

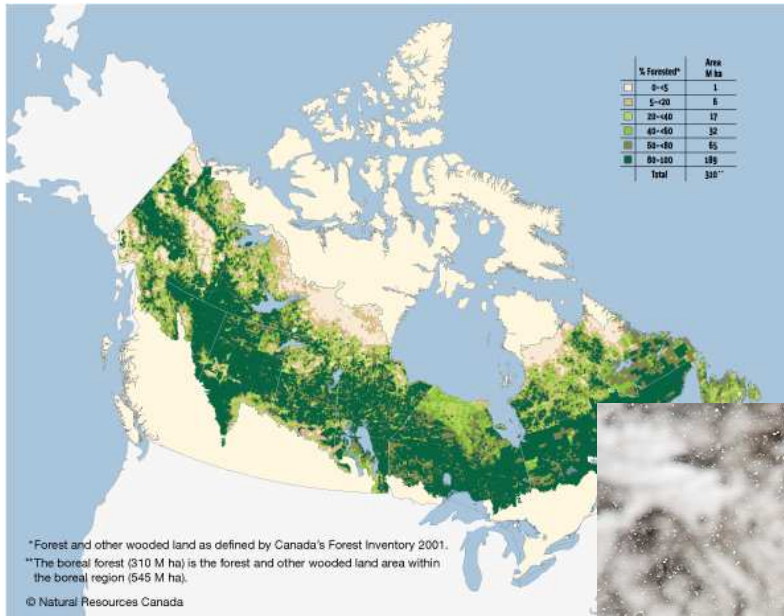
# Sarcopenia predicts treatment toxicity, mortality and functional status of patients with advanced cancer

Vickie Baracos PhD

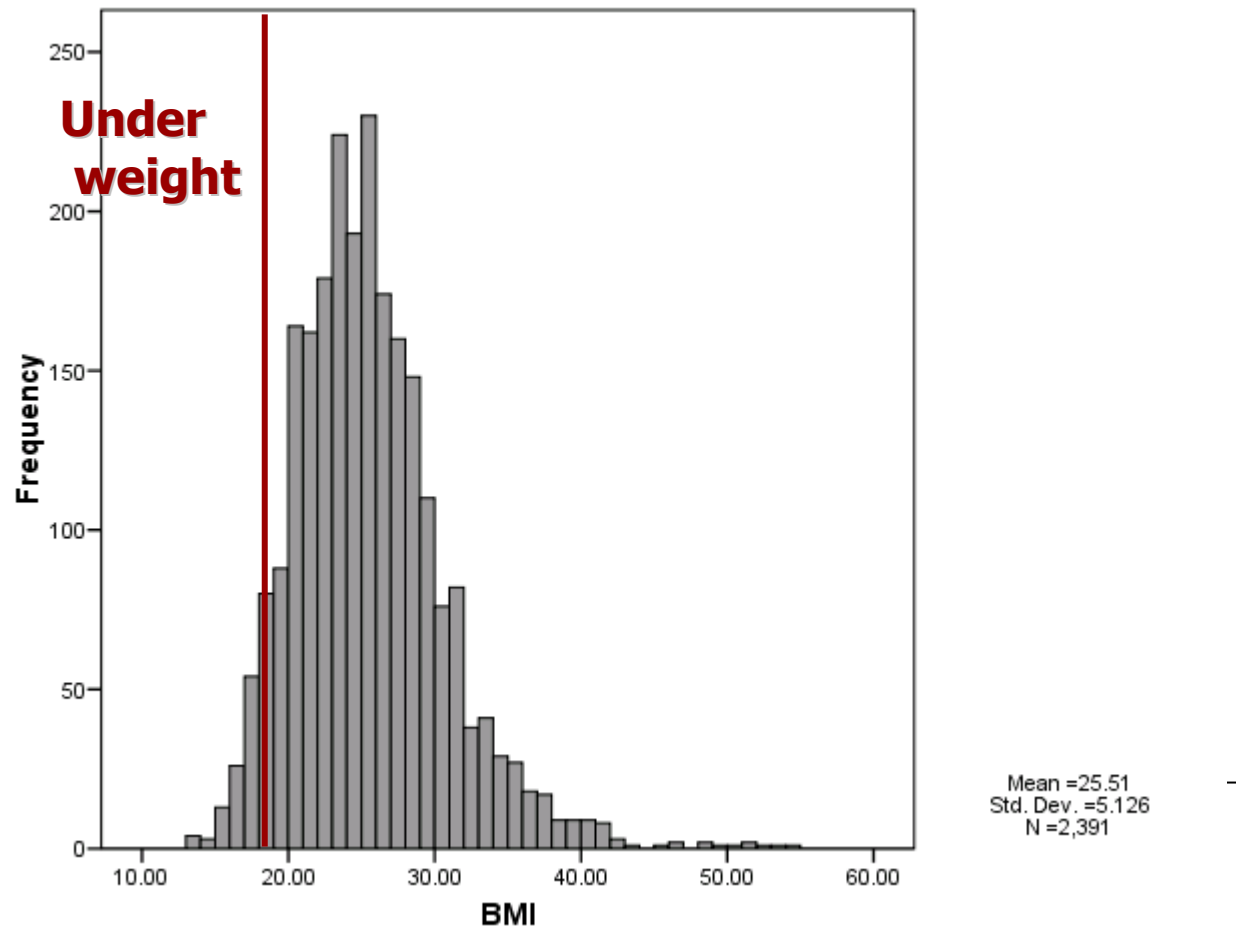
Professor and Alberta Cancer Foundation  
Chair in Palliative Medicine, University of  
Alberta, Department of Oncology, Edmonton,  
Alberta, Canada



# Welcome to Alberta



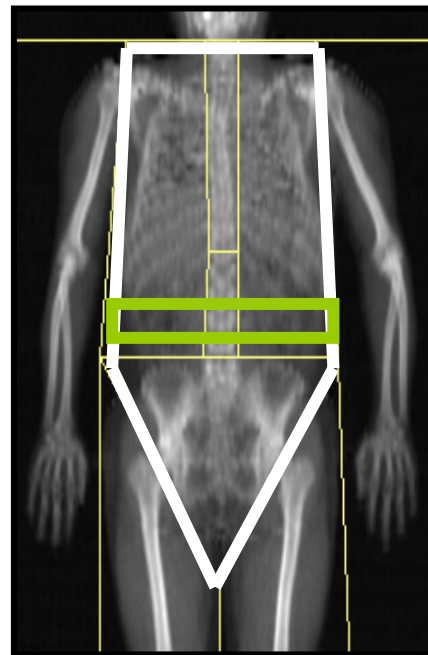
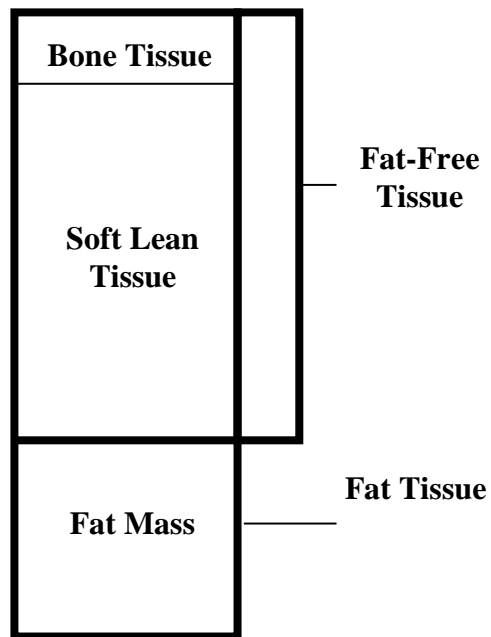
BMI Distribution for Cross Cancer Institute (n=2391 patients newly referred to Medical Oncology clinics with advanced lung or GI malignancies)



