

Cancer related cachexia and anorexia syndrome

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Cachexia – kakos hexis
"bad condition"

Anorexia – an-orexis
"absence of appetite"



Cancer cachexia

- A multifactorial condition
- Ongoing **loss of skeletal muscle mass** (+/- loss of fat mass)
- Cannot be fully reversed by conventional nutritional support
- Leads to progressive functional impairment

Fearon et al., Lancet Oncol, 2011

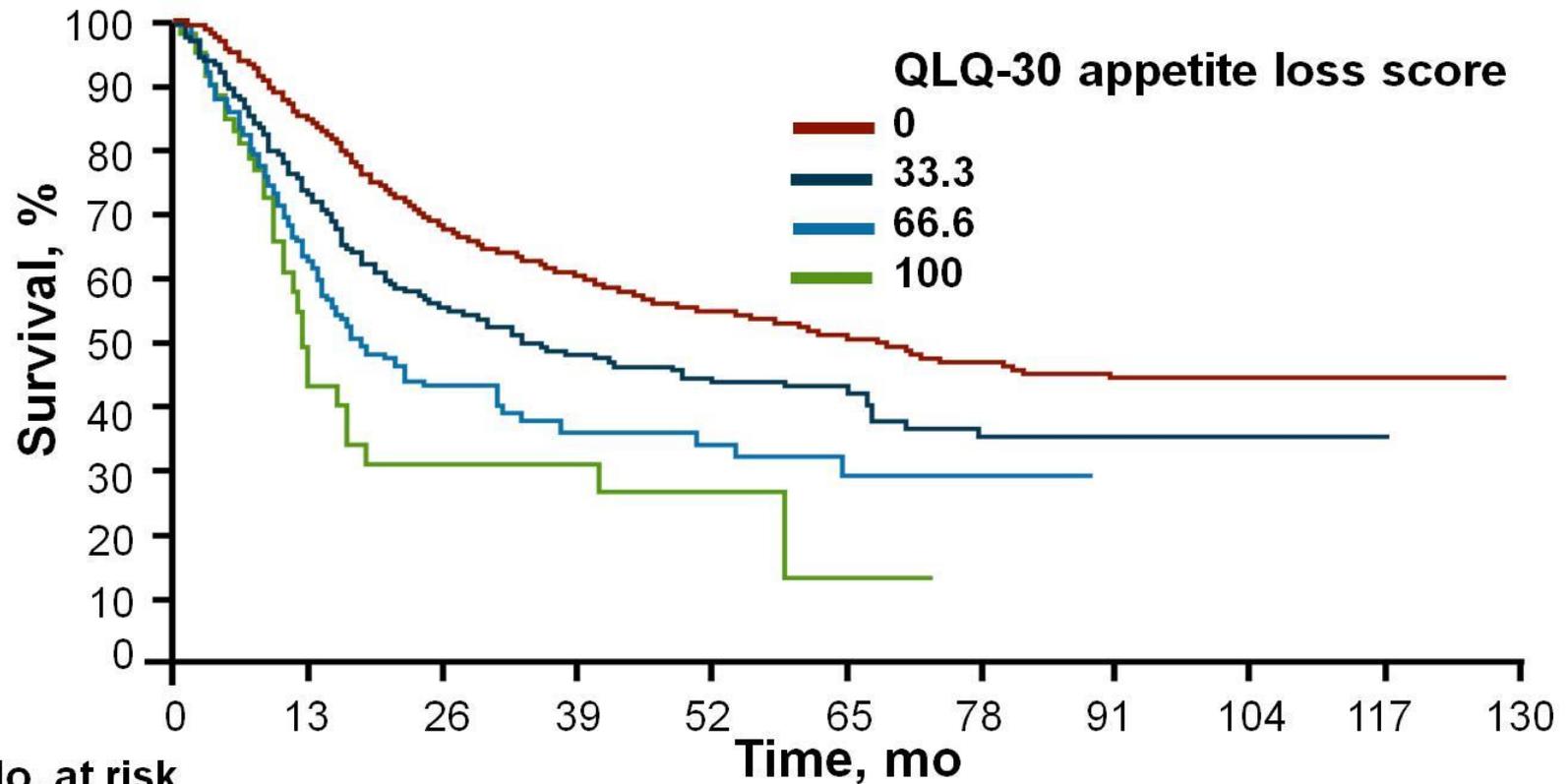
- Frequency:
 - End-stage cancer patients 80%
 - Major cause of death 20%
- Prevalence is depending of cancer type

Incidence of weight loss according to the primary cancer type

Table 1 Incidence of weight loss in cancers of different sites (adapted, with permission, from ref 22).

Tumor site	Incidence of weight loss (%)
Pancreas	83
Gastric	83
Esophagus	79
Head and neck	72
Colorectal	55–60
Lung	50–66
Prostate	56
Breast	10–35
General cancer population	63

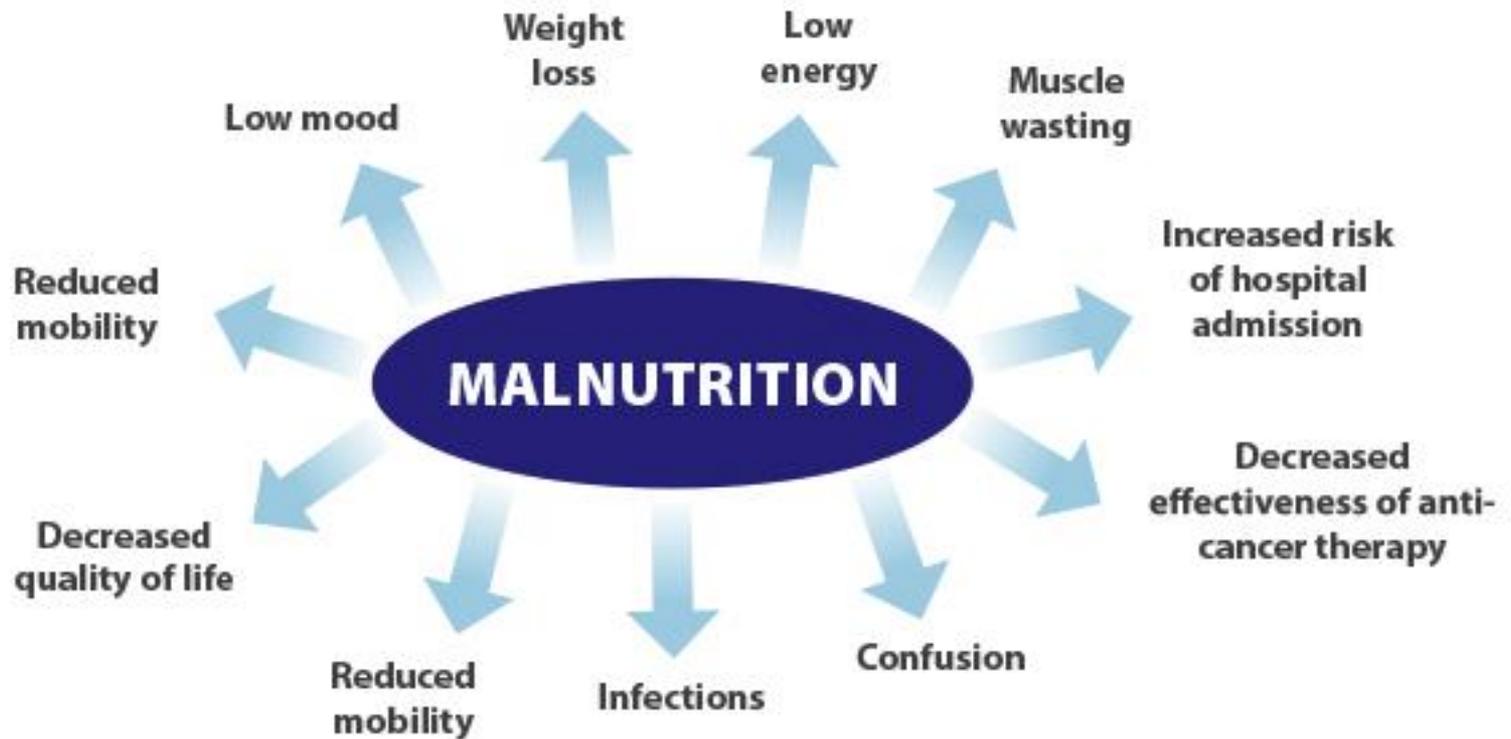
Loss of Appetite Affects Survival



No. at risk

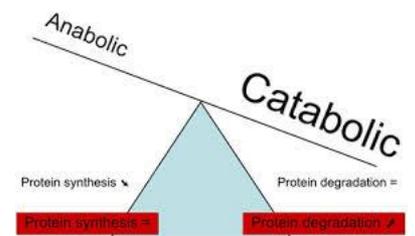
0	1314	984	686	486	310	195	128	46	9	1
33.3	348	205	132	90	60	42	27	12	4	1
66.6	133	65	37	22	17	10	6	0	0	0
100	63	17	9	8	5	1	0	0	0	0

