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Sarcopenia e tossicità oncologica: evidenze emergenti e algoritmi decisionali

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Pharmacology & Therapeutics 196 (2019) 135–159

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Body composition and sarcopenia: The next-generation of personalized oncology and pharmacology?

Marc Hilmi [a], Anne Jouinot [a], Robert Burns [b], Frédéric Pigneur [b], Rémi Mounier [d], Julien Gondin [d], Cindy Neuzillet [c,*,1], François Goldwasser [a,1]

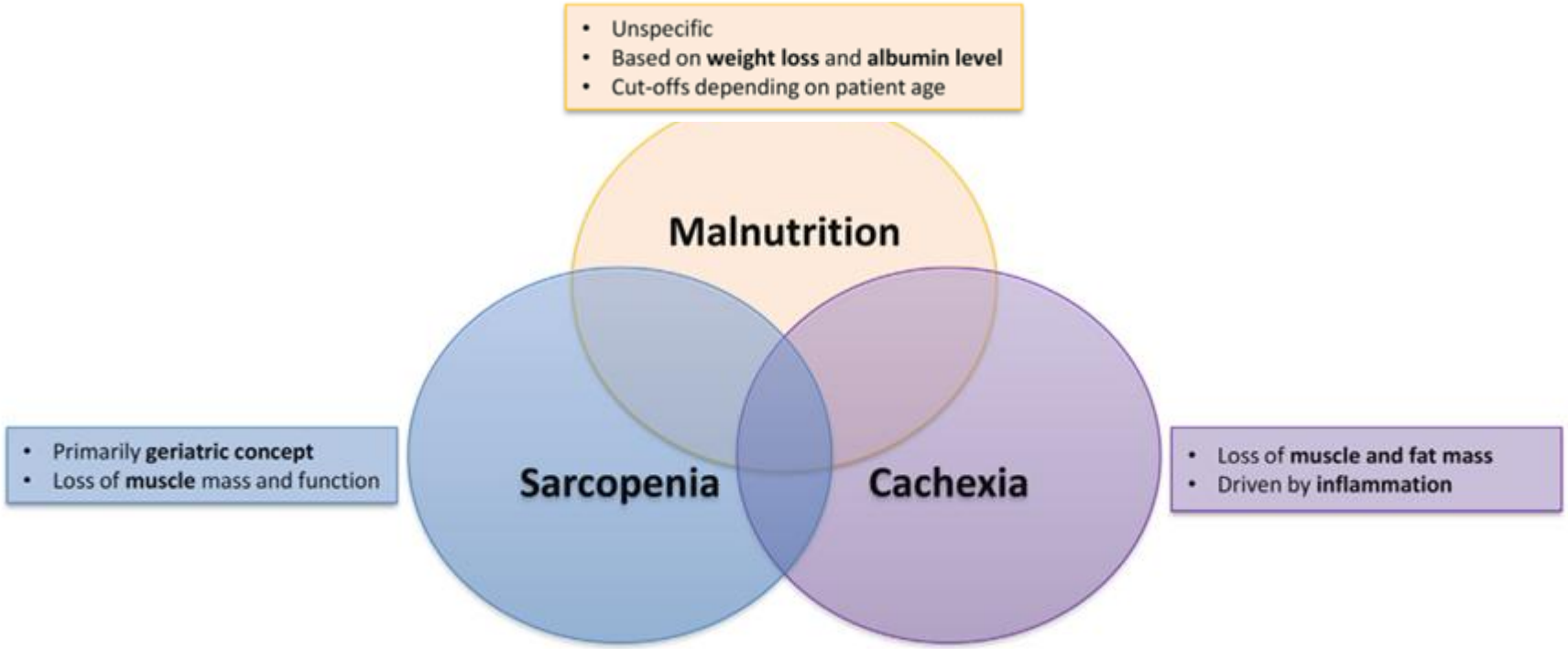


Fig. 1. Overlap and distinctions between sarcopenia, cachexia and malnutrition definitions.

Table 3
Prevalence of sarcopenia.

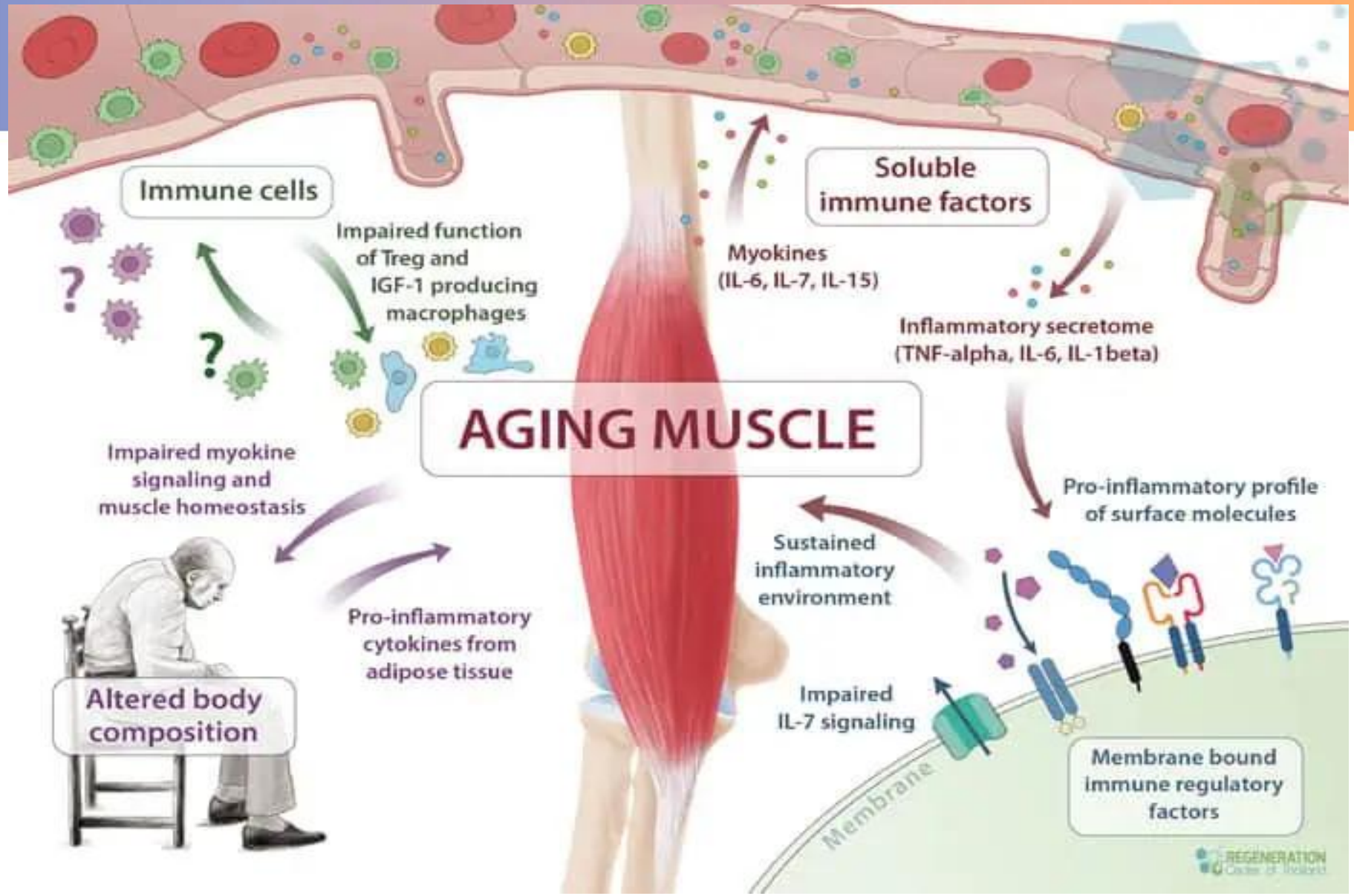
Tumor type	Stage	Study	Sarcopenia evaluation	Prevalence of sarcopenia
Head and neck	Locally advanced	Wendrich et al., 2017	L3 CT scan	54%
Breast	Localized	Shachar, Deal, Weinberg, Williams, et al., 2017	L3 CT scan	3% obese sarcopenic
		Del Fabbro et al., 2012	L3 CT scan	14%
				3% obese sarcopenic
	Metastatic	Carla M. M. Prado et al., 2009	L3 CT scan	25%
		Shachar, Deal, Weinberg, Nyrop, et al., 2017	L3 CT scan	58%
Lung	Metastatic	Srdic et al., 2016	L3 CT scan	47%
		Stene et al., 2015	L3 CT scan	74%
		Arrieta et al., 2015	L3 CT scan	69%
	All stages	Kim et al., 2015	L3 CT scan	79%
		Go et al., 2016	T4 CT scan	25%
		Baracos, Reiman, Mourtzakis, Gioulbasanis, & Antoun, 2010	L3 CT scan	47%
Oesophagus	Localized	Anandavadivelan et al., 2016	L3 CT scan	43%
				14% obese sarcopenic
		B. H. L. Tan et al., 2015	L3 CT scan	49%
		Tamandl et al., 2016		65%
	Locally advanced	Murimwa et al., 2017	L4 CT scan	41%
		Awad et al., 2012	L3 CT scan	57%
		Yip et al., 2014	L3 CT scan	43%
		Miyata et al., 2017	BIA	47%
Stomach	Locally advanced	Palmela et al., 2017	L3 CT scan	23%
				10% obese sarcopenic
		Tegels et al., 2015	L3 CT scan	58%
		Wang et al., 2016	L3 CT scan	12%
Liver	Localized	Meza-Junco et al., 2013	L3 CT scan	30%
		Levolger et al., 2015	L3 CT scan	58%
		Voron et al., 2015	L3 CT scan	30%
		Kamachi et al., 2016	L3 CT scan	66%
		(Harimoto et al., 2013)	L3 CT scan	40%
	Advanced	Dhooge et al., 2013	L3 CT scan	50%
		Mir, Coriat, Blanchet, et al., 2012	L3 CT scan	27%
		Nault et al., 2015	L3 CT scan	76%
		Mir, Coriat, Boudou-Rouquette, et al., 2012	L3 CT scan	50%
	All stages	Fujiwara et al., 2015	L3 CT scan	11%
		Iritani et al., 2015	L3 CT scan	11%
Pancreas	Localized	Amini et al., 2015	L3 CT scan	25%
		Cooper et al., 2015	L3 CT scan	52%
		Joglekar et al., 2015	L3 CT scan	26%
	Advanced	Rollins et al., 2016	L3 CT scan	60%
				25% overweight/obese sarcopenic