## A new term

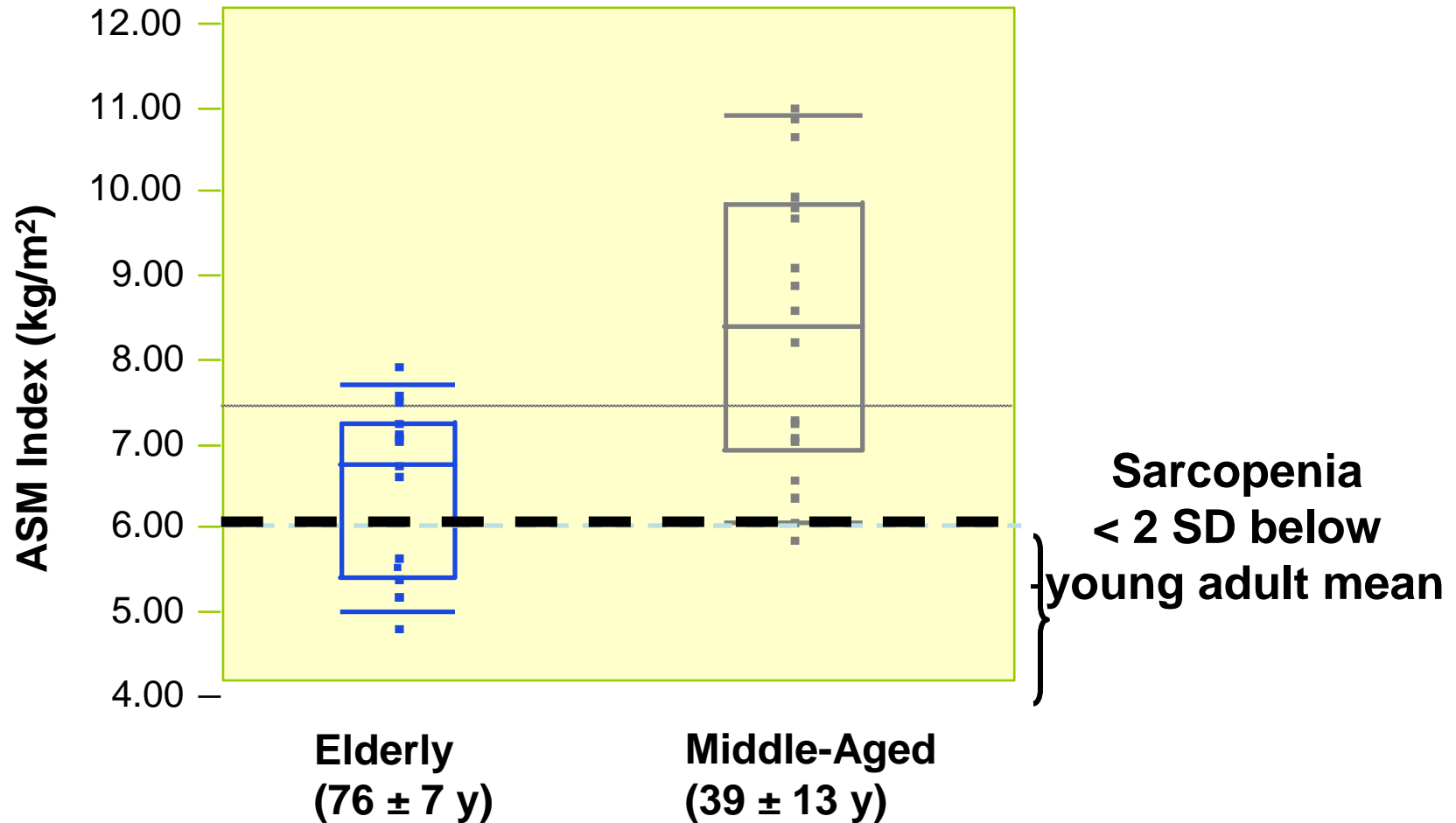
- Sarcopenia – “poverty of muscle”
- Working definitions:
  - absolute skeletal muscle mass
    - > 2 standard deviations below that expected for healthy middle age adults

# Dual energy X ray: total appendicular skeletal muscle



Sarcopenia=  
Men:  $<7.26$   
Women  $< 5.45$   
Kg of total  
appendicular  
skeletal muscle /  
 $\text{height}^2$

# Distribution of Skeletal Muscle Index (Total Appendicular Skeletal Muscle / Stature<sup>2</sup>) in Elderly versus Middle-Aged Men and Women



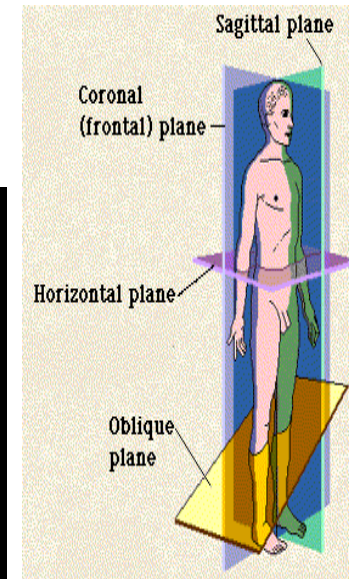
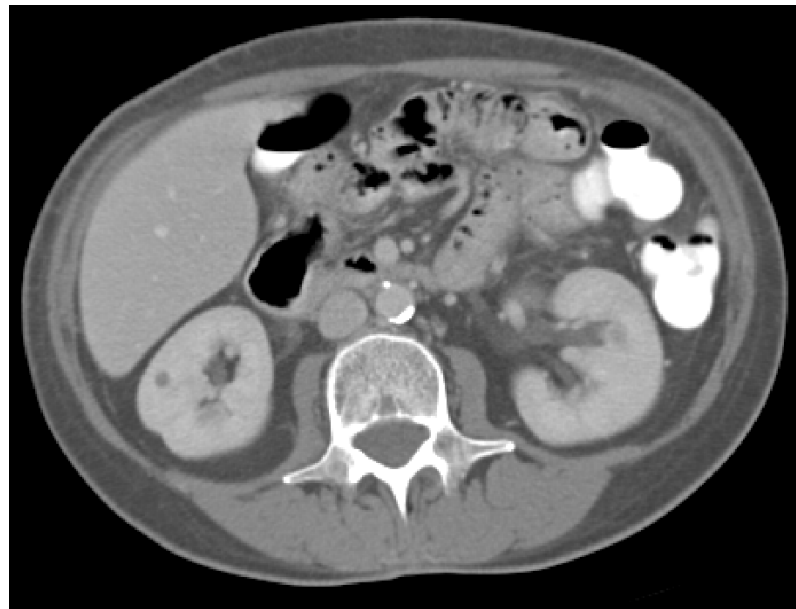
## **(In non-malignant disease) sarcopenia associates with**

- **Frailty, falls, fractures**
- **extended hospitalization**
- **infections and non-infectious complications in  
hospital and nursing home inpatients**
- **mortality**

**Baumgartner RN, et al. Epidemiology of sarcopenia among  
the elderly in New Mexico. *Am J Epidemiol* 1998;147(8):755-63**

