



A new era of therapeutics for cancer cachexia

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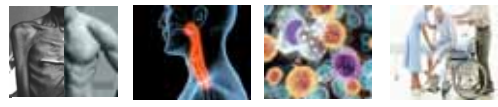


Definition and classification of cancer cachexia: an international consensus

Lancet Oncol 2011; 12: 489-95

Kenneth Fearon¹, Florian Strasser², Stefan D. Antke³, Ingrid Baracos⁴, Eduardo Bruhn⁵, Robin L. Finkelstein⁶, Anand Jais⁷, Charles Lippman⁸, Nef Mau-Dumont⁹, Catherine Morinsson¹⁰, Mike Davis¹¹, Maurizio Muscaritola¹², Faith Ottag¹³, Lukas Radbruch¹⁴, Paolo Ravasco¹⁵, Debra Walsh¹⁶, Andrew Wilcock¹⁷, Sora Kanao, Vickie F. Baracos

I. Depletion of Reserves	II. Limitation of food intake	III. Catabolic Drivers	IV. Impact and outcomes
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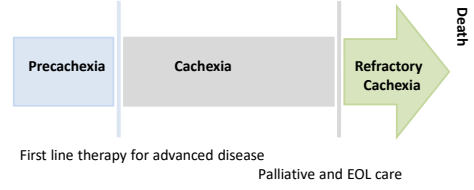
Consensus definition (Fearon et al.)

- a multi-factorial syndrome of **involuntary weight loss**
- characterized by an **ongoing loss of skeletal muscle mass (with or without loss of fat mass)**

Cachexia is not the same as starvation or simple malnutrition

- a negative protein and energy balance driven by a **variable combination of reduced food intake and abnormal metabolism.**

Cachexia is a continuum with 3 stages of clinical relevance



Death

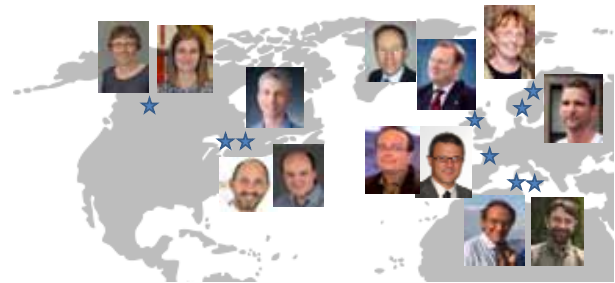
Precachexia Cachexia Refractory Cachexia

First line therapy for advanced disease Palliative and EOL care

Definition and classification of cancer cachexia, an international consensus Fearon K et al. *Lancet Oncology* 2011; 12(5):489-495

Definitive diagnostic criteria could be determined from **large contemporary datasets** by determining the values that relate optimally to meaningful patient-centred outcomes, such as loss of function or decreased survival.

Diagnostic criteria for the classification of cancer-associated weight loss Martin L et al *J Clin Oncol* 2015;33(1):90-9.



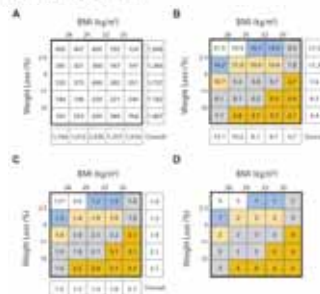
International Cancer Cachexia Data Repository

Definition and classification of cancer cachexia, an international consensus Fearon K et al. *Lancet Oncology* 2011; 12(5):489-495

•**Severity** classified according to the **rate of ongoing loss** of weight in combination with the concurrent **degree of depletion** of energy stores and body protein mass

