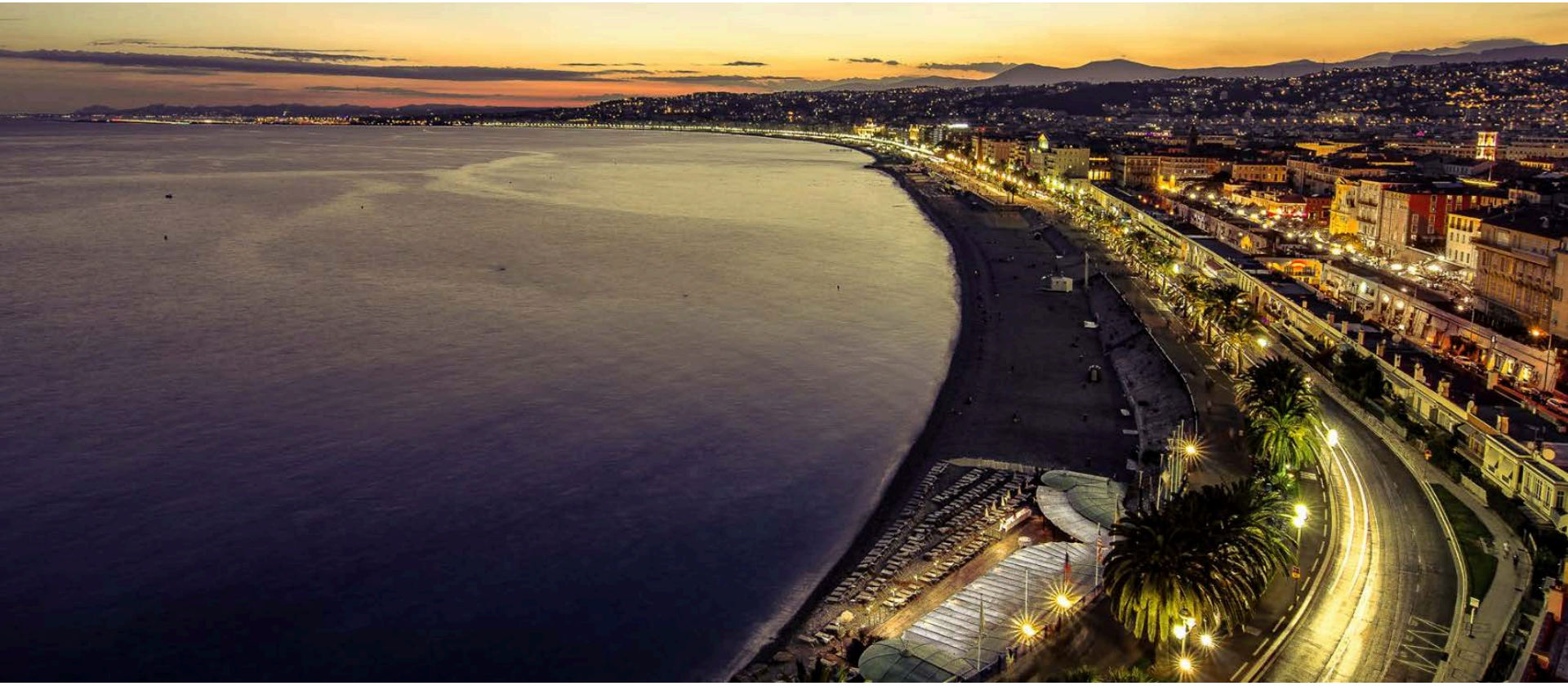
malnutrition matters

BAPEN 2016 Annual Conference

Hilton Brighton Metropole Hotel – 8th & 9th November



Nutrition Nice

Université Nice Sophia Antipolis

Centre Hospitalier Universitaire de Nice

Member of UNIVERSITÉ CÔTE D'AZUR

LUTTE CONTRE LA DÉNUTRITION

LE COLLECTIF DE LUTTE CONTRE LA DÉNUTRITION

Preserving muscle in cancer patients

Stéphane M. Schneider, MD, PhD, FEBGH

Nutrition Nice

Links of interest

- B. Braun
- Baxter
- Danone
- Fresenius-Kabi
- Grand Fontaine
- Nestlé Health Sciences
- Nutricia
- Shire

Cancer cachexia

Consensus findings

Definition and diagnosis

Cancer cachexia is defined as a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism.

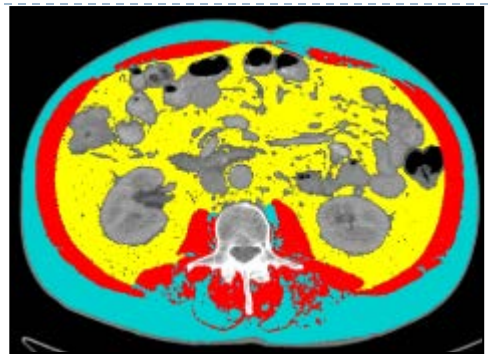
Fearon *et al.* Lancet Oncol 2011

Cancer cachexia

- Involuntary weight loss > 5% over 6 months *or*
- BMI < 20 *and* weight loss > 2% *or*
- "Sarcopenia" defined by:
  - appendicular skeletal muscle mass (M < 7.26 kg/m^2, F < 5.45)
  - *or* mid-arm muscle circumference (M < 32 cm, F < 18)
  - *or* CT-scan lumbar muscle surface (M < 55 cm^2/m^2, F < 39)
  - *or* BIA FFM (H < 14.6 kg/m2, F < 11.4)
  - *and* weight loss > 2%

Fearon *et al.* Lancet Oncol 2011

CT scan imaging for body composition



Subcutaneous adipose tissue

Muscle mass

Perivisceral adipose tissue

-190 -150 -50 -29 0 +150

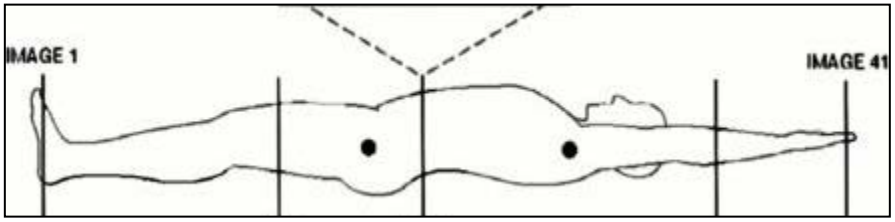
water

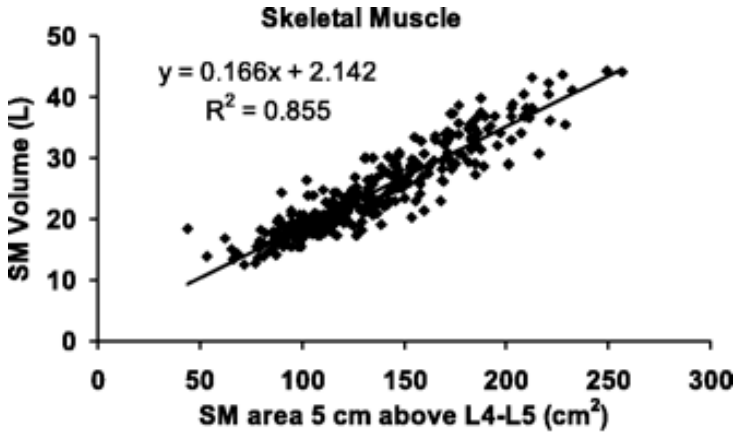
Perivisceral adipose tissue

muscle

Subcutaneous adipose tissue

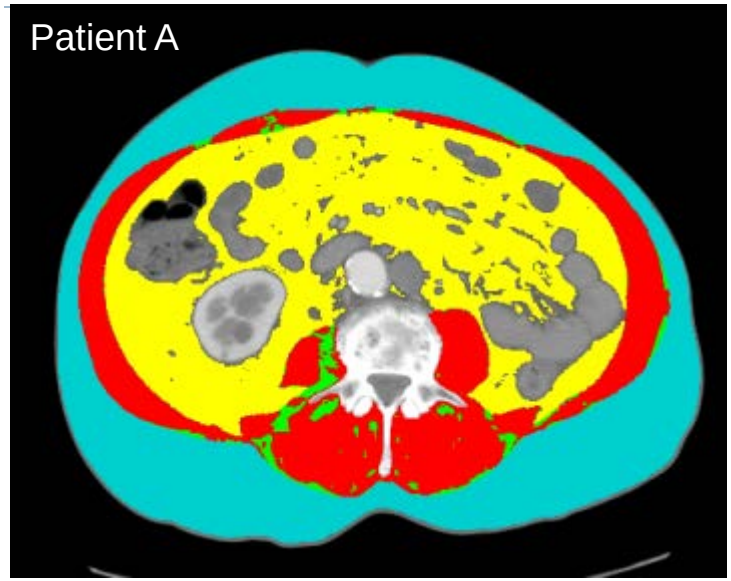
L3 vertebra

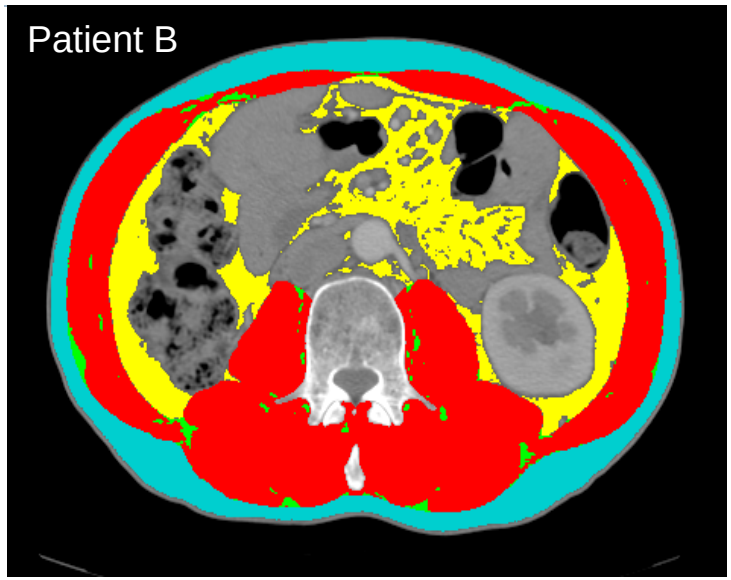




Shen *et al.* J Appl Physiol 2004

CT scan imaging for body composition





Tissue surface measurement in two patients with renal carcinoma with same BMI and BSA

	BMI	BSA	SM	VAT	SAT	Mean density
Patient A	25.5	1.8	131.0	208.4	224.9	36.0
Patient B	25.9	1.9	189.9	75.9	80.6	47.1

BSA: body surface area (m^2); SM: skeletal muscle area (cm^2); VAT: visceral adipose tissue area (cm^2); SAT: subcutaneous adipose tissue area (cm^2);

Prevalence of muscle wasting in cancer

Pancreas Tan, Fearon Clin Cancer Res 2009		
BMI (kg/m^2)	Total	Sarc*
BMI <18.5	11 (10%)	11 (100%)
18.5< BMI <24.9	56 (50%)	33 (59%)
BMI>25	44 (40%)	18 (41%)
* Sarcopenia n (% of total)		

Colon and rectum Lieffers, Baracos Br J Surg 2012		
BMI (kg/m^2)	Total	Sarc*
BMI <18.5	1 (0.5%)	1 (100%)
18.5< BMI <24.9	47 (24%)	28 (60%)
BMI>25	151 (76%)	47 (31%)
* Sarcopenia n (% of total)		