(continued on next page)

Table 3 (*continued*)

Tumor type	Stage	Study	Sarcopenia evaluation	Prevalence of sarcopenia
		Dalal et al., 2012	L3 CT scan	63%
		Benjamin H. L. Tan, Birdsell, Martin, Baracos, & Fearon, 2009	L3 CT scan	40%
				16% overweight/obese sarcopenic
		Choi et al., 2015	L3 CT scan	21%
	All stages	Di Sebastiano et al., 2013	L3 CT scan	48%
Colorectal	Localized	Broughman et al., 2015	L3 CT scan	57%
		Miyamoto et al., 2015	L3 CT scan	25%
		Reisinger et al., 2015	L3 CT scan	48%
		Huang et al., 2015	L3 CT scan	12%
	Locally advanced	Chemama et al., 2016	L3 CT scan	40%
		Van Vugt et al., 2015	L3 CT scan	44%
	Metastatic	Lene Thoresen et al., 2013	L3 CT scan	39%
		L. Thoresen et al., 2012	L3 CT scan	20%
		Van Vledder et al., 2012	L3 CT scan	19%
		Barret et al., 2014	L3 CT scan	71%
		Blauwhoff-Buskermolen et al., 2016	L3 CT scan	57%
		Parsons, Tsimberidou, et al., 2012	L3 CT scan	42%
	All stages	Lieffers, Bathe, Fassbender, Winget, & Baracos, 2012	L3 CT scan	39%
Kidney	Localized	Psutka et al., 2016	L3 CT scan	47%
	Metastatic	(Fukushima et al., 2016)	L3 CT scan	68%
		Sharma, Zargar-Shoshtari, Caracciolo, Fishman, et al., 2015	L3 CT scan	29%
		Huillard et al., 2013	L3 CT scan	53%
		Cushen et al., 2017	L3 CT scan	33%
				13% overweight sarcopenic
		Ishihara et al., 2016	L3 CT scan	63%
		Antoun et al., 2010	L3 CT scan	55%
Bladder	Localized	Psutka et al., 2015	L3 CT scan	83%
				5% obese sarcopenic
	Advanced	Fukushima, Yokoyama, Nakanishi, Tobisu, & Koga, 2015	L3 CT scan	60%
Prostate	Metastatic	Cushen et al., 2016	L3 CT scan	47%
				27% obese sarcopenic
Penile	Locally advanced	Sharma, Zargar-Shoshtari, Caracciolo, Richard, et al., 2015	L3 CT scan	51%
Hematological malignancies		Sucak et al., 2012	LBM: Cunningham formula*	13%
		Morishita et al., 2012	BIA	50%
		Camus et al., 2014	L3 CT scan	55%
		Nakamura et al., 2015	L3 CT scan	56%
Melanoma	Metastatic	Heidelberger et al., 2017	L3 CT scan	50%
				16% overweight sarcopenic
		Daly et al., 2017	L3 CT scan	20%
Mixed	All stages	Carla M. M. Prado et al., 2008	L3 CT scan	15%
		Bretagne et al., 2017	Cr/CysC ratio	62%
	Advanced	Parsons, Baracos, Dhillon, Hong, & Kurzrock, 2012	L3 CT scan	51%
		Cousin et al., 2014	L3 CT scan	50%

Abbreviations: BIA: bioelectrical impedance analysis, Cr: creatinine, CysC: cystatin C, L3 CT scan: computed tomography at the third lumbar vertebra level, LBM: lean body mass.
* Male; $[(79.5–0.24 \times \text{mass (kg)} - 0.15 \times \text{age (years)})] \times \text{mass (kg)} + 73.2$ which is divided by square of height (m^2).
Female; $[(69.8–0.26 \times \text{mass (kg)} - 0.12 \times \text{age (years)})] \times \text{mass (kg)} + 73.2$ which is divided by square of height (m^2).


Immune cells
Impaired function of Treg and IGF-1 producing macrophages
Soluble immune factors
Myokines (IL-6, IL-7, IL-15)
Inflammatory secretome (TNF-alpha, IL-6, IL-1beta)
AGING MUSCLE
Impaired myokine signaling and muscle homeostasis
Pro-inflammatory profile of surface molecules
Sustained inflammatory environment
Pro-inflammatory cytokines from adipose tissue
Altered body composition
Impaired IL-7 signaling
Membrane bound immune regulatory factors
Membrane

Geriatrics & Gerontology International

DOI: 10.1111/ggi.14770

INVITED REVIEW

Drug-related sarcopenia as a secondary sarcopenia

Masafumi Kuzuya[1,2]

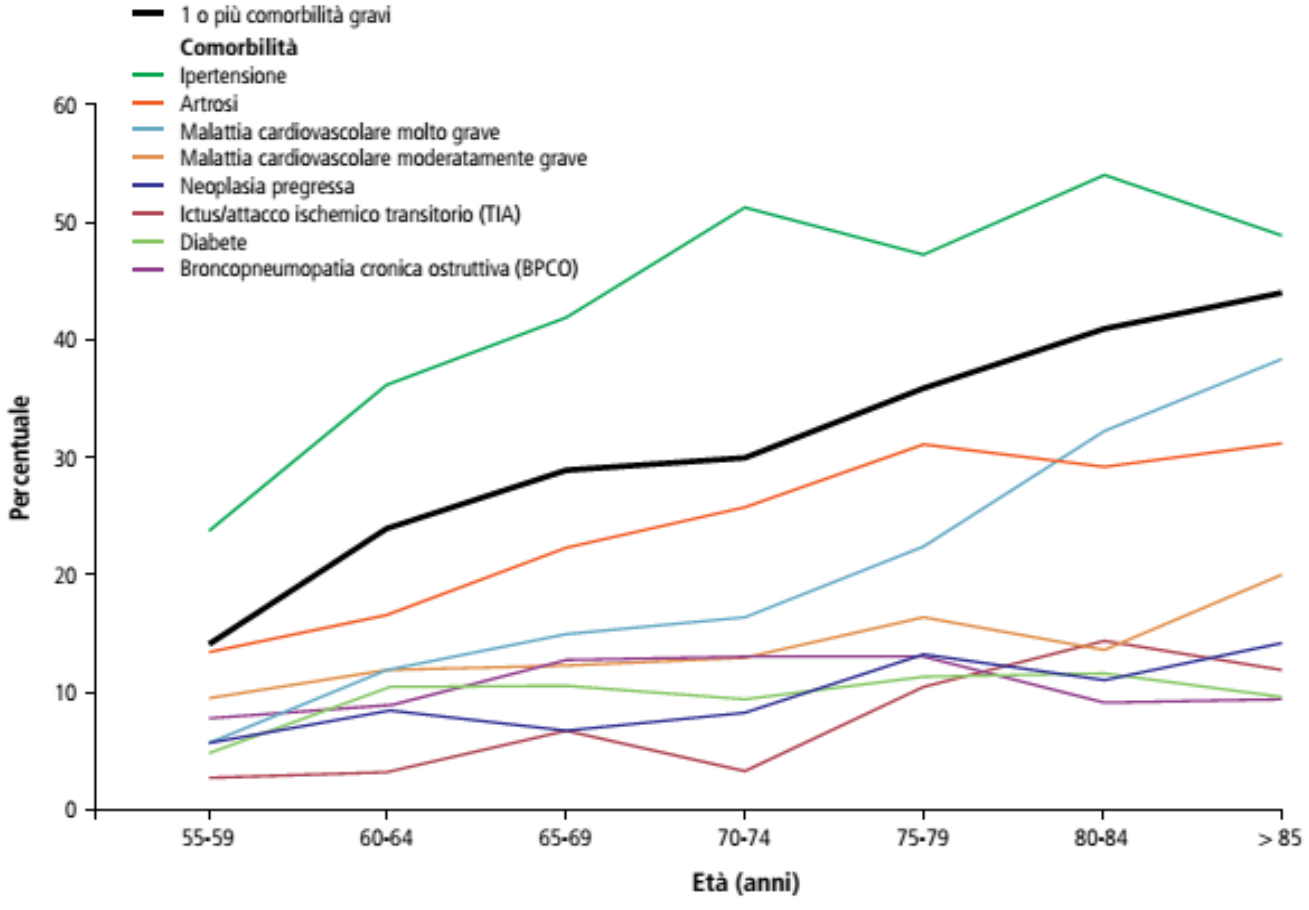


Table 2 Drugs that may cause sarcopenia and their direct effects on muscle

Drugs	Effects on skeletal muscle
Statin	Mitochondrial function ⬇, coenzyme Q10 ⬇, apoptosis ⬆, muscle protein catabolism ⬆
Sulfonylureas/insulin secretagogue (glinides)	Apoptosis ⬆
SGLT2 inhibitors	Muscle protein ⬇[a]
Antineoplastic drugs	Various[b]
Immune checkpoint inhibitors	Cytotoxic T cell ⬆, inflammation in muscle ⬆
Glucocorticoids	Muscle protein ⬇, satellite cell differentiation ⬇, muscle IGF-I production ⬇
Androgen deprivation therapy	Muscle protein ⬇, inflammation ⬆
Chloroquine/ hydroxychloroquine	Autophagy ⬇
Colchicine	Autophagy ⬇
Nucleoside analogues	Mitochondrial function ⬇
Loop diuretics	Myoblast fusion ⬇
D-penicillamine	Inflammation in muscle ⬆

Abbreviations: SGLT2, sodium–glucose cotransporter 2; ⬆, increase; ⬇, decrease.

[a]Indirect action on muscles.