Consequences of malnutrition

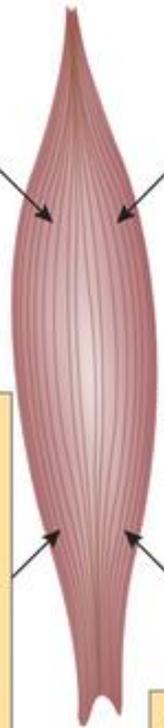
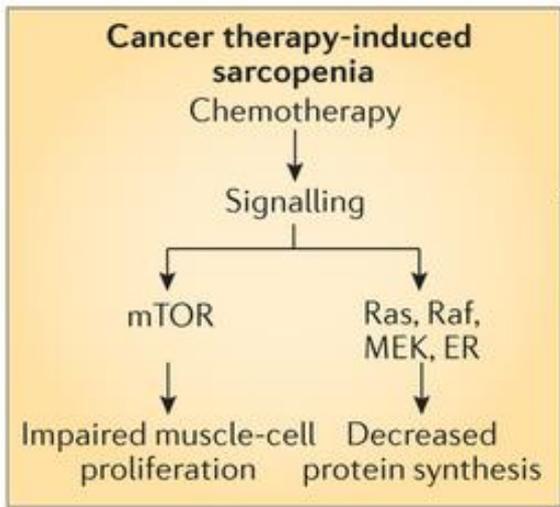
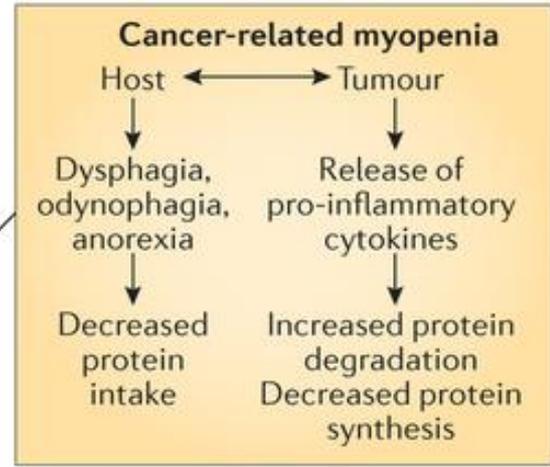


Consequences of cancer-related malnutrition

Sarcopenia



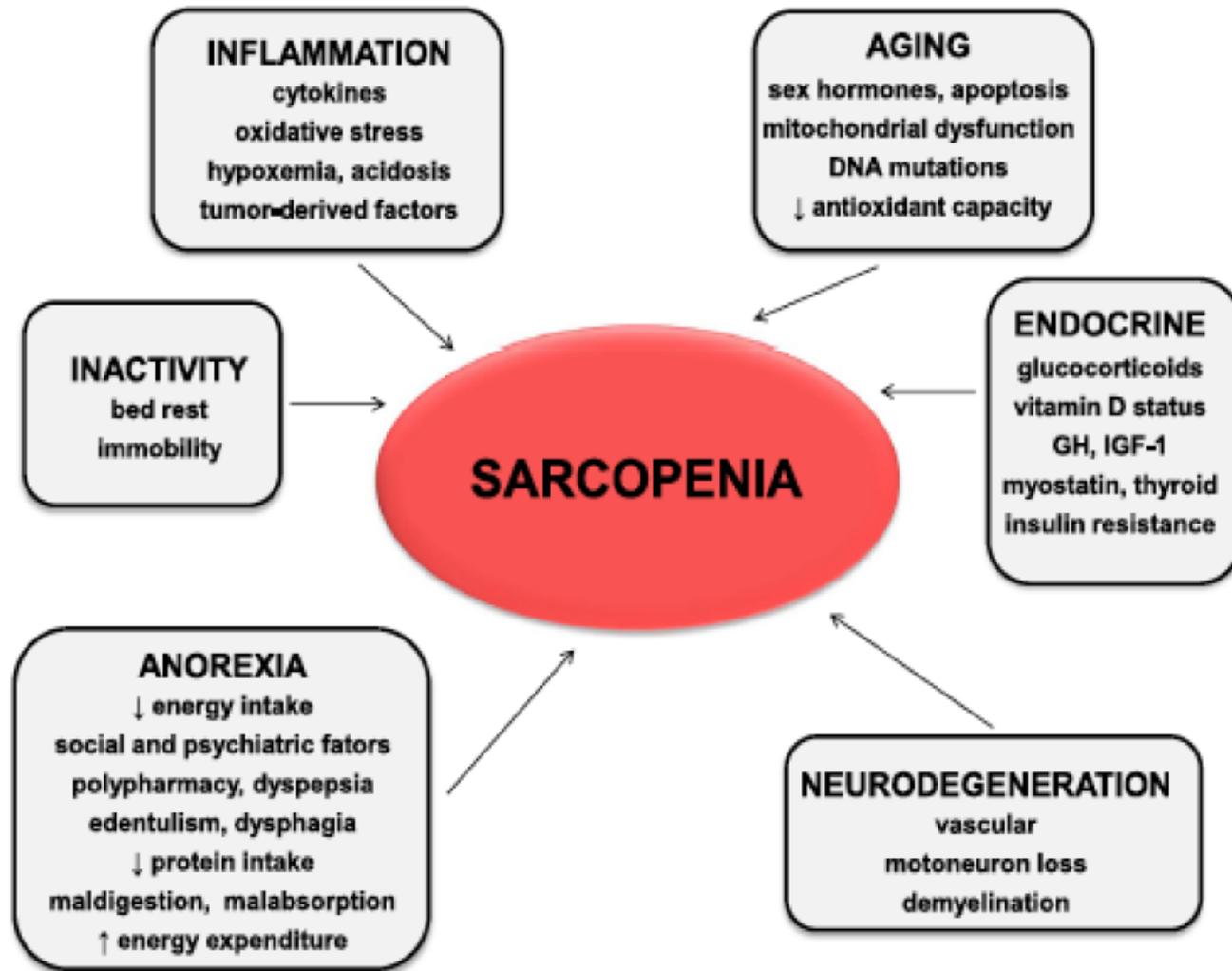
- Pre-existing sarcopenia**
- Genetic predisposition
 - Ageing
 - Co-morbidities
 - Reduced physical activity



Skeletal muscle wasting

- Oesophagectomy-related sarcopenia?**
- SIRS
 - Decreased ghrelin levels
 - Eating difficulties

Sarcopenia (other contributing factors)



Reprinted from Clin Nutr 2014; 33(5), Biolo G, *et al.*, Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: From sarcopenic obesity to cachexia; 737-748. Copyright (2014), with permission from Elsevier

Muscle wasting → Sarcopenia

- ↑ morbidity
- ↑ risk of falls
- ↓ tolerance to therapy
- ↓ quality of life
- ↓ survival

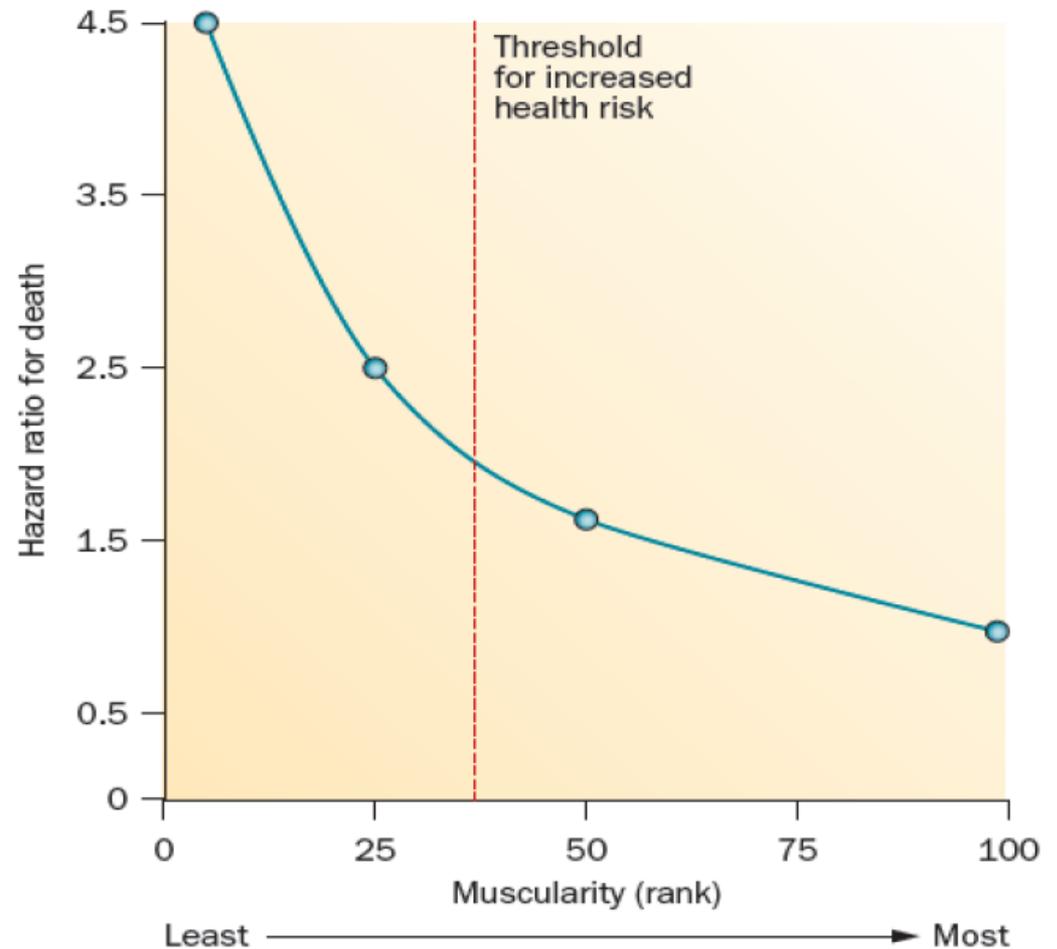
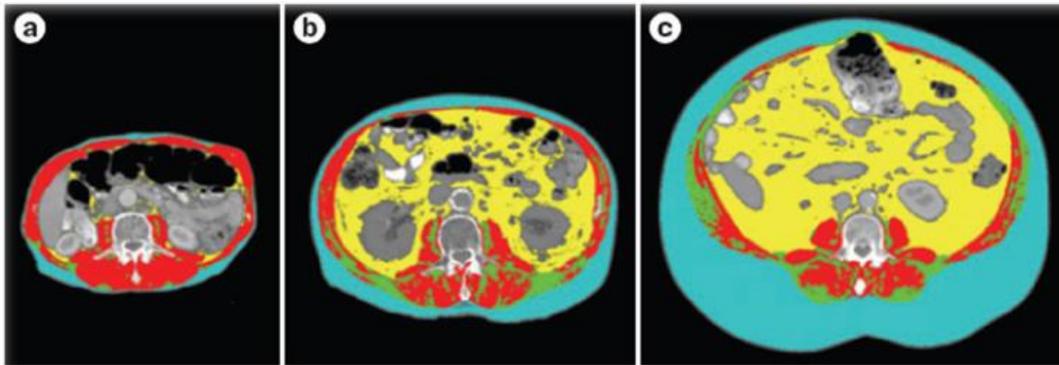
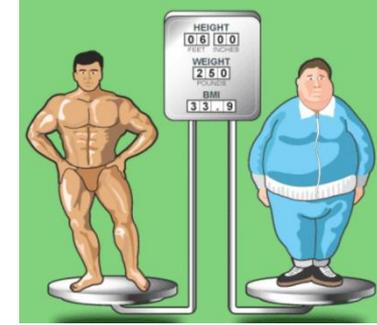


