Table 1: Characteristics of the included studies

Author (year)	Country	Chemo/ RT	Cancer	N	Dietary intervention (immunonutrient)	Control	Dietary support (timing)	Intervention duration	Data collection point	Primary Outcome	Secondary Outcome	Compliance
Akita (2019) (35)	Japan	NACRT (Gem)	Pancreatic (PDAC)	I-31 C-31	ONS (Omega-3) + Normal diet	Normal diet	3 times during RT (day 0, wk 3, end tx)	5 wk	Immediately before and after RTx	Pre-to-post ratio SMM and PMA	Post/pre ratios pre-albumin, albumin, BMI, CRP, lymphocyte count and severity tx related toxicity (CTACE), intervention compliance, progression of diabetes	I:12.9% (full dose)* (45.2% ≥50%$) C: NA
Chitapanarux (2020) (30)	Thailand	CCRT	H&N	I-20 C-20	ONS (arginine + glutamine + fish oil) +/- normal diet	Normal diet	Weekly	47-63 d	Weekly	Acute CCRT toxicities (AE)	CCRT completion rate, hospital admission, 2-year overall survival	NR
			Cervical	I-10 C-10				33-34 d				
			Oeso	I-14 C-14	PEG (arginine + glutamine + fish oil feed) +/- Normal diet	Isocaloric feed + Normal diet		35-38 d				
Fietkau (2013) (32)	Germany	CCRT	H&N	I-51 C-51	PEG (Omega-3 feed + isocaloric feed) +/- normal diet as able	Isocaloric feed + Normal diet as able	NR	14 wk^	Start CRT, end CRT, 6-7 wk post CRT	Change in body cell mass	FFM, lipid mass, TBW, LM, weight, BMI, SF, MAC, SGA, Karnofsky index, EORTC QLQ-C30, hand grip strength, CTCAE, IL-6, TNF-α	I: 82.7% ± 17.9 C: 76.9 +/-28.7
			Oeso	I-4 C-5								
Pastore (2014) (33)	Brazil	Chemo	GI*	I-26 C-24	ONS (EPA) +/- diet	Standard ONS + diet	None (ONS intake only)	Start d-3 for 4 wk	Post randomisation and end of treatment (AE – wkly)	Supplement compliance, inflammation (us-CRP)	Weight, height, SGA, TNF-α	I: 71.4% C:88.2% (p=0.08)^
			Lung	I-9 C-10								
Sanchez Lara (2014) (34)	Mexico	Chemo	NSCLC	I-46 C-46	ONS (Omega-3) +/- standardised calorie-controlled diet	Standardised calorie-controlled diet	NR (1 wk prior to cycle – protocol)	6-8 wk^ (2 cycles)	0-7 d prior to chemo, 0-7 d post 1st and 2nd cycle chemo	Nutritional status (Unintentional wt loss, SGA, energy consumption, FM, LBM, phase angle). Inflammatory response (FBC, albumin, NLR, PLR, CRP, TNF-α, IL-6) QOL: EORTC-QLQC30 and QLQ-LC13, toxicity (CTCAE)	Response to chemotherapy and survival	I: >73% target volume C: N/A
Sunpawer avong (2014) (36)	Thailand	CCRT	Oeso	I-35 C-36	PEG (Arginine, glutamine, fish oil feed) + Isocaloric/ isonitrogenous feed +/- diet	Isocaloric/ isonitrogenous feed (Otsuka) +/- diet	NR	28 d (Pre to post tx)	Bloods - Prior to CCRT, d 7, 14, 28. Immune – prior to & d 28	Immune &, inflammatory markers (IL-6, IL-10, TNF-α, IFN-σ and CRP, WBC, CD3,4,8, PMN), CCRT-related AE	Weight, tumour response	NR