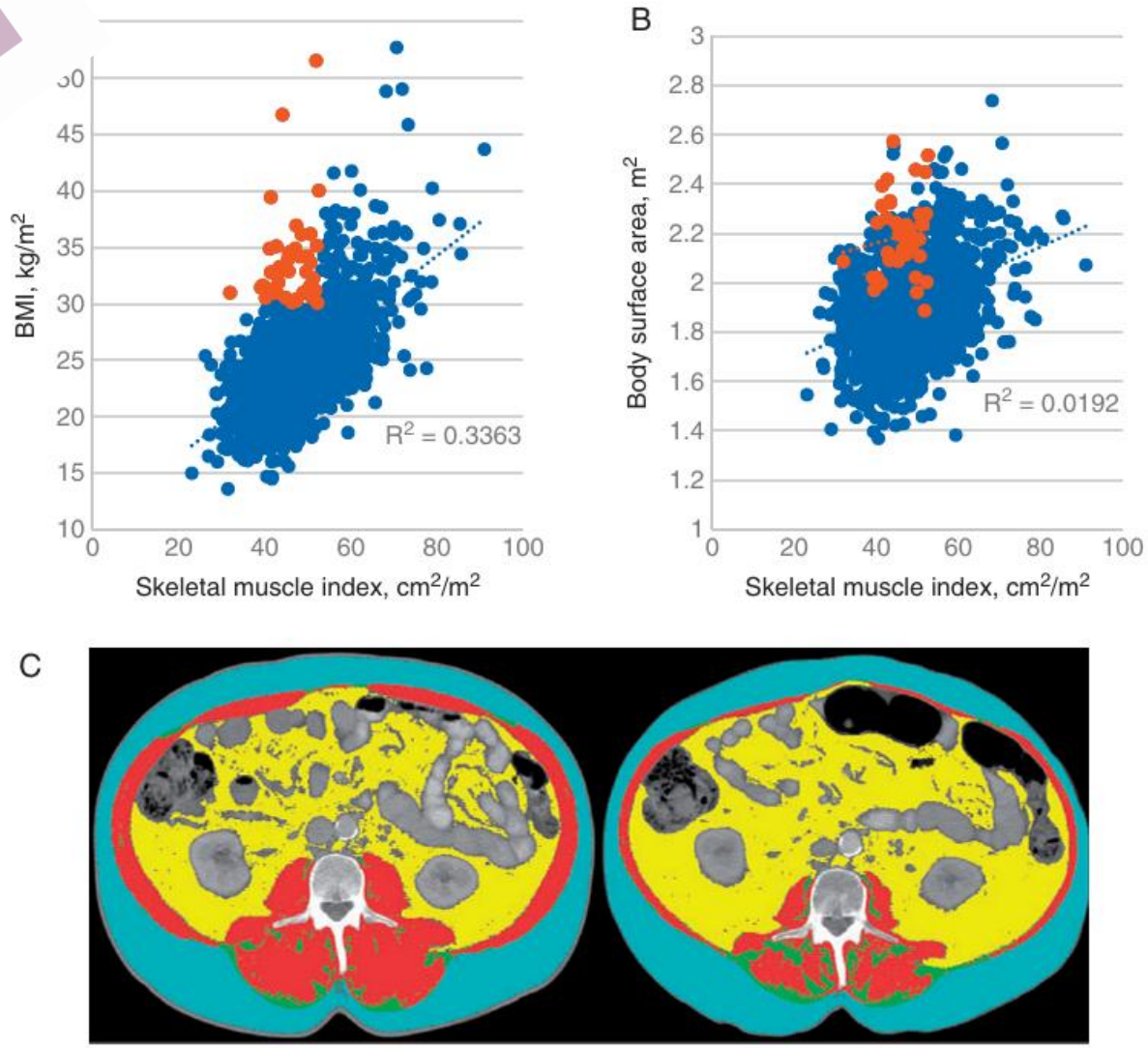
Annals of Oncology 29 (Supplement 2): ii1–ii9, 2018
doi:10.1093/annonc/mdx810

SUPPLEMENT ARTICLE

Sarcopenic obesity: hidden muscle wasting and its impact for survival and complications of cancer therapy

V. E. Baracos[1]* & L. Arribas[2,3,4]

Annals of Oncology



Orange dots represent sarcopenic obese patients

Figure 1. Variation in muscularity of patients with solid tumors. Data presented are for a population cohort of male patients with advanced solid tumors of the lung or gastrointestinal tract (*n*=2760). (A) Body mass index (BMI) and lumbar skeletal muscle index are poorly correlated.

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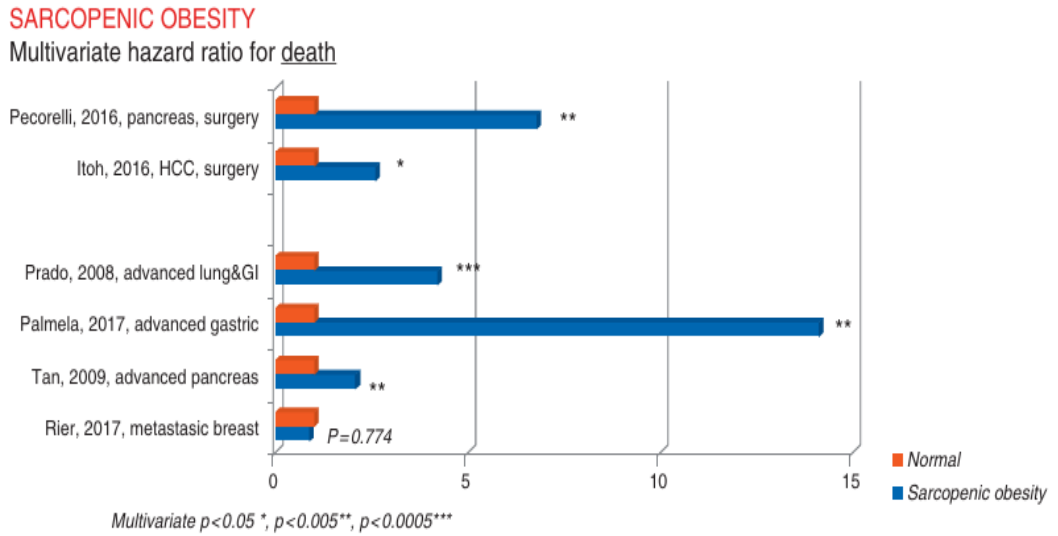

Figure 2. Multivariate odds ratio for mortality in sarcopenic obese patients.

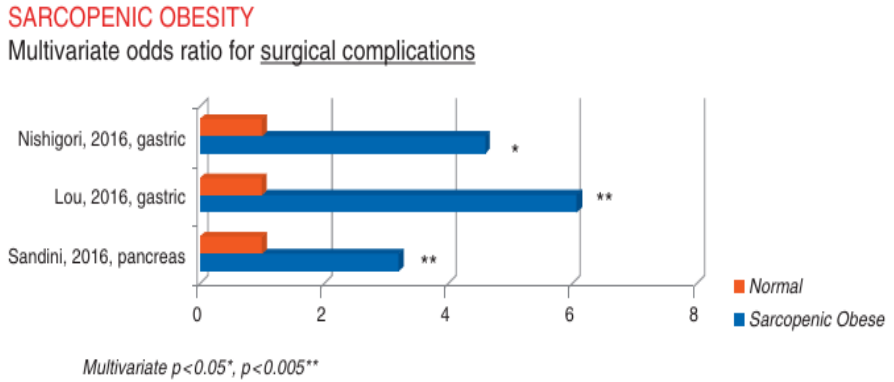

Figure 3. Multivariate odds ratio for surgical complications in sarcopenic obese patients.

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SUPPLEMENT ARTICLE

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Annals of Oncology Supplement article

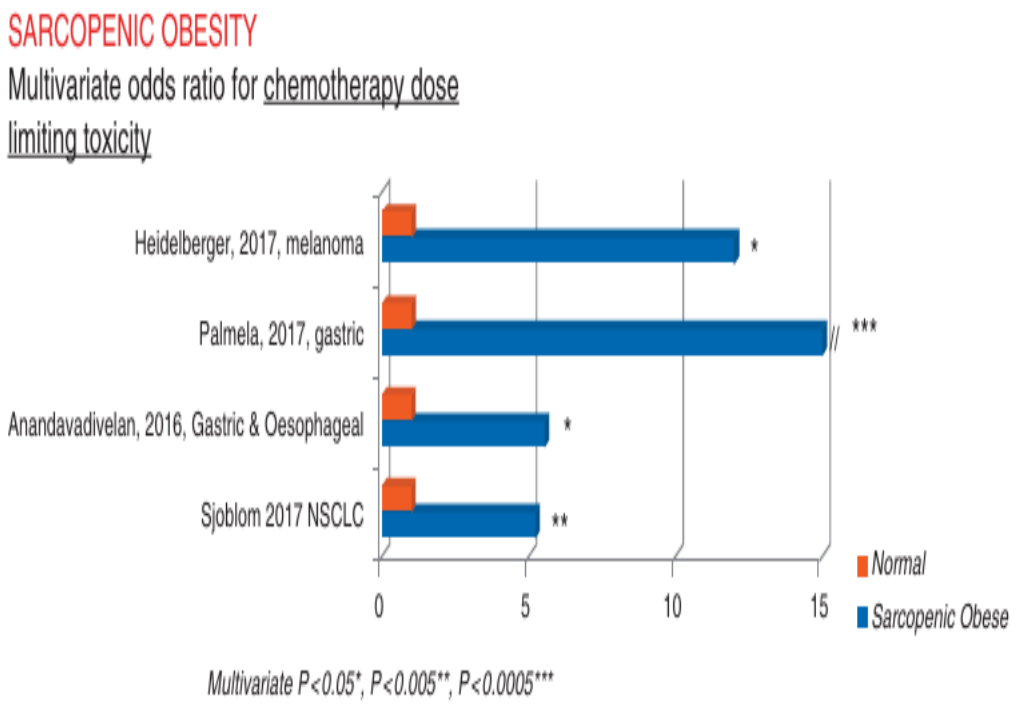
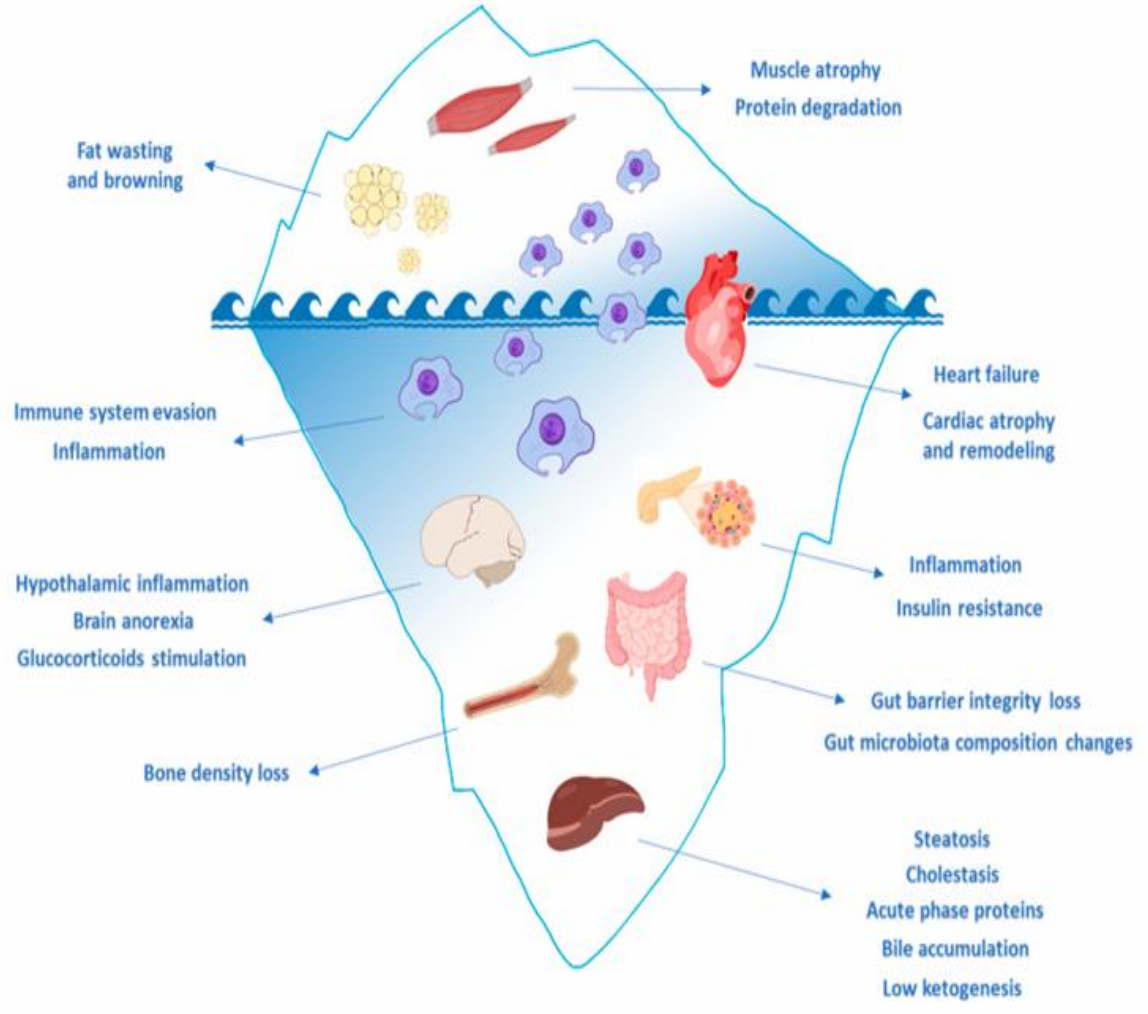