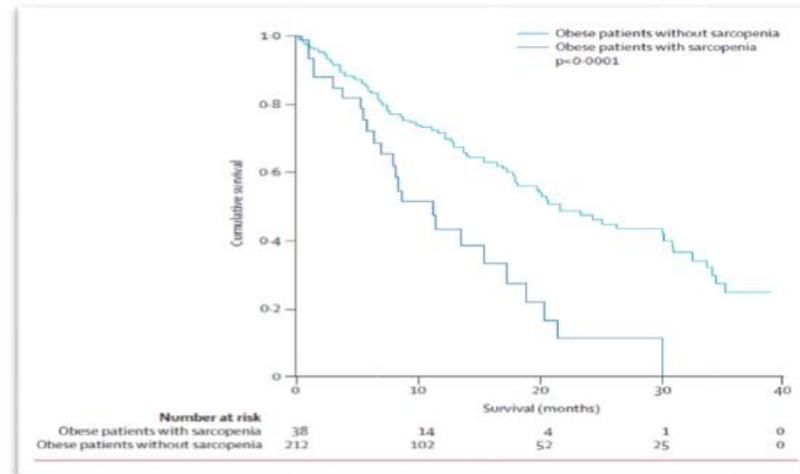
Figure 1. Cachexia's impact on the dimensions of quality of life. Adapted from the City of Hope Quality of Life Model 2008 (Ferrell and Coyle, 2008).

Physical Impact	Psychological Impact
<ul style="list-style-type: none">• Weight loss• Loss of appetite• Weakness• Fatigue• Reduced performance status• Anorexia	<ul style="list-style-type: none">• Anxiety• Worry• Fear• Depression• Distress
Social Impact	Spiritual Impact
<ul style="list-style-type: none">• Social Isolation• Family conflicts• Alterations in body image• Anger• Emotional distancing• Low self-esteem	<ul style="list-style-type: none">• Hopelessness• Uncertainty• Questioning the meaning of life• Helplessness

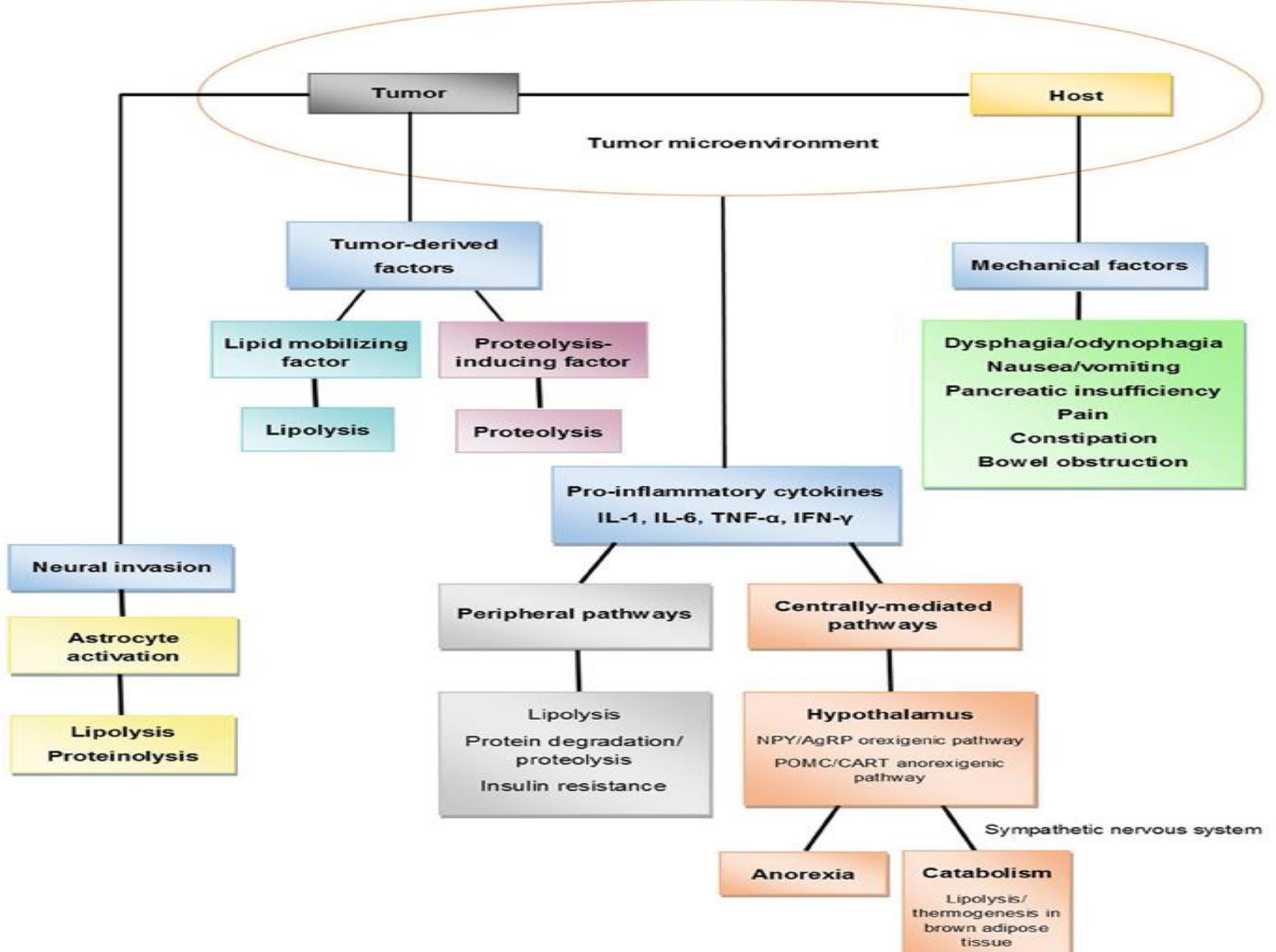
Look behind the BMI – sarcopenic obesity

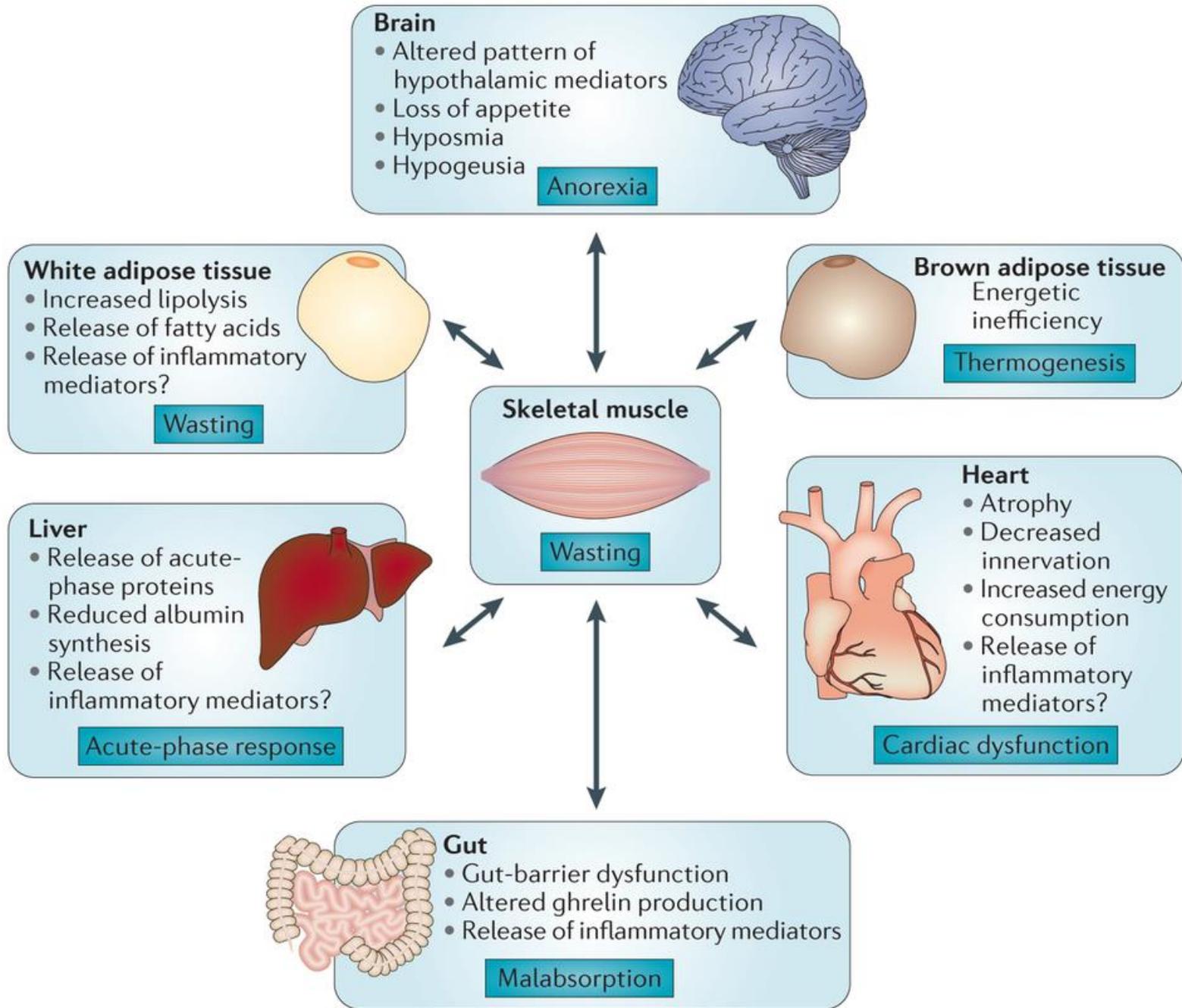


- Total skeletal muscle (parapinal, psoas, transverse/oblique abdominus, rectus abdominus)
- Visceral adipose tissue
- Subcutaneous adipose tissue
- Intermuscular adipose tissue

