

# Cancer cachexia, resilience and impact on anti-cancer treatment

Cardiff Palliative Care Masterclass 2019



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## Overview

- Current clinical frameworks for definition and assessment
- Current research focus on underlying mechanisms and targets
- Broadening the focus: looking beyond the weight loss
- Concept of phenotypical resilience in cancer patients
- How might we better represent 'fitness' for anti-cancer treatment?
- The future MDT: algorithms and A.I. - where is the patient?
- SMARTER MDT ways of working



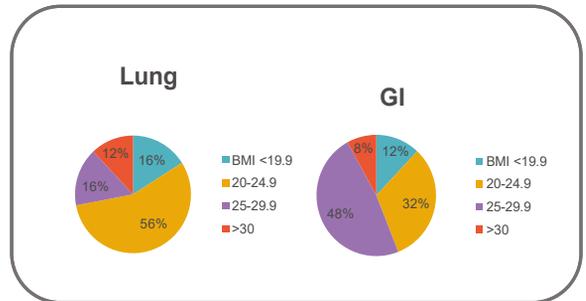
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# Cancer Associated Cachexia Syndrome

Not what it used to be.....?

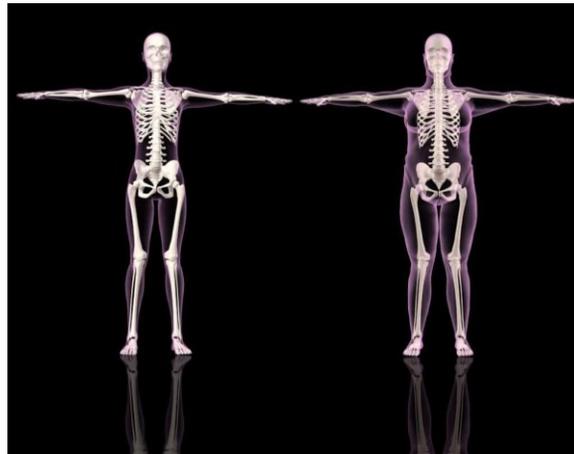


Cardiff data on 50 patients with criteria for cachexia



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## Cancer cachexia: what does it look like now?



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# Cancer cachexia: a definition

- What does a definition give us?
  - The framework to assess key factors consistently
  - The potential to understand when to treat – and not
  - The ability to classify severity – and the implications for anti-cancer treatment
  - The opportunity to target specific components effectively
    - As MDTs
    - As part of clinical trials



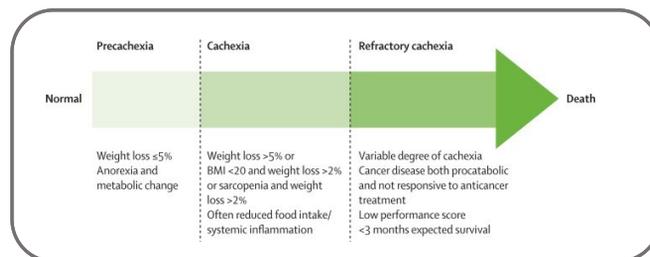
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## Definition and classification of cancer cachexia: an international consensus



Kenneth Fearon\*, Florian Strasser\*, Stefan D Anker, Ingvar Bosaeus, Eduardo Bruera, Robin I. Fainsinger, Aminah Jatoi, Charles Loprinzi, Neil MacDonald, Giovanni Mantovani, Mellar Davis, Maurizio Muscaritoli, Faith Ottery, Lukas Radbruch, Paula Ravasco, Declan Walsh, Andrew Wilcock, Stein Kaasa, Vickie E Baracos

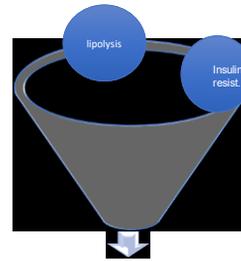
Fearon K et al. Lancet Oncology. 2011;12:489–495.



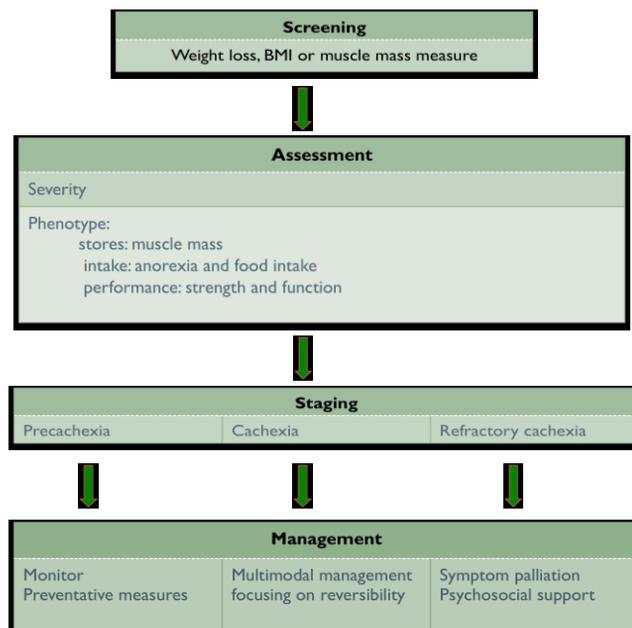
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## Definition of cancer cachexia