# Computed tomography

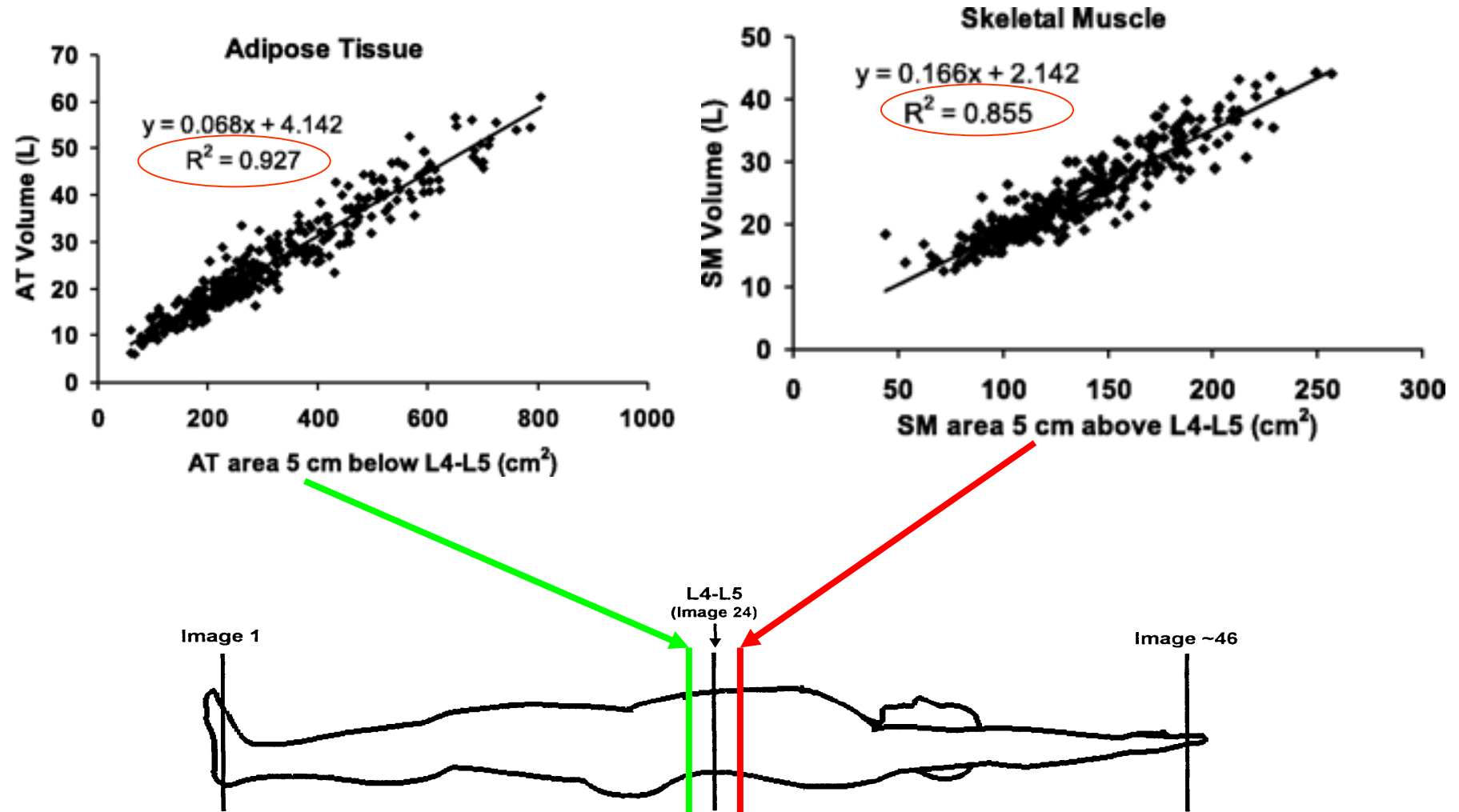
Fat-Free Tissue	Bone Tissue
	Liver Kidneys Spleen Tumor Intestines
	Specific Skeletal Muscle Groups
Fat Tissue	Visceral
	Intramuscular
	Subcutaneous



Lumbar skeletal muscles

# Association Between Whole Body Tissue Volume (L) and Single Abdominal Surface Area (cm<sup>2</sup>)

Shen, W. et al. *J Appl Physiol* 97:2333-2338 2004



# Methods

## **The emerging role of computerized tomography in assessing cancer cachexia**

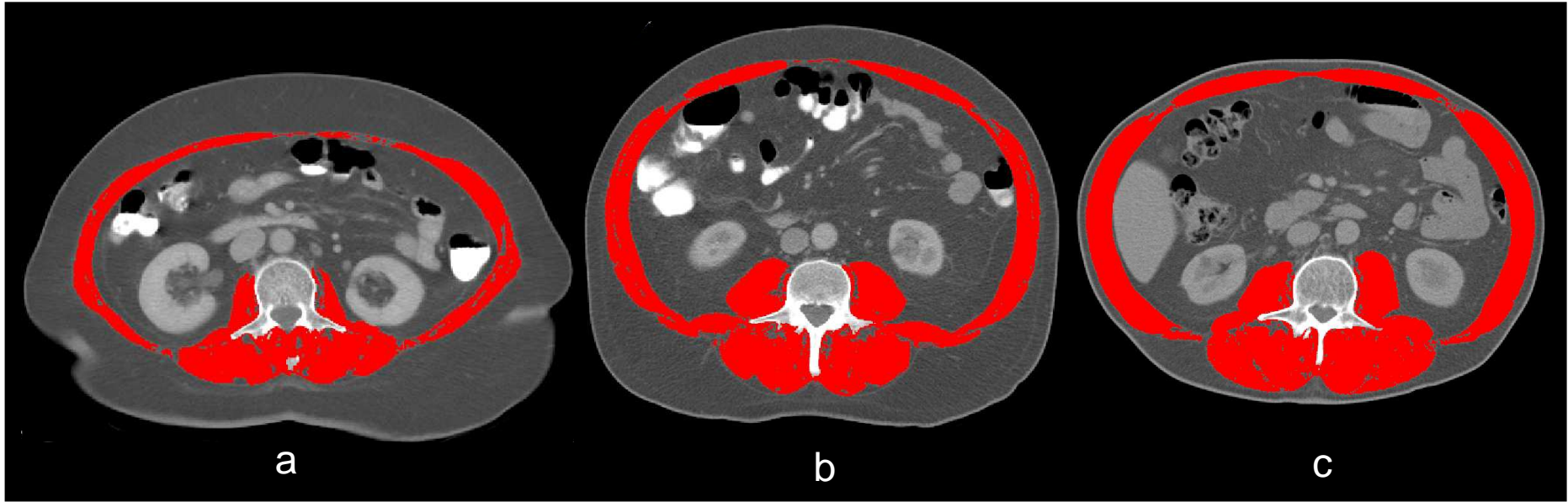
Carla M.M. Prado, Laura A. Birdsell and Vickie E. Baracos

**Current Opinion in Supportive and Palliative  
Care** 2009, 3:269–275

## **A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care.**

Mourtzakis M, Prado C, Lieffers JR, et al.

**Appl Physiol Nutr Metab.** 2008;33(5):997-1006.



Figure\_. Differences in lumbar skeletal muscle index (L3SMI;  $\text{cm}^2/\text{m}^2$ ) between three male patients with colorectal cancer and a BMI of 30. A) L3SMI of  $38.3 \text{ cm}^2/\text{m}^2$ ; sarcopenic\* b) L3SMI of  $57.4 \text{ cm}^2/\text{m}^2$ ; non-sarcopenic c) L3SMI of  $74.1 \text{ cm}^2/\text{m}^2$ ; non-sarcopenic. \*Sarcopenia is defined as lumbar skeletal muscle index  $<52.4 \text{ cm}^2/\text{m}^2$  for males (Prado et al. 2008).