Kidney Antoun, Baracos J Clin Oncol 2010		
BMI (kg/m^2)	Total	Sarc*
BMI <18.5	4 (5%)	4 (100%)
18.5< BMI <24.9	35 (44%)	26 (74%)
BMI>25	41 (51%)	12 (29%)
* Sarcopenia n (% of total)		

Nutrition Nice

Cachexia accounts for 20% of deaths

Table 1 Estimated clinical impact of cachexia in different chronic illnesses in Europe in 2014. Estimates are assumed to be rather conservative

	Prevalence of illness in population (%)	Patients at risk (%)	Prevalence in patients at risk (%)	Absolute number of patients with cachexia[a]	1-year mortality of patients with cachexia (%)
COPD, moderate	3.5	15	35	1.4 m	15–25
Chronic HF, NYHA II–IV	2.0	80	10	1.2 m	20–40
Cancer, all types	0.5	90	30	1.0 m	20–60
Rheumatoid arthritis, severe	0.8	20	10	120,000	5
End-stage chronic kidney disease	0.1	50	50	185,000	20

[a] Assumptions are based on a total population of 742 million in Europe. By comparison, the assumed population of the US is 300 million, and of Japan 100 million

von Haehling and Anker. J Cachexia Sarcopenia Muscle 2014

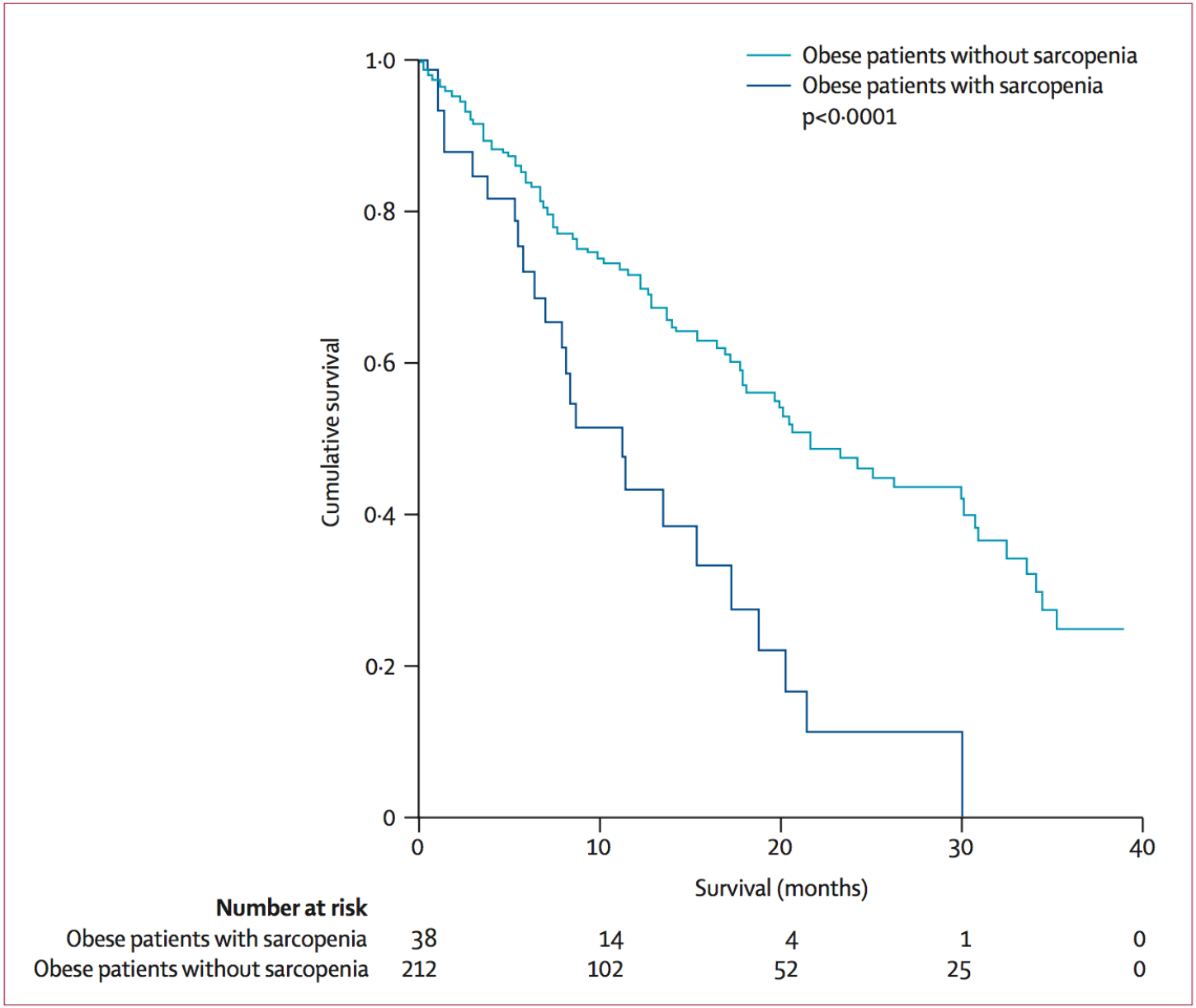
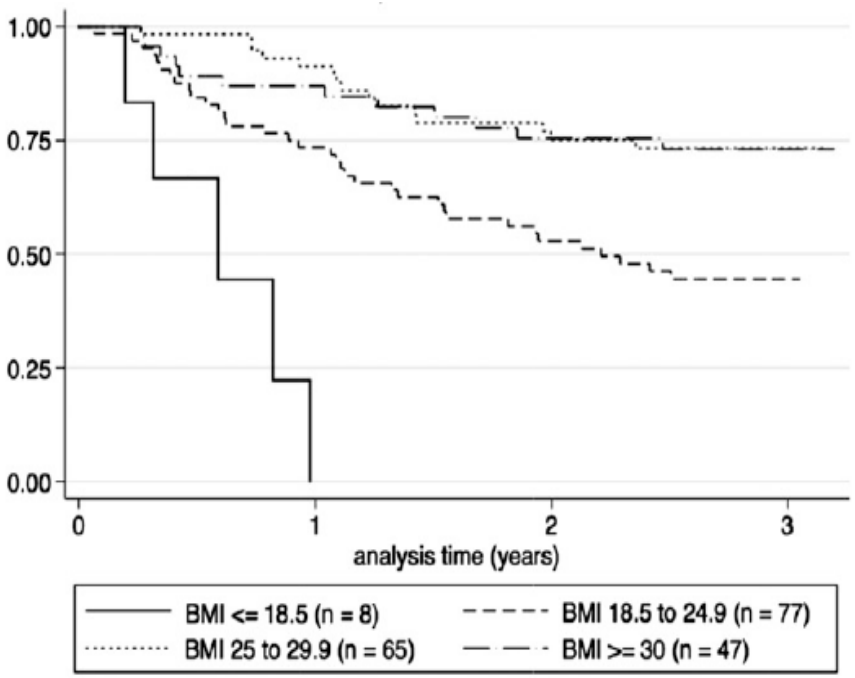


***Figure 3*: Survival of obese patients who had sarcopenia and obese patients who did not have sarcopenia**

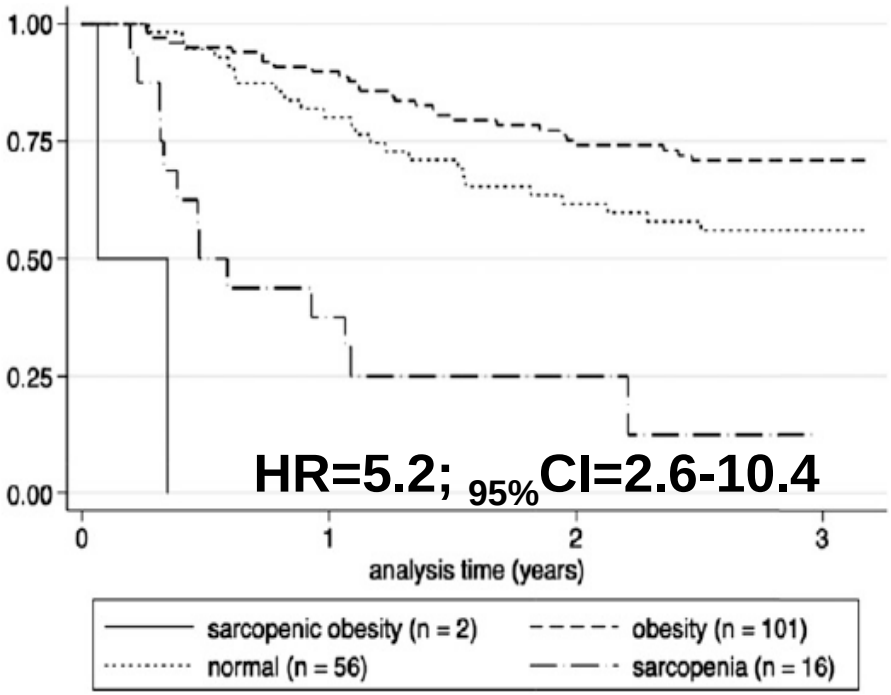
Prado *et al.* Lancet Oncol 2008

Sarcopenic obesity and survival

Kaplan-Meier survival based on BMI



Kaplan-Meier survival based on FMI & FFMI



Gonzalez *et al.* Am J Clin Nutr 2014

Sarcopenia as a determinant of chemotherapy toxicity and time to tumour progression in metastatic breast cancer patients receiving capecitabine

	Sarcopenic n = 14	Non-sarcopenic n = 41	p-value
Anthropometry			
Weight (kg)	65.6 (11.4)	71.4 (16.7)	0.23
BMI (kg/m^2)	24.6 (4.0)	27.8 (5.7)	0.06
BSA (m^2)	1.7 (0.2)	1.8 (0.2)	0.42
Lumbar skeletal muscle index (cm^2/m^2)	35.0 (3.3)	47.4 (5.0)	<0.0001
Whole body lean mass (kg)	34.0 (3.3)	42.5 (5.0)	<0.0001
Treatment			
mg capecitabine / kg FFM	104.2 (16.1)	86.9 (13.7)	<0.0001
Toxicity			
Present	7 (50.0%)	8 (20%)	0.03
Absent	7 (50.0%)	33 (80%)	

Prado *et al.* Clin Cancer Research 2009

Nutrition Nice

Performance Status Definition

ECOG PERFORMANCE STATUS[1]