Figure 4. Multivariate odds ratio for dose-limiting toxicity of chemotherapy in sarcopenic obese patients.



The tip of the iceberg

Multi-organ dysfunctions are parallelly ongoing during tumor growth by promoting muscle wasting

Main molecular mechanisms of cancer cachexia

Adipose tissue breakdown
- ↑ in lipolysis, ↑ turnover of glycerol and FFA
- elevated levels of lipid mobilising factor (**LMF**), a tumour-induced catabolic factor directly acting on the adipose tissue with the release of FFA and glycerol.

Inflammation
- elevated levels of **TNF-α**, **IFN-γ**, **IL-1** and **IL-6** act in a synergistic manner, driving mechanisms responsible for the progressive muscle wasting

Increased muscle protein breakdown
- via various proteolytic pathways

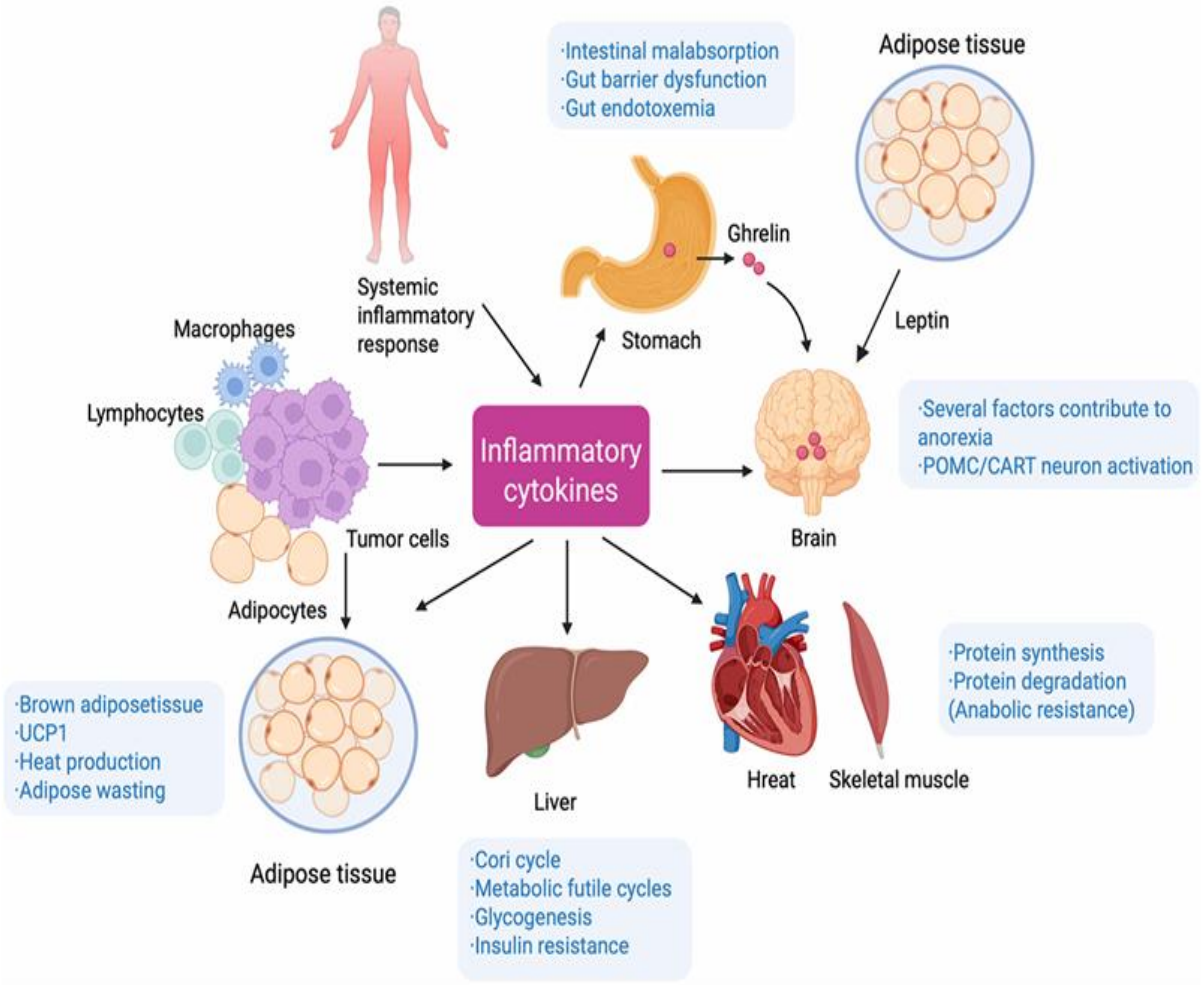
Decreased protein synthesis

Decreased insulin sensitivity of the skeletal muscle
- prevents the AA uptake, suppressing protein synthesis

Loss of physical activity

may also significantly affect the suppression of protein synthesis

Oxidative stress
- due to increased production levels of ROS



Key proteolytic systems in muscle wasting

Proteolytic systems act synergistically to degrade both myofibrillar and non-myofibrillar cellular proteins, thereby contributing to muscle wasting.

- **Ubiquitin–proteasome system**
  This pathway degrades myofibrillar proteins, which constitute the structural components of muscle fibers

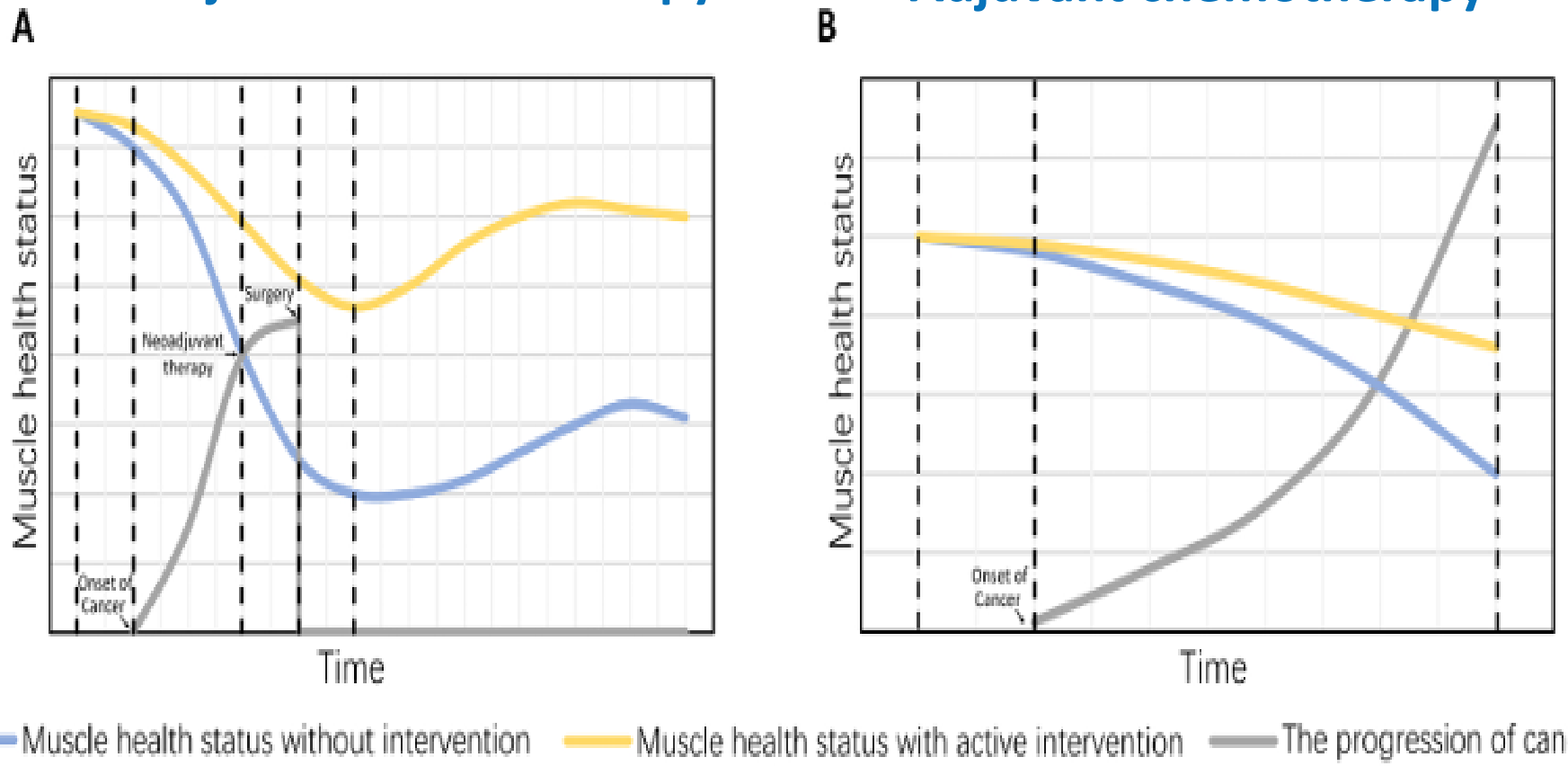
- **Inappropriately upregulated lysosomal autophagy**