- Loss of skeletal mass (+/- fat mass)
- Negative protein and energy balance
- Complex multifactorial syndrome:
  - Reduced food intake (anorexia)
  - Abnormal metabolism
  - Physical deconditioning



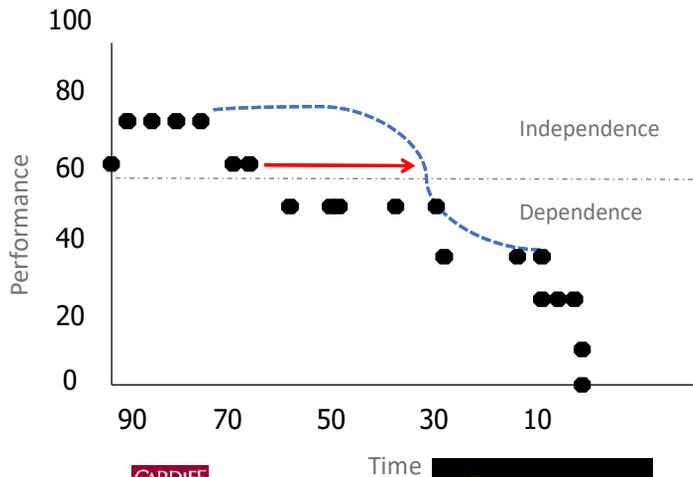
7



Adapted from: Fearon K et al. Lancet Oncology 2011;12: 489-495

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## The value of palliative rehabilitation



9

## Where has the focus of attention been?

- Assessment
- Quantifying the implications for prognosis
- Understanding the underlying pathophysiology
- The holy grail of therapeutic targets



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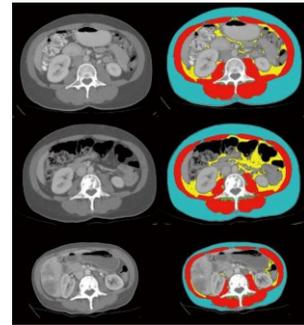
# Assessment

**Assessment**

Severity

Phenotype:  
 stores: muscle mass  
 intake: anorexia and food intake  
 performance: strength and function

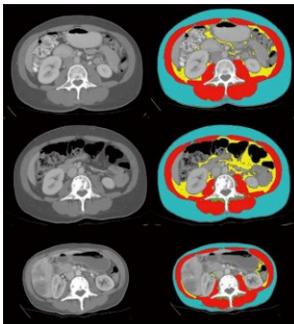
PHYSIOLOGICAL	CLINICAL	PROGNOSIS
Energy Expenditure	Resting Metabolic Rate (RMR)	1500 kcal
Energy Intake	Energy Intake	1500 kcal
Energy Balance	Energy Balance	0 kcal
Body Mass	Body Mass	70 kg
Lean Body Mass	Lean Body Mass	50 kg
Adipose Tissue	Adipose Tissue	20 kg
Water	Water	40 kg
Minerals	Minerals	3 kg
Proteins	Proteins	10 kg
Carbohydrates	Carbohydrates	1 kg
Lipids	Lipids	5 kg
Other	Other	1 kg



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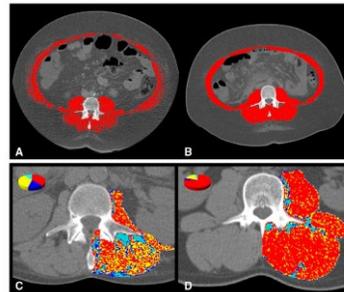
# Staging and prognosis

Staging		
Precachexia	Cachexia	Refractory cachexia



Quantity

TABLE FOR THE STAGING OF CACHEXIA (WHO 2005)