0. Fully active, able to carry on all pre-disease performance without restriction

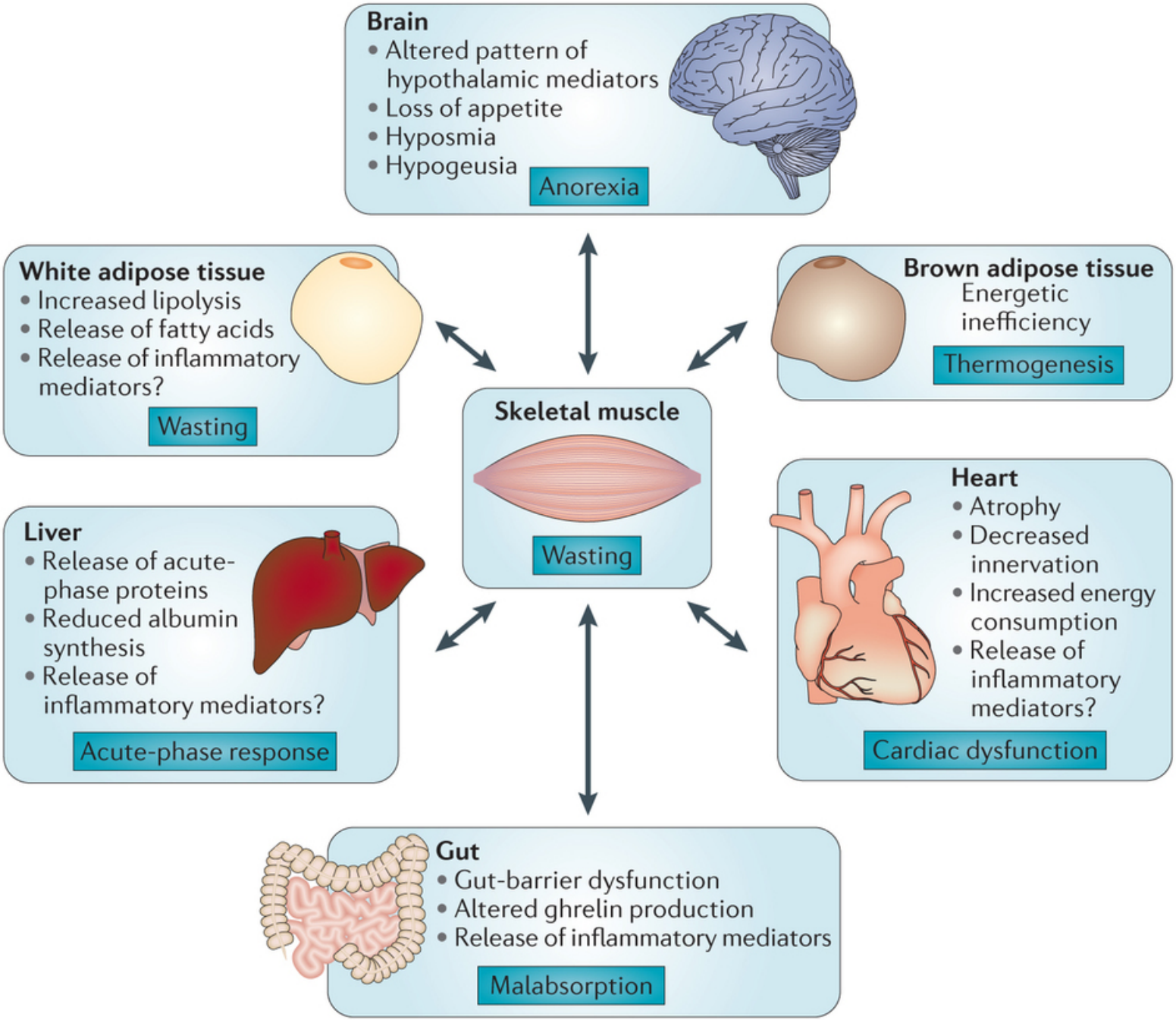
1. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work

2. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours

3. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

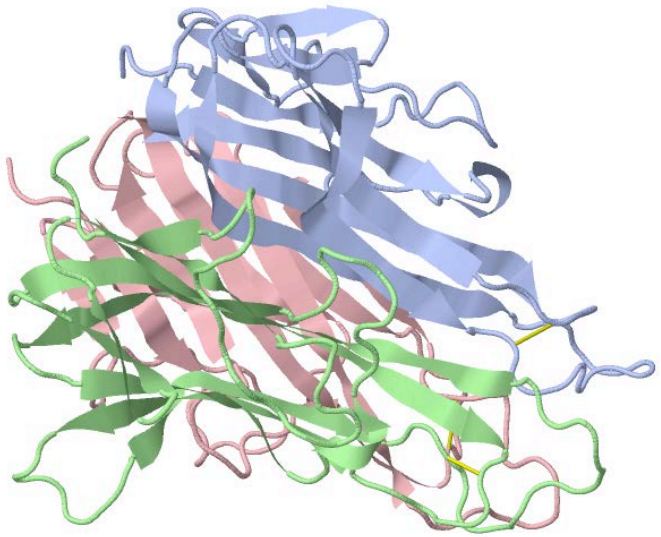
4. Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair

Oken *et al.* Am J Clin Oncol 1982



Argilès *et al.* Nat Rev Cancer 2014

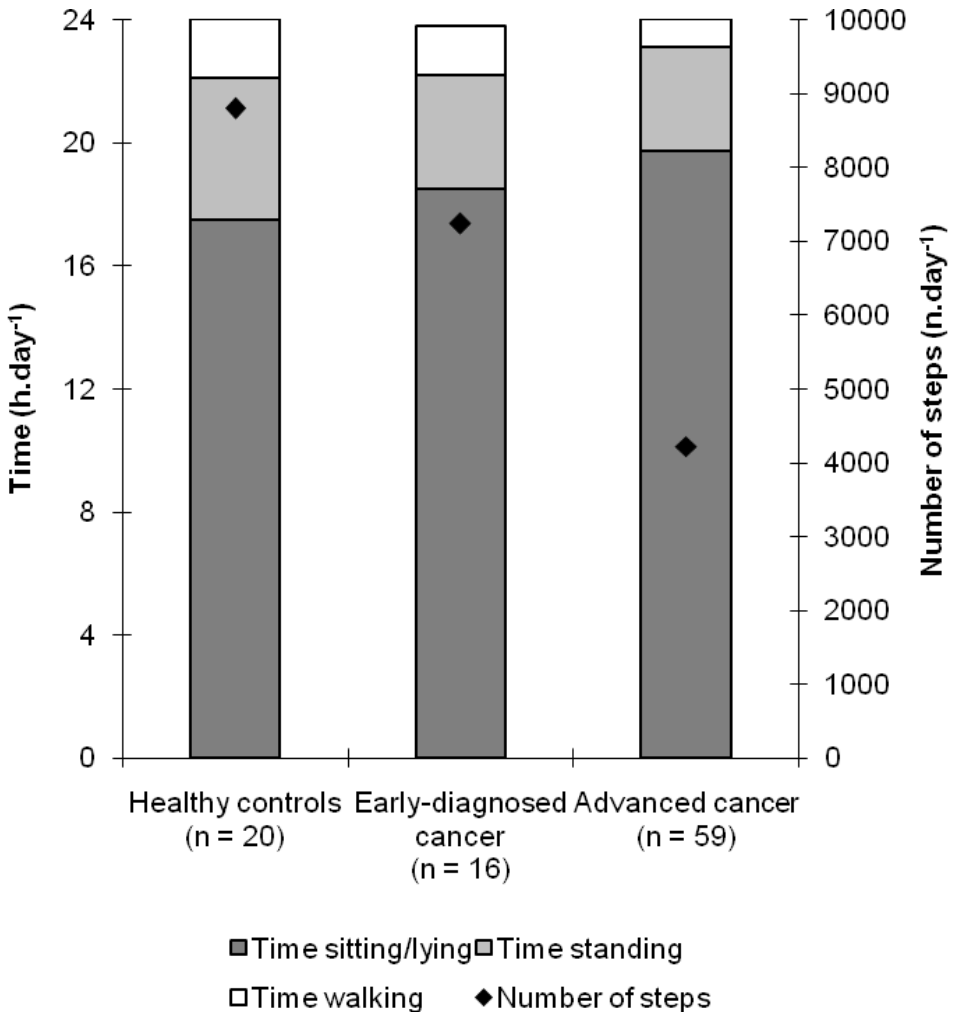
Cachexia mediators



	Animal models	Humans
TNF-α	++	+/–
	Yoshida hepatoma/sarcoma, LLC, Leydig cell tumor, Morris hepatoma	Various types of solid tumors
TRAF-6	+	+
	LLC	Gastric cancer
IL-6	++	+/–
	C26, Morris hepatoma, ApcMin/+	Various types of solid tumors
IL-1	+	+/–
	Methylcholanthrene-induced Sarcoma, Prostate ADK	Various types of solid tumors
INF-γ	+	+/–
	MAC16	Various types of solid tumors
Myostatin/ TGF-ß	++	+
	C26, MAC16	Gastric cancer
PIF	+	+/–
	MAC16	GIT cancers
Angiotensin II	+	+
	C26	NSCLC, congestive heart failure
Ubiquitin-Proteasome system	++	+
	C26, Yoshida hepatoma, LLC	GIT cancers
Autophagy-lysosomal system	+	+
	C26, Yoshida hepatoma, LLC	Lung cancer
IGF-1/Pi3K/Akt/mTOR	+/–	+/–
	C26, ApcMin/+	Various types of solid tumors
MRFs (Myo D, Pax7)	+	+
	C26	Pancreatic cancer