- **Calcium-dependent proteases**
  Calpains are activated by elevated intracellular calcium concentrations

- **Mitochondrial dysfunction**
  It impairs energy metabolism in muscle cells, increases oxidative stress, leading to excessive production of ROS

Neoadjuvant chemotherapy

Adjuvant chemotherapy



Ageing Research Reviews 91 (2023) 102057

Clinical Nutrition 35 (2016) 1103–1109

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma

Katie E. Rollins [a, 1], Nilanjana Tewari [a, 1], Abigail Ackner [a], Amir Awwad [b], Srinivasan Madhusudan [c], Ian A. Macdonald [d], Kenneth C.H. Fearon [e], Dileep N. Lobo [a, *]

Does quantity or quality of muscle mass matter?

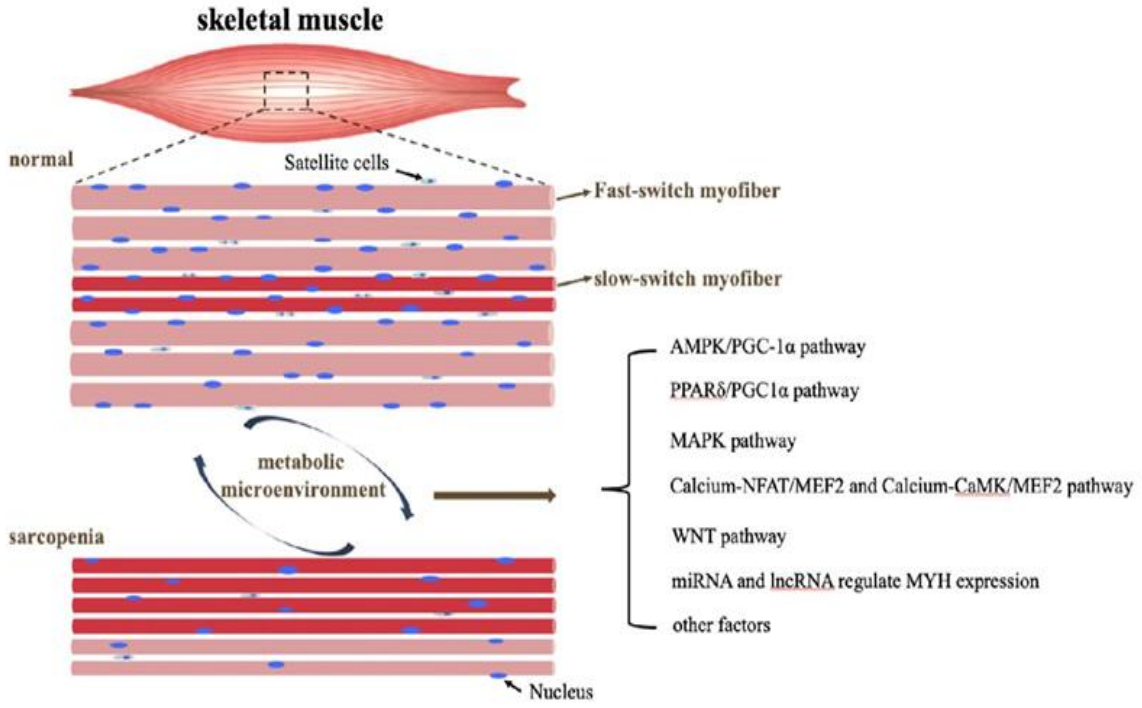


Figure 3. The model of signaling pathways and transcription factors that regulate metabolic microenvironment in skeletal muscle. AMPK/PGC-1α signaling, MAPK signaling, Calcium-NFAT/MEF2 and Calcium-CaMK/MEF2 signaling, WNT signaling, miRNA and lncRNA and other transcription factors.

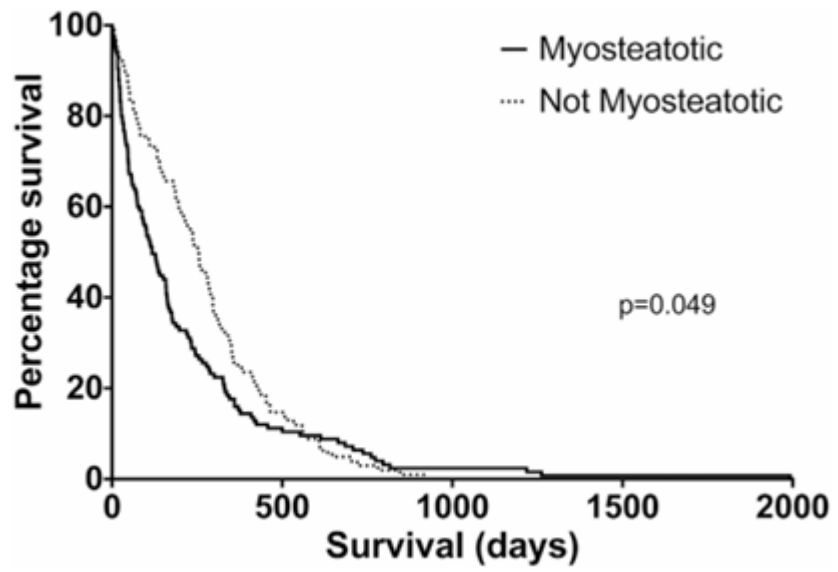


Fig. 3. Survival by presence and absence of myosteatosis in the whole patient cohort.

Table 3. Risk of mortality due to sarcopenia

Author (year)	Primary tumour	Hazard ratio (CI)
	Colorectal	
Van Veddler [45] (2012)		2.69 (1.67–4.33)
Thoresen [46] (2013)		1.74 (0.99–3.04)
Myamoto [44] (2015)		2.27 (1.15–4.49)
	Hepatocellular carcinoma	
Dhooge [52] (2012)		2.87 (0.41–20.27)
Mir [50] (2012)		1.66 (0.64–4.27)
Mir [51] (2012)		4.84 (1.20–19.44)
Fujwara [56] (2013)		1.52 (1.18–1.96)
Harimoto [53] (2013)		1.11 (1.04–1.19)
Moza-Junco [54] (2013)		2.53 (1.35–4.74)
Itoh [117] (2014)		1.96 (1.04–3.68)
Iritani [58] (2015)		3.18 (1.68–6.03)
Levolger [59] (2015)		3.76 (1.78–7.93)
Veron [55] (2015)		3.19 (1.28–7.96)
Kaido [118] (2017)		95% versus 57% 3-year survival
	Pancreas/biliary tract	
Tan [68] (2009)		1.28 (0.86–1.91)
Dalal [62] (2012)		1.48 (0.76–2.87)
Mir [50] (2012)		3.27 (0.80–13.44)
Choi [70] (2015)		1.72 (1.39–2.28)
Cooper [66] (2015)		0.99 (0.96–1.02)
Rollins [71] (2015)		1.10 (0.77–1.58)
	Oesophagus/gastric	
Yip [73] (2013)		2.38 (0.48–11.69)
Harada [76] (2015)		1.07 (0.69–1.67)
Tamandl [77] (2015)		1.87 (1.15–3.03)
Tan [107] (2015)		1.80 (0.95–3.42)
	Kidney/bladder/urothelial	
Psutka [91] (2015)		1.48 (1.02–2.15)
Sharma [88] (2015) Smith [89] (2014)		2.13 (1.15–3.93)
Fukushima [87, 90] (2015, 2015)		2.58 (1.16–5.74), 1.11 (1.07–1.15)
Psutka [91, 84] (2015, 2016)		1.93 (1.24–3.01), 1.71 (1.14–2.57)
	Other	
Prado [32] (2008)		4.20 (2.42–7.27)
Martin [33] (2013)		1.20 (1.05–1.38)
Sharma [99] (2015)		1.95 (0.68–5.64)
Lanic [119] (2014)		3.22 (1.73–5.98)

Sarcopenia decreases response to chemotherapy and survival

If patients are sarcopenic, the response to chemotherapy may be lower.

Poor outcomes may be related to higher toxicity rates that, in turn, may lead to dose reduction and delivering lower doses of effective oncological treatment.