Talvas (2015) (31)	France	CCRT	Oeso	I- 8, C-5	Gastrostomy or NGT (Arginine, EPA, DHA, nucleotide) +/- isocaloric/isonitrogenous feed +/- diet	Isocaloric/ isonitrogenous enteral feed +/- diet	NR	5 d pre RCT for 5-7 wk end tx	Beginning and end RCT	Cell blood count, Leukocyte phenotype, leukocyte function, PBMC transcriptome	Weight, BMI, weight loss, NRI, patient compliance	4.5 x EPA and 2.5 x DHA in fatty acids of leukocytes in intervention arm ($p<0.05$)
			H&N	I-7, C-8								

Abbreviations: N, number of patients available to be included in the intention to treat analysis at the end of treatment time points; I, intervention; C, control; Oeso, oesophageal cancer; H&N, head and neck cancer; GI*, gastrointestinal cancer (oesophageal, gastric, colorectal, pancreatic or gallbladder); PDAC, pancreatic ductal adenocarcinoma; NACRT, neoadjuvant chemoradiotherapy; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; RCT, radiochemotherapy; SGA, subjective global assessment; FFM, fat free mass; TBW, total body water; LM, lean mass; BMI, body mass index; SF, skin fold thickness; PMA , psoas major muscle area; MAC, mid-arm circumference; FM, fat mass; QOL, quality of life; EORTC-QLQC30, European Organisation for Research and Treatment of Cancer quality of life questionnaire C30; EORTC-QLQ-LC13, European Organisation for Research and Treatment of Cancer quality of life questionnaire LC13; CTCAE, Common Terminology Criteria for Adverse Events; PMBC, peripheral blood mononuclear cell; PMN, polymorphonuclear cell; CD3, cluster of differentiation 3; PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein; usCRP, ultra sensitive CRP; TNF-alpha, tumour necrosis factor alpha; IL-6, interleukin-6; AE, adverse event; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PEG, percutaneous endoscopic gastrostomy; NGT, nasogastric tube; ONS, oral nutritional supplement; NR, not reported.

Table 2: Inflammatory markers

a) CRP: Intention to treat reported outcomes						CRP (mg/dL)					
						Intragroup changes			Between group difference		
Author (year)	**Population**			**Tx**	**N**	**Baseline**	**End tx**	**P-value**	**Difference**	**P-value**	**Units**
Akita (2019) (35)	Pancreatic	ONS	Omega-3	I	31	0.45 ± 0.78	0.84 ± 2.13	0.338	-	-	mean ± SD
				C	31	0.46 ± 1.27	0.31 ± 0.46	0.539	-	-	
Sanchez- Lara (2014) (34)	NSCLC	ONS	Omega-3	I	46	3.2 ± 4	1.9 ± 2	**0.02**	-1.3	0.07	mean ± SD
				C	46	3.7 ± 4	3.9 ± 2	0.305	0.19 +/- 0.02		
Pastore (2014) (33)	GI	ONS	Omega-3	I	20	-	-	-	0.35 (-9.7;10.2)	0.9	median ± IQR
				C	21	-	-	-	-0.3 (-13.8; 10.9)		
	Lung			I	8	-	-	-	-3.95 (-56.4; 20.6)	0.7	
				C	8	-	-	-	-8.8 (89.8; 5.25)		
Talvas (2015) (31)	H&N or Oeso	EN	Arginine, omega-3, nucleotides	I	15	10.8 ± 6.3	-	-	-	-	mean ± SD
				C	13	9.3 ± 7.7	-	-	-	-	
Sunpaweravong (2014) (36)	Oeso	EN	Arginine, glutamine, omega-3	I	35	0.92 (0.53, 1.6)	0.37 (0.21, 0.64)	-	-	**0.001**	% change (95% CI)
				C	36	0.97 (0.58, 1.62)	1.16 (0.69, 1.93)	-	-		
b) TNF-α: Intention to treat reported outcomes						**TNF-alpha (pg/ml)**					
						Intragroup changes			**Between group difference**		
Author (year)	**Population**			**Tx**	**N**	**Baseline**	**End tx**	**P-value**	**Difference**	**P-value**	**Units**
Sanchez- Lara (2014)	NSCLC	ONS	Omega-3	I	46	69.8 ± 56.5	58.7 ± 57	**0.05***	0.16 ± 0.8	0.541	mean ± SD
				C	46	67 ± 61	67.2 ± 56	0.934	-11.1		
Fietkau (2013)	H&N / oeso	EN	Omega-3	I	34	33.56 ± 47.41	-	-	-29.93 ± 5.76	0.154	mean ± SE
				C	27	19.28 ± 50.85	-	-	-11.4 ± 6.47		
Talvas (2015)	H&N/oeso	EN	Arginine, omega-3, nucleotide	I	13	3.5 ± 0.5	5.8 ± 0.9	**P<0.05**	-	-[a]	mean +/- SE
				C	15	3.2 ± 0.4	5.7 ± 0.7	**P<0.05**	-		
Sunpaweravong (2014)	Oeso	EN	Arginine, glutamine, omega-3	I	35	0.96 (0.79 - 1.18)	0.96 (0.8-1.16)	-	-	**0.0014**	% change (95% CI)
				C	36	0.84 (0.84-0.69)	1.21 (1-1.45)	-	-		

