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

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ABSTRACT

Body composition has gained increasing attention in oncology in recent years due to fact that sarcopenia has been revealed to be a strong prognostic indicator for survival across multiple stages and cancer types and a predictive factor for toxicity and surgery complications. Accumulating evidence over the last decade has unraveled the "pharmacology" of sarcopenia. Lean body mass may be more relevant to define drug dosing than the "classical" body surface area or flat-fixed dosing in patients with cancer.

Since sarcopenia has a major impact on patient survival and quality of life, therapeutic interventions aiming at reducing muscle loss have been developed and are being prospectively evaluated in randomized controlled trials. It is now acknowledged that this supportive care dimension of oncological management is essential to ensure the success of any anticancer treatment.

The field of sarcopenia and body composition in cancer is developing quickly, with (i) the newly identified concept of sarcopenic obesity defined as a specific pathophysiological entity, (ii) unsolved issues regarding the best evaluation modalities and cut-off for definition of sarcopenia on imaging, (iii) first results from clinical trials evaluating physical activity, and (iv) emerging body-composition-tailored drug administration schemes.

In this context, we propose a comprehensive review providing a panoramic approach of the clinical, pharmacological and therapeutic implications of sarcopenia and body composition in oncology.

Contents

Abbreviations: 5-FU, 5-Fluorouracil; ACF, 5-FU, Cisplatin, and adriamycin; APA, Adapted physical activity; AUC, Area under the curve; BIA, Bioelectrical impedance analysis; BMI, Body mass index; BSA, Body surface area; CMF, Cyclophosphamide, methotrexate, 5FU; Cr, Creatinine; CRP, C Reactive protein; CT, Computed tomography; CYP, Cytochrome; CysC, Cystatin C; DCF, Docetaxel, cisplatin, and 5FU; DXA, Dual-energy X-ray absorptiometry; DLT, Dose-limiting toxicity; FM, Fat mass; FOLFOX, 5FU, Leucovorin and oxaliplatin; GFR, Glomerular filtration rate; HRQoL, Health-related quality of life; HU, Hounsfield unit; IL-1, Interleukin-1; IL-6, Interleukin-6; L3, Third lumbar vertebra; LBM, Lean body mass; mAb, Monoclonal antibody; MKI, Multikinase inhibitor; MRI, Magnetic resonance imaging; NLR, Neutrophil-to-lymphocyte ratio; NSCLC, Non-small cell lung cancer; OS, Overall survival; OR, Odds ratio; PK, Pharmacokinetics; PS, Performance status; SCLC, Small cell lung cancer; SMA, Skeletal muscle area; SMI, Skeletal muscle index; TGF-β, Transforming growth factor beta; TMA, Total muscle area; TNF, Tumor necrosis factor.

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1. Introduction

Sarcopenia (i.e. loss of muscle mass and function) is a hallmark of cachexia, a multi-organ syndrome characterized by negative protein and energy balance, weight loss (including muscle with or without fat), anorexia, and decreased physical function (Fearon et al., 2011). Cachexia has been defined in the setting of underlying inflammatory disease as: (i) unintended weight loss of >5% over the past 6 months; or (ii) body mass index (BMI) < 20 kg/m^2 and any degree of weight loss >2%; or (iii) muscle atrophy (i.e. reduced muscle mass) as determinable by various modalities of body composition analysis and any degree of weight loss >2% (Fearon et al., 2011). Not all cachectic patients have sarcopenia, and not all sarcopenic patients meet consensus criteria for cachexia, while most cancer patients in this context have both sarcopenia and cachexia (Fig. 1). Sarcopenia is observed in >50% of patients with metastatic cancers (Morishita et al., 2012). It negatively affects survival and health-related quality of life (HRQoL) of patients due to decreased tolerance to anticancer treatments and increased susceptibility to infections and other complications (Bozzetti, 2017). Therefore, sarcopenia and cachexia represent a major clinical target in oncology.

Cancer-related sarcopenia is multifactorial in origin, involving mainly inflammatory and hypercatabolic syndrome, anxiety/depression, and chemotherapy adverse effects (nausea/vomiting, mucitis, diarrhea, and loss of appetite) (Fearon et al., 2011). Given this multifaceted pathophysiology, a multimodal therapeutic approach to sarcopenia management including nutritional support and exercise on a background of personalized oncology care and family-centered education is advocated for (Morley et al., 2010). Several techniques and markers are used to characterize sarcopenia. Lean body mass (LBM) may be more relevant to adapt drug dosing than the "classical" body surface area or flat-fixed dosing. Sarcopenia and changes in body composition present a rapidly developing field of oncology, with the newly identified concept of sarcopenic defined as a specific pathophysiological entity, unsolved issues regarding evaluation modalities and best cut-off for imaging definition of sarcopenia (probably not a "one-size-fits-all" value), first results from clinical trials evaluating physical activity, and emerging body-composition-tailored drug administration schemes.

