.006 ○ Moon face: 31.7% vs. 3.3%, p<0.001 ○ Oedema: 14.9% vs. 4.4%, p=0.029 ○ Vaginal bleeding: 13.9% vs. 2.2%%, p=0.008 • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: not reported • Performance status: not reported • Survival: 50% survival duration 82.4 vs. 94.8 weeks, p=0.21	cyclophosphamide (CPA) plus doxorubicin (ADR) plus 5-fluorouracil(5FU) (CAF therapy) • Unclear if anorexia or weight loss was present at inclusion
Willemse 1990	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single centre, the Netherlands • Sample size: N=98 • Duration: median follow-up 9 months • Study ID: unclear	• Eligibility criteria: postmenopausal patients with locally advanced or metastatic breast cancer • Exclusion criteria: patients with rapidly progressive disease, liver metastases or pulmonary lymphangitis; patients aged 80 years or more, WHO performance grade 3 or a life expectancy less than 3 months, or patients with a second malignancy • *A priori* patient characteristics: ○ Median age: 64 vs. 65y	Megestrol acetate 160 mg/day (N=50) vs. Medroxyprogesterone acetate 1000 mg/day (N=48)	CRITICAL OUTCOMES • Weight: increase of at least 5%, 26% vs. 59%, p<0.05 • Anorexia / appetite: not reported IMPORTANT OUTCOMES • Adverse events: ○ % with at least one adverse event: 83% vs. 74% ○ Pyrosis: 10% vs. 2%, p<0.05 ○ Breathlessness: 8% vs. 0%, p<0.05 ○ Hot flashes: 4% vs. 12%, p<0.05 ○ Sweating: 12% vs. 31%, p<0.05 ○ Tremor: 6% vs. 17% • Calorie/food intake: not reported • Lean body mass: not reported • Quality of life: not reported • Performance status: not reported • Survival: median overall survival 20 vs. 16 months	Level of evidence: unclear risk of bias • Unclear randomization method and allocation concealment • Unclear blinding • No ITT analysis for adverse events (92/98)
Zuijdgeest-Van Leeuwen 2000	• Design: RCT • Funding: Numico Research BV, Wageningen, The Netherlands; CoI: not reported • Setting: single centre, the Netherlands • Sample size: N=17 • Duration: 7 days • Study ID: unclear	• Eligibility criteria: weight-losing cancer patients • Exclusion criteria: patients treated with chemotherapy or radiation therapy 2 weeks before start of the study, or elective surgery in the last 2 months were excluded from the study; patients with corticosteroid treatment, insulin-dependent diabetes mellitus, uncontrolled hyper- or	Supplement of 6 g of EPA-EE per day (N=9) vs. 6 g of oleic acid (OA)-EE (N=8)	CRITICAL OUTCOMES • Weight: not reported • Anorexia / appetite: not reported IMPORTANT OUTCOMES • Adverse events: not reported • Calorie/food intake: mean energy intake at day 7, 7847 vs. 6033, NS • Lean body mass: not reported	Level of evidence: unclear risk of bias • Unclear randomization method and allocation concealment • Double-blinded • Unclear if assessor was blinded

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		hypothyroidism, edema or fever • *A priori* patient characteristics: ○ Mean age: 64 vs. 64y ○ M/F: 13/4 ○ Cancer type: upper GI N=4, pancreas N=1, rectal N=1, renal N=1, breast N=1, NSCLC N=1		• Quality of life: not reported • Performance status: not reported • Survival: not reported	• Also 16 healthy subjects included in study, but not reported here

Abbreviations: 95%CI: 95% confidence interval; ACS-12: Anorexia/Cachexia Subscale; AE: adverse event; BMI: body mass index; CI-QOL: Cancer Institute's Quality of Life; CoI: conflict of interest; CTCAE: Common Terminology Criteria for Adverse Events; DHA: docosahexaenoic acid; ECOG: Eastern Cooperative Oncology Group; EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EPA: eicosapentaenoic acid; EQ-5D: EuroQol- 5 Dimension; ESAS: Edmonton Symptom Assessment Scale; FAACT: Functional Assessment of. Anorexia Cachexia Therapy; FACT-G: Functional Assessment of Cancer Therapy – General; FLIC: Functional Living Index-Cancer; HR: hazard ratio; IV: intravenous; ITT: intention-to-treat; KPS: Karnofsky performance status; LASA: Linear analogue self assessment; MA: megestrol acetate; MD: mean difference; MPA: medroxyprogesterone acetate; MSAS: Memorial Symptom Assessment Scale; NCCTG: North Central Cancer Treatment Group; NOSIE: Nurses Observation Scale for Inpatient Evaluation; NS: not significant; OR: odds ratio; RCT: randomised controlled trial; RoB: risk of bias; RR: relative risk; SC: subcutaneous; SF-36: short form 36; SGA: Subjective Global Assessment; SMD: standardised mean difference; THC: tetrahydrocannabinol; VAS: visual analogue scale.

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