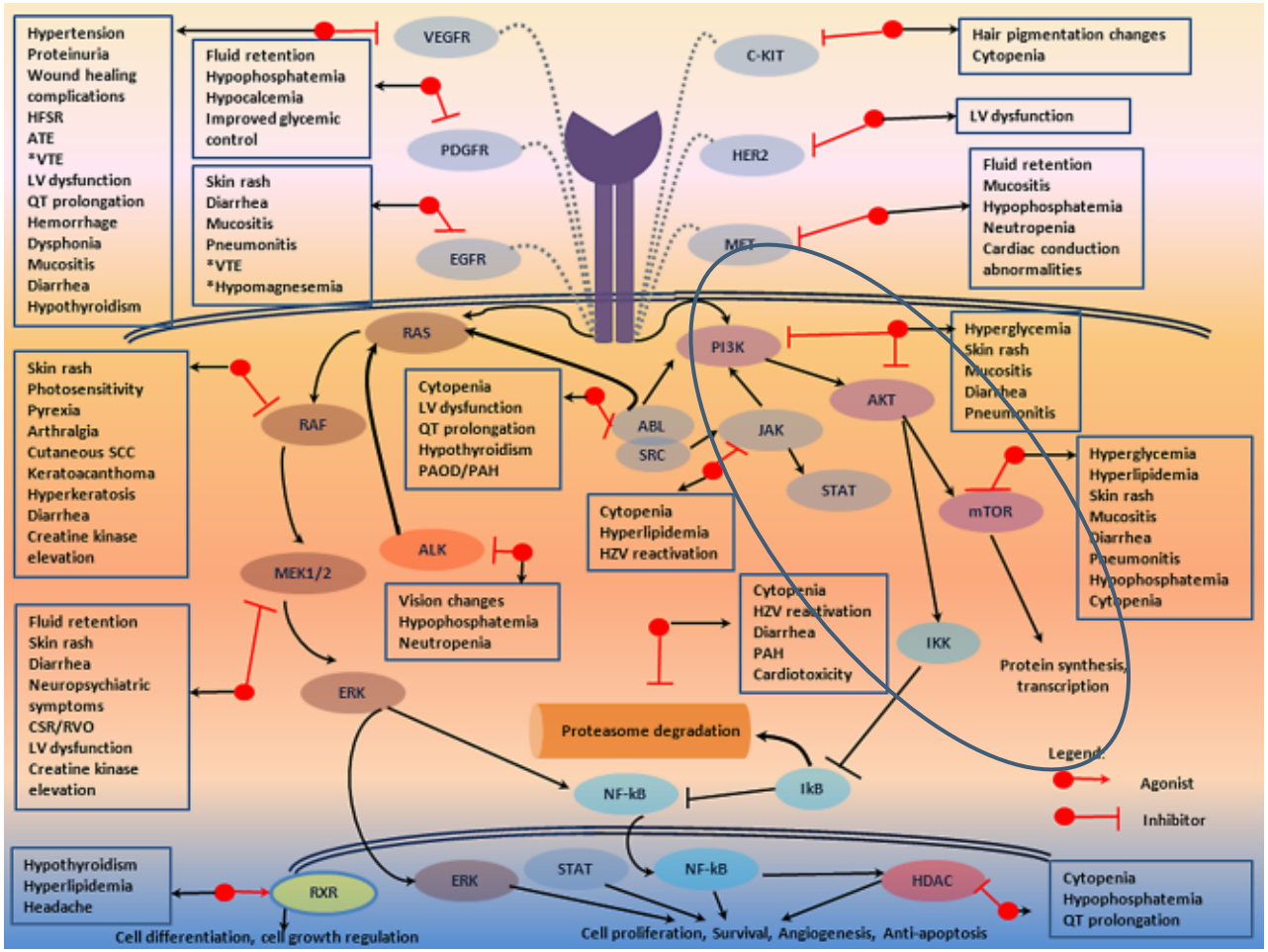
Mueller *et al.* BMC Cancer 2016

Spontaneous physical activity in cancer patients



Ferrioli *et al.* J Pain Symptom Manage 2012

Impact of targeted therapies



Dy and Adjei. CA Cancer J Clin 2013

Impact of targeted therapies

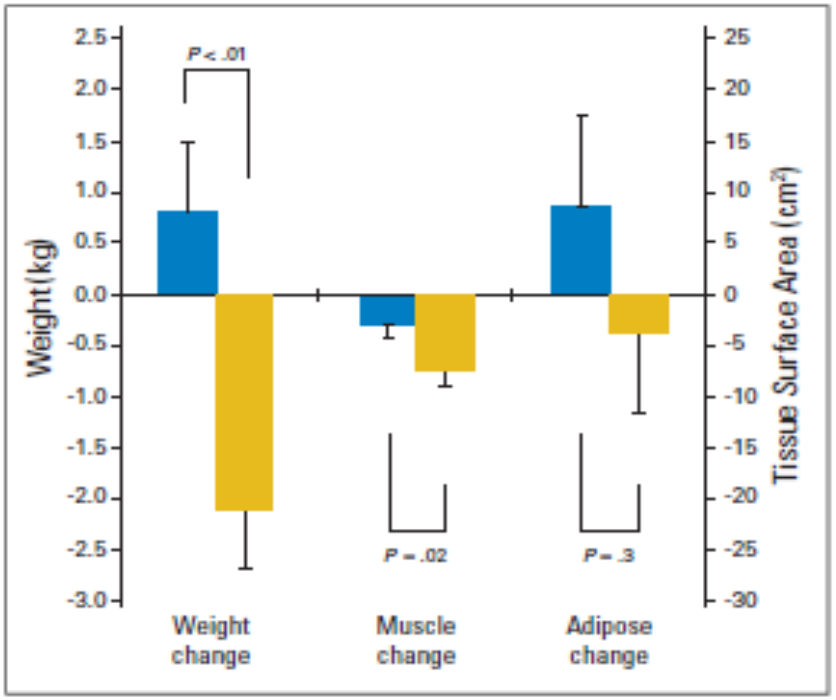


Fig 2. Evolution of body weight, muscle area, and adipose area during 6 months of treatment with sorafenib (gold; n = 48) *v* placebo (blue; n = 32). Statistical indications are for unpaired *t* test were as follows (mean ± SE; black error bars above and below color blocks indicate SE): body weight (in kilograms), 0.8 ± 0.7 *v* −2.1 ± 0.6 ($P < .01$); and skeletal muscle area (in square centimeters), −3.1 ± 1.3 *v* −7.4 ± 1.7 ($P = .02$).

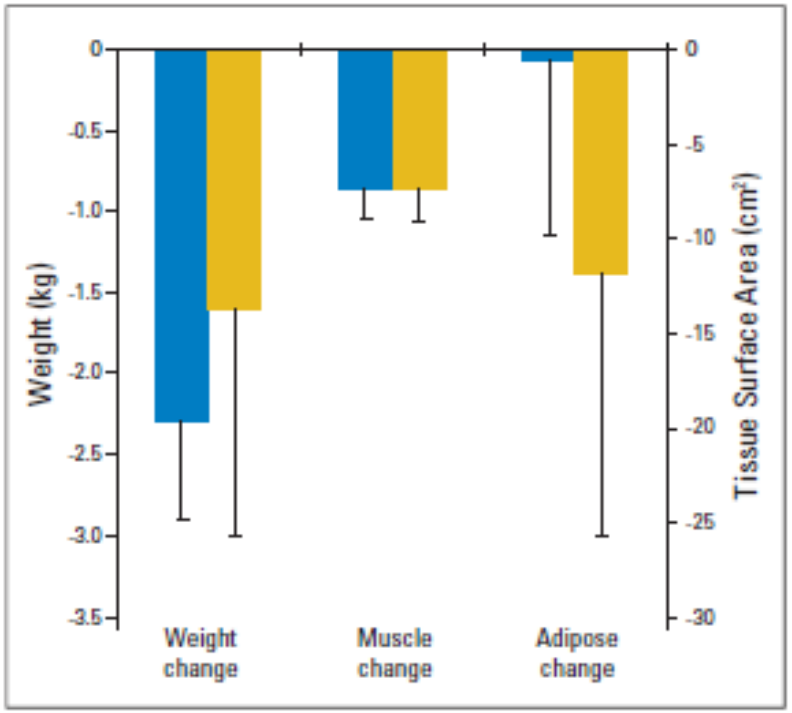
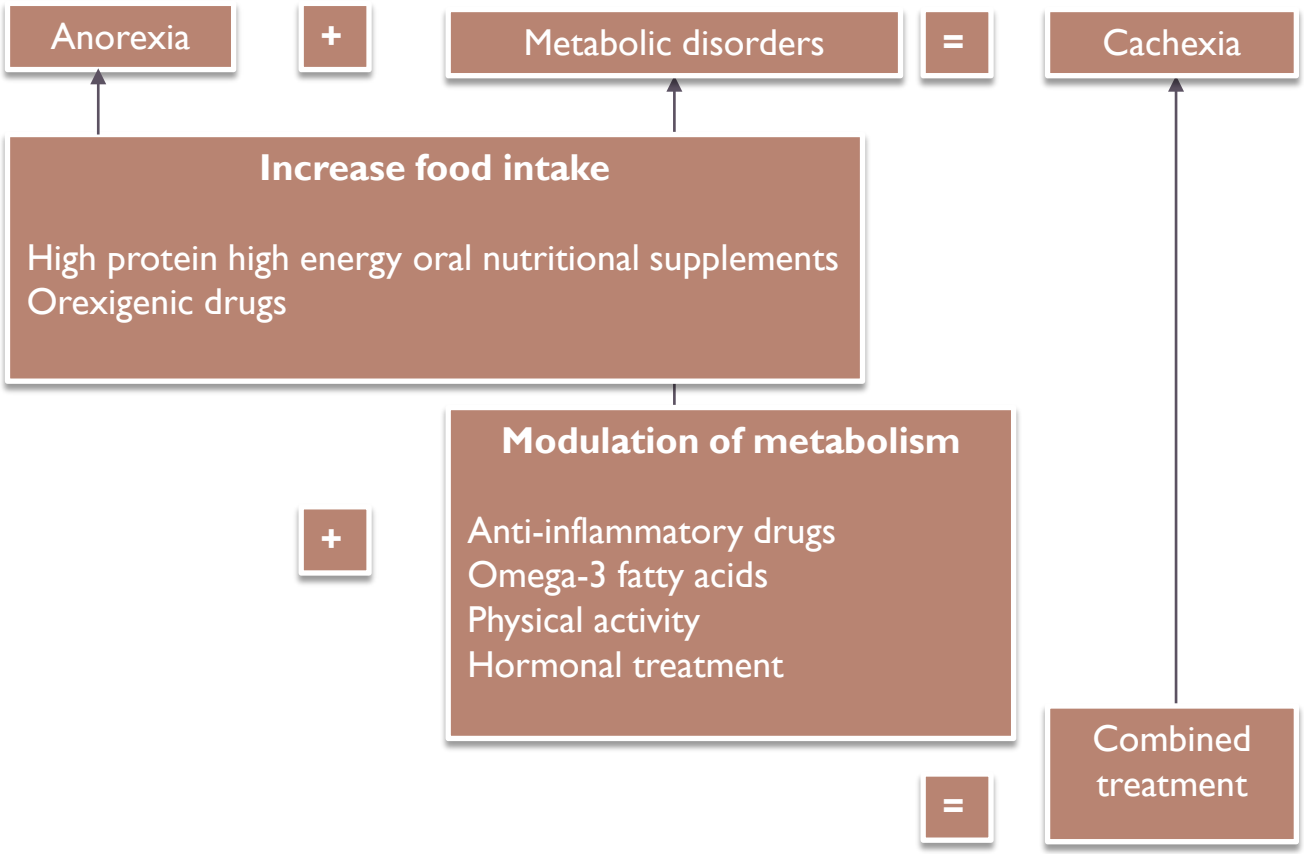


Fig 5. Overall change (mean ± SE; black error bars below color blocks indicate SE) of body weight (kilograms), muscle area, and adipose area (square centimeters) in patients responding to treatment (blue) versus progressive disease (gold). No statistically significant differences were noted ($P > .05$, unpaired *t* test).