Table 2. Increased toxicity due to sarcopenia

Author (year)	Primary	Drugs	Comments
	Colon		
Prado [105] (2007)		5-FU	1.7↑ toxicity if > 20 mg/kg LMB
Barret [48] (2014)		Fluoropyrimidine±oxaliplatin, irinotecan	13.5↑ grade 3–4 toxicity at oxaliplatinum 3 mg/Kg LBM
Ali [106] (2016)		FOLFOX	44% versus 0 in nonsarcopenic
Jung [41] (2015)		FOLFOX	1.5↑ grade 3–4 toxicity/1PI*SD<ref. value
	Oesophago-Gastric J		
Anandavalivedan [74] (2015)		Cisplatinum +5-FU	5.5↑ DLT in obese sarcopenic patients
Tan [107] (2015)			2.9↑ DLT in sarcopenic patients
	Breast		
Prado [93] (2009)		Capecitabine	2.5↑ toxicity
Prado [108] (2011)		Epirubicine	Lower LBM in patients with toxicity
Shachar [109] (2016)		Taxane	3.1↑ grade 3–4 toxicity
	Renal cell		
Antoun [82] (2010)	Carcinoma	Sorafenib	6.4 ↑ toxicity
Houillard [85] (2013)		Sunitinib	4.1 ↑ toxicity
Cushen [86] (2014)		Sunitinib	1.6 ↑ dose-limiting toxicity
	Other		
Mir [50, 51] (2012)		Safeni, vandetanib,	2.6↑ DLT, 5.2↑ DLT
Massicotte [110] (2013)		Phase 1 drugs	6↑ toxicity
Sjoblom [111] (2016)		carboplatinum,pemetrexed/ gemcitabine/vinorelbine	2↑ toxicity
Choi [70] (2016)		rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone	2.4↑ early discontinuation
Go [112] (2016)		R-CHOP	1.3 ↑ discontinuation

LMB: lean body mass; PI; psoas index; DLT:dose lethal toxicity; R-CHOP: radiotherapy-cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone

The excess of toxicity ranges from 1.6 to a 13 factor, mainly depending on the drug investigated in the different studies

Table 4
Sarcopenia and chemotherapy toxicity.

Study	Tumor type	Treatment	N	Sarcopenia evaluation	Toxicity assessment	Main results	Significant association
Wendrich et al., 2017	Locally advanced head and neck cancer	Primary radiochemotherapy	112	L3 CT scan SMI < 43.2 cm^2/m^2	Entire length of chemotherapy Retrospective	More DLT in sarcopenic pts. (OR = 0.93)	Yes $p = .005$
Carla M. M. Prado et al., 2011	Localized breast cancer	Adjuvant epirubicin	24	L3 CT scan LBM as continuous variable	First cycle Retrospective	Lower LBM (mean 41.6 vs 56.2 kg) in pts. with toxicity Correlation of LBM with neutrophil nadir (r = 0.5)	Yes p = .002 p = .023
Shachar et al., 2017	Localized breast cancer	Anthracycline and taxane-based chemotherapy	151	L3 CT scan Skeletal muscle gauge (SMG) = SMI x SMD	Entire length of chemotherapy Retrospective	More hematological (RR = 2.12), gastrointestinal grade 3–4 toxicities (RR = 6.49), and hospitalizations (RR = 1.91) in pts. with lower SMG (<1475 units)	Yes p = .02 p = .02 p = .05
Shachar, Deal, Weinberg, Nyrop, et al., 2017	Metastatic breast cancer	Taxane-based chemotherapy	40	L3 CT scan SMI < 41 cm^2/m^2	Entire length of chemotherapy Retrospective	More grade 3–4 toxicity (57% vs 18%) in sarcopenic pts. More toxicity-related hospitalizations (39% vs 0%) in sarcopenic patients	Yes p = .02 p = .005
Carla M. M. Prado et al., 2009	Metastatic breast cancer	Capecitabine	55	L3 CT scan SMI < 38.5 cm^2/m^2	First cycle Prospective	More toxicity ≥ grade 2 (50% vs 20%) in sarcopenic pts.	Yes p = .03
Go et al., 2016	Localized and metastatic SCLC	Platinum plus etoposide or irinotecan	117 Men only	T4 CT scan (pectoralis muscle) Lowest quartile SMI	First cycle Retrospective	More dose reduction in sarcopenic pts. (51.7% vs 29.5%) Higher treatment-related mortality (50.0 vs. 8.4%) in sarcopenic pts. with high NLR	Yes p < .001
Suzuki et al., 2015	Metastatic lung cancer	Mostly platinum-based chemotherapy	25	Cr/c ratio as continuous variable	First cycle Retrospective	Higher Cr/CysC ratio (0.83 vs 0.7) in pts. with grade 3–4 toxicity	Yes p < .05
Stene et al., 2015	Metastatic NSCLC	Carboplatin plus vinorelbin or gemcitabine	35	L3 CT scan SMI ≤ 38.5 cm^2/m^2 for women SMI ≤ 52.4 cm^2/m^2 for men	Cycles 1–3 Retrospective	No association between sarcopenia and grade 3–4 toxicity	No p = .33
Sjøblom et al., 2015	Metastatic NSCLC	Gemcitabine vinorelbine	153	L3 CT scan LBM as continuous variable	First cycle Retrospective	Higher dose/kg LBM of gemcitabine (41.9 vs 38.2 mg/kg) and vinorelbine (2.5 vs 2.3 mg/kg) in pts. with grade 3–4 hematological toxicity	Yes p = .008 p = .18
Sjøblom et al., 2017	Metastatic NSCLC	Carboplatin-doublet (gemcitabine, pemetrexed, vinorelbine)	424	L3 CT scan LBM as continuous variable	Cycle 1–4 Retrospective	Regarding grade 3/4 hematological toxicity, higher risk for dose/kg LBM > 20% above mean (OR = 1.93) and lower risk for dose/kg LBM < 20% below mean (OR = 0.52)	Yes p = .004

Table 4 (*continued*)

Study	Tumor type	Treatment	N	Sarcopenia evaluation	Toxicity assessment	Main results	Significant association
	pancreatic cancer			SMI < 41 cm^2/m^2 for women	Retrospective	and toxicity	p = .4321
C. M.M. Prado et al., 2007	Stage II/III colon cancer	5FU	62	SMI < 43 cm^2/m^2 for men and < 53 cm^2/m^2 for overweight/obese men Yes LBM as continuous variable	L3 CT scan Retrospective	First cycle p = .036	Higher dose of 5FU mg/kg LBM in pts. with DLT (17.9 vs 16.3) Threshold of 20 mg 5FU/kg LBM for developing overall toxicity
p = .05							
Jung et al., 2015	Stage III colon cancer	Adjuvant FOLFOX	229	L4 CT scan (psoas muscle) Sex-adjusted lowest quartile SMI	Cycles 1–12 Retrospective	No association between decreased psoas index and toxicity (OR = 1.36 in multivariate analysis)	No p > .05
Cespedes Feliciano et al., 2017	Stage II/III colon cancer	Adjuvant FOLFOX	533	L3 CT scan Sex-adjusted lowest tertile SMI	Cycles 1–12 Retrospective	More neutropenia in pts. in the lowest tertile (54.9 vs 38.4%) More thrombocytopenia in pts. in the lowest tertile (13.2% vs 5.1%)	Yes p = .008 p = .02
Barret et al., 2014	Metastatic colorectal cancer	Mostly fluoropyrimidine based chemotherapy	51	L3 CT scan SMI ≤ 38.9 cm^2/m^2 for women SMI ≤ 55.4 cm^2/m^2 for men	Two first months Prospective	More grade 3–4 toxicity in sarcopenic pts. (OR = 13.35 in multivariate analysis)	Yes p = .043
Blauwhoff-Buskermolen et al., 2016	Metastatic colorectal cancer	Mostly capecitabine oxaliplatin + − bevacizumab	67	L3 CT scan SMI ≤ 38.9 cm^2/m^2 for women SMI ≤ 55.4 cm^2/m^2 for men	Period between two CT scans Prospective	No association between SMI and DLT	No p = .99
Ali et al., 2016	Metastatic colorectal cancer	FOLFOX	138	L3 CT scan LBM as continuous variable	Cycles 1–4 Retrospective	Stratification into three groups based on oxaliplatin dose/kg LBM. More DLT in pts. with highest dose/LBM (39.9% including 25% of neuropathy vs 8.3% including no neuropathy).	Yes p < .01

Cancer Chemotherapy and Pharmacology (2018) 82:1–29
https://doi.org/10.1007/s00280-018-3614-8

REVIEW ARTICLE

Interactions of lean soft-tissue and chemotherapy toxicities in patients receiving anti-cancer treatments

Jessica J. Hopkins[1] · Michael B. Sawyer[2]