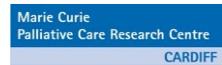
Quality

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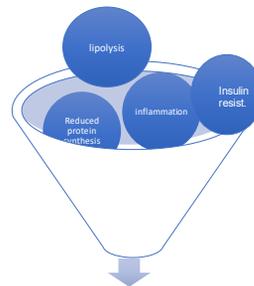
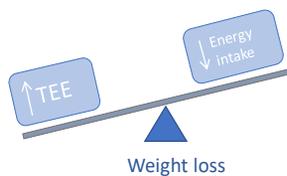
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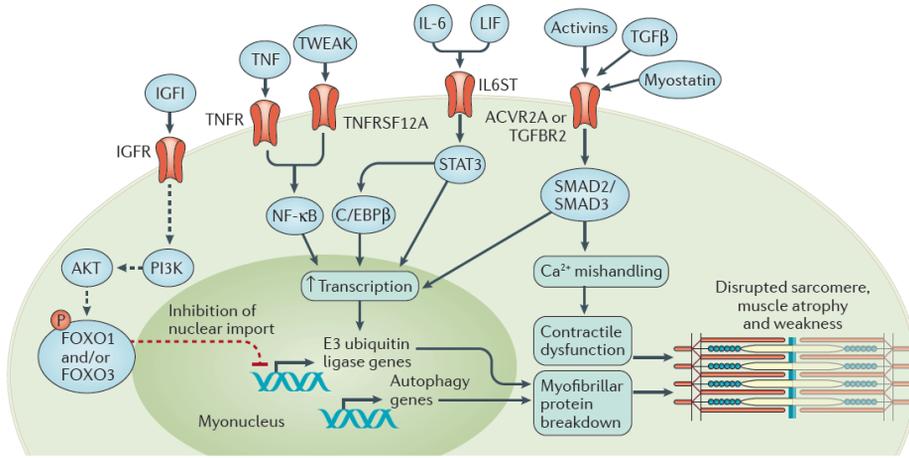
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## What lies beneath?



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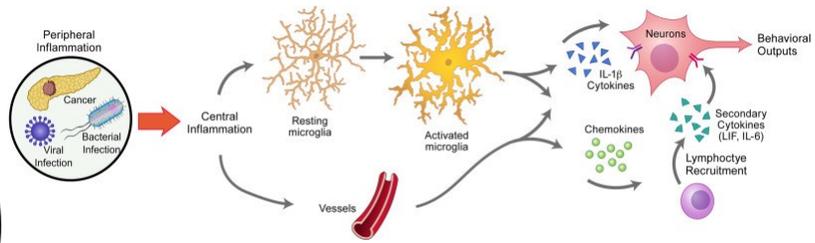
### Skeletal muscle atrophy: the acronym soup of cancer cachexia signalling pathways



Baracos et al. Nature Reviews Disease Primers 2018;4:17105. doi:10.1038/nrdp.2017.105

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CNS,  
sickness  
behaviours  
and cancer  
cachexia



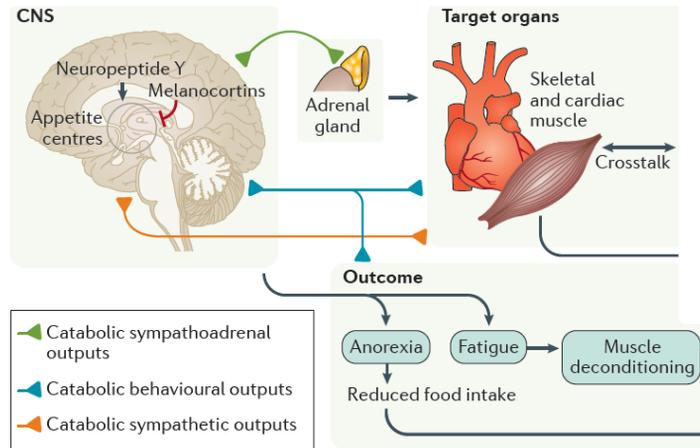
Initiation, amplification, and perpetuation of hypothalamic inflammation.

Burfeind KG et al. Semin Cell & Development Biol 2016;54:42-52



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## CNS, sickness behaviours and cancer cachexia



Baracos et al. Nature Reviews Disease Primers 2018;4:17105. doi:10.1038/nrdp.2017.105

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## Where has the focus of attention been?

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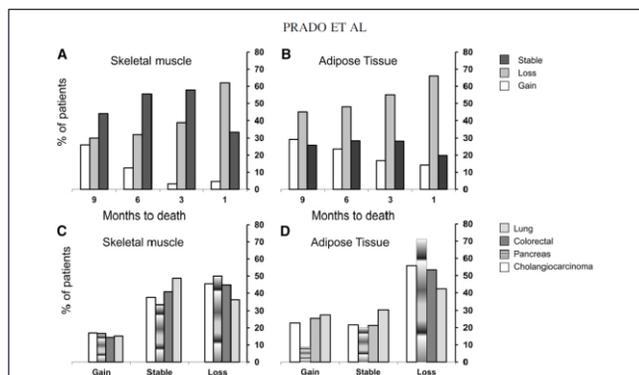
Study	n	Cancer type	Intervention	Outcome
Bourdel-Marchasson et al RCT	335	pancreatic	Structured nutritional intervention	No improvement in mortality or weight gain
Sanchez-Lara et al Double blind RCT	92	NSCLC	PUFA ONS	Improved LBM and weight gain
Temel et al: Romana I&II Double blind RCT	975	NSCLC	Anamorelin	Improved LBM but no improvement in grip strength
Golan et al Phase II RCT	125	Pancreatic cancer	Antimycostatin antibody	Higher deaths in intervention; no improvement in LBM
Dobs et al Phase II RCT	100	Mixed cancers	Enobosarm	Within group improvements in LBM
Hickish et al Double blind RCT	303	Advanced colorectal	Anti IL-1 Monoclonal Ab	Improvement in composite endpoint: LBM/symptoms
NCT02330926	240	Pancreatic and lung	NSAID/exercise/PUFA ONS	recruiting