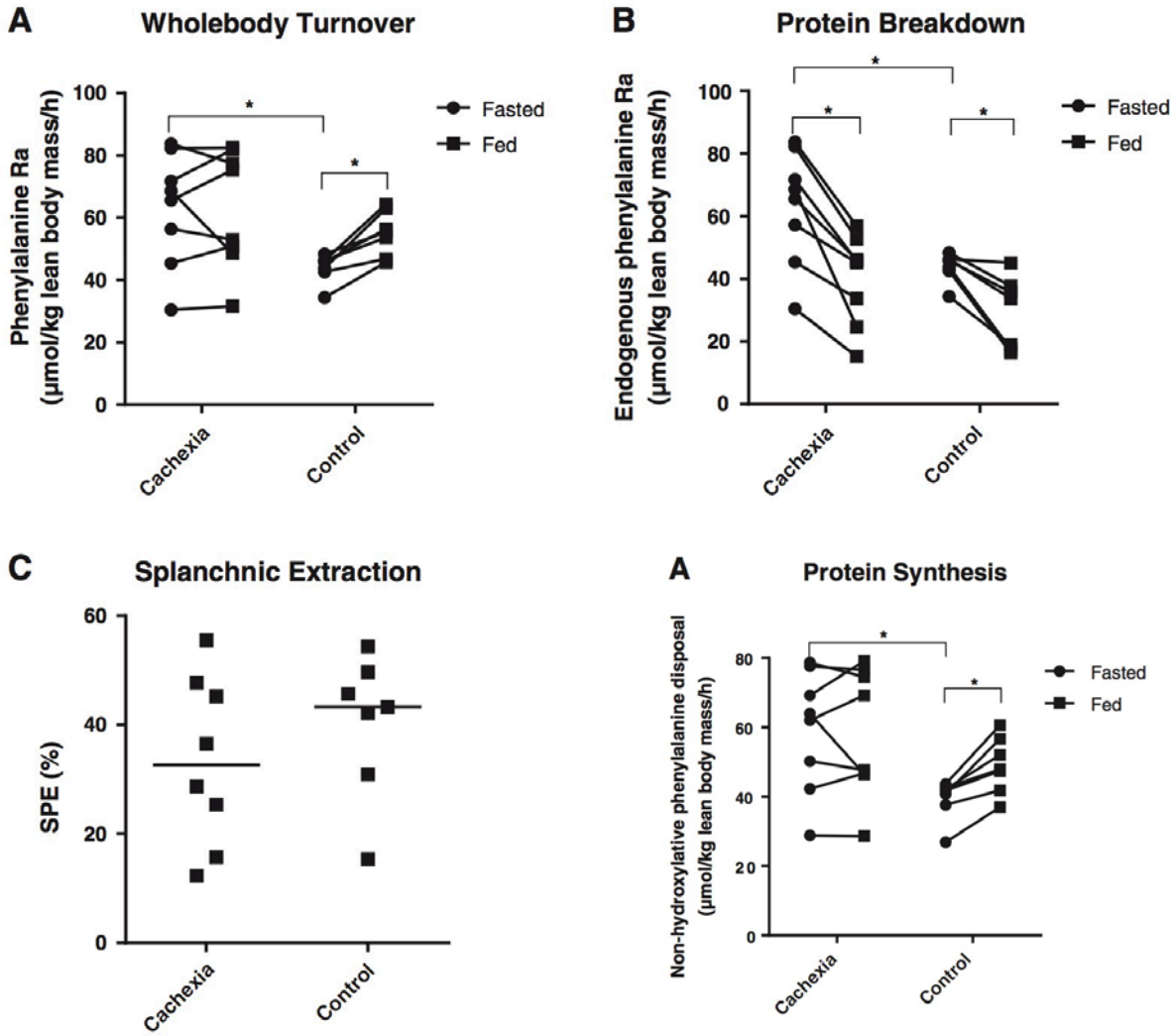
Antoun *et al.* J Clin Oncol 2011

Promoting anabolism in cachexia



Fearon. Clin Nutr 2012

Protein metabolism in 8 cachectic pancreatic cancer patients



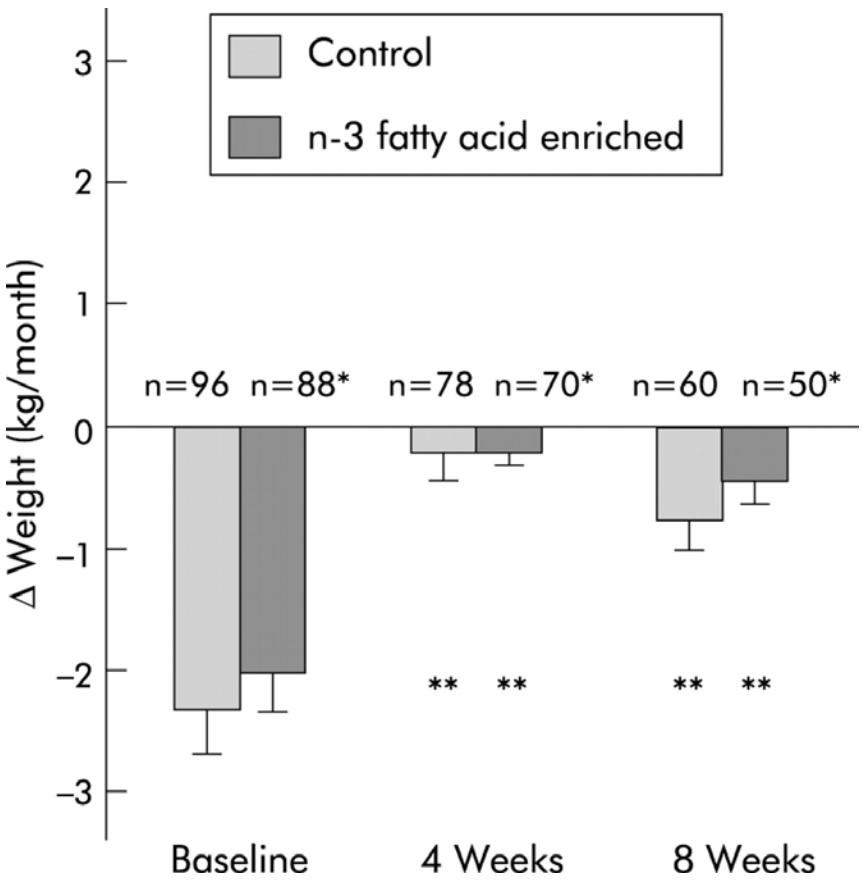
van Dijk *et al.* J Cachexia Sarcopenia Muscle 2015

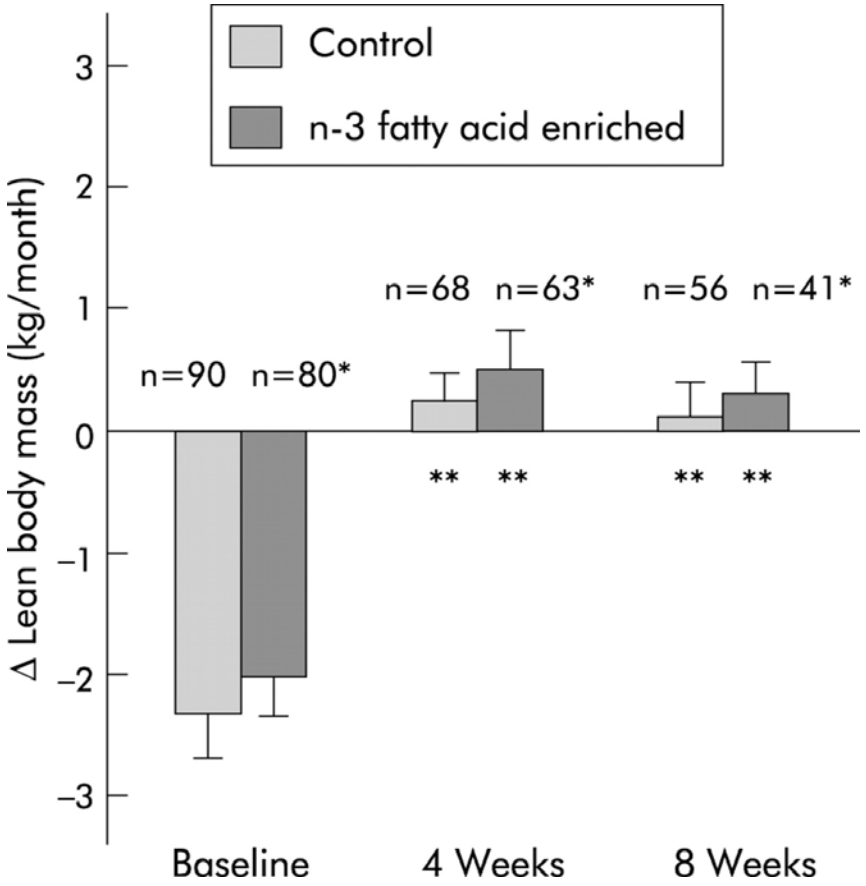
Omega-3 PUFA in cancer

- 200 patients with advanced pancreatic cancer, losing 3.3 kg/month
- Supplement bringing in 480 mL 620 kcal and 32 g proteins
  - 2.2 g EPA + vitamins A, C, E and Se
  - Controls
- Follow-up at 4 and 8 weeks
- Actual intake: 1.5 g EPA per day