Population – based study of 2115 consecutively referred patients with solid tumors of the respiratory or gastrointestinal tracts

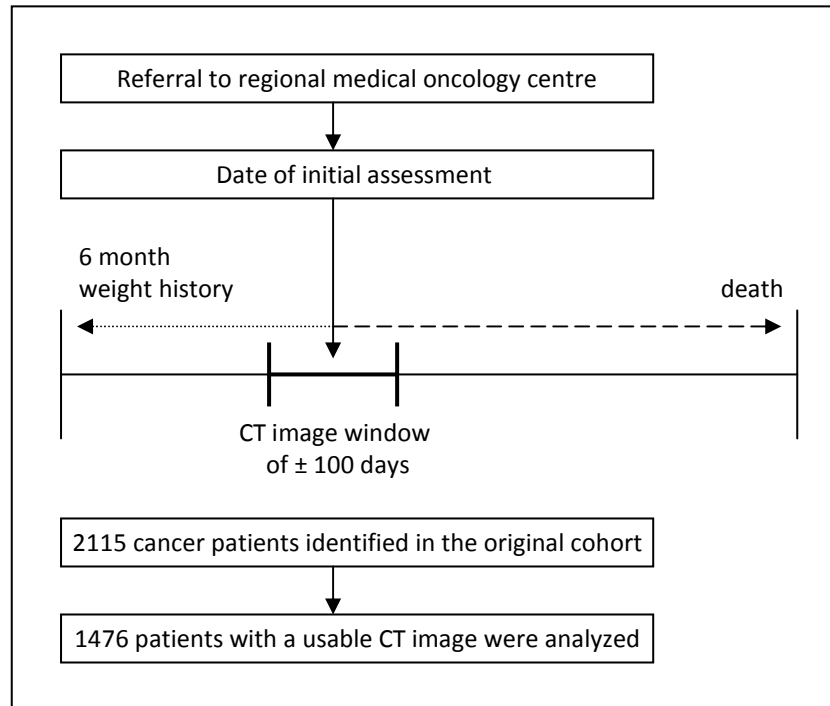



Figure 1. Study timeline and patient selection.

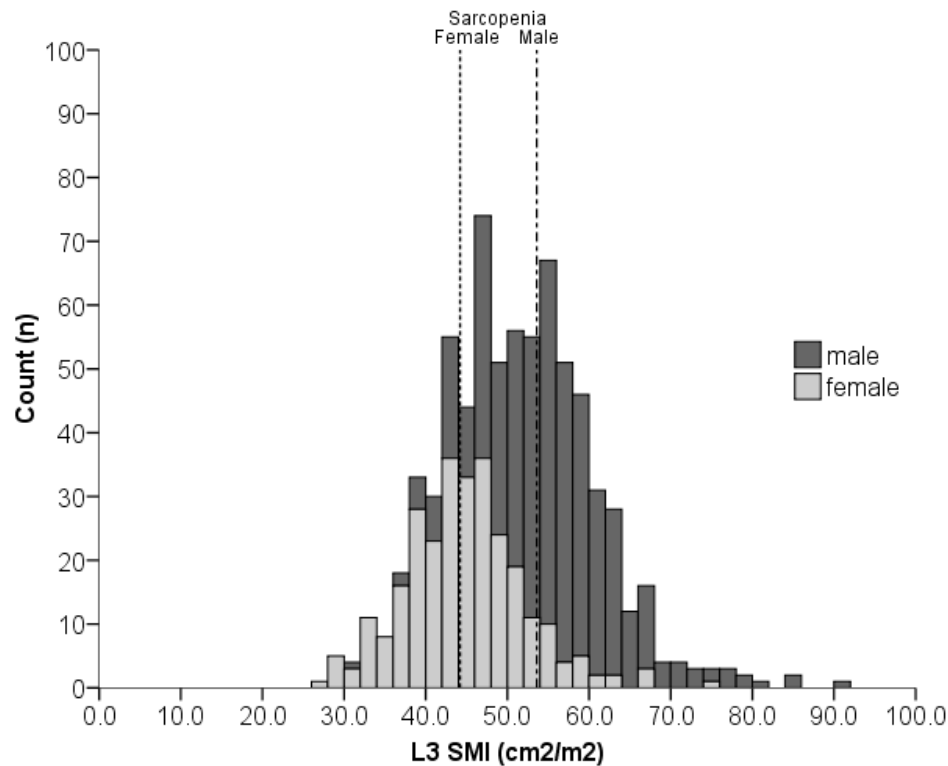
# Sarcopenia & cancer outcomes

- Mortality

Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study 

*Carla M M Prado, Jessica R Lieffers, Linda J McCargar, Tony Reiman, Michael B Sawyer, Lisa Martin, Vickie E Baracos*

# Defined sarcopenia in cancer patients



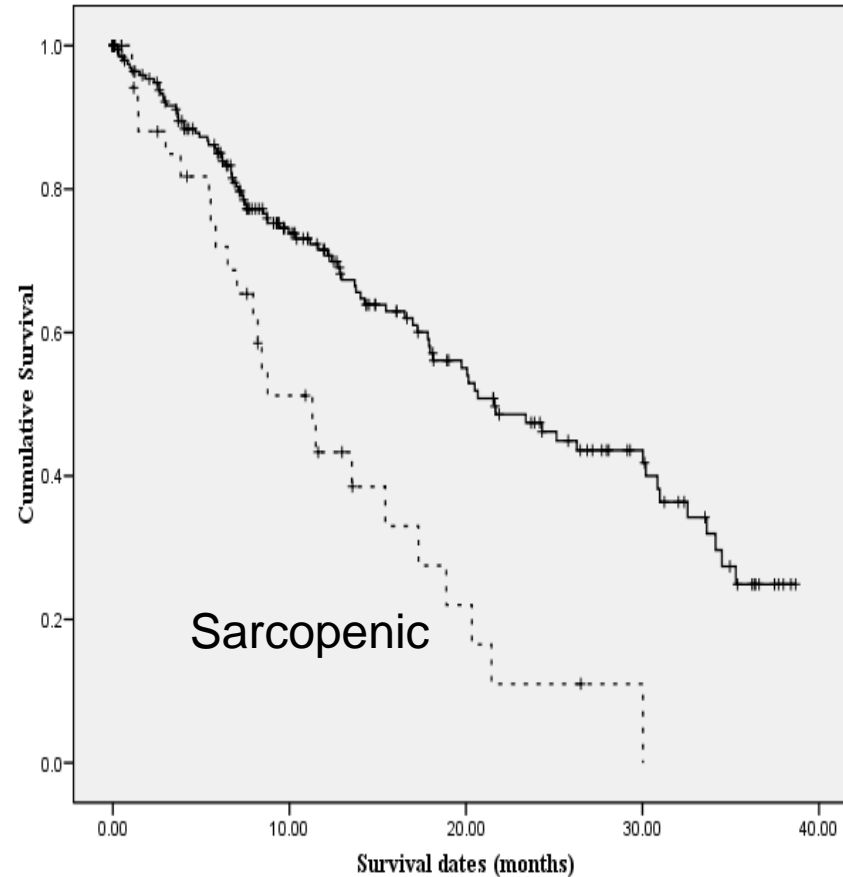
Level of muscle  
(cut point)  
significantly  
associated with  
decreased survival

Statistical method,  
Optimal  
Stratification

←  
Increased risk of death

## Survival is related to sarcopenia in obese patients with solid tumors

- independent of age, disease stage and performance status
- 11 months vs 21 months median survival



Results from 250 obese cancer patients with solid tumors of the respiratory or gastrointestinal tract

Sarcopenic obesity was shown to be a significant independent predictor of survival (HR 4.2 [2.4 – 7.2],  $p < 0.0001$ ) in a model which included age, stage, functional status

# Sarcopenia in an Overweight or Obese Patient Is an Adverse Prognostic Factor in Pancreatic Cancer

Benjamin H.L. Tan,<sup>1</sup> Laura A. Birdsell,<sup>2</sup> Lisa Martin,<sup>2</sup> Vickie E. Baracos,<sup>2</sup> and Kenneth C.H. Fearon<sup>1</sup>