2. Sarcopenia definition and modalities of body composition analysis

2.1. Definition and pathophysiology

Sarcopenia was first described in 1989 as an age-related loss of muscle mass (Rosenberg, 1989). Later, the definition was expanded to a syndrome combining three criteria: (i) loss of skeletal muscle mass, (ii) loss of function, and (iii) loss of physical performance (Rosenberg, 1997; Roubenoff, 2000). Three consensus papers established a definition of sarcopenia based on these three parameters (Cruz-Jentoft, Baeyens, et al., 2010; Fielding et al., 2011; Muscaritoli et al., 2010). The European Working Group on Sarcopenia in Older People (EWGSOP) proposed three stages of sarcopenia: pre-sarcopenia (presence of one criterion), sarcopenia (two criteria), and severe sarcopenia (three criteria) (Table 1). The techniques used to diagnose sarcopenia include (i) cross sectional imaging, dual-energy X-ray absorptiometry (DXA), or bioelectrical impedance analysis (BIA) for the assessment of muscle mass, (ii) handgrip test for the assessment of muscle strength, and (iii) a short physical performance battery (i.e., a group of measures that combines gait speed, chair stand, balance tests, and walk speed) (Guralnik et al., 2000) (Fig. 2). The muscle function was added into the sarcopenia definition based on the results demonstrating that its decrease is correlated with mortality (Baumgartner et al., 1998). Nevertheless, beside motor functions, skeletal muscle mass plays an important role in the endocrine regulation of metabolism (Janssen & Ross, 2005). Overall the motor function is overly narrow and does not reflect the endocrine function of the muscle. Thus, muscle mass should take the priority over muscle function and be considered as the

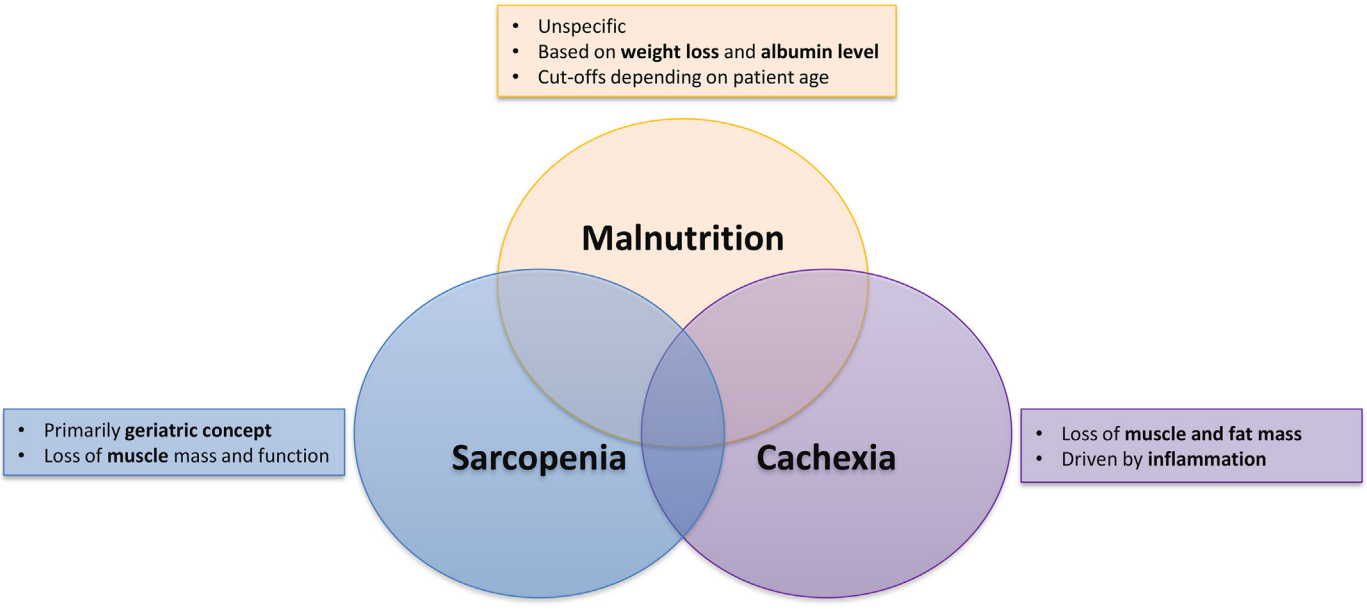

Fig. 1. Overlap and distinctions between sarcopenia, cachexia and malnutrition definitions.