c) IL-6: Intention to treat reported outcomes						IL-6 (pg/ml)					
						Intragroup changes			Between group difference		
Author (year)	**Population**			**Tx**	**N**	**Baseline**	**End tx**	**P-value**	**Difference**	**P-value**	**Units**
Sanchez- Lara (2014)	NSCLC	ONS	Omega-3	I	46	13.4 ± 10	17.5 ± 12	0.267	4.09	0.602	mean ± SD
				C	46	11 ± 11	14.9 ± 37	0.354	3.9 ± 1.2		
Fietkau (2013)	H&N / oeso	EN	Omega-3	I	34	10.34 +/- 12.97	5.2 +/- 3.57	-	-	**0.031**	mean ± SE
				C	27	9.12 +/- 8.67	17.15 +/- 4.01	-	-		
Sunpaweravong (2014)	Oeso	EN	Arginine, glutamine, omega-3	I	35	1.58 (1.05-2.38)	1.06 (0.7-1.6)	-	-	0.083	% change (95% CI)
				C	36	1.65 (1.13-2.42)	1.69 (1.6-1.15)	-	-		

a) IL-6: Intention to treat reported outcomes						IL-6 (pg/ml)					
						Intragroup changes			Between group difference		
Author (year)	**Population**			**Tx**	**N**	**Baseline**	**End tx**	**P-value**	**Difference**	**P-value**	**Units**
Talvas (2015)	H&N/oeso	EN	Arginine, omega-3, nucleotide	I	13	5.5 ± 0.7	5.1 ± 1.3	-	-	**<0.05**	mean ± SE
				C	15	6.7 ± 0.91	4.0 ± 0.9		-		
Sunpaweravong (2014)	Oeso	EN	Arginine, glutamine, omega-3	I	35	1.23 (0.97-1.57)	1.06 (0.7-1.6)	-	-	0.669	% change (95% CI)
				C	36	1 (0.78-1.27)	1.05 (0.84 -1.32)		-		

Sunpaweravong does not provide an absolute baseline values reported as % change based on differences between days 1-7 (baseline) and 1-28 (end of treatment). [a] Reported as not significant but no value provided.