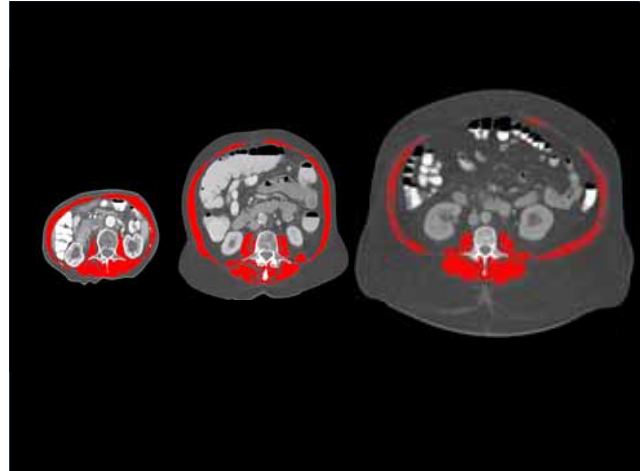
Diagnostic Criteria for the Classification of Cancer-Associated Weight Loss Martin L et al *J Clin Oncol* 2015

Lisa Martin, Pierre Senesse, Ioannis Gialeltsakis, Sami Antman, Federico Bezzetti, Chris Deam, Florian Strasser, Lone Thoresen, R. Thomas Jayose, Martin Chasen, Kent Lundholm, Ingar Børseth, Kenneth H. Fearon, and Vickie E. Baracos

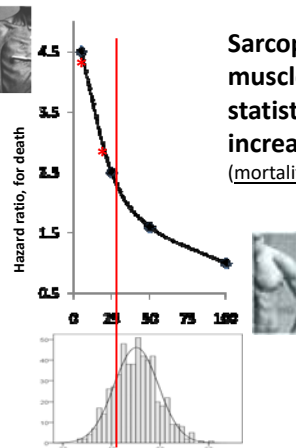


Definition and classification of cancer cachexia, an international consensus Fearon K et al. *Lancet Oncology* 2011; 12(5):489-495

- characterized by an **ongoing loss of skeletal muscle mass (with or without loss of fat mass)**



Sarcopenia: a low level of muscle, characterized by statistically significant* increase in health risk (mortality, toxicity, physical disability).



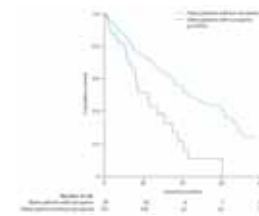
*statistical test for a threshold value -i.e. Optimal stratification

Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study *Lancet Oncol* 2008; 9: 629-35

Linda M M Prado, Jessica R Lefrere, Linda J McCarroll, Tony Brismar, Michael P Sweeney, Lisa Martin, Victor E Baracos

Cancer Cachexia in the Age of Obesity: Skeletal Muscle Depletion Is a Powerful Prognostic Factor, Independent of Body Mass Index *J Clin Oncol* 2013

Lisa Martin, Laura Rinkel, Neil MacDonald, Tony Brismar, M. Thomas Choudhry, Linda J McCarroll, Rachel Murphy, Susana Ghosh, Michael R. Sweeney, and Victor E. Baracos



Vickie

100-15

ate

① Gastric pump ✓ (-100)

② muscle biopsy results ? → cognition / behavior

③ CRP in the cache

④ MENAC Trial → recruiting

⑤ Review for Nature Disease Process Unit

⑥ NADIC: track

⑦ Lancet Oncology Consensus

⑧ Stefan Antler → phone call


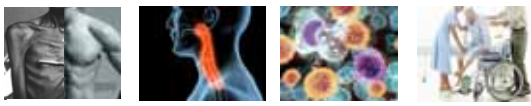


Diagram showing a circle with 'E. coli' and arrows pointing to 'ate'.

Conceptual Framework

I. Depletion of Reserves	II. Limitation of food intake	III. Catabolic Drivers	IV. Impact and outcomes
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Sarcopenia

← Malnutrition →

← Cachexia →

Weakness/
Fatigue
Frailty
Toxicity
Infection
Complication
Costs
Poor QOL
Mortality

Promoting food intake in the cancer patient



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ESPEN Guideline

ESPEN guidelines on nutrition in cancer patients[®]