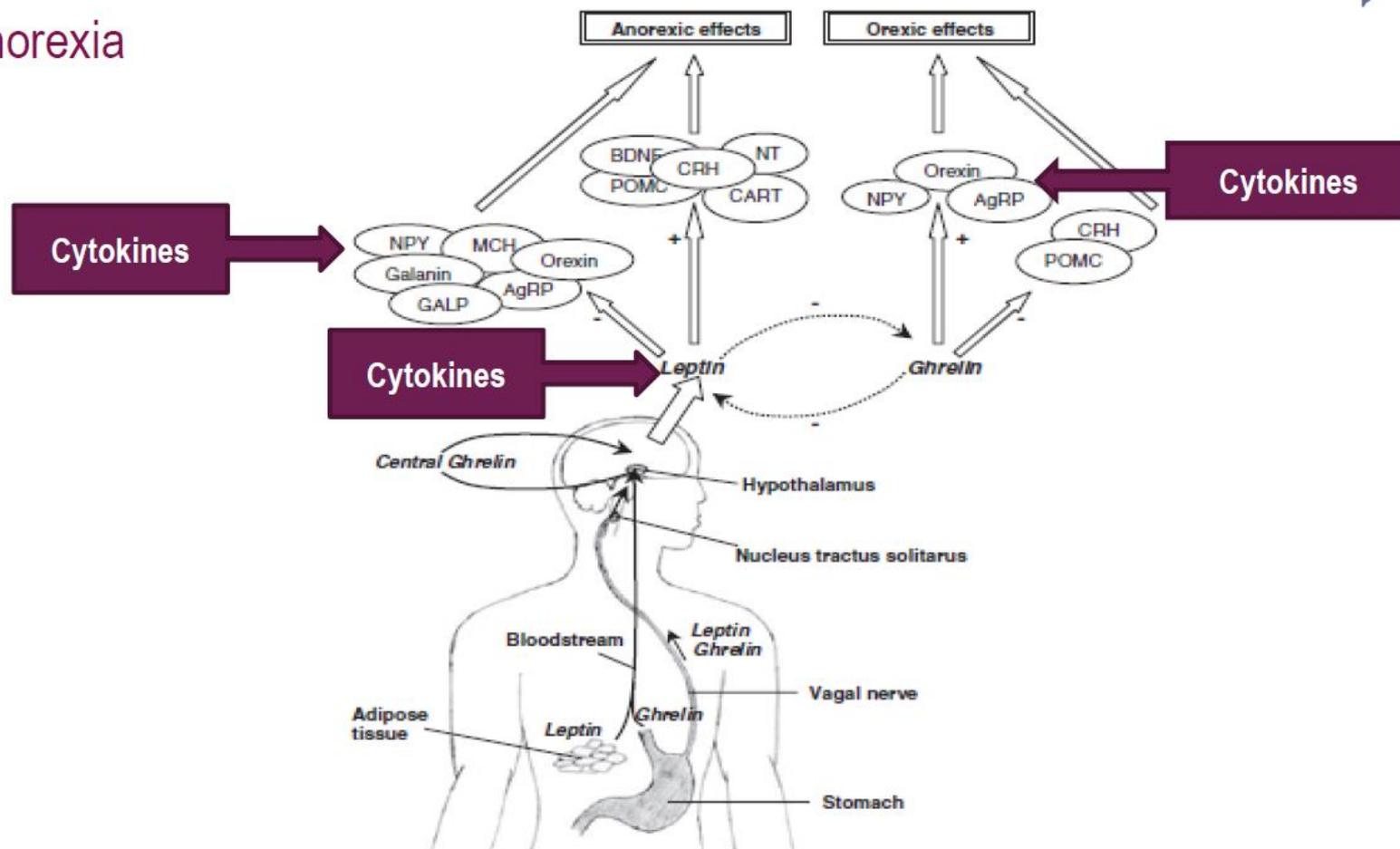


Fearon K, *et al.*, Nat Rev Clin Oncol 2013;10(2):90-99. Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Clin Oncol copyright (2013); Reprinted from Lancet Oncol 2008;9(7), Prado CM, *et al.*, Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study: 629-635. Copyright (2008), with permission from Elsevier





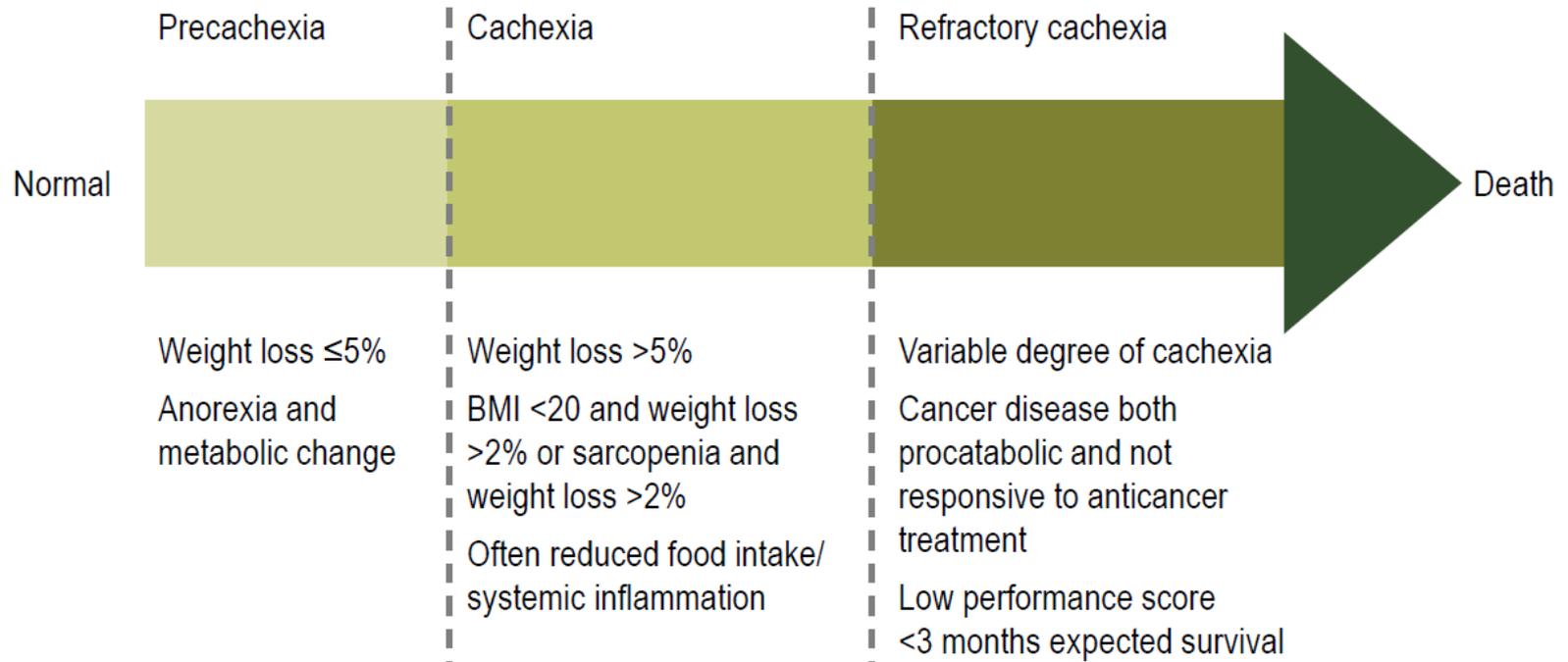
Anorexia



Klok MD, *et al.*, *Obes Rev* 2007;8(1):21-34, copyright © 2006, John Wiley and Sons