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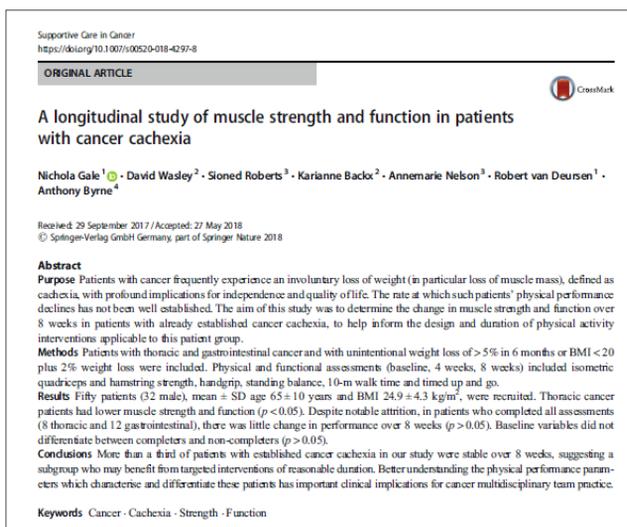
## Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential?<sup>1-3</sup>

Carla M Prado, Michael B Sawyer, Sunita Ghosh, Jessica R Lieffers, Nina Esfandiari, Sami Antoun, and Vickie E Baracos

Prado et al. Am J Clin Nutr 2013;98:1012-1019



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Study	n	Cancer type	Intervention	Outcome
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## Looking beyond the weight loss

- Sarcopenia – we all develop it as we get older
- Elderly care: sophisticated approach to loss of *strength and function* as well as mass
- Loss of strength can predate loss of mass: a chance to intervene early and understand cachexia as reducing our participatory abilities and resilience



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# Sarcopenia: definitions from elderly care

Age and Aging 2018, 6: 1-16  
doi: 10.1093/ageing/afy169

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## GUIDELINES

### Sarcopenia: revised European consensus on definition and diagnosis

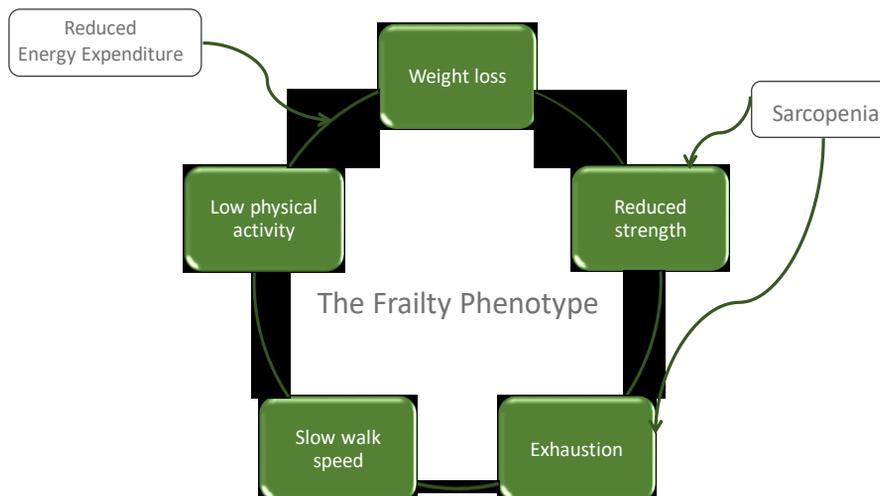
ALFONSO J. CRUZ-JENTOFF<sup>1</sup>, GOLUSTAN BAHAT<sup>2</sup>, JURGEN BAUER<sup>3</sup>, YVES BOIRIE<sup>4</sup>, OLIVIER BRUYERE<sup>5</sup>, TOMMY CEDERHOLM<sup>6</sup>, CYRUS COOPER<sup>7</sup>, FRANCESCO LANDI<sup>8</sup>, YVES ROLLAND<sup>9</sup>, AVAN AIHE SAYER<sup>10</sup>, STEPHANIE M. SCHNEIDER<sup>11</sup>, CORNEL C. SIEBER<sup>12</sup>, EVA TOPINKOVA<sup>13</sup>, MAURITS VANDEVOUDE<sup>14</sup>, MARIJOLEN VISSER<sup>15</sup>, MAURO ZAMBONI<sup>16</sup>, WRITING GROUP FOR THE EUROPEAN WORKING GROUP ON SARCOPEINIA IN OLDER PEOPLE 2 (EWGSOP2), AND THE EXTENDED GROUP FOR EWGSOP2

