Nutritional pathology in stage 4 oesophagogastric cancer

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Outline

1. Identification and definitions
2. Scale of the problem
3. What factors contribute to cachexia?
4. Interventions

Cachexia: Definition

Not just an end stage issue!

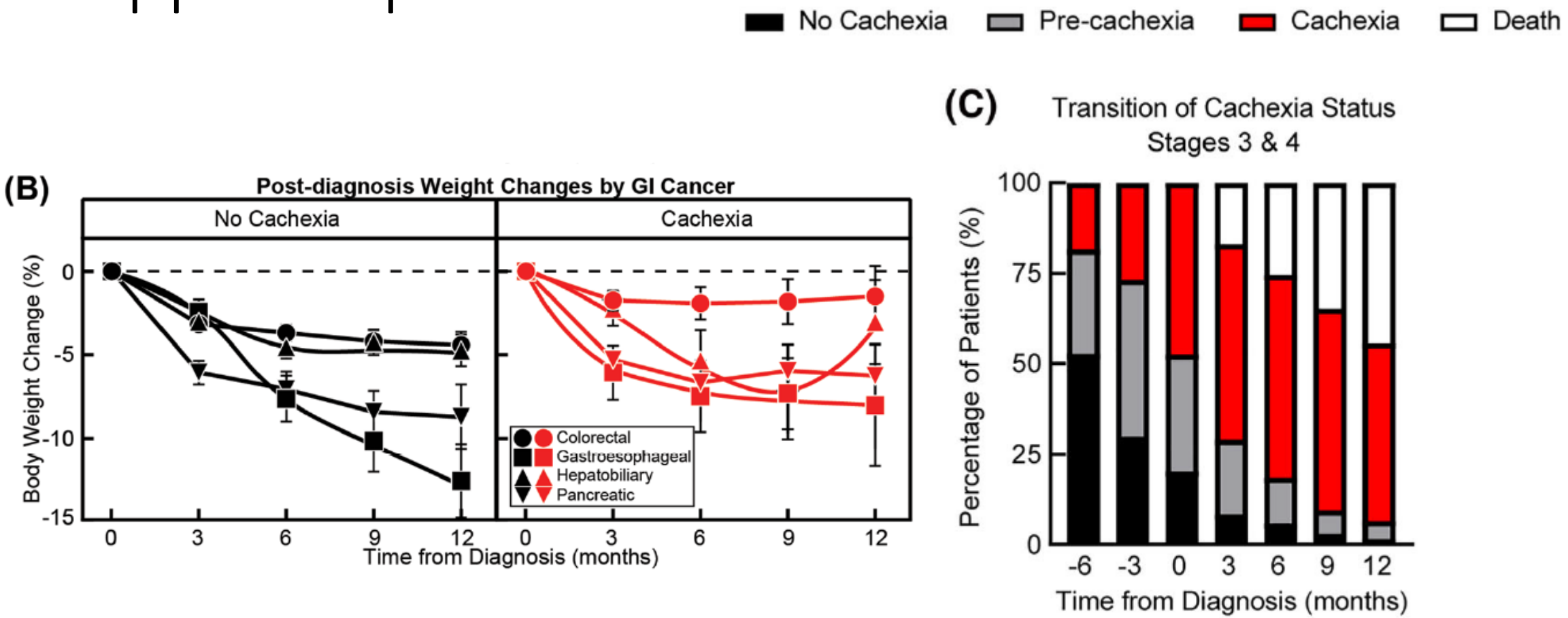
Ralph et al, Dermatol online 2020

Cachexia: Definition
ESMO Cachexia guidelines 2021

Malnutrition	Defined by three criteria: a positive malnutrition screening test combined with one phenotypical and one aetiological criterion:[8]	
	Mandatory screening	Malnutrition risk predicted by a validated screening test, e.g. NRS-2002, MUST, SNAQ, MST or other
	Phenotypical criteria	Loss of or low body mass as defined by at least one of the following: A1: weight loss >5% in 6 months A2: body mass index below 20 kg/m^2 A3: low muscle mass
	Aetiological criteria	Reduced food availability (B1) and/or increased catabolism (B2) B1 (starvation type): reduction in food availability B1a: food intake <50% for >1 week B1b: any reduction in food intake for >2 weeks B1c: chronic malabsorption B2 (cachexia type): increased acute or chronic systemic inflammation
Cachexia	A disease-related subtype of malnutrition identified by malnutrition screening, at least one phenotypical criterion and systemic inflammation:[8,11]	
	Malnutrition screening	As described above
	Phenotypical criteria	As described above
	Aetiological criterion	B2 (systemic inflammation; described above)
Sarcopenia	Defined by two criteria: low muscle strength combined with low muscle mass or quality:[17]	
	Optional screening	SARC-F questionnaire[132]
	Criterion A	Low muscle strength
	Criterion B	Low muscle mass or quality