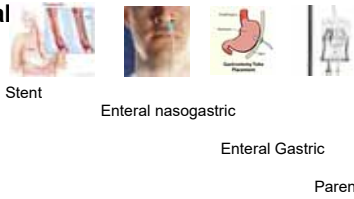
Jann Arends¹, Patrick Bachmann², Vickie Baracos³, Nicole Barthelemy⁴, Hartmut Bertz⁵, Federico Bozzetti⁶, Ken Fearon⁷, Elisabeth Hütterer⁸, Elizabeth Isenring⁹, Stein Kaasa¹⁰, Zeljko Krznaric¹¹, Barry Laird¹², Maria Larsson¹³, Alessandro Laviano¹⁴, Stefan Mühlbacher¹⁵, Maurizio Muscaritoli¹⁶, Line Oldervoll¹⁷, Paula Ravasco¹⁸, Tora Solheim¹⁹

Cachexia continuum: options for nutrition, volitional and non-volitional feeding

Volitional

Diet modification Dietitian Oral nutritional supplements

Non-volitional



What are the risks of parenteral nutrition in cancer patients on home parenteral feeding?

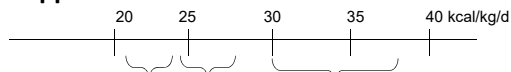


<1 catheter-related bloodstream infection/ 2857 catheter-days

<1 catheter related thrombosis /16,000 catheter-days

Catheter-related complications in cancer patients on home parenteral nutrition: a prospective study of over 51,000 catheter days.
[Cotogni P J Parenteral Enteral Nutrition 2013 ;37\(3\):375-83](#)

Very large shortfall of volitional intake with Dietitian consultation and/or Oral Nutritional Supplements



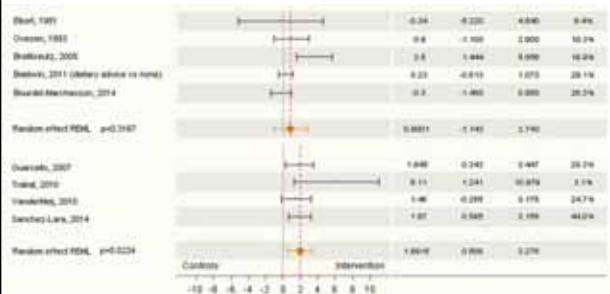
Typical basal intakes 23-24 kcal/kg
 Hutton et al. 2006
 Fearon et al. 2004

Intakes in RCT dietitian + ONS 24-27 kcal/kg

Intakes to maintain weight & lean mass 30-38 kcal/kg
 Lundholm. 2004;
 Fearon et al 2004
 Arends et al 2016



Meta-analysis of response of body weight to volitional nutrition intervention in cancer patients during active chemotherapy Tx



Therapeutic approach: pharmacological activation of ingestive behavior (anorexia) & food reward (anhedonia)

- Corticosteroid
- Progestational agent
- Cannabinoid
- Ghrelin
- Melanocortin antagonist



Pharmacological management of anorexia in advanced cancer patients

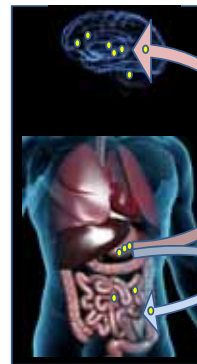
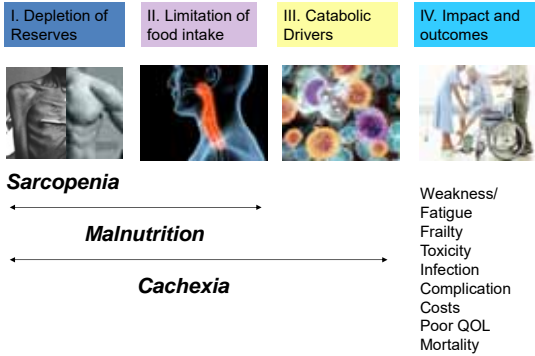
•**Corticosteroids** eg dexamethasone 4-10 mg bid causes temporary increase in appetite of up to 4 weeks (side effects: infection, poor glycemic control, loss of muscle)

- 6 studies in 637 patients. Results for appetite (VAS) favor corticosteroids

•**Progestational agents** eg megestrol acetate, 480-800 mg/day; lasts longer than corticosteroids, weight gain is fat; \$\$, (side effects : impotence; thromboembolic episodes, muscle loss)

- 23 trials in 3436 patients. Results for appetite (VAS) and weight gain favored megestrol acetate over placebo.