- Original definition included importance of muscle function as a core component which defines sarcopenia
- New definition upholds importance of muscle strength
- Muscle mass and quality challenging to interpret
- Emphasis on measures of integrated task performance



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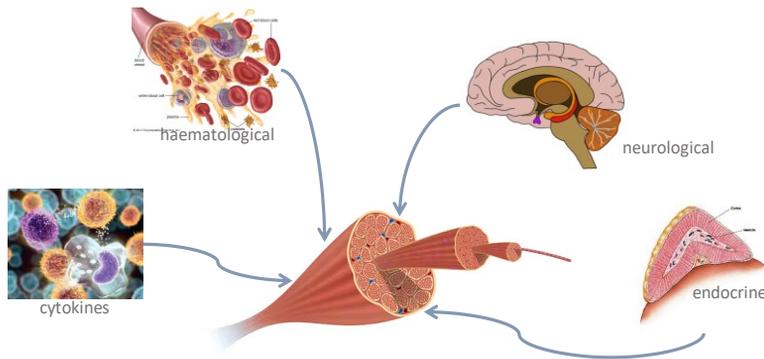
## Sarcopenia and...frailty



Modified from Fried et al. J Gerontol A Biol Sci Med Sci 2009;64:1049-1057

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## Muscle as the substrate of frailty and the pathway for its effects.....



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## Frailty as a cumulative deficits syndrome

- We are complex, resilient organisms
- Redundancy in our integrated physiological systems to cope with stressors
- Loss of resilience occurs when the *number* of systems compromised reaches a threshold
- Cumulative smaller deficits rather than obvious single large deficits produce risk



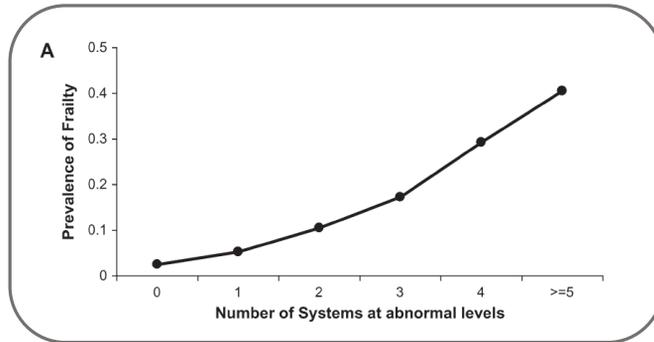
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Journal of Gerontology: MEDICAL SCIENCES  
 The Journal of Gerontology: A Biol Sci Med Sci  
 2009, Vol. 64A, No. 10, 1049-1057  
 doi:10.1093/geronb/gpn076

© The Author 2009. Published by Oxford University Press on behalf of The Gerontological Society of America.  
 All rights reserved. For permission, please e-mail: journals.permissions@oxfordjournals.org  
 Advance Access publication on June 16, 2009

### Nonlinear Multisystem Physiological Dysregulation Associated With Frailty in Older Women: Implications for Etiology and Treatment

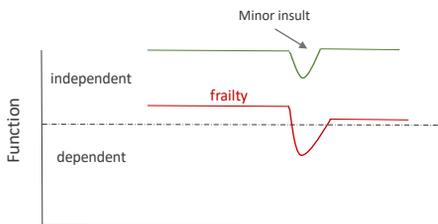
Linda P. Fried,<sup>1</sup> Qian-Li Xue,<sup>2,3,4</sup> Anne R. Cappola,<sup>5</sup> Luigi Ferrucci,<sup>6</sup> Paulo Chaves,<sup>2,3</sup> Ravi Varadhan,<sup>2,3,4</sup> Jack M. Guralnik,<sup>7</sup> Sean X. Leng,<sup>2</sup> Richard D. Semba,<sup>2</sup> Jeremy D. Walston,<sup>2,3</sup> Caroline S. Blaum,<sup>8,9</sup> and Karen Bandeen-Roche<sup>2,3</sup>