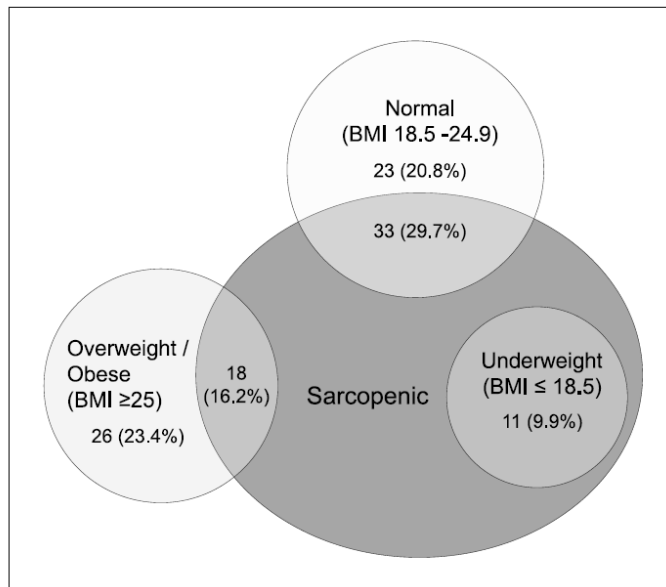
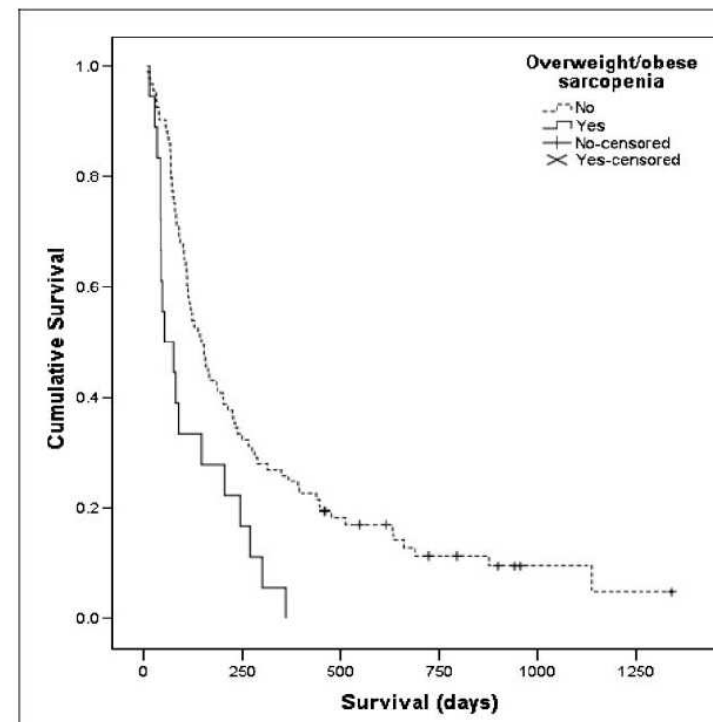


Fig. 1. Venn diagram of BMI classes and sarcopenic patients.



Clin Cancer Res 2009 Sarcopenia independently prognostic of survival.

Body composition in patients with non–small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis<sup>1–4</sup>

*Vickie E Baracos, Tony Reiman, Marina Mourtzakis, Ioannis Gioulbasanis, and Sami Antoun*

**AJCN. First published ahead of print February 17, 2010**

**TABLE 1**

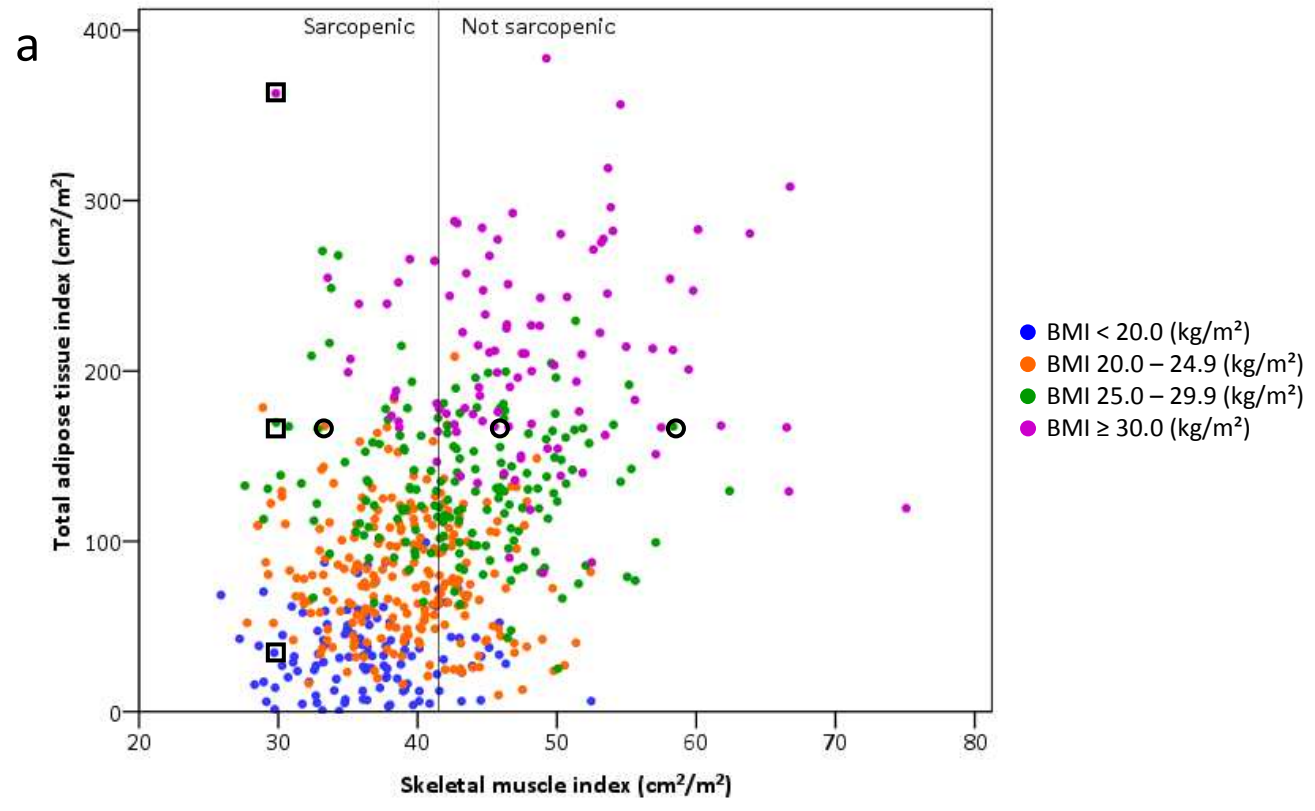
Anthropometric and demographic characteristics of the patients with lung cancer

	Men ( <i>n</i> = 229)	Women ( <i>n</i> = 212)	<i>P</i> value (sex)
Age (y)	67.0 ± 10.0 <sup>1</sup>	65.0 ± 10.7	0.035
Stage III (%)	51	42	0.24
Stage IV (%)	49	58	
Height (cm)	175 ± 7.1	168 ± 9.8	<0.001
Weight (kg)	77.0 ± 13.7	64.0 ± 16	<0.001
BMI (kg/m <sup>2</sup> )	25.2 ± 4.1	24.6 ± 5.9	0.26
BMI <18.5% (%)	2.6	12.3	—
BMI 18.5–24.99% (%)	46.7	43.4	—
BMI 25.0–29.99% (%)	35.8	28.8	—
BMI ≥30 (%)	14.9	15.6	—
Weight loss in preceding 6 mo (%)	−6.39 ± 7.76	−5.58 ± 8.06	0.3
Lumbar skeletal muscle area (cm <sup>2</sup> )	154 ± 25.9	109 ± 19.4	<0.001
Lumbar total adipose area (cm <sup>2</sup> )	310 ± 162	257 ± 170	<0.001
Lumbar skeletal muscle index (cm <sup>2</sup> /m <sup>2</sup> )	50.6 ± 8.5	42.1 ± 7.6	<0.001
Lumbar total adipose index (cm <sup>2</sup> /m <sup>2</sup> )	101 ± 53	99 ± 65	0.67
Sarcopenic (%)	61.1	31.3	<0.001
Estimated fat-free mass (kg)	52.4 ± 7.8	38.8 ± 5.8	<0.001
Estimated fat mass (kg)	24.2 ± 6.8	22.0 ± 7.1	<0.001
Vital status (% deceased)	83.8	78.7	0.16
Median time to death (d)	244	320	0.22

<sup>1</sup> Mean ± SD (all such values).