Fearon *et al.* Gut 2003

Evolution of weight and FFM

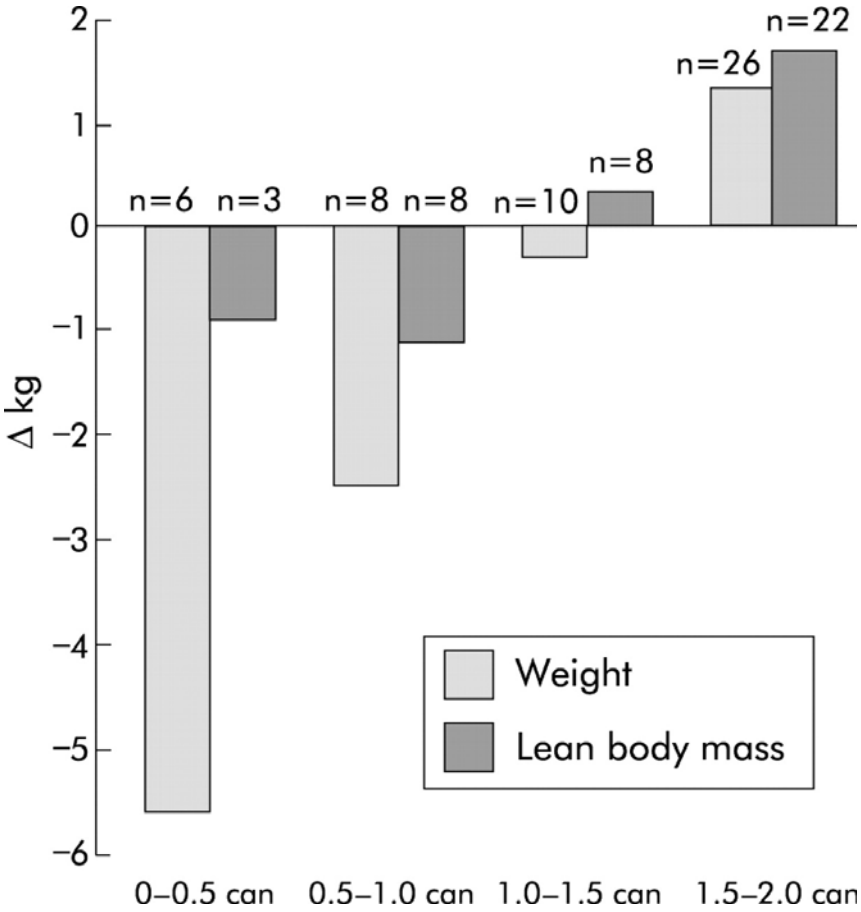


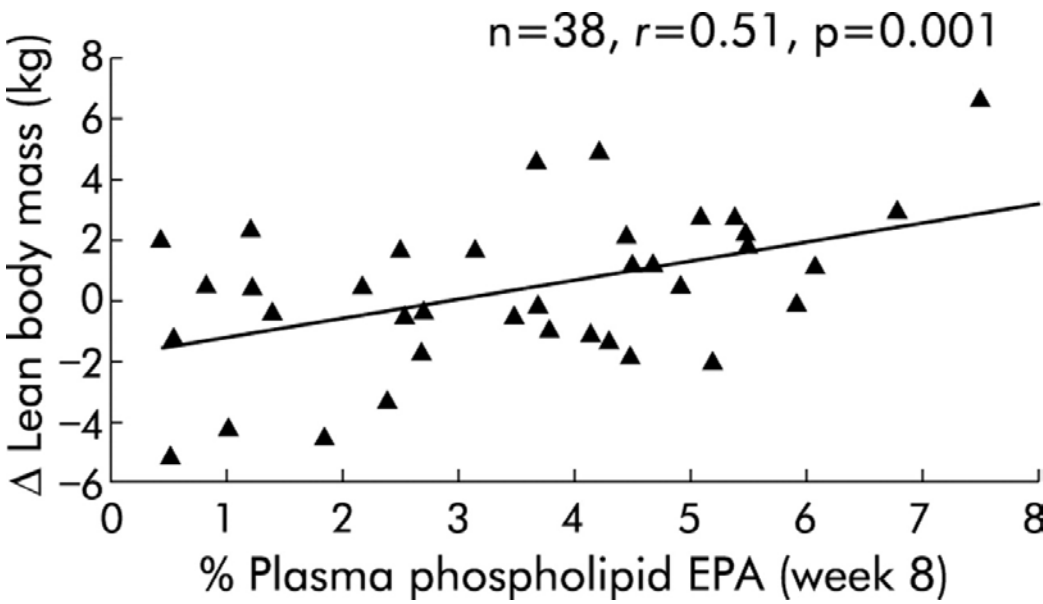


** P<0.001 vs D0

Fearon *et al.* Gut 2003

However…

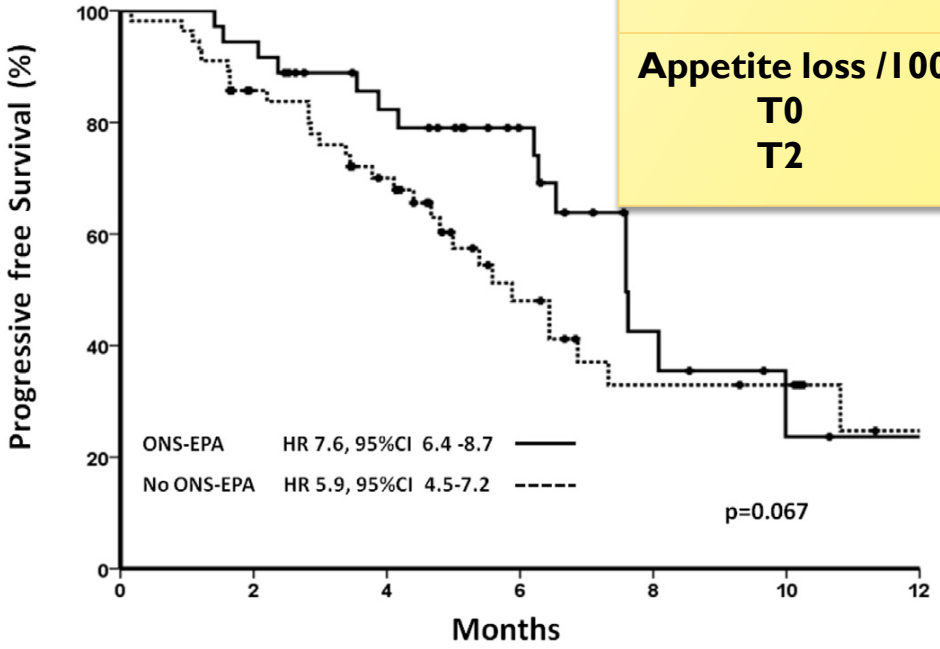




Fearon *et al.* Gut 2003

Omega-3 PUFA in lung cancer

	Controls	n-3	p
LBM (BIA) kg			
T0	43.9±14	36.2±10	0.01
T2	42.0±13	37.8±9	
Protein intake g/d			
T0	69.5±32	62.2±31	<0.001
T2	57.5±29	62.3±48	
Appetite loss /100			
T0	36.8±34	41.5±34	0.05
T2	28.2±30	34.9±31	



92 patients with stage III-IV NSCLC
(60 years-old, weight loss 8%)
Standard ONS vs n-3 (0.5 mg/mL)
and antioxidant-enriched ONS

Sanchez-Lara *et al.* Clin Nutr 2014

Omega-3 PUFA in lung cancer

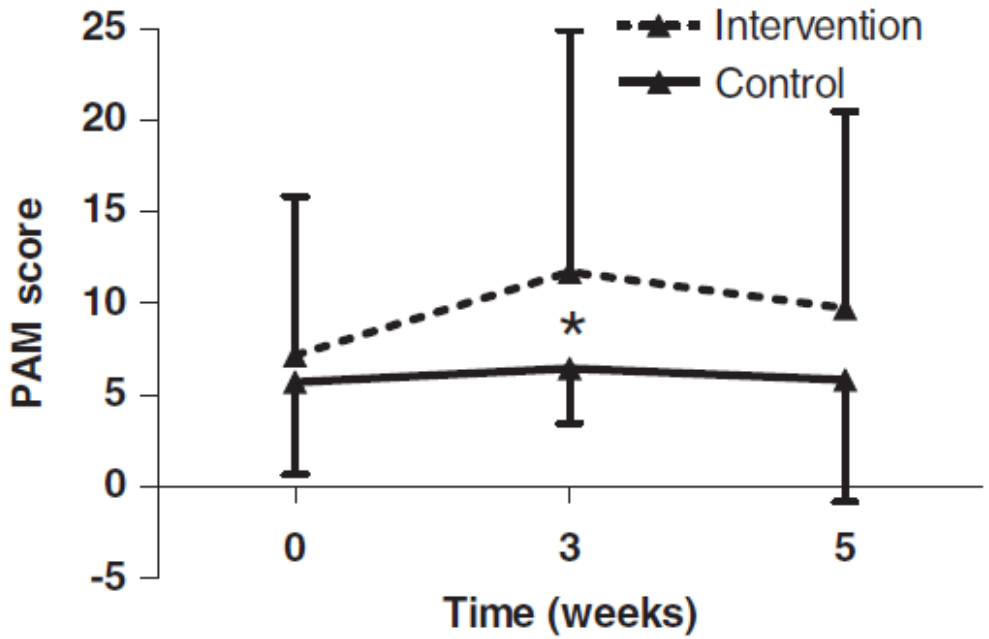
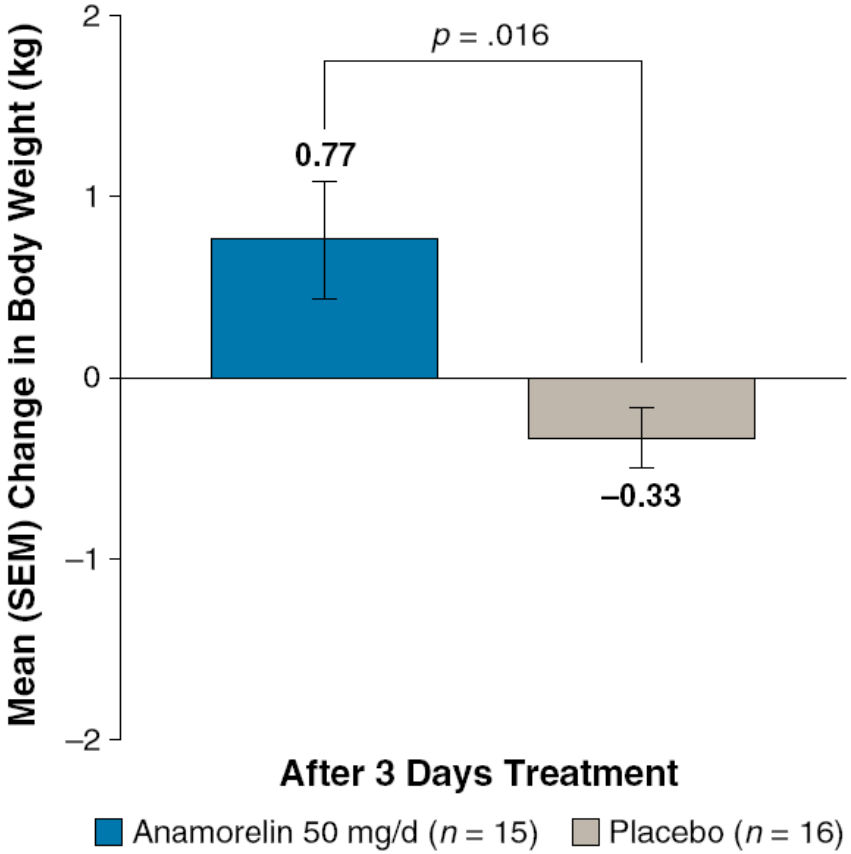


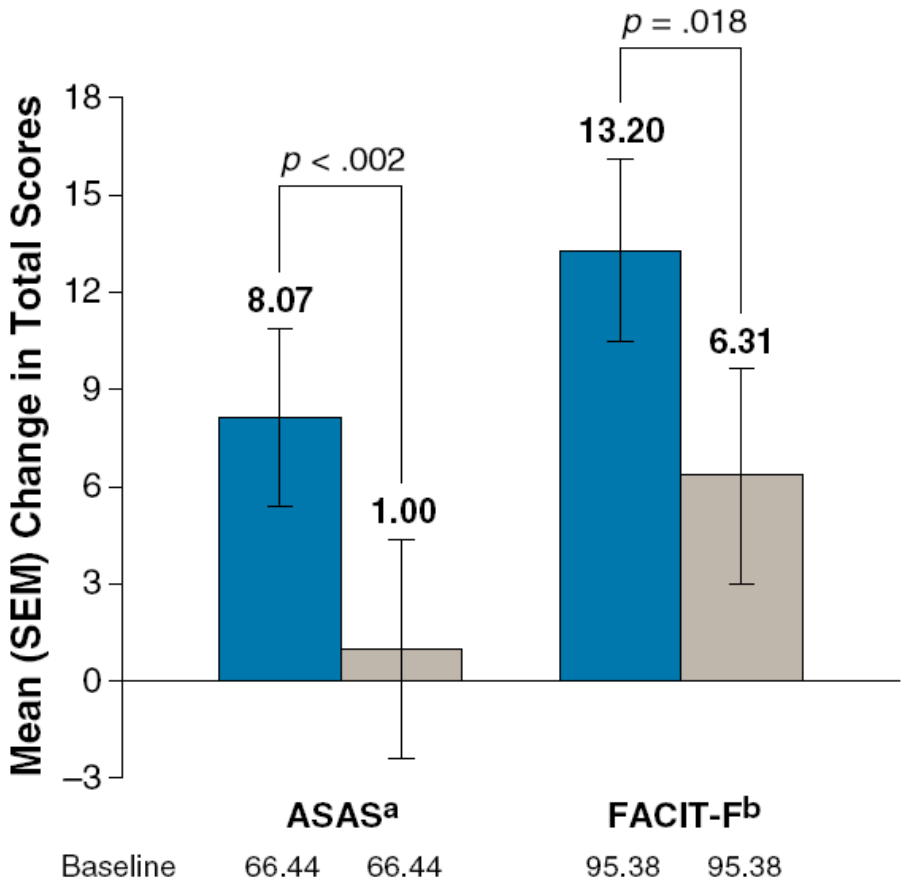
Figure 1. Physical activity (daily PAM score) over time for the I and C groups. Values are mean ± s.d., baseline: $n = 12$ (I), $n = 16$ (C); week 3: $n = 13$ (I) and $n = 17$ (C); week5: $n = 8$ (I), $n = 13$ (C). $^*P < 0.05$, difference between the I and C group (analysed by generalised estimating equations, with baseline value and sex as covariate).

van der Meij *et al.* Eur J Clin Nutr 2012

Anamorelin

16 patients with locally advanced or metastatic cancer (62 years-old, 6/16 with weight loss> 15%)
Cross-over trial between anamorelin 50 mg/d for 3 days and placebo.