Arends et al, 2021

Weight loss and cachexia are common in upper GI patients



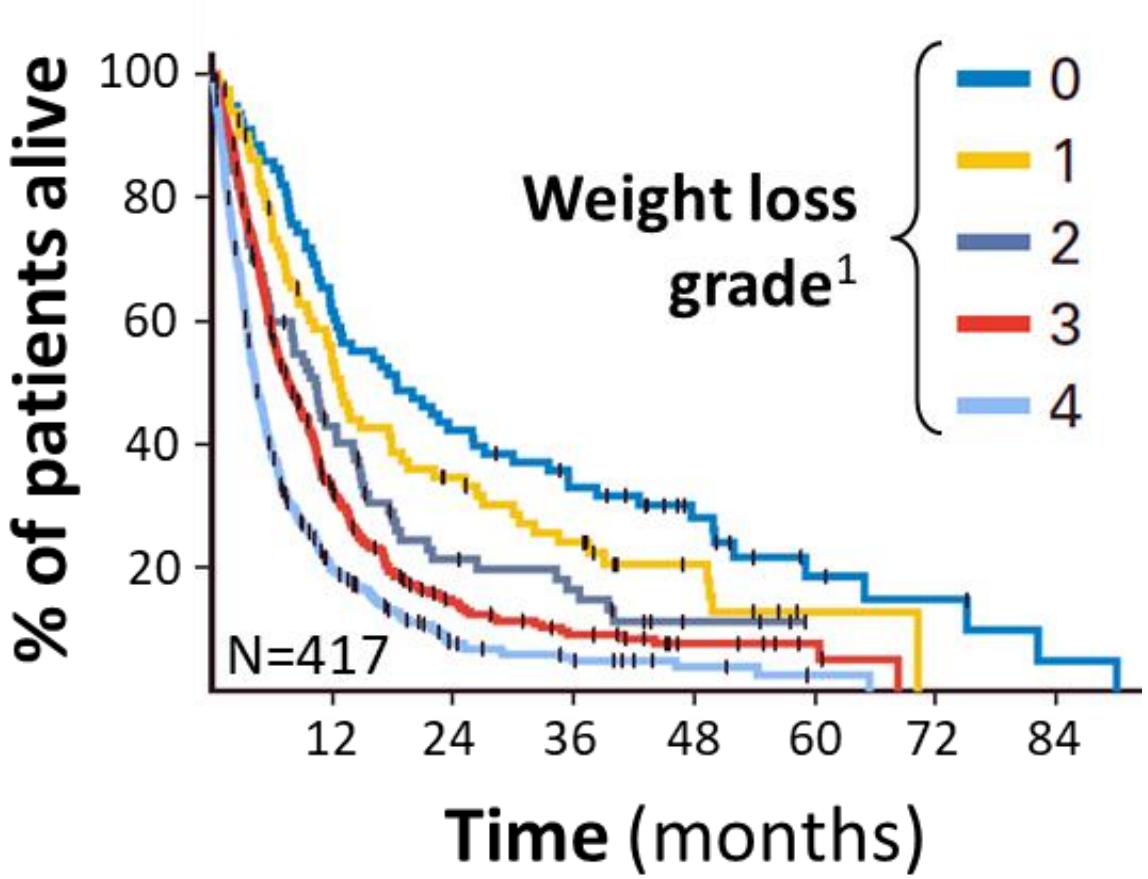
Gillmore et al 2022

Weight loss and cachexia are common in upper GI patients?

- 70-80% of mOG patients have weight loss at baseline
- 60-70% of patients presenting to the Christie had lost >10% body weight prior to presentation

Weight loss as a prognostic factor

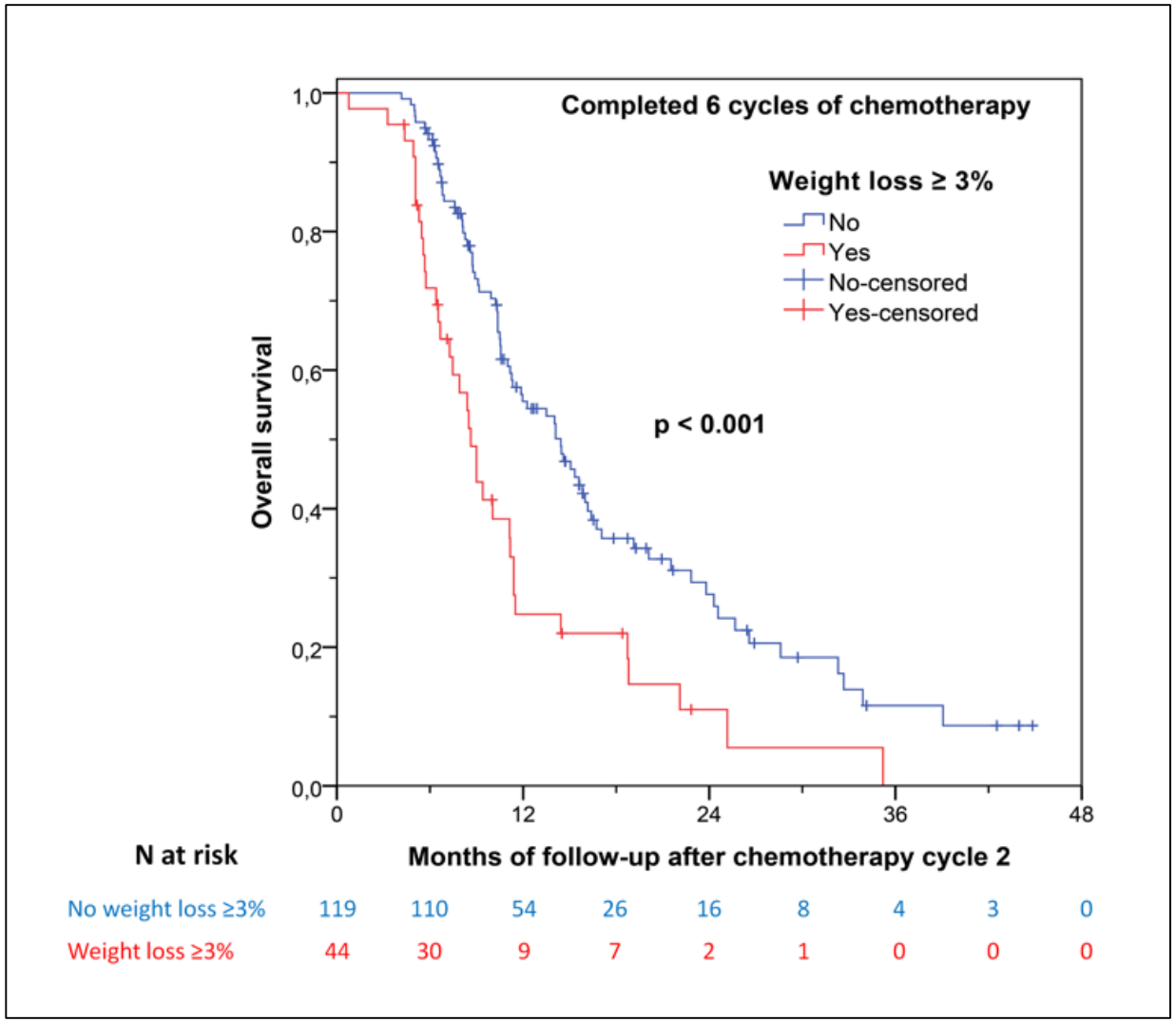
Weight loss (%) \ BMI (kg/m²)	28	25	22	20
2.5	0	0	1	1	3
6	1	2	2	2	3
11	2	3	3	3	4
15	3	3	3	4	4
	3	4	4	4	4