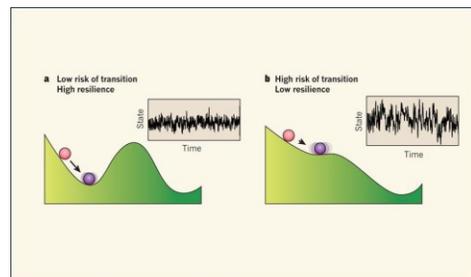
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## Accumulation and the continuum...tipping points

### Stressor and recovery



### Predicting the tipping point



Scheffer M. Nature 2010;467:411-412



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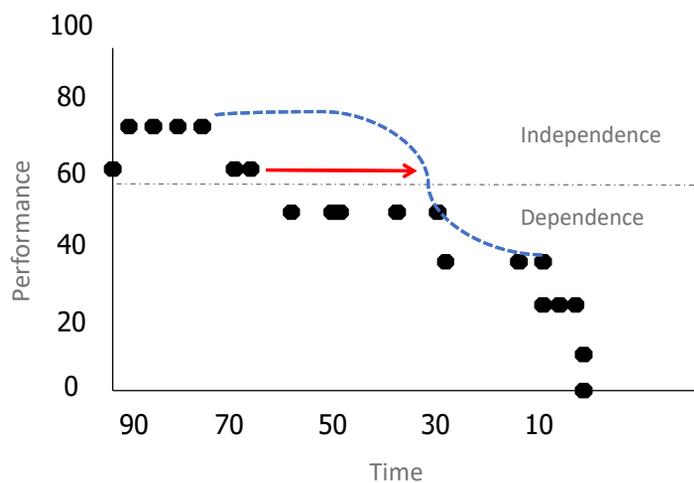
## Adopting the concept of 'cancer frailty'

- Beyond muscle loss to a better understanding of:
  - What are the deficits that accumulate and threaten our resilience?
  - Are they cancer specific and how do we describe this frailty?
  - What can they tell us about 'fitness' for anti-cancer treatment?



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## Why does that matter?



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# Why does that matter?

**BMJ Open** A population-based observational study on the factors associated with the completion of palliative chemotherapy among patients with oesophago-gastric cancer

Oliver Green,<sup>1,2</sup> Tom Dwyer,<sup>3</sup> Richard Henry Hardwick,<sup>4</sup> Stuart Riley,<sup>5</sup> Katherine Greenaway,<sup>6</sup> David Cromwell<sup>7</sup>

**OBJECTIVE** Oesophago-gastric cancer is a world-wide leading cause of cancer death. However, the majority of patients with oesophago-gastric cancer die with symptoms and are likely to have completed palliative chemotherapy.

**DESIGN** A population-based observational study.

**SETTING** A large tertiary care hospital.

**PARTICIPANTS** All patients with oesophago-gastric cancer who were registered with the hospital in 2010 and 2011.

**MEASUREMENTS AND MAIN RESULTS** We identified 1000 patients with oesophago-gastric cancer who were registered with the hospital in 2010 and 2011. We identified 473 patients who had completed palliative chemotherapy.

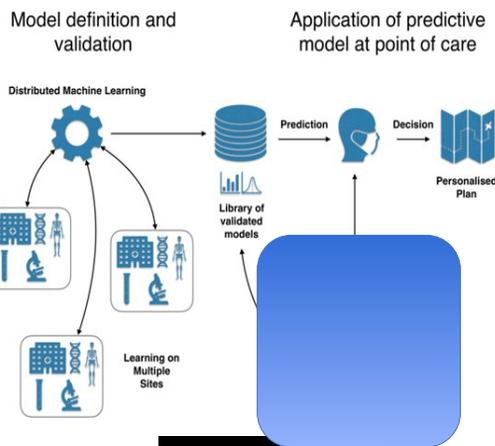
**CONCLUSIONS** The majority of patients with oesophago-gastric cancer who were registered with the hospital in 2010 and 2011 had completed palliative chemotherapy.

- Of patients with complete data: 47.3% did not complete SACT
- For youngest (<55): over 40% did not complete
- For >65 age group: 52% did not complete



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# Why does that matter?



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# Better profiling risk

PUBLISHED IN **LANCET ONCOLOGY** AS  
*Radiother Oncol*. 2014 October ; 113(1): 47-53. doi:10.1016/j.radonc.2014.08.013.