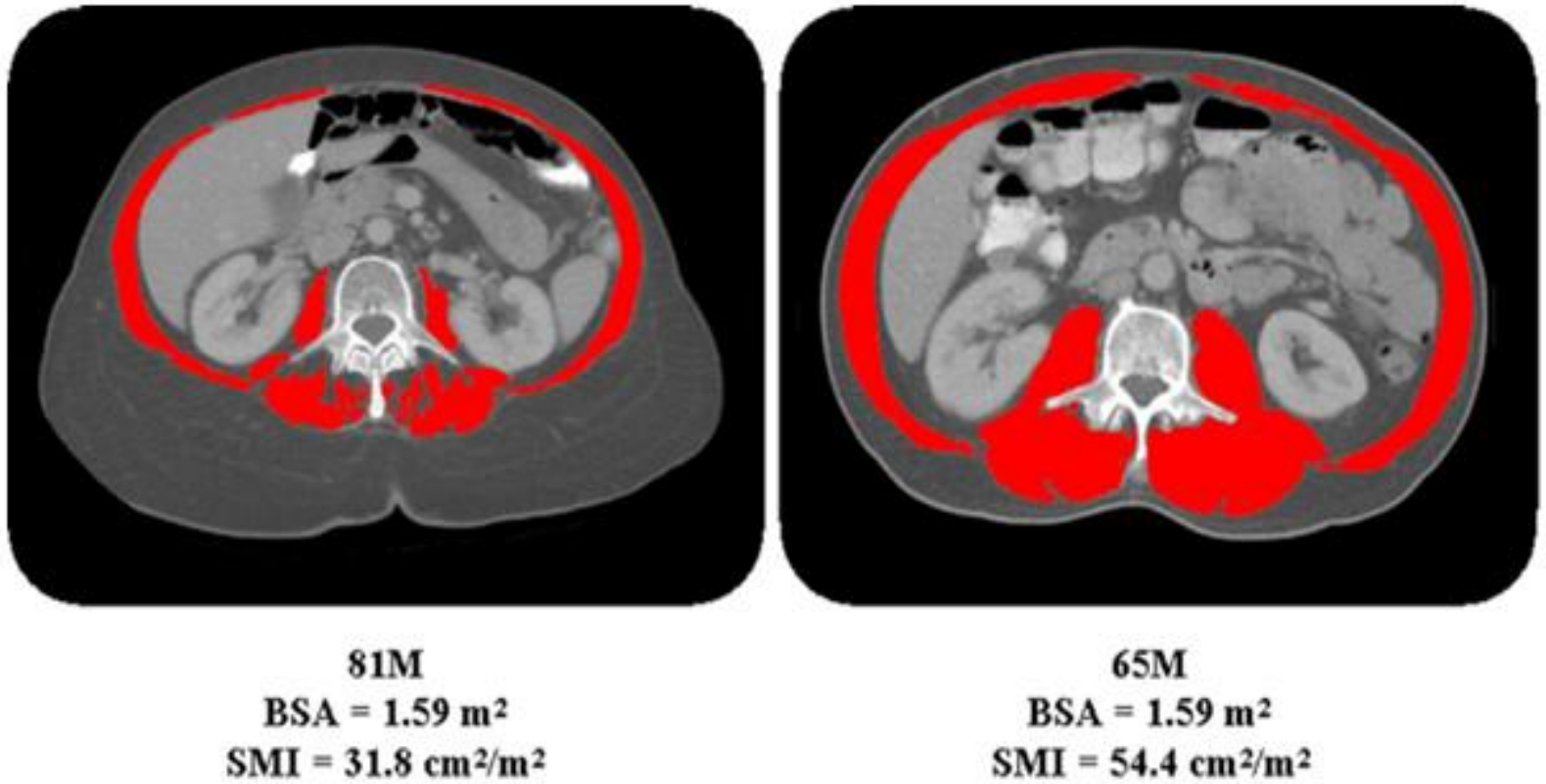


Fig. 1 Using CT-derived body composition analysis to compare two patients with identical BSA but differing skeletal muscle area at L3

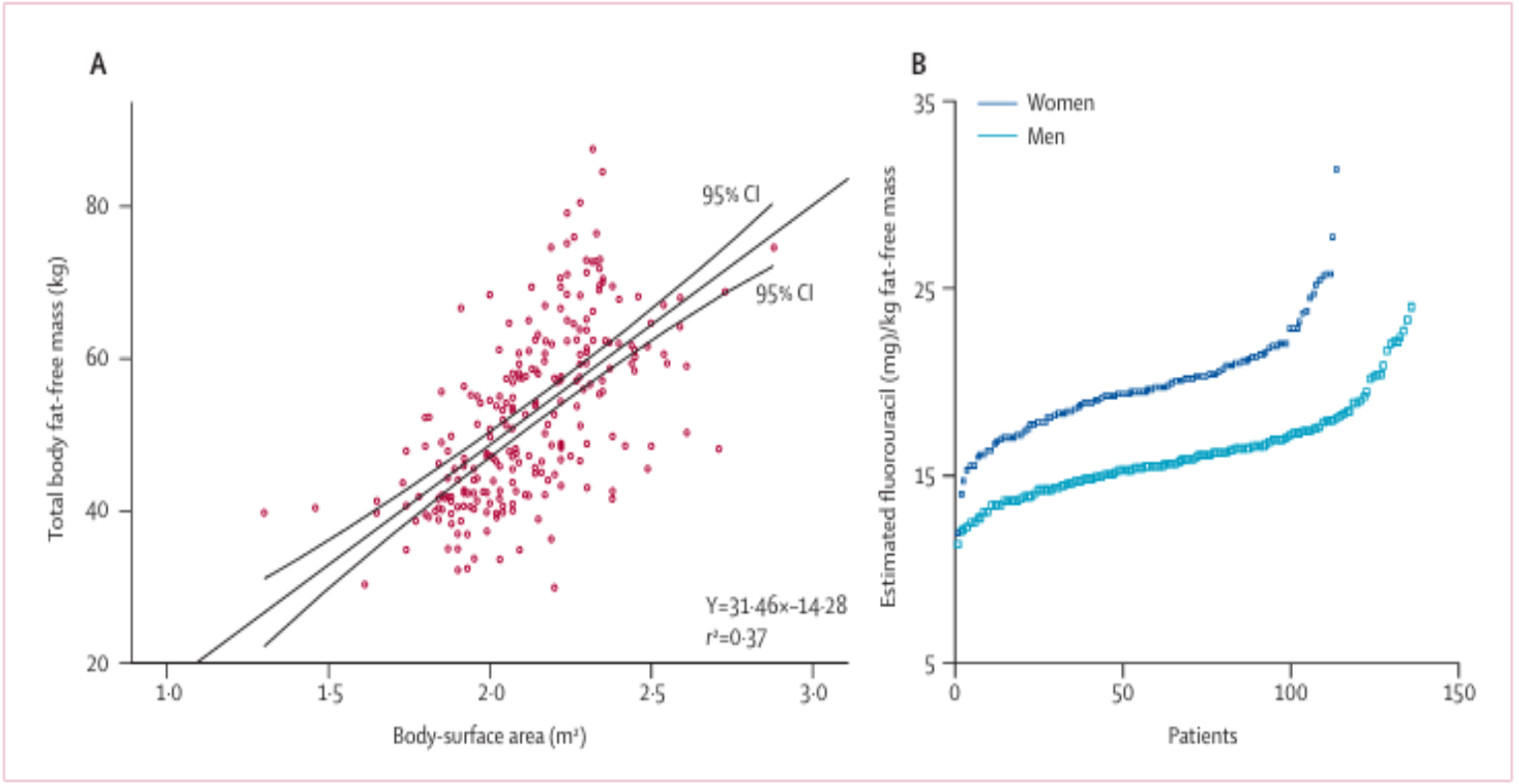


Figure 4: **Findings for obese patients with cancer**
(A) Association between lean body mass and body-surface area in obese patients with cancer. (B) Estimated fluorouracil dose per kg fat-free mass in obese male and female patients based on 425 mg fluorouracil/m² of body-surface area; all patients ranked from lowest to highest fluorouracil dose per kg fat-free mass.

The association between estimated total body **FFM** and **BSA** was poor even though both are associated with height. A consequence of low FFM would be a low volume of distribution of cytotoxic chemotherapy drugs, with a higher incidence of overall toxicity.

C. Prado, The Lancet oncol 2008

How does sarcopenia influence drug toxicity?

Pharmacokinetic alterations due to changes in body composition (FFM)

Hypoalbuminemia
Increases the unbound plasma fraction of drugs with high protein binding (e.g., carboplatin, etoposide, cisplatin, docetaxel, paclitaxel, irinotecan).

Reduced CYP450 activity

cancers

MDPI

Article

Prognostic Impact of Sarcopenia's Occurrence during Radiotherapy in Oropharyngeal Cancer Patients

Luca Bergamaschi [1,†], Giulia Marvaso [1,2,†], Mattia Zaffaroni [1,*], Maria Giulia Vincini [1,*], Oriana D'Ecclesiis [3], Stefania Volpe [1,2], Annamaria Ferrari [1], Stefano Filippo Zorzi [4], Maria Cossu Rocca [5], Annarita Sabbatini [6], Giulia Cannillo [6], Emanuela Zagallo [6], Anna Starzyńska [7], Mohssen Ansarin [4], Federica Cattani [8], Sara Gandini [3], Roberto Orecchia [8,9], Daniela Alterio [1,‡] and Barbara Alicja Jereczek-Fossa [1,2,‡]

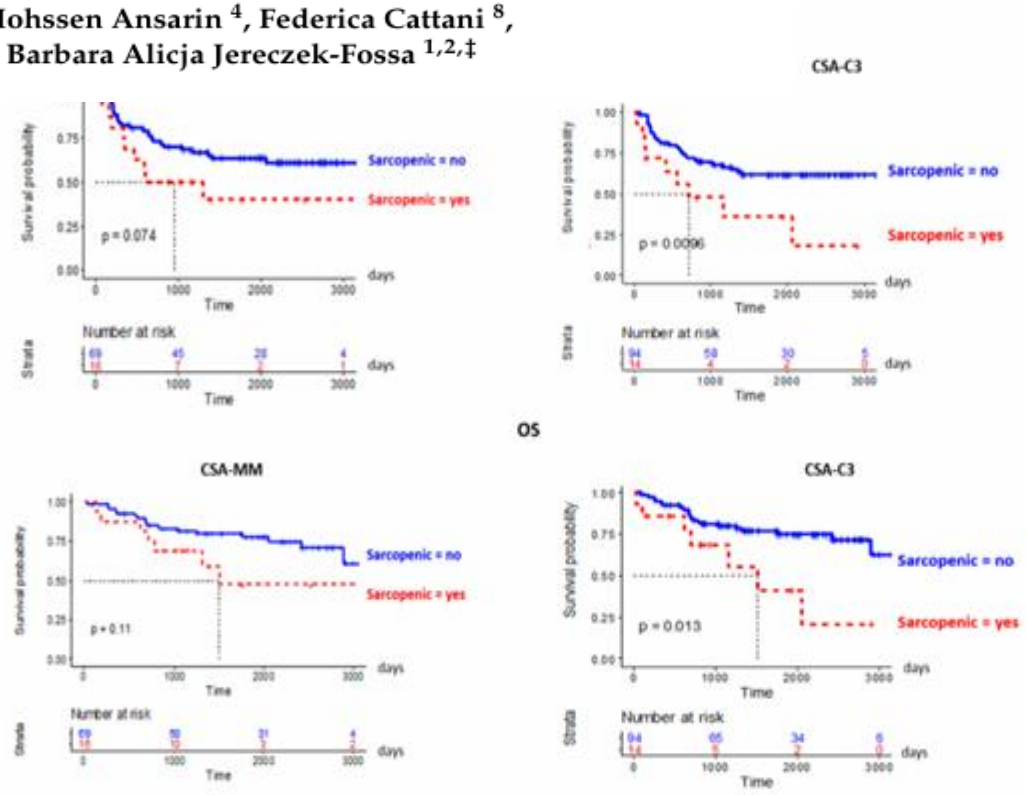


Figure 3. KM curves for OS and PFS of patients become sarcopenic during RT vs. never sarcopenic, based on MM-CSA and C3-CSA.