Large international study
>8000 cancer patients
>400 OG pts

Martin et al. 2015

Weight loss as a prognostic factor



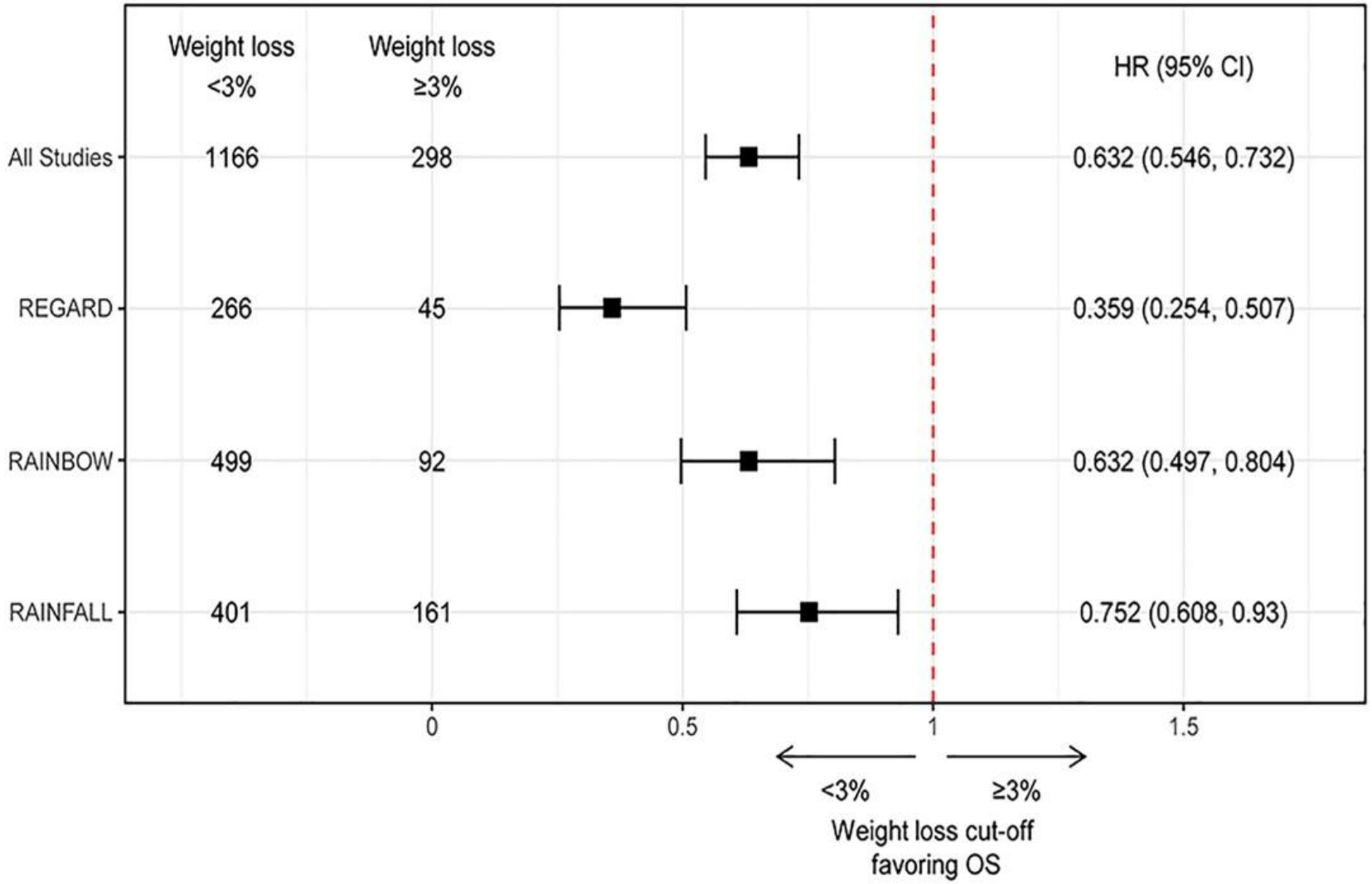
Weight loss is present even in OG patients who are responding to chemotherapy and effects prognosis

Steele et al (manuscript in preparation)

Weight loss as a prognostic factor

Post-hoc analysis of three, Phase 3, 2nd line chemotherapy trials.

Patients categorised according to weight loss of < or ≥3% during 1st cycle of chemotherapy.