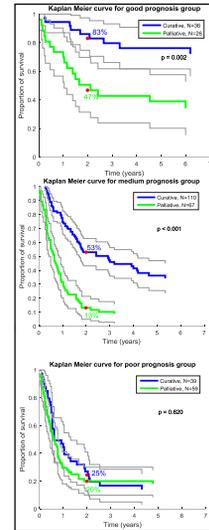
**Rapid learning in practice: A lung cancer survival decision support system in routine patient care data**

Andre Dekker<sup>a,b,c</sup>, Shalini Vinod<sup>a,d</sup>, Lois Holloway<sup>a,c,d,f</sup>, Cary Oberije<sup>b</sup>, Armia George<sup>a</sup>, Gary Goozee<sup>a,d</sup>, Geoff P. Delaney<sup>a,d,g</sup>, Philippe Lambin<sup>b</sup>, and David Thwaites<sup>g</sup>

<sup>a</sup> Liverpool and Macarthur Cancer Therapy Centres and Ingham Institute, Australia <sup>b</sup> Department of Radiation Oncology (MAASTRO), GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre\*, The Netherlands <sup>c</sup> Institute of Medical Physics, School of Physics, University of Sydney <sup>d</sup> South Western Sydney Clinical School, University of New South Wales, Liverpool <sup>e</sup> School of Medicine, University of Western Sydney <sup>f</sup> Centre for Medical Radiation Physics, University of Wollongong, Australia

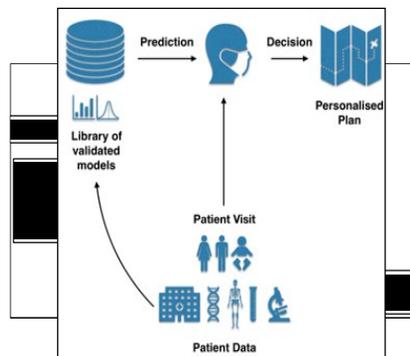
**Abstract**

**Background and purpose**—A rapid learning approach has been proposed to extract and apply knowledge from routine care data rather than solely relying on clinical trial evidence. To validate this in practice we deployed a previously developed decision support system (DSS) in a typical, busy clinic for non-small cell lung cancer (NSCLC) patients.



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# Reframing precision and personalized medicine – with the person



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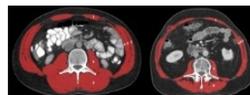
# Single systems approach to cancer frailty

Eur Radiol (2018) 28:5998–6005  
DOI 10.1007/s00309-018-1104-4

ONCOLOGY

## Assessment of sarcopenia and changes in body composition after neoadjuvant chemotherapy and associations with clinical outcomes in oesophageal cancer

Connie Yip · Vicky Goh · Andrew Davies · James Gossage · Rosalind Mitchell-Hay · Orla Hyman · Nick Maisey · Paul Ross · Andrew Gaya · David B. Landau · Gary J. Cook · Nyree Griffin · Robert Mason



## Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG-ps) in patients receiving palliative chemotherapy for gastroesophageal cancer

Andrew B C Crumley, Robert C Stuart, Margaret McKernan, Alexander C McDonald, Donald C McMillan



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# Task performance and chemo toxicity

Support Care Cancer (2018) 26:4049–4057  
ORIGINAL ARTICLE

### The value of physical performance measurements alongside assessment of sarcopenia in predicting receipt and completion of planned treatment in non-small cell lung cancer: an observational exploratory study

Jamini T. Collins<sup>1\*</sup>, Simon Nade<sup>1</sup>, John Chero<sup>2,3</sup>, Helen E. Dwyer<sup>4</sup>, William B. Evans<sup>5</sup>, Daniel Farrow<sup>6</sup>, Jason F. Lopez<sup>7</sup>, Rhona Parry<sup>8</sup>, Rebecca Pratt<sup>9</sup>, Anthony Ryan<sup>10</sup>

Received: 1 April 2017 / Accepted: 3 July 2017  
© Springer-Verlag GmbH Germany 2017

**Abstract** Introduction: The presence of muscle mass depletion is associated with poor outcomes and survival in cancer. Objective muscle mass, assessment of muscle strength or physical performance is essential for the diagnosis of sarcopenia. Non-small cell lung cancer (NSCLC) is a prevalent form of cancer with high mortality, and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) is commonly used to assess patient suitability for treatment. However, a significant proportion of patients with good PS are unable to complete multidisciplinary team (MDT) planned treatment. Little is known about the ability of objective measurements of physical performance in predicting patients' ability to complete MDT-planned treatment and outcomes in NSCLC. Objective: The sought to establish whether physical performance, utilizing the short physical performance battery (SPPB), alongside muscle mass measurements, was able to predict receipt and completion of MDT-planned treatment, with a focus on chemotherapy in NSCLC. Materials and methods: Participants with NSCLC treated through a single lung cancer MDT and ECOG PS 0–2 were recruited and the following assessed: body composition (lean-tissue impedance (LTI) and whole body dual-energy X-ray absorptiometry (DXA)), a validated physical performance (SPPB), PS and nutritional status. We recorded receipt and completion of chemotherapy, as well as any adverse effects, hospitalisations, and treatment delays. Results: We included a total of 62 participants with NSCLC, and in 29 of these, the MDT-planned treatment was chemotherapy. Participants with earlier age, disease and weight loss of <math>10\%</math> were more likely to complete MDT-planned treatment ( $p < 0.001$ ) and  $p < 0.05$ , patients with a higher total SPPB score were more likely to complete more cycles of chemotherapy as well as the full course (Quick gait speed and sit-to-stand times were associated with completion of three or more cycles of chemotherapy ( $p = 0.01$ ). For every unit increase in SPPB score, there was a 28.2% decrease in all-cause hospitalisations and delays of chemotherapy (incidence rate ratio 0.718,  $p = 0.001$ ), while ECOG PS showed no correlation with these outcomes. Conclusion: Assessing physical performance by SPPB is quick and simple to do in clinical settings and may give better indication of likely chemotherapy treatment course completion than muscle mass alone and ECOG PS. In turn, this may identify specific targets for early nutritional intervention and impact on MDT decision-making and patient care of importance.