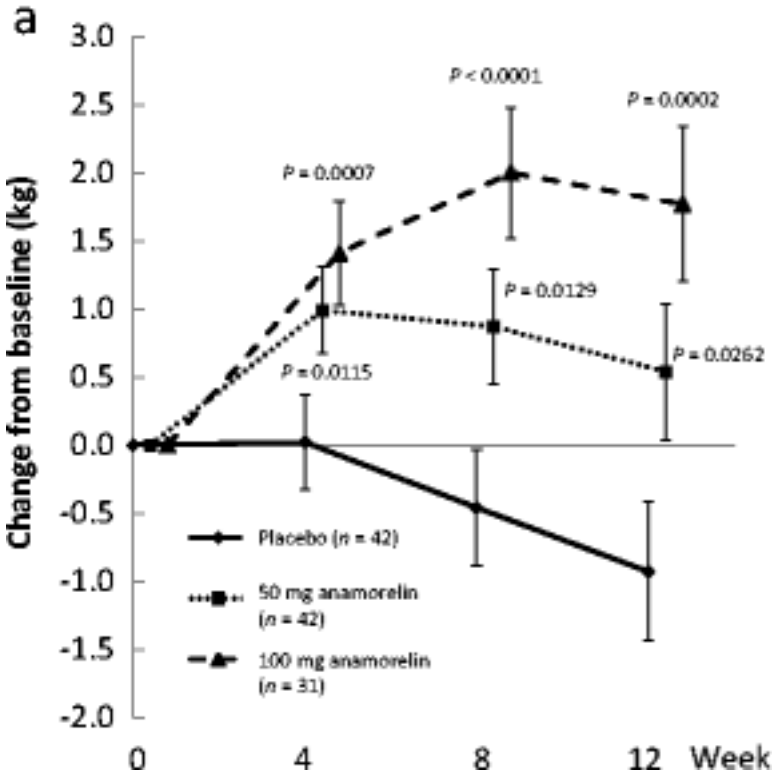




Garcia *et al.* Support Care Cancer 2012

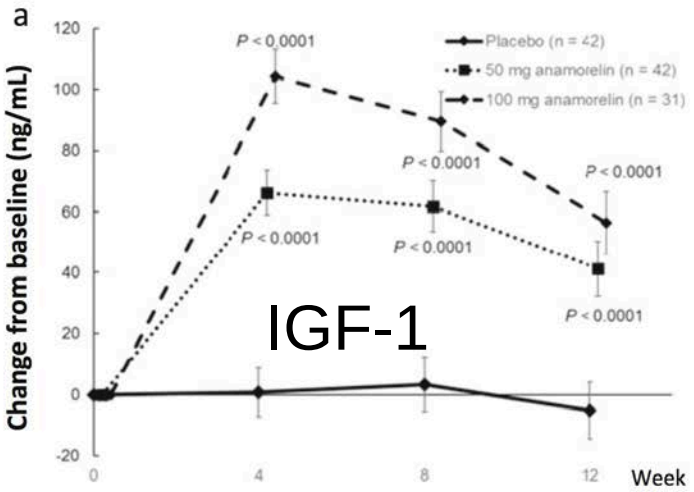
Anamorelin

- 181 patients with NSCLC and cachexia (weight loss ≥ 5% over 6 months)
- Placebo, 50 mg or 100 mg anamorelin PO
- Weight and KPS gains higher in the 100 mg group
- No effect on muscle strength

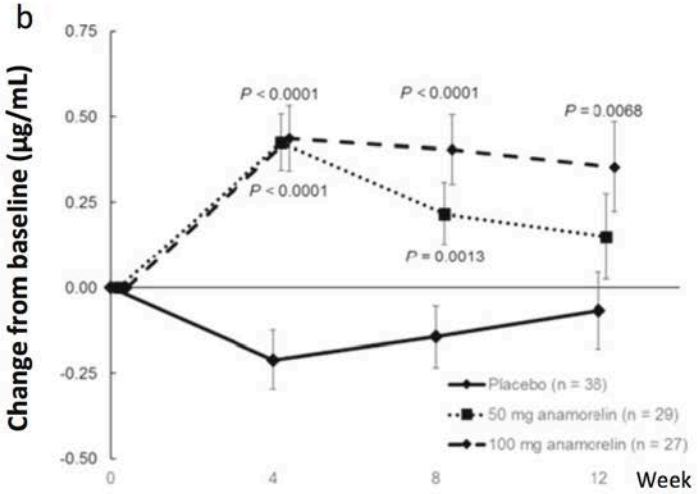


Takayama *et al.* Support Care Cancer 2016

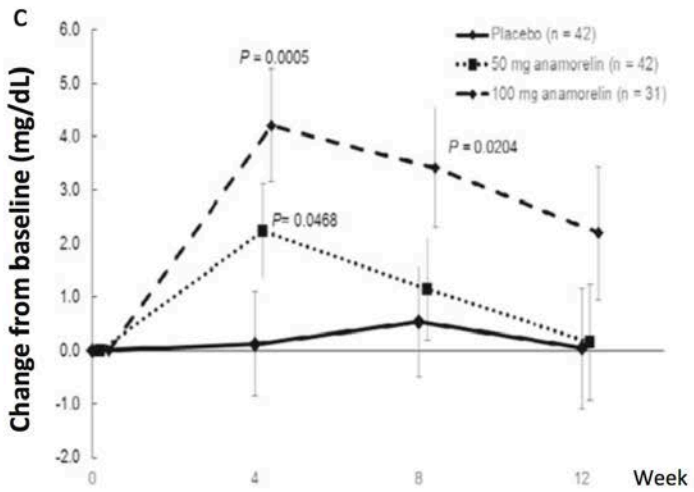
Anamorelin



IGF-1



TTR



IGFBP-3

Takayama *et al.* Support Care Cancer 2016

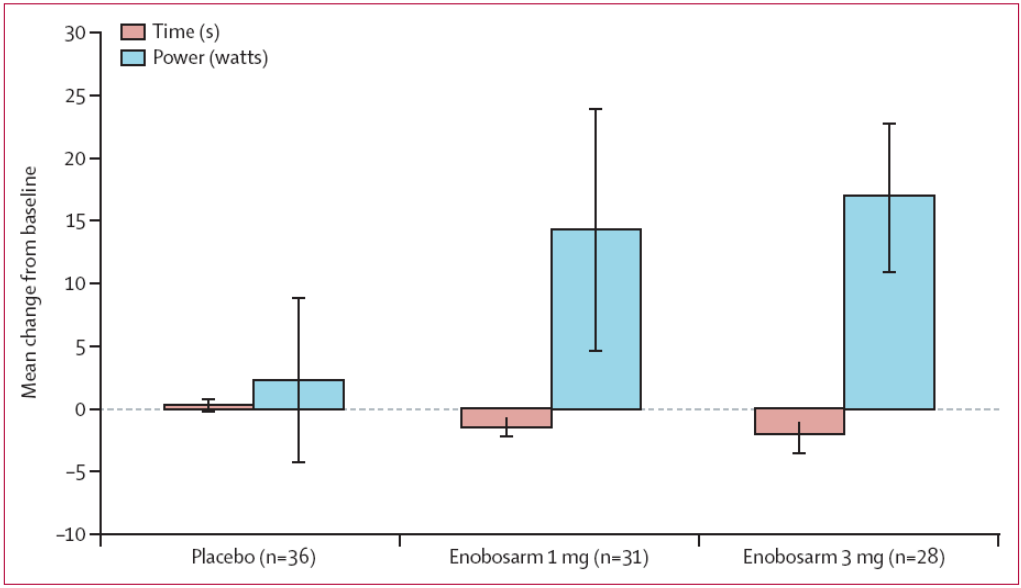
Enobosarm

159 precachectic SCLC patients (66-years old)
Placebo vs. Enobosarm 1 mg vs. Enobosarm 3 mg for 113 days

	Placebo	Enobosarm 1 mg	Enobosarm 3 mg
N	34	32	34
Mean (SD), kg	0·1 (2·7)	1·5 (2·7)	1·3 (3·5)
Median (range), kg	0·02 (−5·8 to 6·7)	1·5 (−2·1 to 12·6)	1·0 (−4·8 to 11·5)
p value*	0·88	0·0012	0·046

These analyses were done for patients for whom efficacy data were evaluable; no adjustments have been made for missing data. p value for enobosarm 1 mg vs placebo is 0·066; for enobosarm 3 mg vs placebo is 0·041. *p values are from an exact Wilcoxon signed rank test.

***Table 2*: Change in total lean body mass at day 113 or end of study compared with baseline**



Improved quality of life
No effect on tumour progression

Dobs *et al.* Lancet Oncol 2013

Combined treatment

332 cancer patients (WL > 5%) – assessment after 4 months of treatment with:
Arm 1: megestrol 320 mg/d; Arm 2: ONS n-3 2-3/d; Arm 3: L-carnitin 4g/d; 4: thalidomide 200 mg/d; Arm 5: 1+2+3+4

Table 2. Comparison of primary efficacy endpoints among arms 3, 4, and 5 by ANOVA

Primary efficacy endpoint	Arm 3 Mean ± SD (95% CI)	Arm 4 Mean ± SD (95% CI)	Arm 5 Mean ± SD (95% CI)	p^a
LBM				
BIA	−0.52 ± 3.14 (−1.2 to 0.18)	−0.02 ± 3.34 (−0.8 to 0.8)	0.44 ± 3.1 (−0.16 to 1.04)	.144
DEXA	−0.7 ± 2.2 (−1.2 to −0.2)	−0.8 ± 2.6 (−1.5 to −0.2)	2.1 ± 2.1 (1.6 to 2.7)	**.007**
REE	12.08 ± 246 (−47.9 to 72.08)	−21.8 ± 241.9 (−90.6 to 46.9)	−133 ± 259 (−200 to −65.4	**.028**
Fatigue	0.85 ± 19.5 (−3.6 to 5.3)	−1.55 ± 15.4 (−5.4 to 2.3)	−7.5 ± 12.8 (−10.4 to −4.6)	**.035**

No difference in quality of life (QLQ-C30 and EQ-5D)
Improvement of appetite, physical activity and ECOG scores