# Predictors of sarcopenia in cancer patients

- Sex male
- Stage IV cancer (advanced)
- Age > 65
- Reduced food intake
- BMI < 20
- BMI > 30 (protective)
- Chronic renal failure
- Diabetes w/ complications
- Hypertension with complications
- Total days in hospital >30 d



# MUSCLE AND ADIPOSE TISSUE DIVORCED!

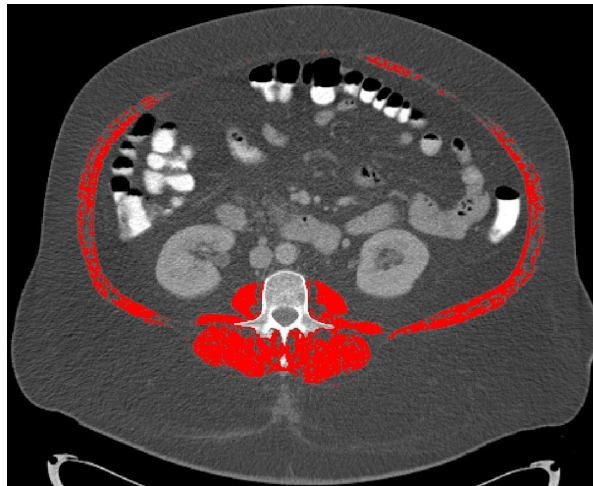
WE KNEW THAT ALL ALONG RIGHT?



## New terms and new definitions

: *Sarcopenic obesity*

- The “confluence of 2 epidemics” (R. Rubenoff)
- Entails the sum of health risks of both conditions



## Cachexia: A new definition

William J. Evans\*, John E. Morley<sup>1</sup>, Josep Argilés<sup>1</sup>,  
Connie Bales<sup>1</sup>, Vickie Baracos<sup>1</sup>, Denis Guttridge<sup>1</sup>,  
Aminah Jatoi<sup>1</sup>, Kamyar Kalantar-Zadeh<sup>1</sup>, Herbert Lochs<sup>1</sup>,  
Giovanni Mantovani<sup>1</sup>, Daniel Marks<sup>1</sup>, William E. Mitch<sup>1</sup>,  
Maurizio Muscaritoli<sup>1</sup>, Armine Najand<sup>1</sup>, Piotr Ponikowski<sup>1</sup>,  
Filippo Rossi Fanelli<sup>1</sup>, Morrie Schambelan<sup>1</sup>, Annemie Schols<sup>1</sup>,  
Michael Schuster<sup>1</sup>, David Thomas<sup>1</sup>, Robert Wolfe<sup>1</sup>, Stefan D. Anker<sup>1</sup>

Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat.

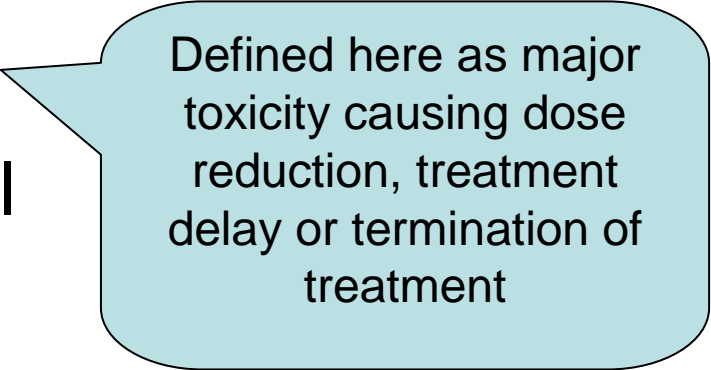
*Clin Nutr. 2008 Dec;27(6):793-9.*

# Sarcopenia & cancer outcomes

- Mortality

- **Chemotherapy toxicity:**

- 5 fluorouracil : colorectal
- Capecitabine : breast
- Sorafenib : renal cell carcinoma
- Adjuvant FEC (5-fluorouracil, epirubicin, cyclophosphamide) : breast
- Platinum-based lung cancer therapy (pilot)

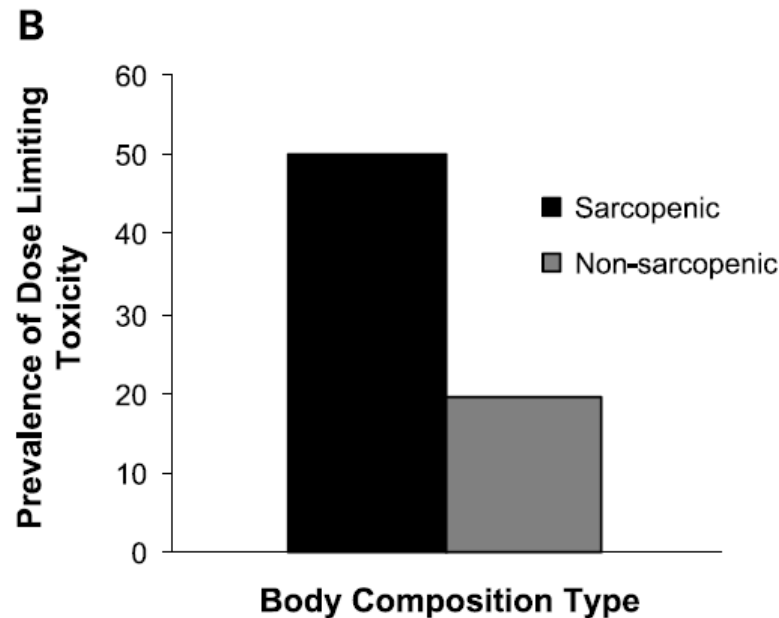


Defined here as major toxicity causing dose reduction, treatment delay or termination of treatment

# Sarcopenia as a Determinant of Chemotherapy Toxicity and Time to Tumor Progression in Metastatic Breast Cancer Patients Receiving Capecitabine Treatment

Carla M.M. Prado,<sup>2</sup> Vickie E. Baracos,<sup>1,2</sup> Linda J. McCargar,<sup>2</sup> Tony Reiman,<sup>1</sup> Marina Mourtzakis,<sup>1</sup> Katia Tonkin,<sup>1</sup> John R. Mackey,<sup>1</sup> Sheryl Koski,<sup>1</sup> Edith Pituskin,<sup>1</sup> and Michael B. Sawyer<sup>1</sup>

Clin Cancer Res 2009;15(8) April 15, 2009



Metastatic breast ca, taxane – or anthracycline resistant.