Conceptual Framework



Brain: Appetite, ingestive behaviour, food preference, food reward, Growth hormone secretion, anabolism, lipogenesis, positive energy balance
Mood, cognitive functions

GHRELIN is an entero-endocrine peptide which induces appetite, food reward & energy storage

Gastrointestinal: secretion & motility
Pancreas: insulin secretion

Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials

Jennifer S Tamiel, Amy P Abernethy, David C Coombs, John P Finnell, Elizabeth M Davis, Ying Fan, Kenneth C Frasure

Ghrelin induces appetite, food reward & energy storage

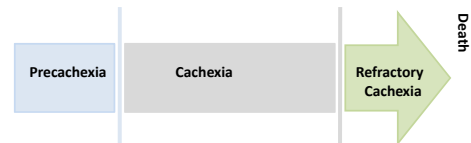
Anamorelin is an orally active small molecule ghrelin receptor ligand.

2:1 randomization Anamorelin vs placebo over 12 weeks 979 patients total

Co-primary endpoints FDA & EMA

- Radiologically determined lean body mass (efficacy)
- Hand grip strength (clinical benefit)

Cachexia is a continuum with 3 stages of clinical relevance

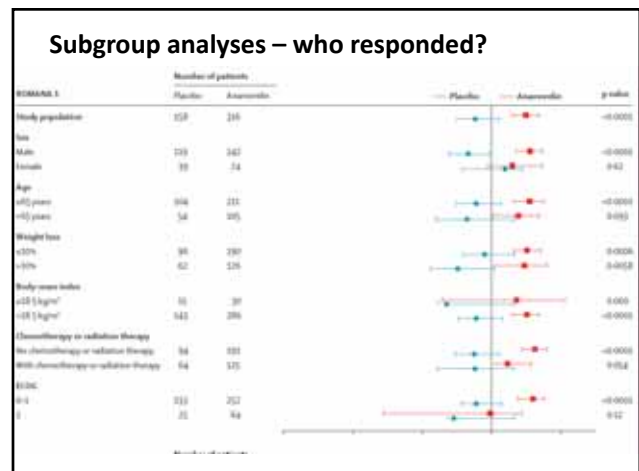


First line therapy for advanced disease
12 weeks Anamorelin therapy
To gain lean body mass

Palliative and EOL care
Corticosteroid, Megestrol
To gain subjective appetite

ROMANA 1			
	Anamorelin	Placebo	p value
Primary endpoints* (n)	323	161	
Median lean body mass (kg)	0.99 (0.61 to 1.36)	-0.47 (-1.00 to 0.21)	<0.0001
Median handgrip strength (kg)	-1.10 (-1.69 to -0.40)	-1.58 (-2.09 to -1.14)	0.15
Secondary endpoints† (n)	284	141	
Mean bodyweight (kg)	2.20 (0.33)	0.14 (0.36)	<0.0001
Mean anorexia-cachexia scale score	4.12 (0.75)	1.92 (0.81)	0.0004
Fatigue scale	0.26 (0.89)	-1.91 (0.93)	0.054

ROMANA 1			
	Anamorelin (n=284)	Placebo (n=141)	p value
Total body mass	2.87 (0.6 to 5.1)	0.07 (-2.9 to 2.7)	<0.0001
Fat mass	1.21 (-0.2 to 2.8)	-0.12 (-0.1 to 1.0)	<0.0001



NCT02330926 : **Multimodal Intervention for Cachexia in Advanced Cancer Patients Undergoing Chemotherapy (MENAC)**

Experimental: Multimodal intervention:



Nutritional supplements aimed at optimal energy balance and protein intake and including 2 g/day n-3 polyunsaturated fatty acids with dietetic consultation

Home-based self-assisted **exercise program** including a walking based aerobic component and resistance training with active physiotherapy input

Anti-inflammatory treatment (Ibuprofen)

Primary Outcome Measure: body weight change [Time Frame: 6 weeks]

Where are we headed?



- Definitive, etiology based diagnostic criteria
- Beyond volitional food intake
- Clarification of approvable endpoints by regulatory agencies
- Multimodal therapy
- Research consortia