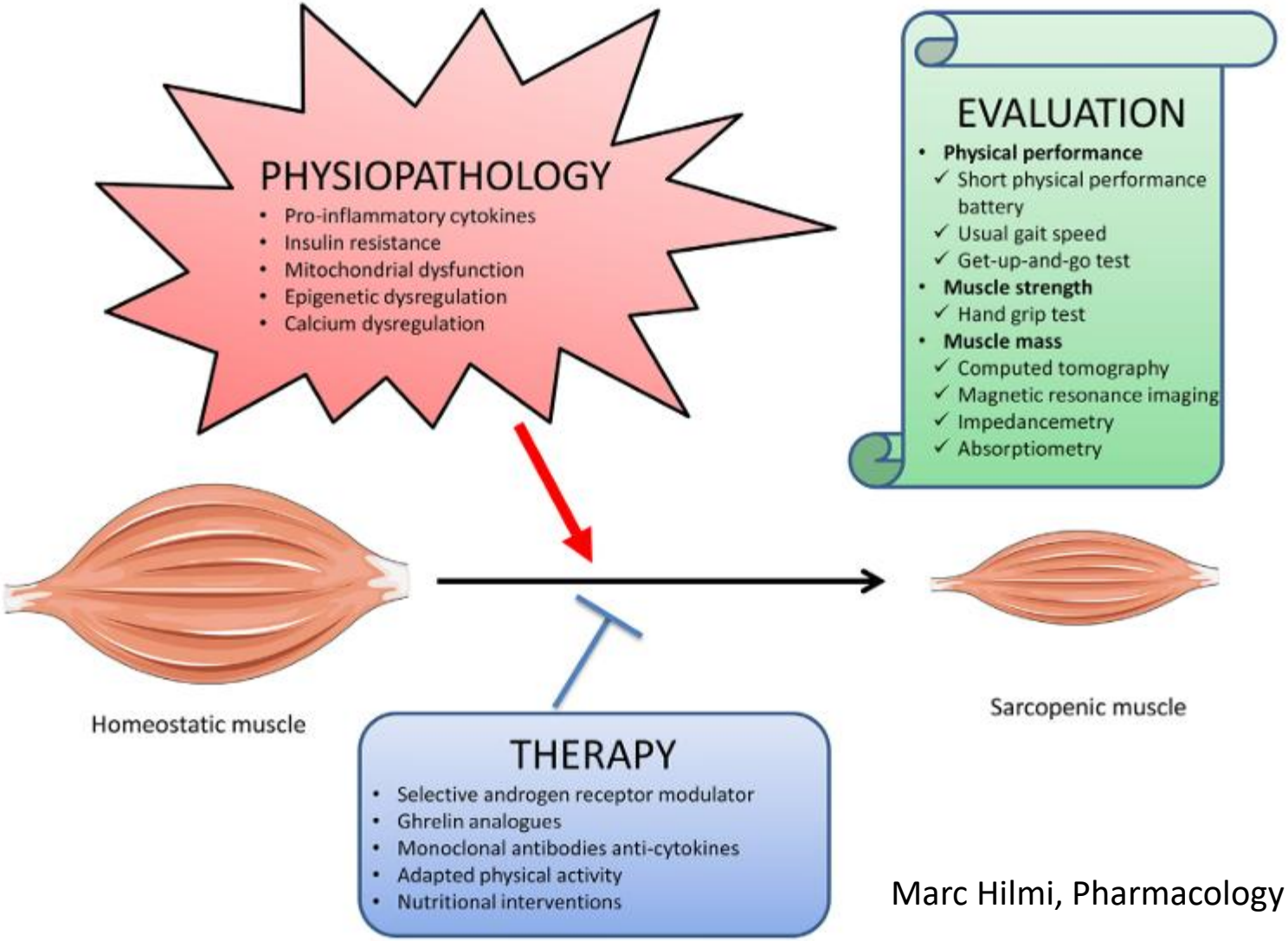


Fig. 2. Physiopathology, treatment and evaluation of sarcopenia.

Marc Hilmi, Pharmacology & Therapeutics 196 (2019) 135 - 159

Strategies to reverse sarcopenia

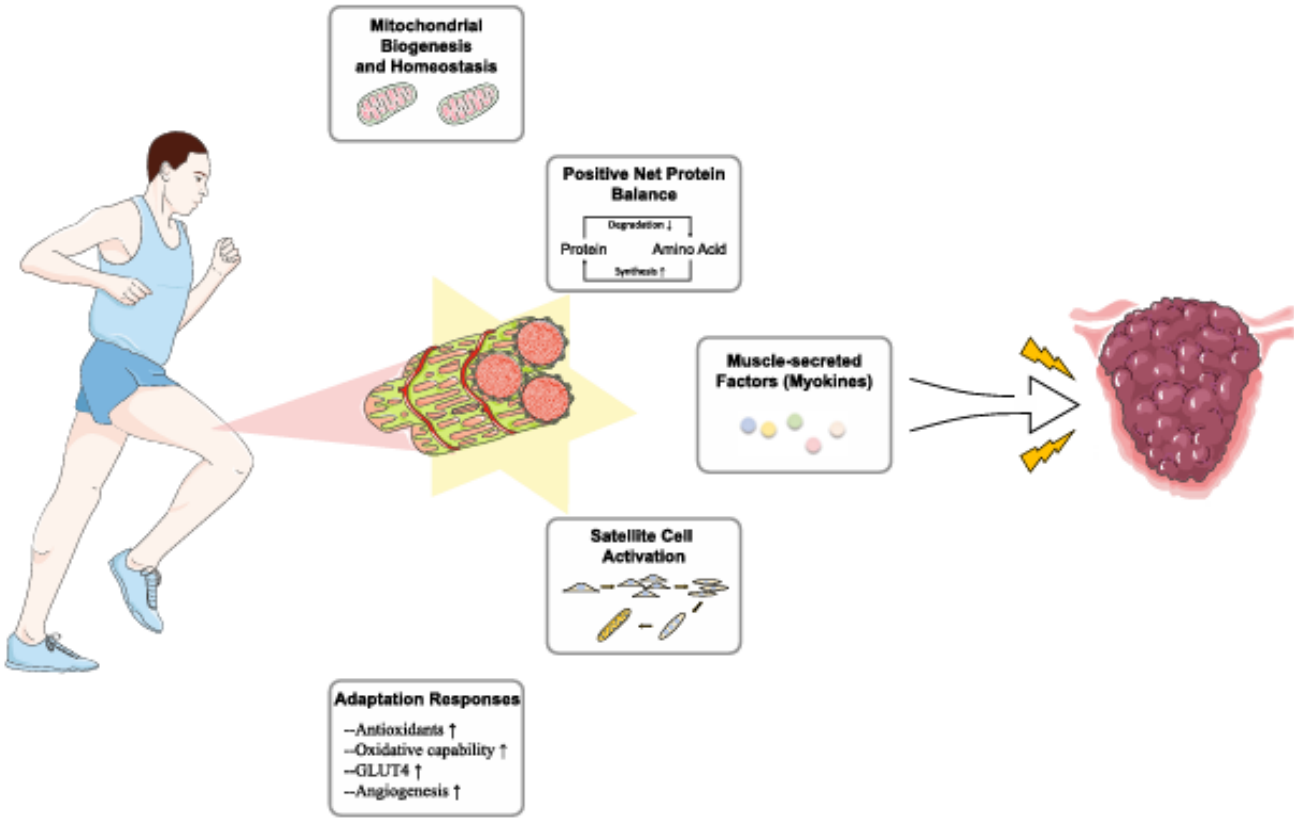
- Adequate intake of nutrients
- Treatments to fight the muscle loss whose efficacy was proved by RCTs
- Anti-inflammatory agents wit both anticatabolic and anabolic effects (omega-3-enriched ONS, orexigenic agents as ghrelin, high protein regimens)
- **Muscle exercise**
- Better results are expected combining different procedures in an **early** and **multimodal approach**.

Table 3
Summary of clinical trials for pharmacological treatment of cancer-induced muscle wasting.

Mechanism	Name	Target	Phase	Status	Clinical Trial
Appetite stimulants	Anamorelin	Ghrelin receptor	III	Completed	NCT01387269
	Ghrelin*	Ghrelin	I/II	Completed	NCT00933361
	CTL-002	GDF-15	I/II	Recruiting	NCT04725474
	Ponsegromab	GDF-15	II	Recruiting	NCT05546476
	NGM120	GDF-15	I/II	Recruiting	NCT04068896
	AZD8853	GDF-15	I/II	Recruiting	NCT05397171
Anabolic agents	Enobosarm	Androgen receptor	II	Completed	NCT00467844
	Testosterone*	Androgen	I	Completed	NCT00878995
Anti-catabolism	Landogrozumab	Myostatin	II	Completed	NCT01505530
	Trevogrumab	Myostatin	II	Completed	NCT01963598
	STM 434	Activin A	I	Completed	NCT02262455
	Bimagrumab	ActRII	II	Completed	NCT01433263
	MT-102	B-adrenergic receptor	II	Completed	NCT01238107
Anti-inflammation	MABp1	IL-1α	III	Completed	NCT02138422
	ALD518	IL-6	II	Completed	NCT00866970
	Lenalidomide	TNF-α	I/II	Completed	NCT01127386
	Ruxolitinib	JAK/STAT signaling	I	Recruiting	NCT04906746

* not trade name.

Muscle exercise



Resistance exercise is a potent stimulant for protein synthesis resulting in increases in muscle fibre cross-sectional area, particularly hypertrophy of myofibrillar proteins, myosin and actin, stimulating both myofibrillar and mitochondrial protein synthesis.

A key regulator of this process appears to be insulin-like growth factor-1 (**IGF-1**)

Ageing Research Reviews 91 (2023) 102057

If exercise could be packed in a pill, it would be the single most widely prescribed and beneficial medicine in the nation.

Robert N. Butler, M.D.
Former Director,
National Institute on Aging

Conclusions

- Cancer patients are susceptible to sarcopenia before and after chemotherapy
- Muscle mass depletion is associated with the risk of discontinuation of chemotherapy and dose reduction
- Sarcopenia worsens chemotherapy mediated toxicity in sarcopenic obese, eutrophic and malnourished subjects, with elevated healthcare costs
- Need for a simple, rapid, and reliable approach to enable timely and effective intervention.


Grazie per l'attenzione!