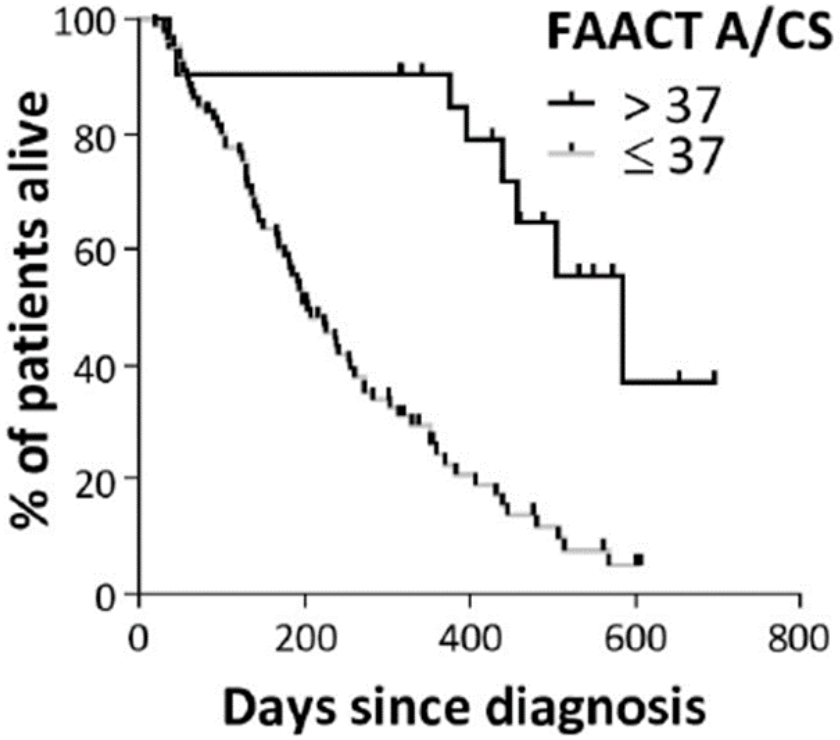


.Mansoor W, et al.2021.

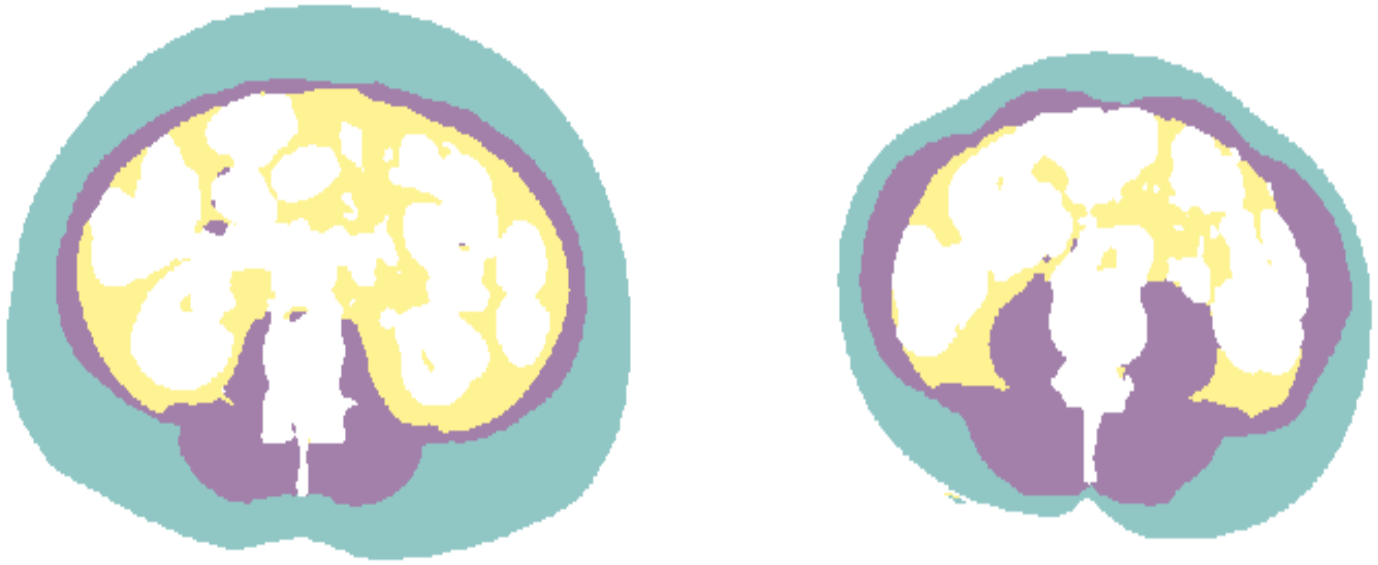
Alternative measures to weight loss: Anorexia

The patient's response applies to the last week		Not at all	A little bit	Somewhat	Quite a bit	Very much
1	I have a good appetite	0	1	2	3	4
2	The amount I eat is sufficient for my needs	0	1	2	3	4
3	I am worried about my weight	4	3	2	1	0
4	Most food tastes unpleasant to me	4	3	2	1	0
5	I am concerned about how thin I look	4	3	2	1	0
6	My interest in food drops as soon as I try to eat	4	3	2	1	0
7	I have difficulty eating rich or 'heavy' foods	4	3	2	1	0
8	My family or friends are pressuring me to eat	4	3	2	1	0
9	I have been vomiting	4	3	2	1	0
10	When I eat, I seem to get full quickly	4	3	2	1	0
11	I have pain in my stomach area	4	3	2	1	0
12	My general health is improving	0	1	2	3	4

Retrospective, single-centre study analyses survival of 182 patients with advanced uGI cancer according to baseline anorexia status as assessed by the FAACT C/S score.
69% anorectic, 31% non-anorectic, mOS 6.7 months vs 19.3.