**Keywords** Sarcopenia · Non-small cell lung cancer · Short physical performance battery

\* Jamini T. Collins  
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<sup>1</sup> Department of Palliative Medicine, University Hospital Llandough, Penarth, UK  
<sup>2</sup> Cardiff University, Cardiff, UK  
<sup>3</sup> Velindre Cancer Centre, Cardiff, UK  
<sup>4</sup> Department of Respiratory Medicine, University Hospital Llandough, Penarth, UK  
<sup>5</sup> Department of Medical Physics and Clinical Engineering, University Hospital of Wales, Cardiff, UK  
<sup>6</sup> Institute of Primary Care and Public Health, Cardiff University, Cardiff, UK

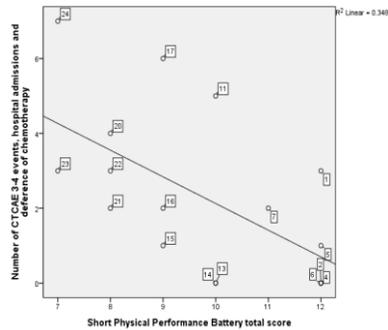
Published online: 18 July 2017



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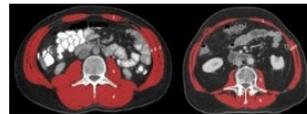
## Task performance and chemo toxicity



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## Paradigm shift: complex host

- Imaging: lean body mass and quality



- Circulating biomolecules

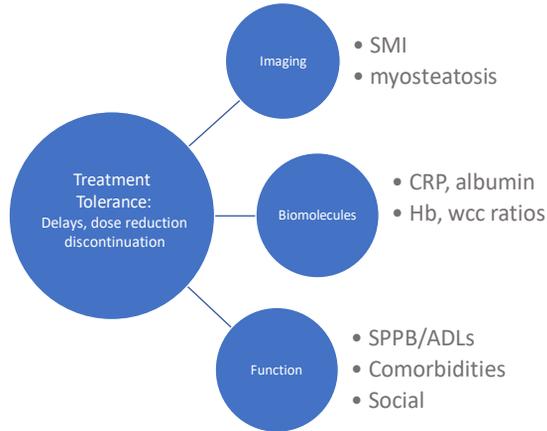


- Function



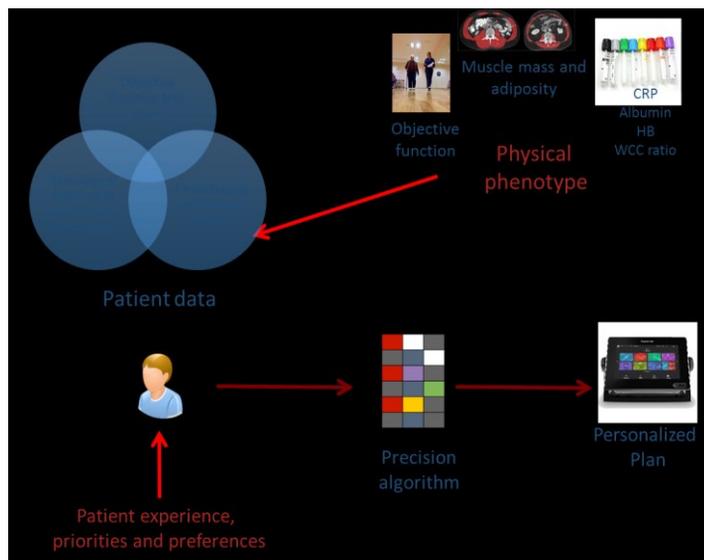
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# PrEdicting Treatment Resilience in Oesophageal cancer Systemic treatment



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# Supporting Multidata Analysis to Refine Treatment: SMART MDT



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# Cachexia and frailty in refining cancer treatment