Table 1
Consensus definitions of sarcopenia.

Society	Low muscle function	Low muscle mass	Low muscle strength	Subgroups
European Working Group on Sarcopenia in Older People (EWGSOP)	Measured by short physical performance battery (SPPB), which is a summation of three tests: Balance, Gait Speed and Chair Stand Score ≤ 8 Measured by Gait Speed Several suggested cut-offs	Measured by BIA or DXA Several suggested cut-offs	Measured by Handgrip Strength Several suggested cut-offs according to age and sex	*Presarcopenia:* decreased muscle mass only *Sarcopenia:* - decreased muscle mass - with decreased muscle function or decreased muscle strength *Severe sarcopenia*: decreased muscle mass, muscle strength and muscle function
International Working Group on Sarcopenia (IWGS)	Measured by Gait Speed Speed below 1.0 m/s over a 4-m walking test	Measured by BIA Appendicular lean mass/height^2 < 20th percentile of values for healthy young adults (i.e. ≤ 7.23 kg/m^2 in men and ≤ 5.67 kg/m^2 in women)	Not specified	Not specified
European Society for Clinical Nutrition and Metabolism Special Interest Groups (ESPEN-SIG)	Measured by Gait Speed Speed below 0.8 m/s over a 4-m walking test	Measured by BIA Percentage of muscle mass ≥ 2 standard deviations below the mean mass in young adults (18–39 years) of the same sex and ethnic group	Not specified	Not specified

Abbreviations: BIA: bioelectrical impedance analysis, DXA: dual-energy X-ray absorptiometry.

cornerstone of the definition criteria for sarcopenia (Bulow, Ulijaszek, & Holm, 2018). Sarcopenia is also classified as "primary" when age-related and "secondary" when activity, nutrition, or disease-related such as in cancer or other chronic diseases (Cruz-Jentoft, Landi, Topinková, & Michel, 2010).

Inflammation is a predominant driving mechanism in cancer-related sarcopenia pathophysiology. C reactive protein (CRP) is a marker for inflammation and has been suggested as a biological marker for sarcopenia (Bano et al., 2017). In a comparable way, neutrophil-to-lymphocyte ratios (NLR) are higher in sarcopenic patients than in those without sarcopenia (Öztürk, Kul, Türkbeyler, Sayıner, & Abiyev, 2018) as well as circulating levels of pro-inflammatory cytokines (e.g. tumor necrosis factor [TNF], interleukin-1 [IL-1], and interleukin-6 [IL-6]) (Narsale & Carson, 2014; Schaap, Pluijm, Deeg, & Visser, 2006; Visser et al., 2002). The cytokines of the transforming growth factor beta (TGF-β) family, i.e., TGF-β, myostatin, GDF11, and activins are major atrophic factors widely involved in cancer-induced cachexia (Wakefield & Hill, 2013). Their circulating levels are increased in most cancers, including pancreatic and colorectal cancers (Wildi et al., 2001; Zhao et al., 2016). These molecules trigger intracellular signals