Alternative measures to weight loss: Sarcopenia



Additional measures to weight loss: Sarcopenia

Association between body composition, survival, and toxicity in advanced esophagogastric cancer patients receiving palliative chemotherapy

Willemieke P.M. Dijksterhuis[1], Maarten J. Pruijt[1], Stephanie O. van der Woude[1], Remy Klaassen[1], Sophie A. Kurk[2], Martijn G.H. van Oijen[1] & Hanneke W.M. van Laarhoven[1]*

[1]Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands, [2]Department of Medical Oncology, University Medical Center Utrecht, University of Utrecht, Utrecht, The Netherlands

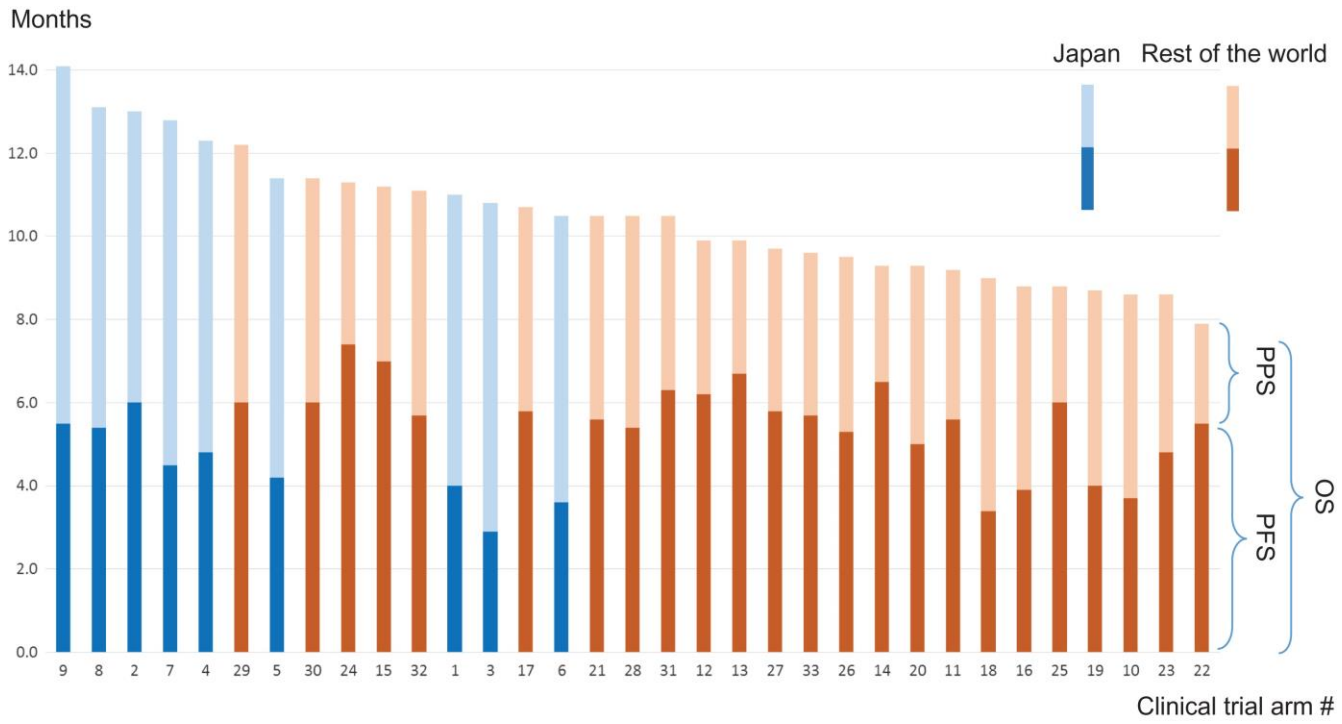
Prognostic role of body composition parameters in gastric/gastroesophageal junction cancer patients from the EXPAND trial

Ulrich T. Hacker[1*†], Dirk Hasenclever[2†], Nicolas Linder[3†], Gertraud Stocker[1], Hyun-Cheol Chung[4], Yoon-Koo Kang[5], Markus Moehler[6], Harald Busse[3] & Florian Lordick[1]

[1]1st Medical Department, University Cancer Center Leipzig (UCCL), University Leipzig Medical Center, Leipzig, Germany, [2]Institute for Medical Informatics, Statistics and Epidemiology (IMISE), Medical Faculty of the University Leipzig, Leipzig, Germany, [3]Department of Radiology, University Leipzig Medical Center, Leipzig, Germany, [4]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea, [5]Division Oncology Department, Medical Center, Seoul, South Korea, [6]First Department of Internal Medicine, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

Why is Cachexia a prognostic factor?