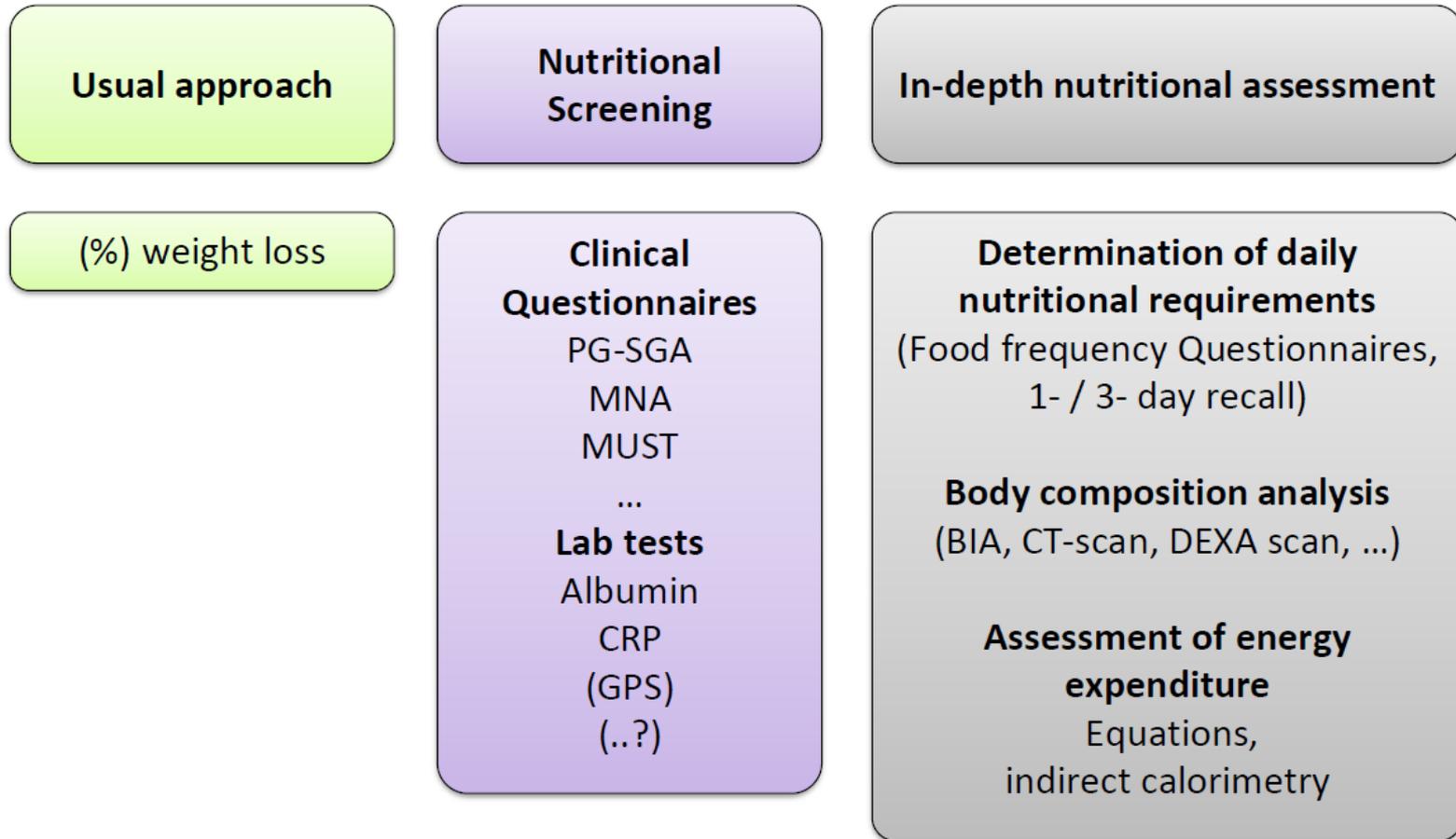
Obes Rev. 2007 Obesity reviews by International Association for the Study of Obesity Reproduced with permission of JOHN WILEY & SONS - JOURNALS in the format Use in an e-coursepack via Copyright Clearance Center

Stages of cachexia



Reprinted from The Lancet Oncol 2011, 12(5), Fearon K, *et al.*, Definition and classification of cancer cachexia: an international consensus; 489-495. Copyright 2011, with permission from Elsevier.

Diagnostic



Diagnostic Criteria for the Classification of Cancer-Associated Weight Loss

Lisa Martin, Pierre Senesse, Ioannis Gioulbasanis, Sami Antoun, Federico Bozzetti, Chris Deans, Florian Strasser, Lene Thoresen, R. Thomas Jago, Martin Chasen, Kent Lundholm, Ingvar Bosaeus, Kenneth H. Fearon, and Vickie E. Baracos

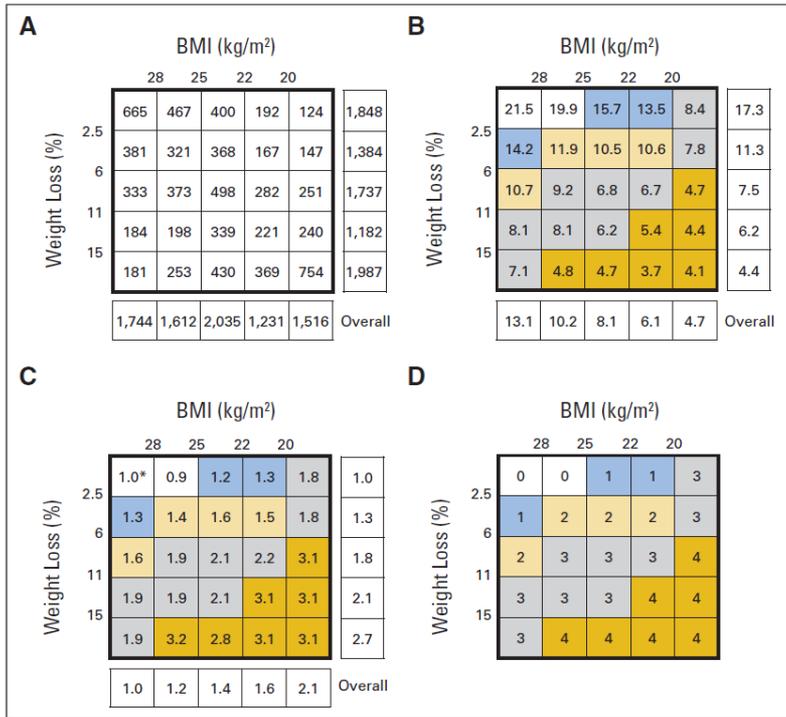
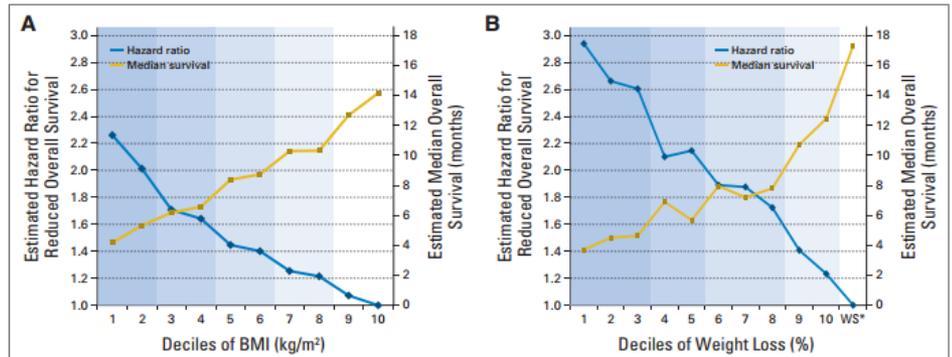


Fig 2. Risk of reduced survival is a function of body mass index (BMI) and percent weight loss (%WL). Panels A to C represent a 5 × 5 matrix analysis of the five categories of BMI and five categories of %WL for a total of 25 possible combinations. The (A) sample size, (B) median overall survival (months), and (C) unadjusted estimated hazard ratios (HRs; HR, 1.0) are presented for each cell. (*) Reference categories are BMI ≥ 28.0 kg/m² and weight stable ± 2.4%. Different colors represent significant differences (*P* < .05) in median overall survival and HRs within and between cells of the matrix. Panel D represents the BMI-adjusted WL grading system (grades 0 to 4). Median survival times by grade were as follows: grade 0, 20.9 months (95% CI, 17.9 to 23.9 months; unadjusted HR, 1.0); grade 1, 14.6 months (95% CI, 12.9 to 16.2 months; HR, 1.3); grade 2, 10.8 months; 95% CI, 9.7 to 11.9; HR, 1.5); grade 3, 7.6 m to



martin et al

We know the problem.

Why do we fail?

FAIL
[F] **F**IRST
[A] **A**TTEMPT
[I] **I**N
[L] **L**EARNING

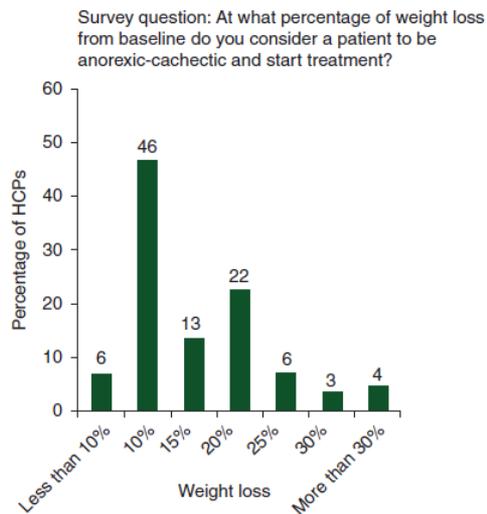
Perspectives of health care professionals on cancer cachexia: results from three global surveys

M. Muscaritoli*, F. Rossi Fanelli & A. Molino

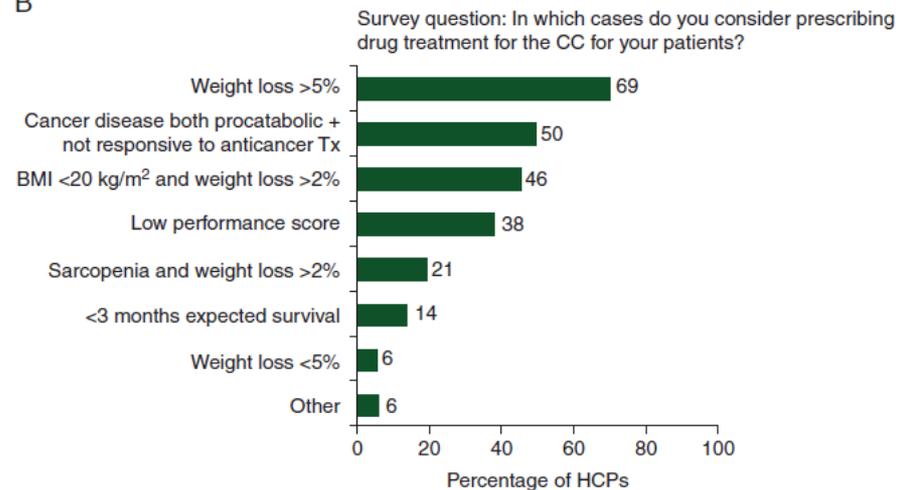
Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy