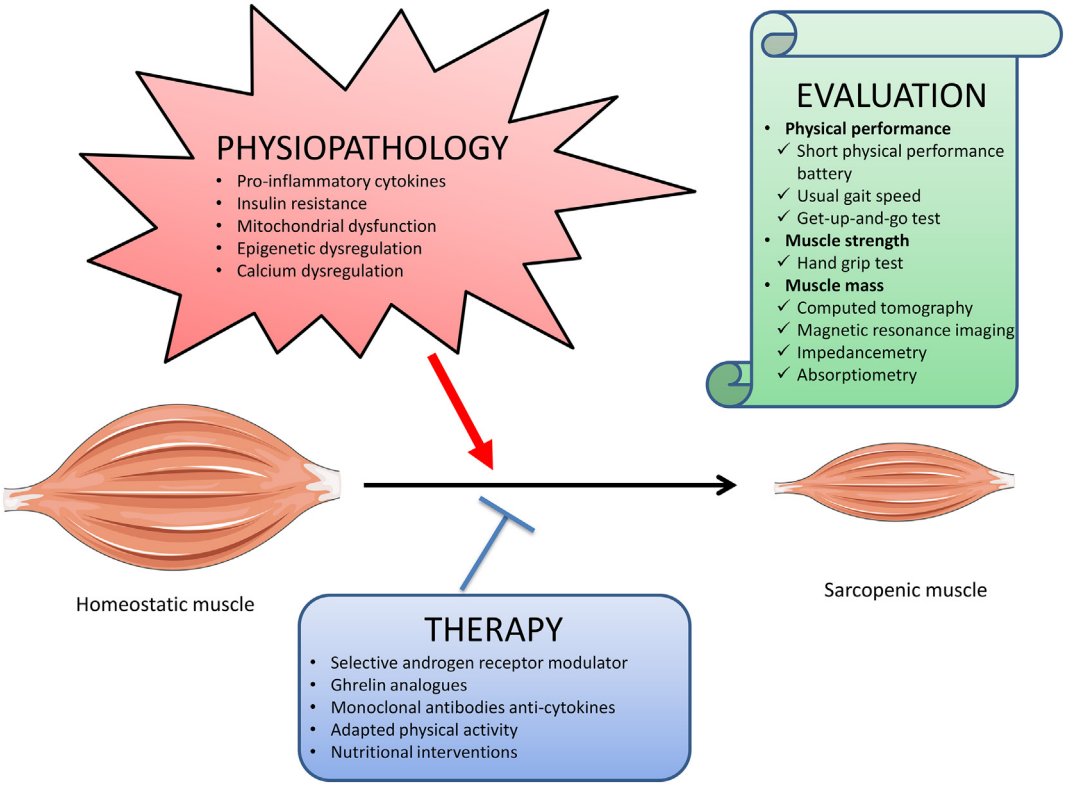

Fig. 2. Physiopathology, treatment and evaluation of sarcopenia.

leading to loss of contractile proteins linked to a decrease in protein synthesis and a significant increase in the degradation of muscle myofibrillar proteins, inevitably impacting muscle strength production (Cohen, Nathan, & Goldberg, 2015). Preclinical studies have shown that ZIP14, a metal-ion transporter, and Twist1, a transcription factor, are overexpressed in muscle progenitor cells, highlighting the roles of zinc homeostasis and activin/myostatin signaling in cancer-related muscle loss (Parajuli et al., 2018; G. Wang et al., 2018). In addition, muscle proteolysis induces an important efflux of muscle amino acids, which constitutes "bricks and fuel" to boost tumor progression (Mayers et al., 2016). However, the mechanisms underlying cancer-related muscle dysfunction appear to be more complex than just a negative balance between muscle protein synthesis and degradation. It has recently been shown that microenvironmental alterations affecting cells located at the periphery of the muscle fiber also play a key role in cancer-related muscle atrophy. Indeed, muscle fibers are surrounded by muscle stem cells called "satellite cells". During muscle injury, these cells become activated and proliferate to produce myoblasts, which differentiate and fuse to form new myofibers and thus restore muscle tissue integrity. In cancer, inflammation induces muscle damage leading to the activation of satellite cells that are engaged in a myogenic muscle tissue repair program, but cannot differentiate (He et al., 2013). Other mechanisms have recently been shown to be involved in cancer-related sarcopenia, such as epigenetic alterations involving bromodomain protein BRD4 (Segatto et al., 2017) and calcium homeostasis involving ryanodine receptors (A. Agrawal, Suryakumar, & Rathor, 2018; Waning et al., 2015). Endocrine and metabolic factors also play a pivotal role in the pathogenesis of sarcopenia. Some publications suggests an association between insulin resistance and mitochondrial dysfunction leading to the development of skeletal muscle lipid deposition (Corcoran, Lamon-Fava, & Fielding, 2007) and to reduced muscle oxidative activity (Simoneau & Kelley, 1997) in sarcopenia and cancer-induced cachexia (Abbatecola et al., 2011; van der Ende et al., 2018). Moreover, insulin promotes amino acids transport into cells through nitric oxide synthase (Mann, Yudilevich, & Sobrevia, 2003). Therefore, insulin resistance may lead to poorer protein synthesis due to reduced internalization of amino acids. These hypotheses may explain why patients with type 2 diabetes mellitus are more at risk of developing sarcopenia (Leenders et al., 2013; Morley, Malmstrom, Rodriguez-Mañas, & Sinclair, 2014; Park et al., 2007).