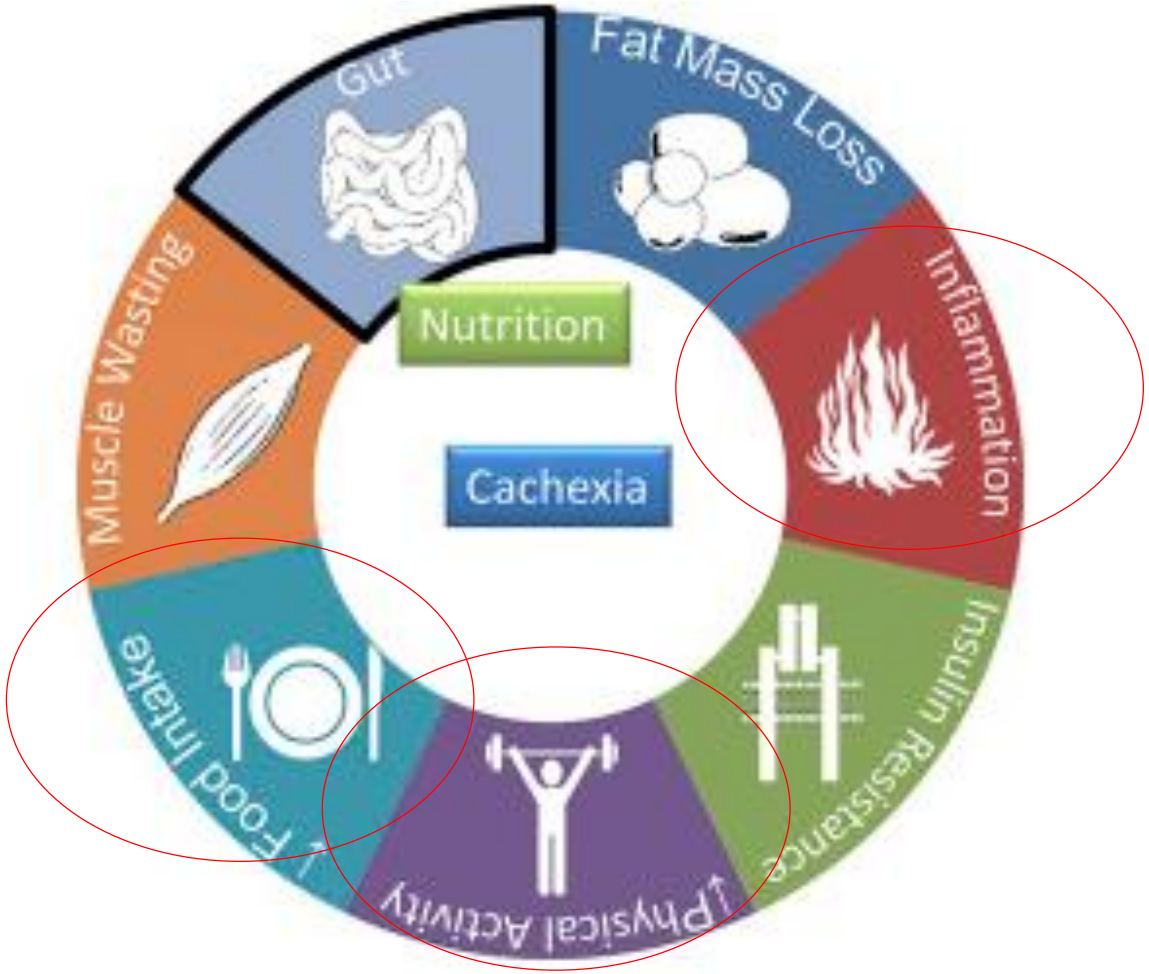
- More aggressive disease biology?
- Increased toxicity on chemotherapy?
- Inability to get patients on to later line therapies?



- Progression-free survival is shown in dark color and post-progression survival in light color
- Increased proportion of patient getting second line therapy (69–85% vs. 11–59%)

Takashima et al 2017

Causes: Cachexia/Sarcopenia in malignancy is multifactorial, weight loss alone is not enough information



- All 3 may be effected by the primary malignancy in a paraneoplastic manner or by local effects and may be worsened by chemotherapy

ANCHOR study: Detailed baseline characterisation of OG patients to identify the relative contributions of causes of cachexia

All new patients attending upper GI clinics

Cohort A
Undergo baseline dietetic and body composition assessments as part of standard of care practice