Received 26 January 2016; revised 15 June 2016; accepted 26 August 2016

C



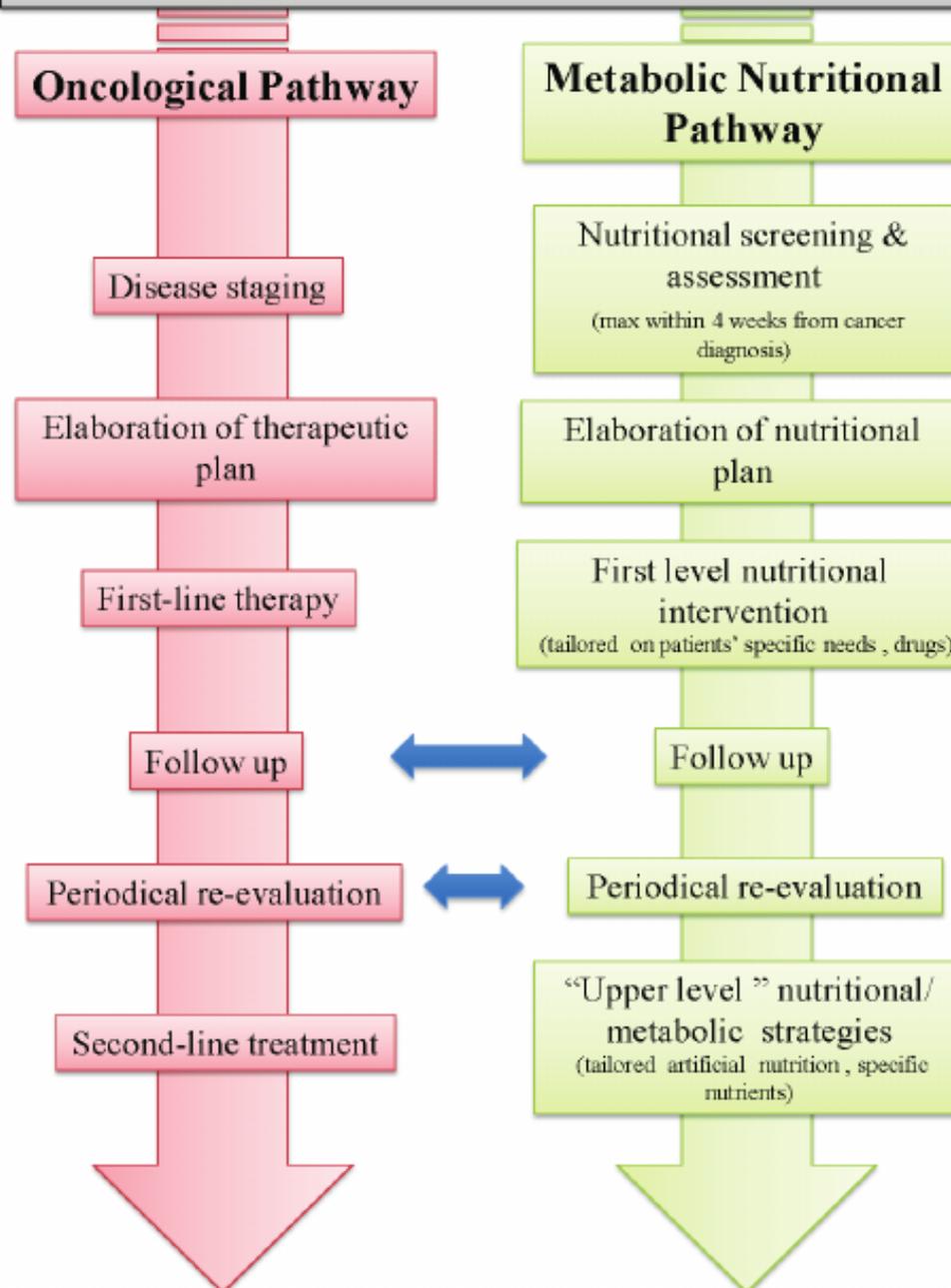
B



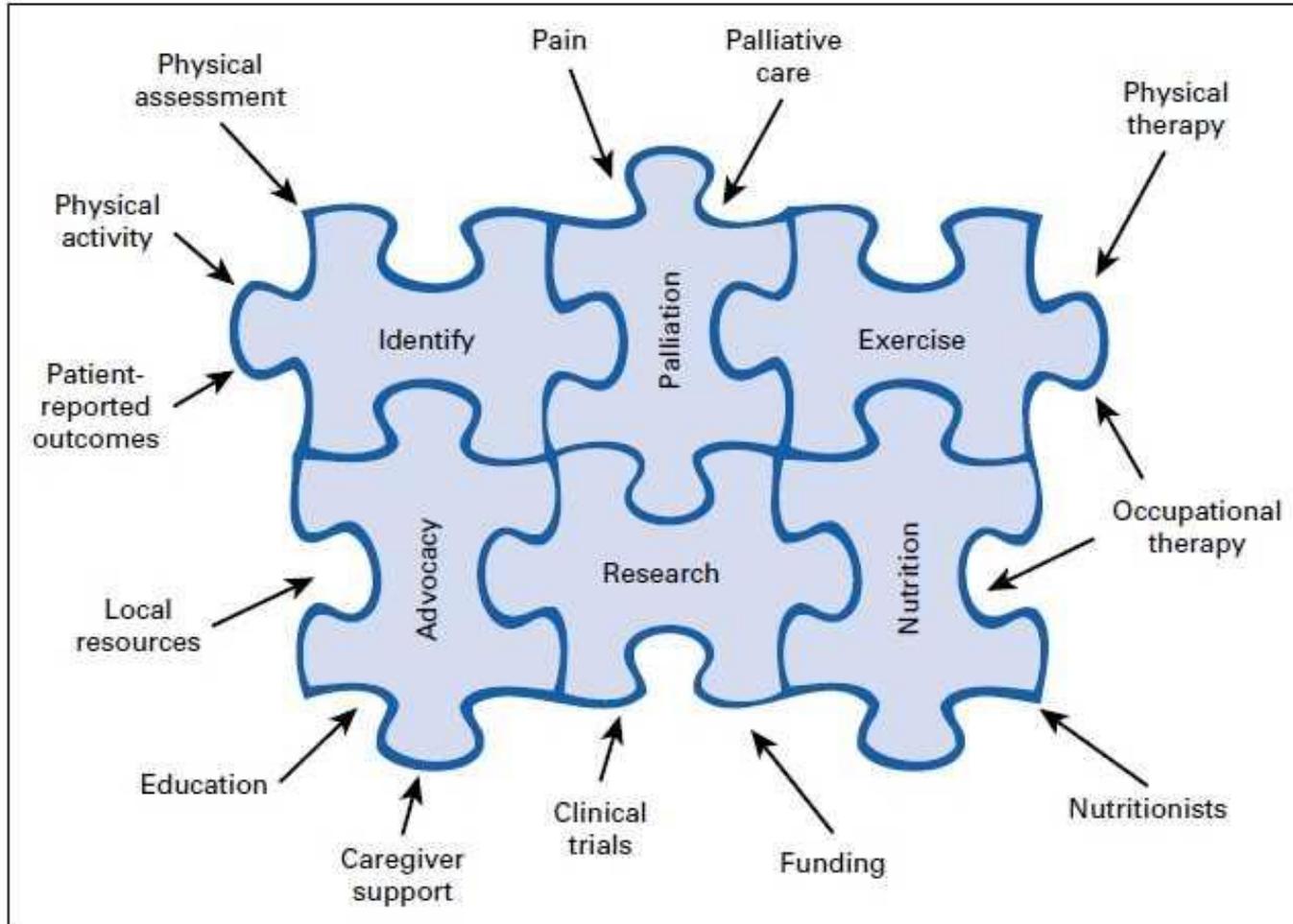
LACK OF.....

- Awareness
- Identification of patients at risk
- Prevention
- Diagnosis
- Early intervention – multimodal approach!
- Education - Patient & Health Care Professionals
- Personalized treatment strategy
- Follow-up