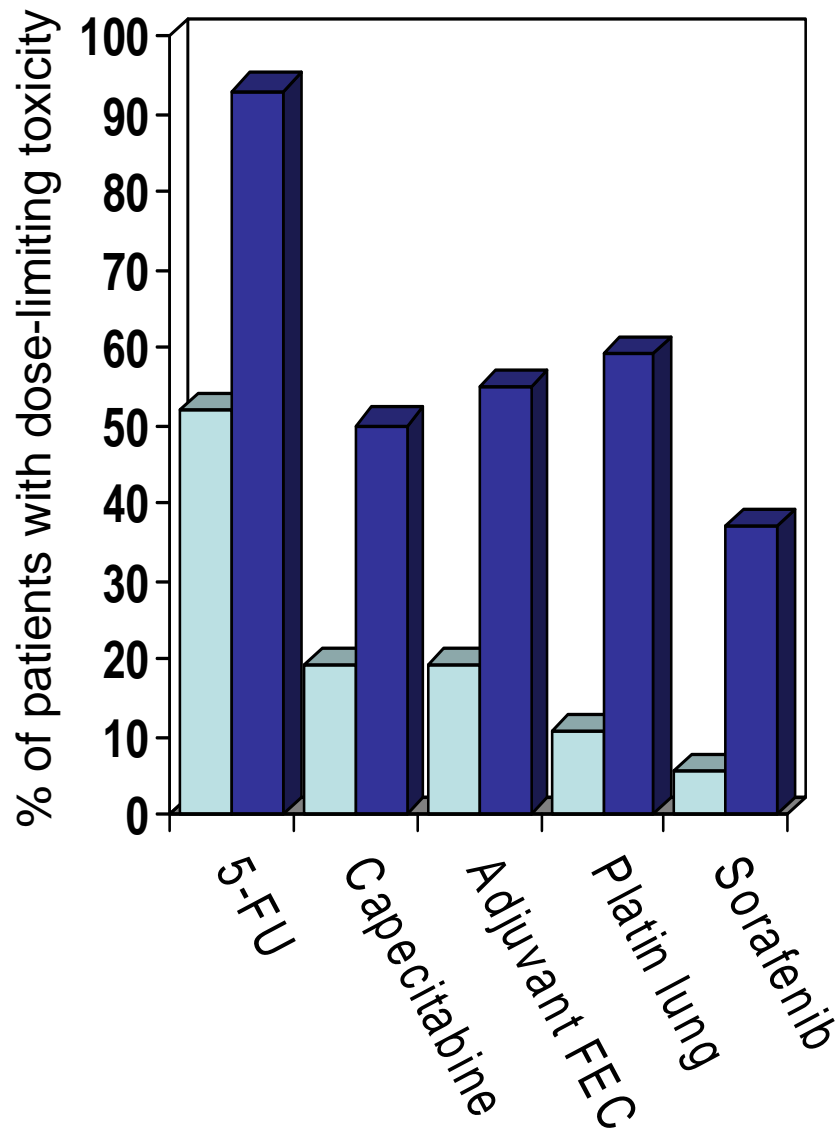
1250 mg/m<sup>2</sup> capecitabine BID

Dose – limiting toxicity defined as  $\geq$  grade 2 and resulting in interruption of treatment (dose reduction or dose delay)

P=0.039

## Sarcopenia significant predictor of chemotherapy toxicity : Fluoropyrimidines, Anthracyclines, Platins and Tyrosine Kinase Inhibitors

- Body composition as an independent determinant of **5-fluorouracil-based chemotherapy** toxicity.
  - Prado et al. *Clin Cancer Res.* 2007; 13(11):3264-8
- Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving **capecitabine** treatment,
  - Prado et al. *Clin Cancer Res.* 2009; 15(8):2920-6.
- Low body mass index and sarcopenia predict dose-limiting toxicity of **sorafenib** in patients with renal cell carcinoma,
  - Antoun et al *Annals of Oncology*, 2010 e pub ahead of print
- An exploratory study of body composition as a determinant of **epirubicin** pharmacokinetics and toxicity,
  - Prado et al, *Cancer Chemotherapy & Pharmacology*, in press
- Unselected lung cancer patients receiving any **platinum-based regimen**; unpublished data