Figure 2. Risk of Bias assessment of studies: Intention to Treat

Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
Akita (2019)	ONS (omega 3) + diet	Diet only	Inflammatory markers	+	+	+	+	!	!
Chitapanarux (2020)	ONS/ enteral feed (glutamine + arginine + fish oil) +/- diet	Normal diet +/- isocaloric feed	Inflammatory Markers and AEs	!	+	+	+	!	!
Fietkau (2013)	Enteral feed (omega-3) + isocaloric feed +/- diet	Isocaloric feed +/- diet	Inflammatory markers	+	+	+	+	!	!
Sanchez-Lara (2014)	ONS (omega-3) + standardised diet	Standardised diet	Inflammatory markers	+	+	+	!	!	!
Pastore (2014)	ONS (EPA) + diet	ONS standard + diet	Inflammatory marker	+	!	+	+	!	!
Sunpaweravong (2014)	Enteral feed (Arginine, glutamine, fish oil) +/- diet	Diet +/- isocaloric/ Isonitrogenous feed	Inflammatory Markers and AEs	!	!	+	+	!	!
Talvas (2015)	Enteral feed (Arginine, EPA, DHA and Nucleotide) +/-	Diet +/- isocaloric/ Isonitrogenous feed	Inflammatory markers	+	+	+	!	!	!

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

Supplementary information

Supplementary Table 1: Intervention details for included studies

Author (year)	Product (manufacturer)	Route	Volume, ml (dose)	Intervention period & timing	Immunonutrient composition and target volume						
					Energy	Protein	Omega-3		Arginine	Glutamine	Other
							EPA	DHA			
Akita (2019) (35)	Prosure *(Abbott)*	ONS	220 ml (bd)	Daily during irradiation (~ 5 wk)	560 kcal/d	29.2 g/d	1.98 g/d	0.88 g/d	NR	NR	9.1 g/d fibre (4.84 g/d FOS)
Chitapanarux (2020) (30)	Neo-mune *(Otsuka)*	PEG/ONS	250 ml (bd)	1 hr pre & post RT (28-33 fractions)	500 kcal/d	31.25 g/d	Y		Y	Y	NR
Fietkau (2013) (32)	Supportan *(Fresenius Kabi)*	PEG	500 ml (od)	14 wk^	750 kcal/d (+std feed 30-33 kcal/kg/d)	50 g/d	2 g/d	1 g/d	NR	NR	NR
Pastore (2014) (33)	Forticare *(Nutricia)*	ONS	125 ml (tds)	Start d-3 for 4 weeks	600 kcal/d	33 g/d	2.2 g/d	1.1 g/d	NR	NR	NR
Sanchez-Lara (2014) (34)	**ProSure** *(Abbott)*	ONS	237ml (bd)	6-8 wk^ (2 cycles)	597 kcal/d	30 g/d	2.1 g/d	0.75 g/d	NR	NR	FOS 4.2 g/d Fibre 7.9 g/d
Sunpaweravong (2014) (36)	Neo-Mune *(Otsuka)*	PEG	Variable (30 kcal/kg/d)	Start d-3 for 4 wk	1100 kcal/L (30 kcal/kg/d)	62.5 g/L	Y		12.5 g/L (20% of protein content)	6.25 g/L (10% of protein content)	NR
Talvas (2015) (31)	Impact *(Nestle)*	Gastrostomy or NGT	1500 ml (minimum volume)	5-7 wk	1010 kcal/L (35-40 kcal/kg/ d)	56 g/L (1.5-1.8 g/kg/L)	3.4g/L (ratio not defined)		13 g/L		RNA 1.3 g/L

Abbreviations: PEG, percutaneous endoscopic gastrostomy; ONS, oral nutritional supplement; NGT, nasogastric feeding tube; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; Y, immunonutrient present but quantity not defined; FOS, fructooligosaccharides; NR, not reported; od, once a day; bd, twice a day.

Supplementary Table 2: Medline exemplar search strategy (Ovid)	
Number	**Search term**
1	cancer.ti,ab.
2	neoplasm.ti,ab.
3	tumor.ti,ab.
4	tumour.ti,ab.
5	malignanc*.ti,ab.
6	leukemia.ti,ab.
7	leukaemia.ti,ab.
8	lymphoma.ti,ab.
9	Myeloma.ti,ab
10	exp hematological malignancy/
11	Neoplasm/
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	immunonutrition.ti,ab.
14	(immune adj3 nutrition).ti,ab.
15	13 or 14
16	arginine.ti,ab.
17	amino acid*.ti,ab.
18	vitamin d.ti,ab.
19	eicosapentaenoic acid.ti,ab.
20	Docosahexaenoic acid.ti,ab.
21	vitamin e.ti,ab.
22	exp amino acids/
23	exp vitamin d/
24	omega 3.ti,ab.
25	exp fatty acids,omega-3/
26	vitamin a.ti,ab.
27	Zinc.ti,ab.
28	Selenium.ti,ab
29	glutamine.ti,ab.