Continue in Cohort A

Cohort B

Undergo CPET testing at baseline in addition to standard of care assessments

Cohort C

Undergo gut hormone assessment in addition to standard of care assessments

Continue standard of care assessments and treatment

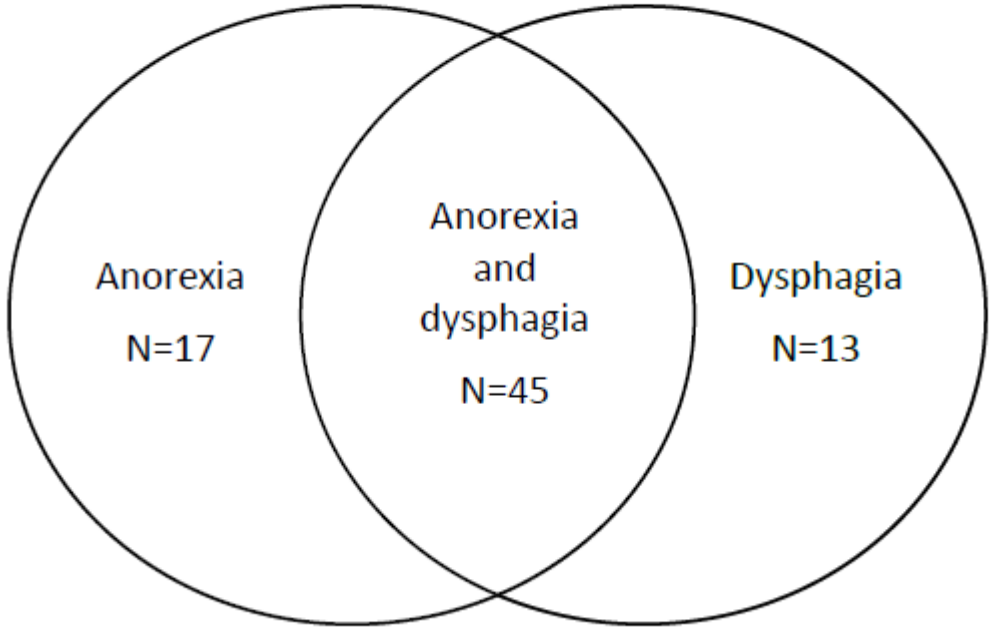
Healthy controls invited to participate

Cohort D

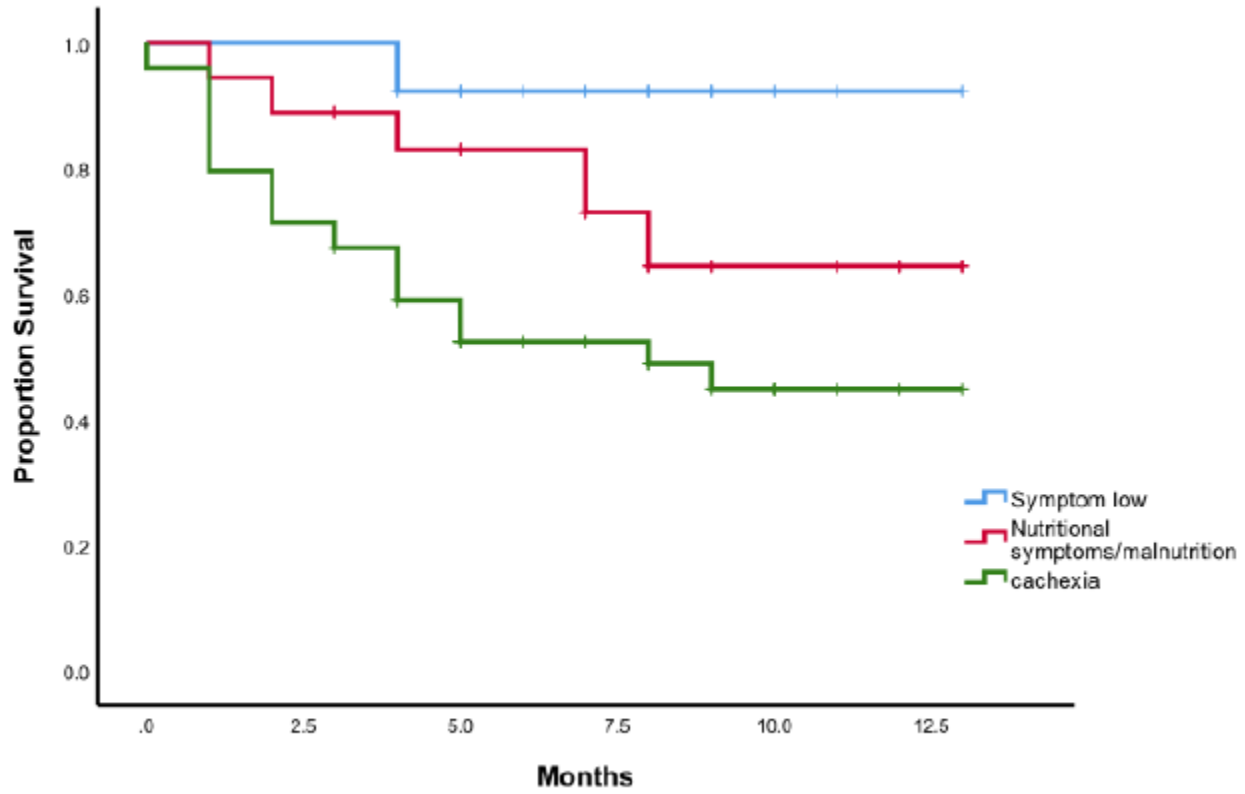
Undergo gut hormone assessment in addition to standard of care assessments

Follow-up call

ANCHOR: Anorexia and dysphagia overlap to a large degree but are also seen independently



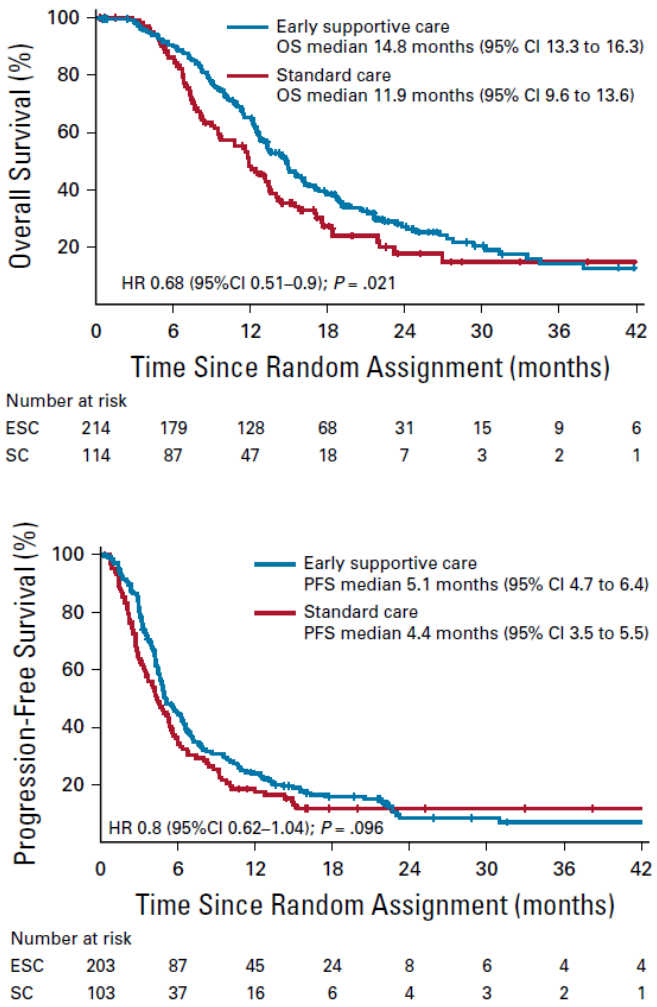
Anchor: Patients with multifactorial weight loss do worst