## Incidence of dose-limiting toxicity is increased in sarcopenic patients:

Colorectal: 5FU p=0.001

Breast: Capecitabine p=0.039

Breast: Adjuvant FEC p= 0.03

Lung: platinum regimen p=0.003

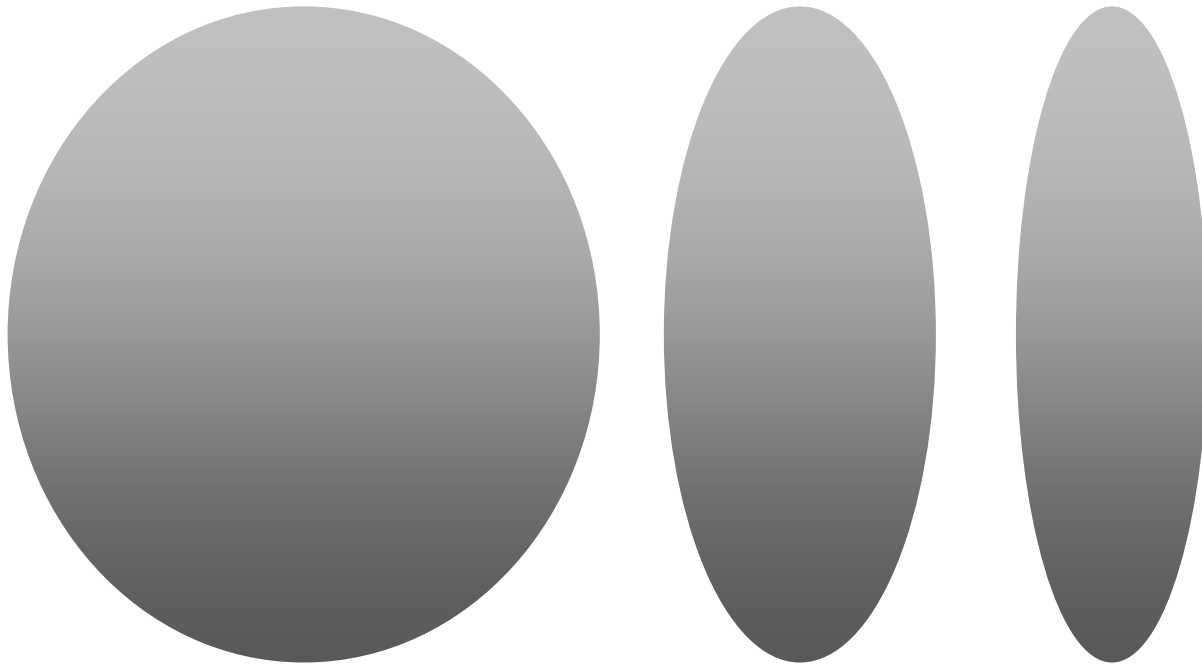
Renal cell: Sorafenib p=0.04

□ Normal

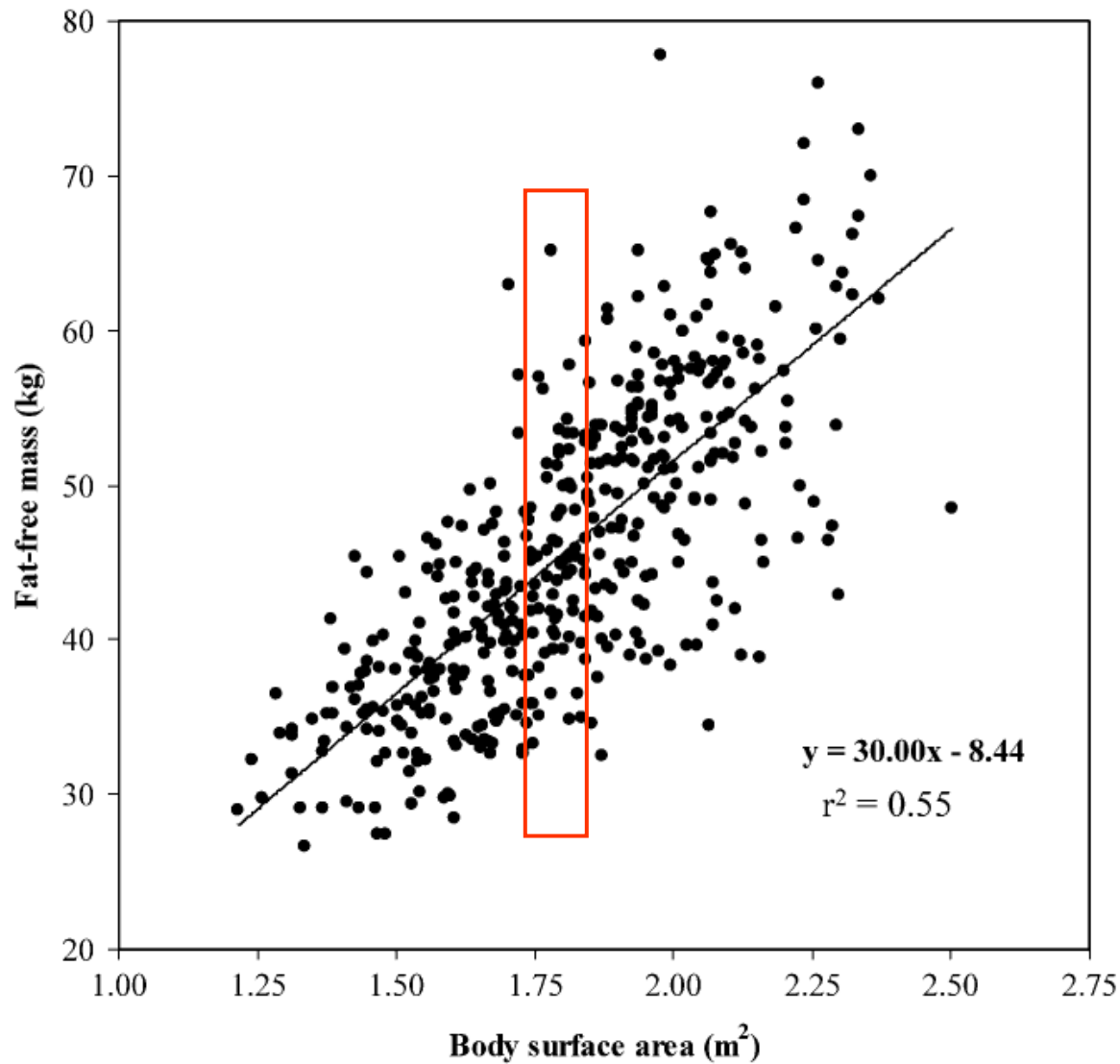
■ Sarcopenic

## Potential mechanisms?

Sarcopenic individuals are **unfit**: lack of physiological reserves for stress / injury / repair & wound healing / immunity?



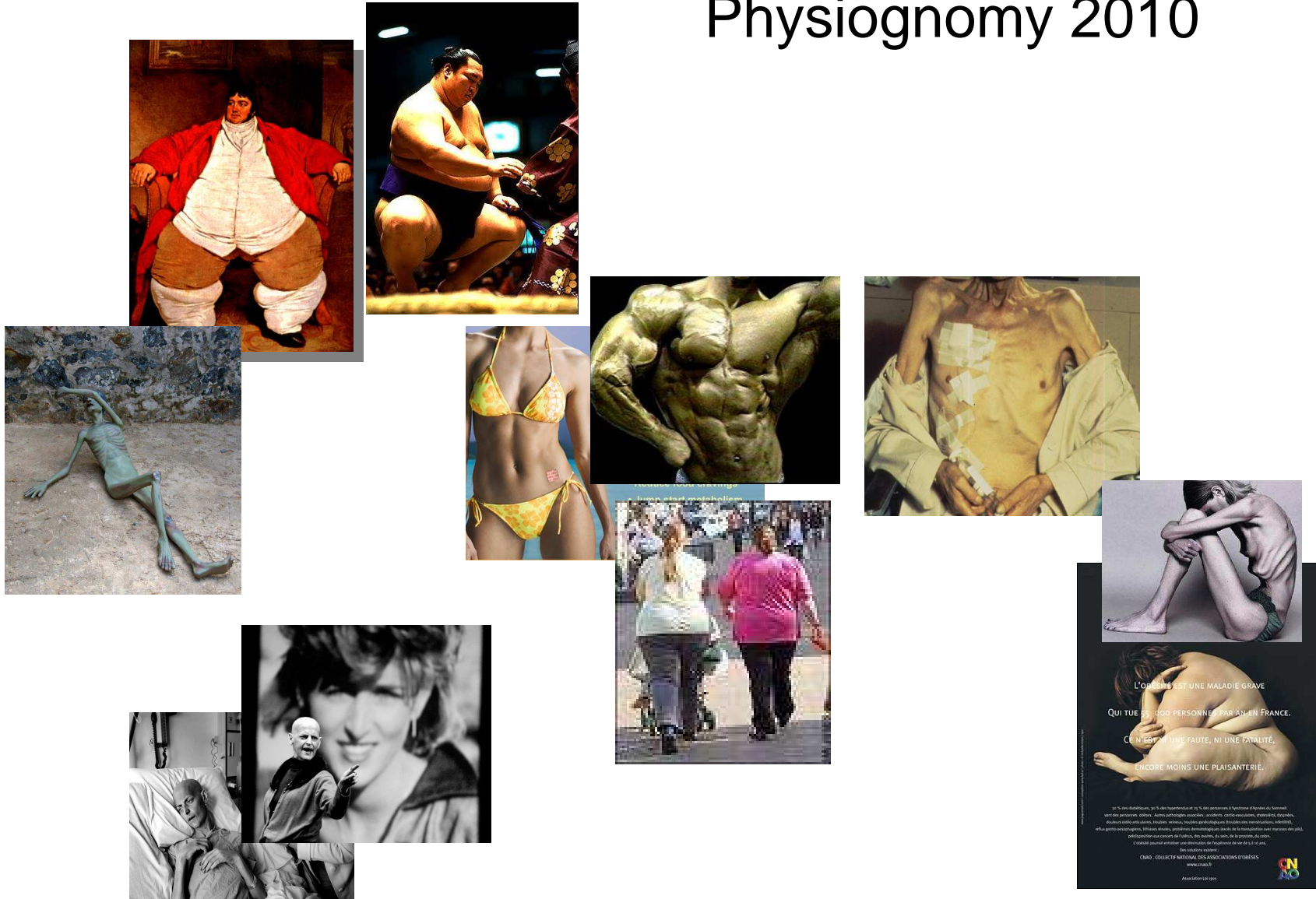
Altered **pharmacokinetics**: drug distribution and metabolism: that 1 kilogram of human being has a constant composition is not a valid assumption



BSA is a poor predictor of fat-free mass in non-small cell lung cancer patients

$$\text{Body surface area (BSA (m}^2\text{))} = ([\text{Height (cm)} \times \text{Weight(kg)}] / 3600)^{\frac{1}{2}}$$

# Oncology meets Physiognomy 2010



# Conclusions

- Oncologic CT images offer high precision and specificity for the determination of body composition; amenable to population – based research
- Body composition variable within patients with identical weight and height
- Sarcopenia prevalent, prognostic for poor survival and treatment toxicity
- Figure sarcopenia into our view of expected survival for individual patients?
- Alter chemotherapy doses for sarcopenic patients?
- Treat muscle wasting?



# Questions & Discussion