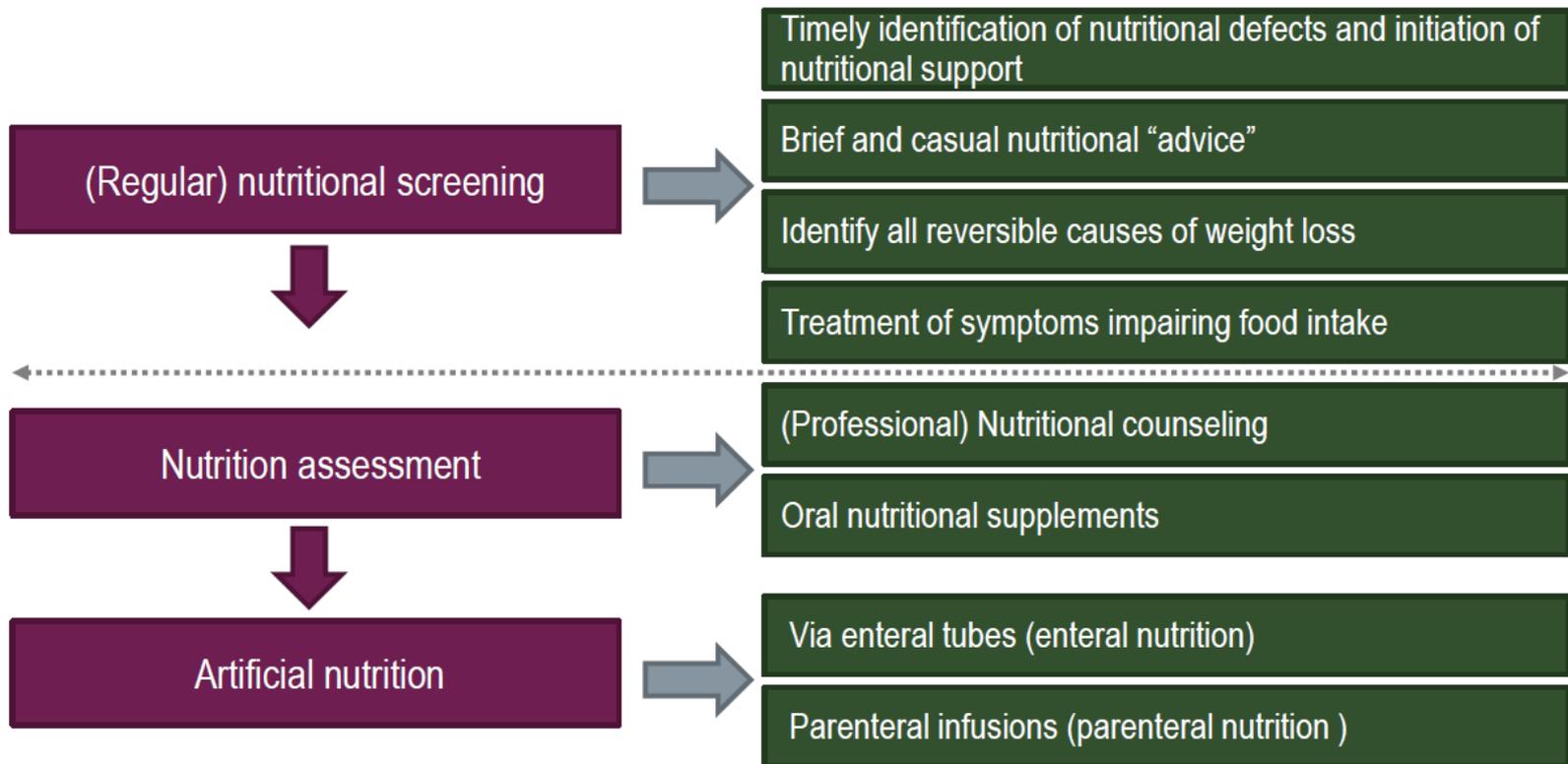
NEOPLASTIC DISEASE UPON DIAGNOSIS



Multimodal approach



Nutritional Care Plan



Reversible causes

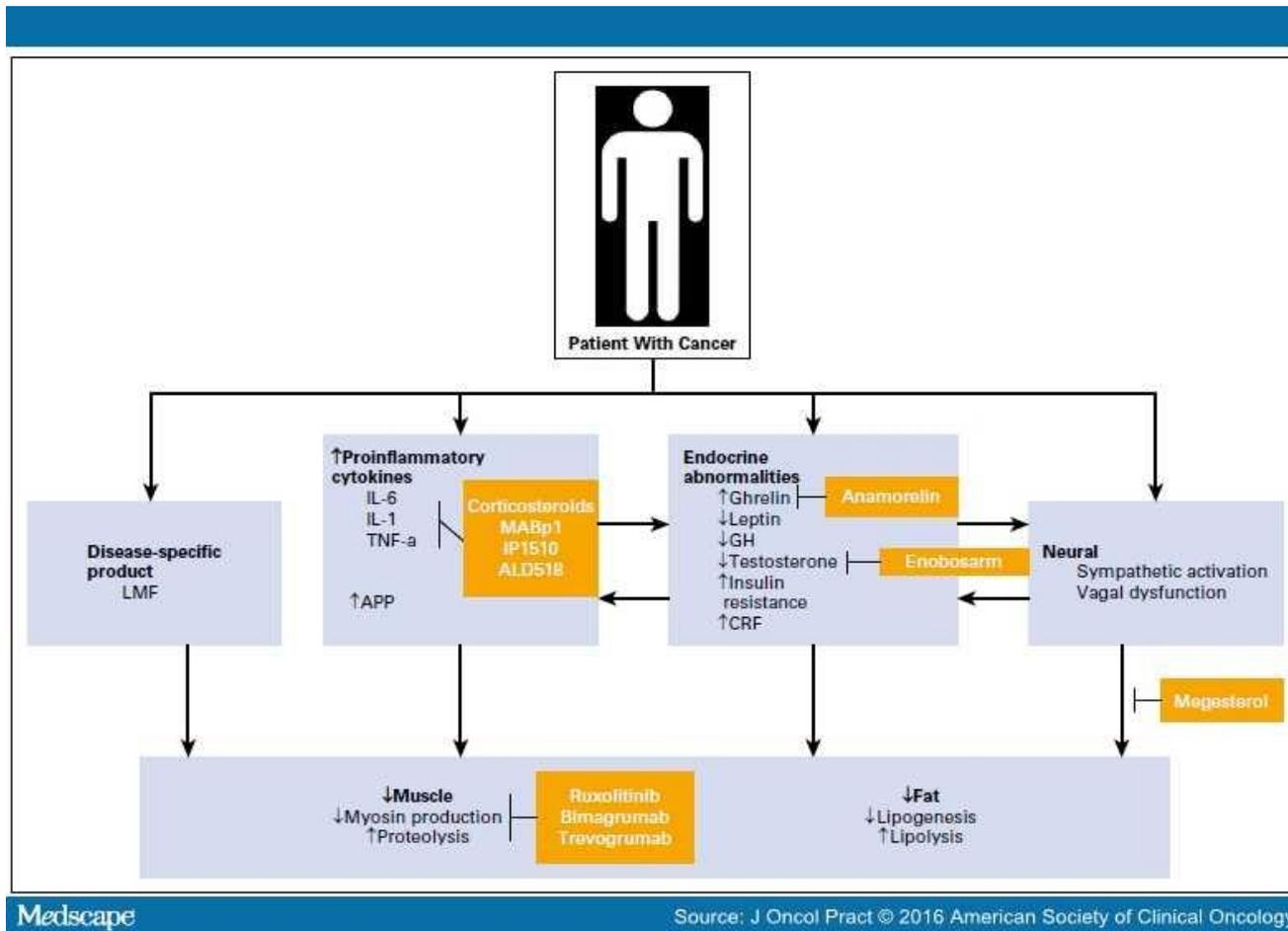
- Obstruction in the GI tract
- Head&Neck cancer
- Pain
- Nausea – vomiting
- Dyspnea
- Depression
- Malabsorption
- Side effects of anticancer therapies

Right strategy to right patient

Prognosis-Based Decision Making Regarding Artificial Nutrition

Nutritional State	Life expectancy: months or longer (active cancer treatments considered; pre-cachexia/ cachexia state)	Life expectancy: days to weeks (progressive cancer with no standard treatment options; refractory cachexia)
Reduced oral intake and normal absorption	Continue with oral intake, consider nutritional supplements	Continue with oral intake, consider nutritional supplements
Significantly compromised oral intake (e.g. dysphagia, severe mucositis) and normal absorption	Consider enteral nutrition	Conservative measures Consider parenteral hydration Artificial nutrition not recommended
Significantly compromised absorption (e.g. bowel obstruction) or failure of enteral nutrition	Consider parenteral nutrition	Conservative measures Consider parenteral hydration Artificial nutrition not recommended

Medical treatment



Cancer cachexia pathophysiology and targeted treatments. APP, acute phase proteins; CRF, corticotropin-releasing factor; GH, growth hormone; IL-1, interleukin-1; LMF, lipid mobilizing factor; TNF- α , tumor necrosis factor α .

Approach to the Patient With Cachexia

Symptomatic patient with incurable, refractory cancer

EDUCATION

Maybe consider pharmacologic treatment

Life expectancy in months

Life expectancy in weeks

Megestrol acetate

History of DVT and/or cost of megestrol acetate prohibitive

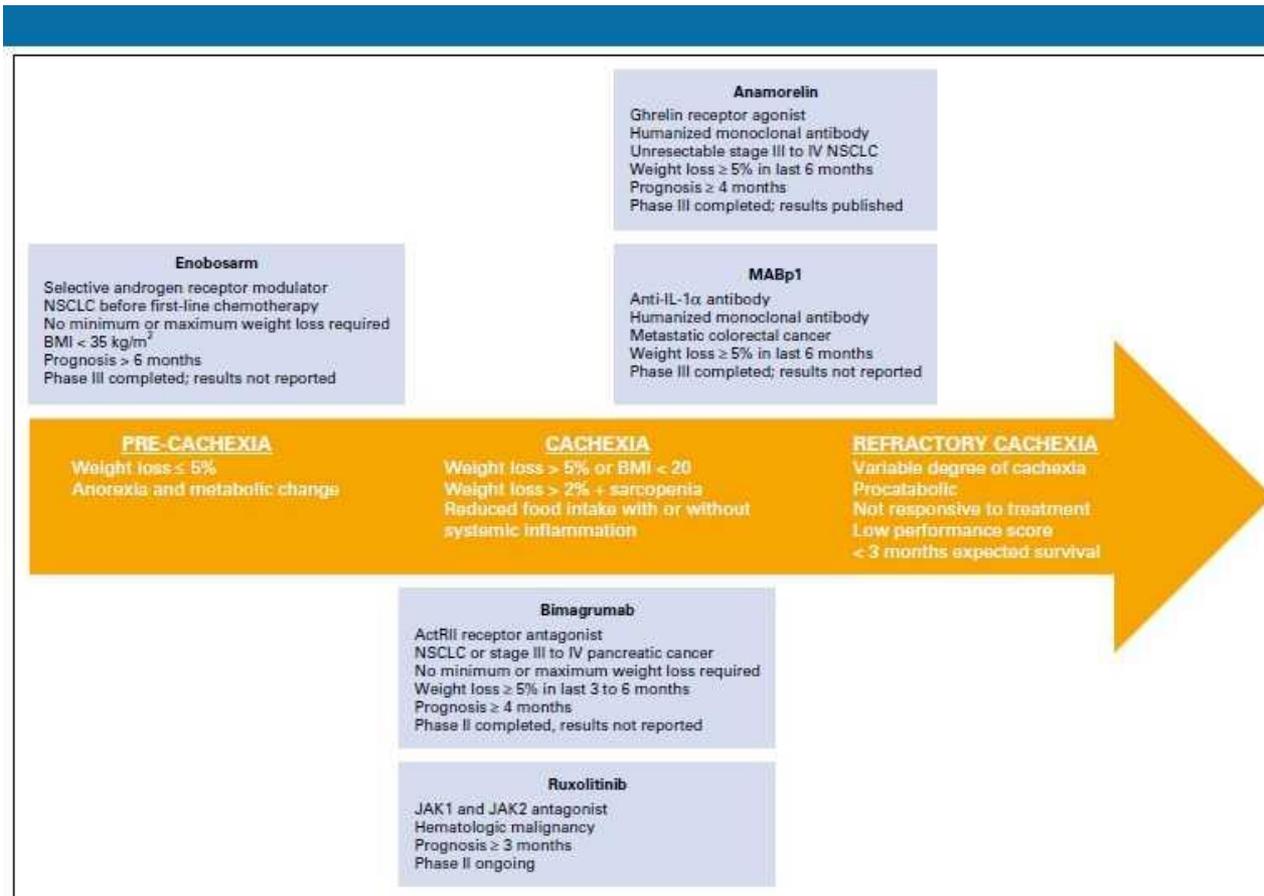
Dexamethasone

Monitor

Novel drugs

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

New drugs – timing



Recommendations – NCCN

For patients with a life expectancy of years to months, the recommendations are as follows:

- Evaluate the severity of weight loss
- Treat reversible causes – Early satiety; symptoms that interfere with food intake (eg, depression, pain, constipation, nausea/vomiting, fatigue, dyspnea)
- Modify medications that interfere with intake
- Consider possible endocrine disorders – Hypogonadism, thyroid dysfunction, metabolic abnormalities (eg, increased calcium)
- Consider appetite stimulant – Megestrol acetate (should be used with caution due to increased risk of blood clots, edema; death occurs in one of every 23 patients, prednisone)
- Consider exercise program
- Consider consultation with a nutritionist
- Consider enteral and parenteral feeding as appropriate

End of life care – NCCN - EPCRC

For patients with a life expectancy of months to weeks to days, the NCCN recommends first determining the importance of the symptoms to patient and family; if considered important, the anorexia/cachexia can be treated with megestrol acetate. Further recommendations are as follows:

- Focus should be on patient goals and preferences
 - Provide emotional support
 - Treat depression, if appropriate
 - Provide education and support to patient and family regarding the emotional aspects of withdrawal of nutritional support
-
- Educate patient and family to minimize eating-related distress; counsel them about weight loss–related distress and end-of-life issues
 - Enteral nutrition therapy may be partially effective for selected patient groups
 - The burden of parenteral nutrition will outweigh any benefits in the majority of patients
 - The use of thalidomide is not recommended
 - The use of cannabinoids is not recommended
 - Progestins should be considered for patients with anorexia as a major distressing symptom
 - Steroids may be given for short periods (at most 2 weeks); longer duration may increase the burden on the patient from side effects and may cause a deterioration in muscle strength

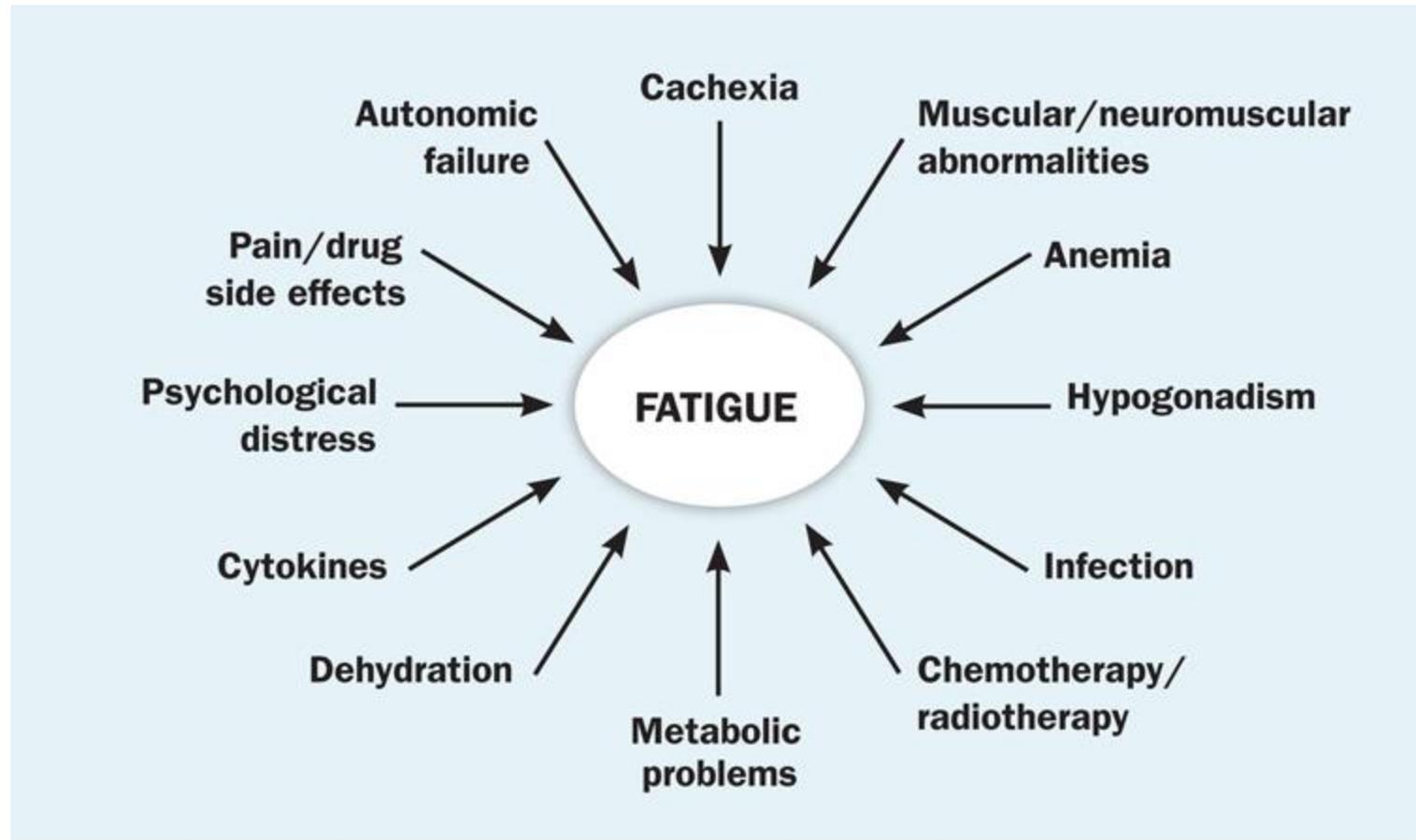
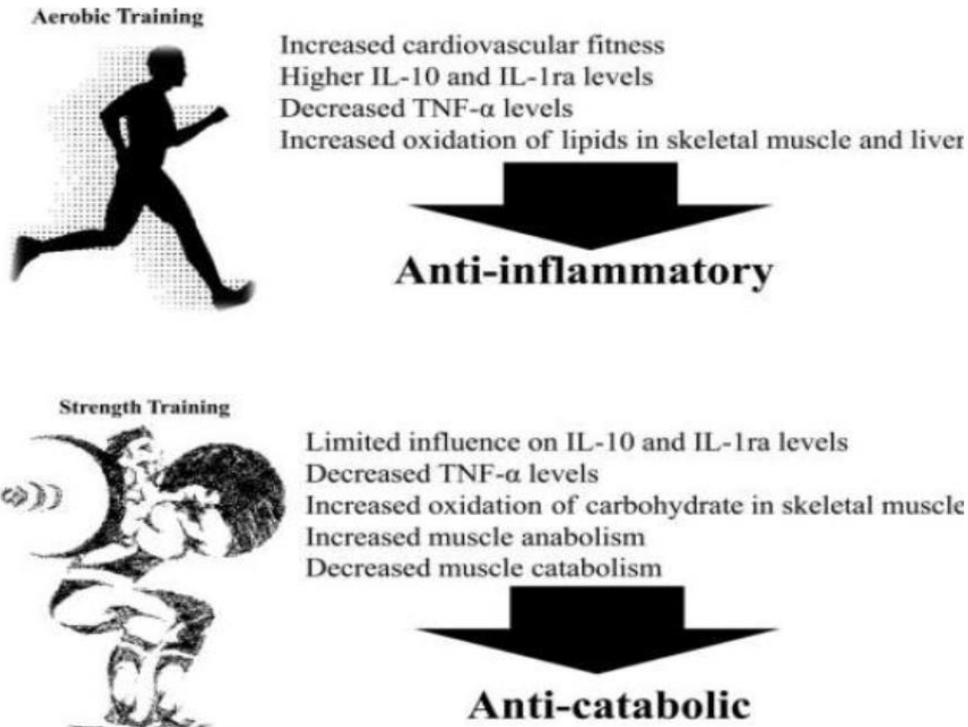


FIGURE 1: Contributors to fatigue in cancer patients.

Exercise, exercise, exercise.....



Limiting factors

- Anaemia
- Fatigue
- Peripheral sensoric neuropathy
- Bone metastases
- Co-morbidities – cardiac disorders, COPD
- Compromised immune function
- Pain
- Indwelling catheters and feeding tubes

New Rx for Advanced Colorectal Cancer:

Exercise

- CALGB 80405 trial – NCI
- 1231 patients with mCRC
- Walking 4 hours/week - 20% ↑ OS
- Walking or yoga 5 hours/week - 25% ↑ OS
- 16 % ↑ PFS
- 19 % ↓ Mortality

Guerico et al. – GICS 2017

Recommendations

Conclusion: Despite a strong rationale for the use of exercise, there is insufficient evidence to determine safety and effectiveness in patients with cancer cachexia. Findings from ongoing studies are awaited. Assessment of cachexia domains, ideally against international criteria, is required for future trials of exercise and supportive care interventions

Strength of recommendation: STRONG	We recommend maintenance or an increased level of physical activity in cancer patients to support muscle mass, physical function and metabolic pattern
Level of evidence	High
Strength of recommendation: WEAK	We suggest individualised resistance exercise in addition to aerobic exercise to maintain muscle strength and muscle mass
Level of evidence	Low

Future perspectives

- MENAC- study

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

Three-step Approach for the Busy Oncologist

- **Recognize Cachexia Early**
- **Refer and Collaborate**
- **Nutrition and Exercise**

[Cancer Cachexia: Beyond Weight Loss](#)

Andrew R. Bruggeman Arif H. Kamal Thomas W. LeBlanc Joseph D. Ma Vickie E. Baracos Eric J. Journal of Oncology Practice 2016 12:11, 1163-1171

Practice changing is practice sharing.

P. Soubeyran