30	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31	Dietary supplements/
32	enteral nutrition/
33	nutrition therapy/
34	nutrition support/
35	nutrition support.ti,ab.
36	nutritional therapy.ti,ab.
37	enteral nutrition.ti,ab.
38	dietary supplement*.ti,ab.
39	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40	15 or 30 (immunonutriiton)
41	39 or 40 (immunonutrition or enteral nutrition)
42	chemotherap*.ti,ab.
43	chemoradiotherap*.ti,ab.
44	hematopoietic stem cell transplant*.ti,ab.
45	haematopoietic stem cell transplant*.ti,ab.
46	bone marrow transplant*.ti,ab.
47	Bone Marrow Transplantation/
48	antineoplastic protocols/
49	chemoprevention/
50	chemoradiotherapy/
51	chemotherapy,adjuvant/
52	consolidation chemotherapy/
53	induction chemotherapy/
54	maintenance chemotherapy/
55	drug therapy/
56	42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 (chemotherapy +/- radiotherapy/HSCT)

57	12 and 41 and 56 (Cancer, immunonutrition,EN, chemo)
58	12 and 40 and 56 (Cancer, immunonutrition, chemo)
59	12 and 40 and 41 and 56
60	randomized controlled trial.pt.
61	controlled clinical trial.pt.
62	randomized.ab.
63	placebo.ab.
64	randomly.ab.
65	groups.ab.
66	58 or 59 or 60 or 61 or 62 or 63
67	exp animals/ not humans.sh.
68	66 not 67
69	57 and 68 (final outcome used to ensure captured papers where EN is not reported)
70	58 and 68
	Cancer
	Immunonutrition
	Enteral nutrition
	Chemotherapy
	Cancer + (immunonutriiton or EN) + chemo
	Cancer + immunonutrition + chemo
	Immunonutrition + cancer + chemotherapy + RCT
	Immunonutrition + cancer + chemotherapy + Enteral nutrition

Supplementary Table 3: Timing of outcome collection relative to chemo/ CCRT and nutrition

Timing of outcome collection relative to chemo / CCRT and nutrition																		
Study (year)	**Patient group**		**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Chitapanarux (2020)		Nutrition			1hr pre	Rtx	Session												
	Head & Neck	Treatment																	
	Oesophageal	Treatment																	
	Cervical	Treatment																	
Talvas (2015)		Nutrition		5days pre															
	Head & Neck	Treatment																	
	Oesophageal	Treatment																	
Fietkau (2013)		Nutrition																	
	Head & Neck	Treatment																	
	Oesophageal	Treatment																	
Pastore (2014)		Nutrition		3 days pre															
	GI	Treatment	NR																
	Lung	Treatment	NR																
Sanchez- Lara (2014)		Nutrition																	
	NSCLC	Treatment																	
Akita (2019)		Nutrition																	
	Pancreatic	Treatment																	
Sunpaweravong (2014)		Nutrition									(cellular immunity days 1 and 18) 1,7,14,28 for blood inflammatory cytokines - pre ccrt								
	Oesophageal	Treatment																	

Where there is insufficient information to report the association, it is left blank. Red denotes time points for outcome collection; **black vertical lines** denote chemotherapy administration where reported; green denotes timing for nutrition delivery unless otherwise stated; blue denotes timing of radiotherapy where reported; Patterned fields denote documented variation in treatment delivery times (nutrition/CCRT/chemo) or in outcome collection.