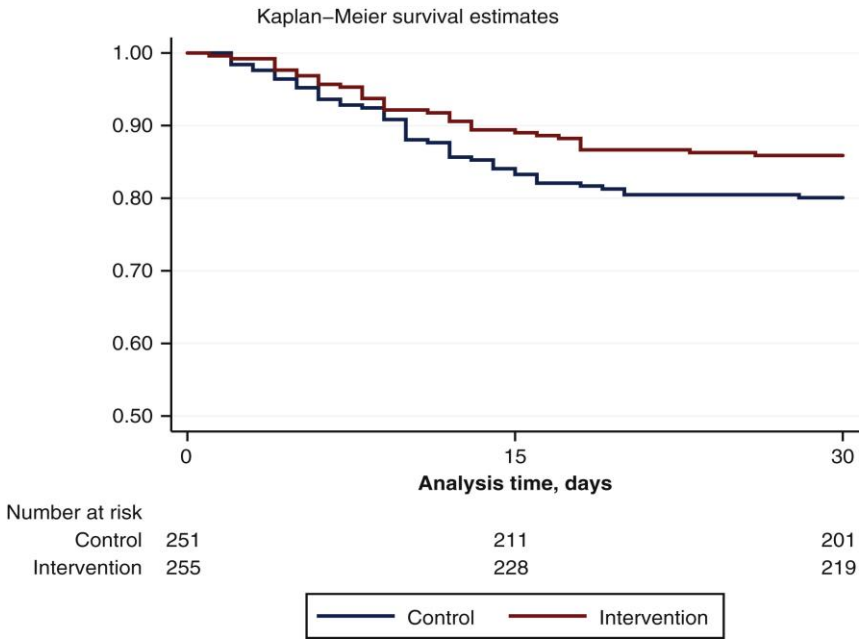
What interventions do we have available?

Anorexia: Dietician support

Prospective Phase 3 RCT of early supportive care vs standard care, 328 patients with GO cancer receiving chemotherapy, dietician and psychology support received q3w through treatment.[1]



EFFORT: prospective, multi-centre RCT, protocol-guided individualised nutritional support (intervention group) vs standard hospital food (control group) regarding mortality at 30-day (primary endpoint) and other clinical outcomes in cancer patients.[2]



Lu et al 2021, Bargetzi et al 2021

Anorexia: Appetite stimulants, Dex or Megesterol

	Megestrol acetate 480 mg/day (n=61)		Dexamethasone 4 mg/day (n=67)		Placebo (n=62)	
	%	N assessable	%	N assessable	%	N assessable
Week 1	79.3	58	65.5	58	58.5	53
Week 2*	92.5	40	96.9	32	78.9	19
Week 3*	89.7	29	100.0	28	100.0	12
Week 4*	100.0	22	100.0	20	100.0	10
	Megestrol acetate		Dexamethasone		Placebo	P value
Weight responders, %	87%		74%		85%	**0.2417**
Change from baseline in FACT-G* Total Score, mean (SD)	− 2.1 (3.4)		− 4.8 (3.4)		− 0.8 (3.4)	**0.576**

- *Note participants that failed to achieve a response at the end of each treatment period ceased treatment and underwent a follow-up visit.

Other therapeutic targets?

Table 1 Randomized-controlled trials of anti-cytokines in the treatment of cancer-related cachexia

Reference	Agent/phase	Population	Size	CRC criteria
Gordon *et al.* 2005	Thalidomide; phase II	Inoperable pancreatic cancer	50 pts; 33 evaluable	Weight loss >10% in last 6 months
Mantovani *et al.* 2010	Thalidomide; phase III	Different advanced cancer types	332 pts; all evaluable	>5% loss of ideal or pre-illness weight in last 3 months, with or without abnormal inflammatory cytokines
Wilkes *et al.* 2011	Thalidomide; phase II	Incurable esophageal cancer	34 pts; 24 evaluable	No specific CRC criteria
Yennurajalingam 2012	Thalidomide; phase II	Different advanced cancer types	31 pts; 21 evaluable	>5% weight loss within last 6 months, reporting anorexia, fatigue, and one more symptom (≥3/10 anxiety, depression, or sleep disorders) in last 24 h
Wen *et al.* 2012	Thalidomide; phase II	Different advanced cancer types	108 pts; 93 evaluable	≥5% loss of ideal or pre-illness weight in last 3 months
Goldberg *et al.* 1995	Pentoxifylline; phase II	Different advanced cancer types	70 pts; all evaluable	Weight loss ≥5 lb within last 2 months, or an estimated caloric intake <20 kcal/kg/day
Mehrzad *et al.* 2016	Pentoxifylline; phase II	Different advanced cancer types	70 pts; 64 evaluable	>5% loss of ideal or pre-illness weight in last 2 months
Jatoi *et al.* 2007	Etanercept; phase II	Different advanced cancer types	66 pts; 63 evaluable	Weight loss of ≥2.27 kg within last 2 months and/or an estimated caloric intake <20 kcal/Kg/day
Wiedenmann *et al.* 2008	Infliximab; phase II	Advanced pancreatic cancer	89 pts; 51 evaluable	≥10% premorbid weight loss or ≥5% within last 90 days
Jatoi *et al.* 2010	Infliximab; phase II	Elderly, and/or poor performance status metastatic NSCLC	64 pts; 61 evaluable	No specific CRC criteria
Del Fabbro *et al.* 2013	Melatonin; phase II	Advanced lung or GI cancer	73 pts; 48 evaluable	Appetite score ≥4 on a 0–10 scale (10= worst) and ≥5% weight loss within last 6 months
Rigas *et al.* 2010	Clazakizumab (ALD518); phase II	Advanced NSCLC	124 pts [§]	>5% weight loss within last 3 months; CRP >10 mg/dL
Hichish *et al.* 2017	MABp1; phase III	Metastatic colorectal cancer	333; 309 evaluable	Any weight loss ≤20% in last 6 months or serum IL-6 ≥10 pg/mL plus anorexia, fatigue or pain (EORTC QLQ-C30 >10), and decreased role, emotional, and social function (score <90)

Summary and future research directions

- Nutritional pathology in oesophagogastric cancer effects the **vast majority** of patients, is associated with **poor prognosis** and is **multifactorial**
- **Dietician input** is essential but its exact form needs clarifying (timing of reviews, advice given, supplements offered)
- But nutrition supplementation can only take us so far we need to address the underlying pathology
  - **Multimodal biomarker driven approach**, nutrition, resistance training, anti inflammatory, appetite stimulants

Thank you for listening!