Mantovani *et al.* Oncologist 2010

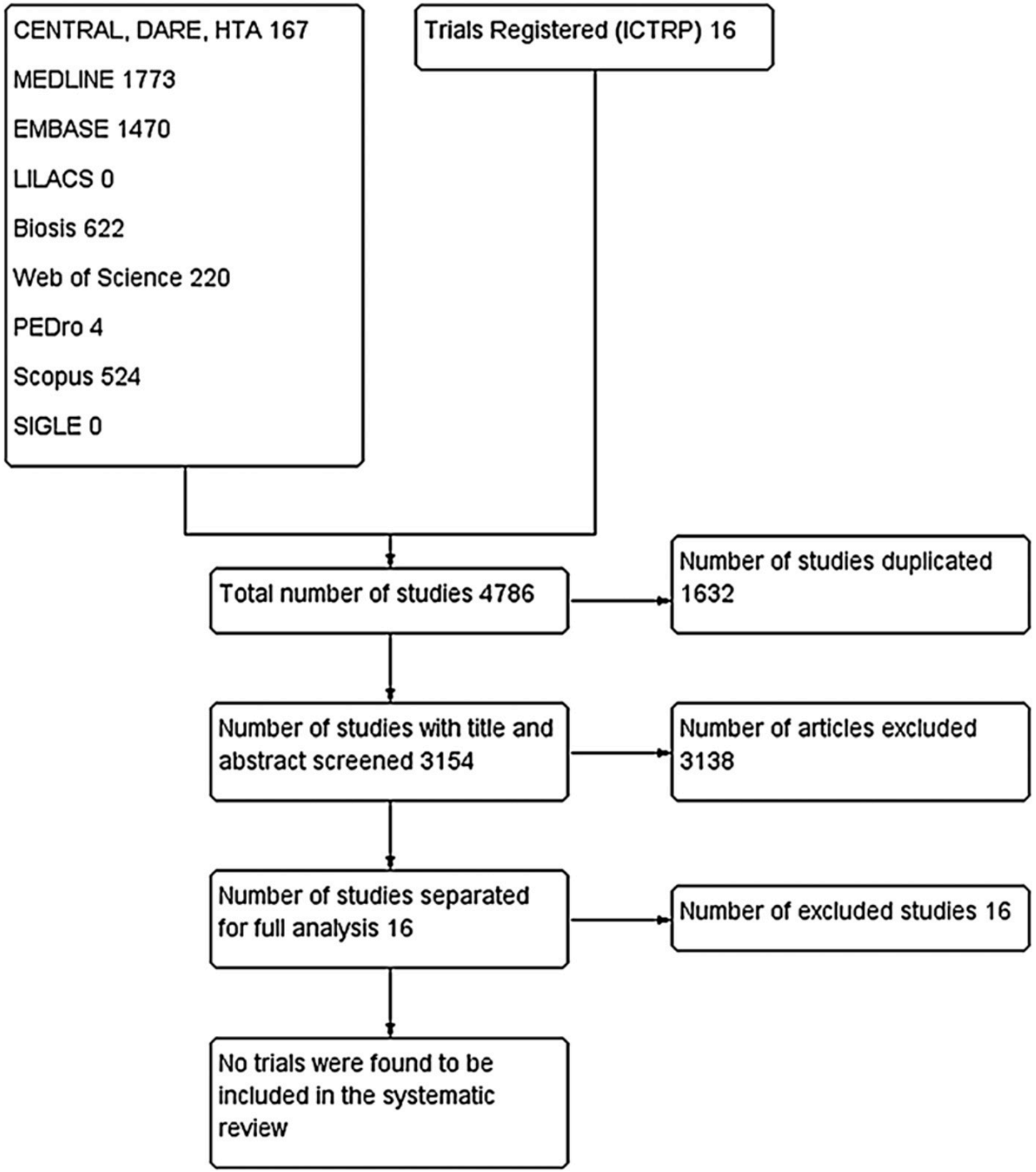
Nutrition Nice

Promising pharmacological agents

Agent	Mechanism of action	Physiological effects	References
Anamorelin	Ghrelin receptor agonist	Appetite-enhancing and anabolic activity	Garcia et al. 2015
Bimagrumab	Anti-ActRII monoclonal antibody	Prevent skeletal muscle atrophy	Lach-Trifilieff et al. 2014
Clazakizumab	Anti-IL-6 monoclonal antibody	Anti-inflammatory activity	Bayliss et al. 2011
Enobosarm	Selective androgen receptor modulator	Anabolic activity	Dobs et al. 2013
IP-1510	IL-1 receptor antagonist	Anti-inflammatory activity	Paspaliaris et al. 2011
MABp1	Anti-IL-1α monoclonal antibody	Anti-inflammatory and anti-neoplastic activity	Hong et al. 2014
REGN1033	Myostatin antagonizing antibody	Prevents skeletal muscle atrophy	Ebner et al. 2014

Petruzzelli and Wagner. Genes Dev 2016

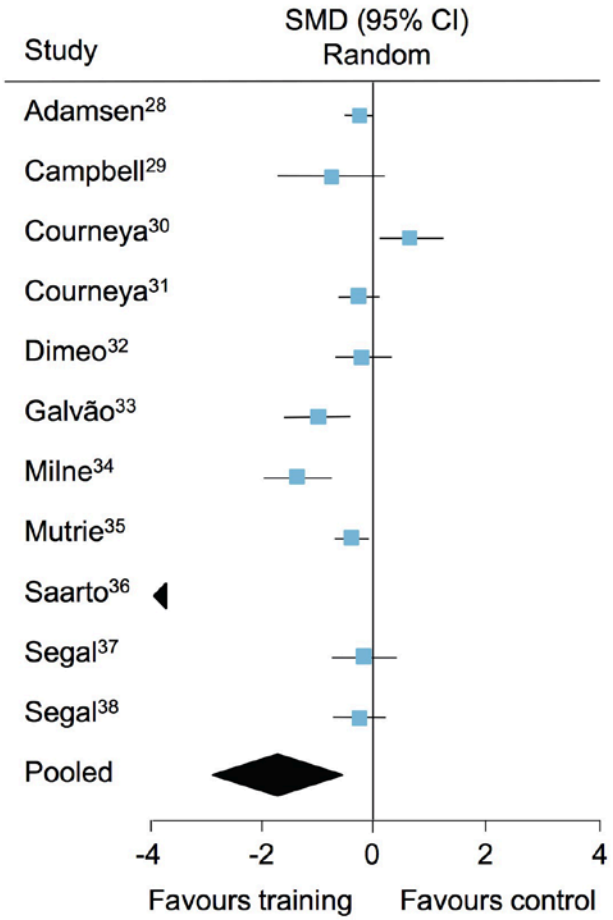
Coch exia



eviews 2014

Effects of supervised physical activity on cancer-related fatigue

- Mostly survivors
- No cachexia assessment
- Increased lean body mass
- Effective on: immune function, insomnia, anxiety, depression, pain, cognitive impairment, reduced quality of life



Meneses-Echávez *et al.* J Physiother 2015

12-week exercise in prostate cancer patients

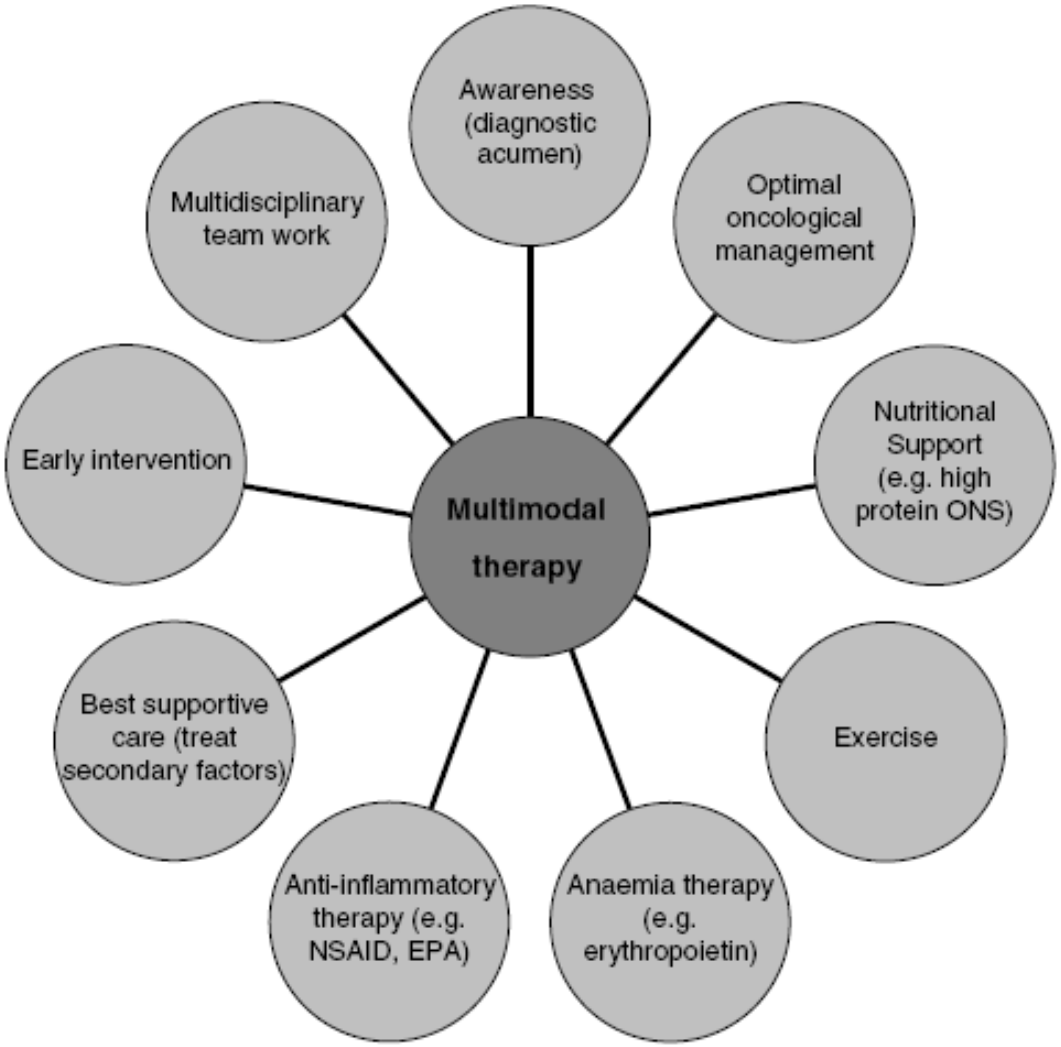
Variable	Mean change (95 % CI)		Mean intervention effect (95 % CI)		
	Intervention ($n = 53$)	Control ($n = 66$)	Intervention—control	p^a	$p_{adj}{}^b$
Fitness and physical function					
6-min walk distance (m)	64.87 (49.76, 79.99)	14.89 (0.47, 29.31)	49.98 (28.54, 71.42)	<0.0001	0.001
Leg—1 repetition maximum (kg)	28.54 (21.54, 35.54)	6.72 (−0.06, 13.49)	21.82 (12.15, 31.49)	<0.0001	0.001
Chest—1 repetition maximum (kg)	10.05 (7.30, 12.80)	3.14 (0.59, 5.69)	6.91 (3.31, 10.51)	<0.0001	0.001
30-s sit-to-stand (reps)	3.89 (2.80, 4.99)	0.51 (−0.54, 1.56)	3.38 (1.87, 4.89)	<0.0001	0.001
Reach distance (cm)	3.17 (0.92, 5.41)	−1.63 (−3.71, 0.45)	4.80 (1.77, 7.82)	0.002	0.024
Anthropometrics					
Body mass index (kg/m^2)	−0.02 (−0.24, 0.20)	0.05 (−0.15, 0.24)	−0.07 (−0.36, 0.23)	0.654	0.788
Chest circumference (cm)	−0.75 (−1.66, 0.16)	−0.01 (−0.82, 0.79)	−0.74 (−1.96, 0.49)	0.238	0.788
Waist circumference (cm)	−1.06 (−2.21, 0.10)	0.06 (−0.98, 1.09)	−1.11 (−2.68, 0.46)	0.165	0.788
Hip circumference (cm)	−1.40 (−2.35, −0.46)	0.25 (−0.61, 1.11)	−1.65 (−2.95, −0.35)	0.013	0.143
Right thigh circumference (cm)	0.55 (−0.15, 1.25)	0.24 (−0.42, 0.90)	0.31 (−0.65, 1.27)	0.526	0.728
Left thigh circumference (cm)	0.66 (−0.03, 1.34)	0.35 (−0.27, 0.97)	0.31 (−0.64, 1.25)	0.523	0.788
Right arm circumference (cm)	−0.39 (−0.99, 0.21)	−0.28 (−0.81, 0.25)	−0.11 (−0.92, 0.70)	0.788	0.788
Left arm circumference (cm)	−0.34 (−0.92, 0.25)	−0.20 (−0.72, 0.32)	−0.14 (−0.93, 0.65)	0.733	0.788

Gaskin *et al.* J Cancer Surviv 2016

8-week exercise in advanced cancer patients

- 23 patients with a life expectancy ≤ 2 years
- Randomised to exercise or usual follow-up
- Lost to follow-up in 36% and 23% of the intervention and control groups
- No effects on fatigue
- Improvement of shuttle walk test and handgrip strength in the exercise group

Oldervoll *et al*. Oncologist 2011



MENAC: The Multimodal Exercise/Nutrition/Anti-inflammatory treatment for Cachexia trial

MENAC is a large-scale open randomised phase III, multimodal intervention trial.

Fearon. Eur J Cancer 2008

Nutrition Nice

Summary

- Cachexia: not only muscle, but muscle wasting linked to complications
- Complex pathophysiology
- Cachexia therapy should be integrated in overall oncology management
- Nutrition, exercise and drugs
- Professionals need adequate knowledge on nutrition and exercise
- Goals should be realistic
- Multimodal care pathways are self-evident but still to be evidence-based

Nutrition Nice