Overall, systemic inflammation, metabolic changes, and secreted "atrophying" cytokines along with the muscle microenvironmental dysfunction alter cell signaling in muscle fibers and lead to imbalance between protein synthesis and degradation (Argilés, Campos, Lopez-Pedrosa, Rueda, & Rodriguez-Mañas, 2016) (Fig. 2). These phenomena are very early in some malignancies, particularly in pancreatic cancer, and may precede cancer diagnosis by several years (Agustsson, D'souza, Nowak, & Isaksson, 2011; Mayers et al., 2014). Moreover, sarcopenia itself is affected by chemotherapy, since a variety of common chemotherapy drugs are known to experimentally induce sarcopenia in rodent cancer models (Hojman et al., 2014; Sakai et al., 2014). Data on humans carry some caveats because chemotherapy agents are not given to healthy adults and it seems that muscle wasting is exacerbated by chemotherapy (Awad et al., 2012; Coletti, 2018) through reduced food intakes (Spotten et al., 2017) and induced NF-kB expression (Damrauer et al., 2018). The decrease in food intakes in cancer patients is multifactorial and classically thought to result from changes to appetite, smell and taste and to behavior-regulating regions of brain occurring as a result of inflammatory mediators (Ezeoke & Morley, 2015).

2.2. Modalities of body composition evaluation

In clinical practice, physical performance assessment by short physical performance battery, usual gait speed, and get up and go test (Cruz-Jentoft, Baeyens, et al., 2010; Owusu, Margevicius, Schluchter, Koroukian, & Berger, 2017) and muscle strength evaluation using handgrip test (Kilgour et al., 2013; Veni et al., 2018) are quite standardized. On contrary, there is no consensus on the optimal modality to assess muscle mass in cancer patients.

Anthropometric measurements include weight variation, BMI, waist and hip circumference, waist-to-hip ratio, and skinfold. These are non-invasive, easy to perform, and routinely used to estimate body surface area (BSA; derived from weight and height) for chemotherapy dosing calculation (Griggs, Mangu, Temin, & Lyman, 2012). However, anthropometry is unreliable in some cancer patients, particularly in case of short-term changes in body water composition (e.g. in presence of ascites or lymphedema), or in obese patients (Di Sebastiano & Mourtzakis, 2012).

Bioelectrical impedance analysis (BIA) is an additional widely available, non-invasive modality that uses reactance and resistance to determine total body water, fat mass (FM), and fat-free mass. However, BIA is highly dependent on patient hydration state and is biased in case of pathological increase in body water content such as ascites and lymphoedema. Other limitations of BIA is the lack of specific predictive equations for cancer patients leading to frequent inaccuracies (under or overestimations) and the lack of standardization resulting in heterogeneity of sarcopenia prevalence rates across studies (Gonzalez, Barbosa-Silva, & Heymsfield, 2018).

Dual energy X-ray absorptiometry (DXA) uses a three-compartment model comprising FM, fat-free mass, and bone mineral content. This method can detect early lean mass variations, is highly accurate and reproducible (Ellis, 2001; Shiel et al., 2018). However, it cannot discriminate between different types of fat tissues (visceral, subcutaneous, and intramuscular) as only an overall assessment of FM at the molecular and not at compartmental tissue level can be provided by DXA and no differentiation of specific lean tissues like skeletal muscle and the internal organs within the thorax or abdomen can be made (Guglielmi et al., 2016; Prado & Heymsfield, 2014). Consequently, muscle mass using DXA is estimated based on the appendicular skeleton.

Finally, it has been shown that cross sectional muscle surface at the third lumbar vertebrae (L3) best reflects total skeletal muscle mass determined by computed tomography (CT) or magnetic resonance imaging (MRI) (Heymsfield, 2008; Mitsiopoulos et al., 1998; Yang et al., 2017). In practice, total muscle area (TMA, in cm^2) is measured at L3 using a semi-automatic segmentation software on a dedicated post-treatment station (with most packages being interchangeable) (Bonekamp et al., 2008). TMA is then normalized to stature (using $height^2$ in m^2, similarly to BMI) (Baumgartner et al., 1998) to obtain the skeletal muscle index (SMI) in cm^2/m^2.

However, uncertainties remain regarding technical aspects of this method. To date, the only technical guideline available for L3 skeletal muscle surface estimation using CT is the one described by Mitsiopoulos et al. in 1998 and recommended by Prado et al. in 2008 (Mitsiopoulos et al., Prado et al.). It recommends measurement of the mean skeletal muscle surface value on two consecutive slices at the L3 level based on Hounsfield unit (HU) thresholds (−29 to +150), followed by manual corrections where necessary. Nevertheless, several technical issues that can influence skeletal muscle surface measurements need clarification such as the effect of intravenous contrast injection (van Vugt et al., 2018), slice thickness (Fuchs et al., 2018), or the influence of tube potential (Morsbach et al., 2018).

Regarding MRI, there are no clear technical recommendations on image acquisition techniques. Most studies used standard T1 and T2-weighted imaging protocols (Heymsfield, 2008; Mitsiopoulos et al., 1998; Yang et al., 2017) and fat-water separated imaging techniques (Dixon, 1984) with manual segmentation to determine L3 skeletal muscle surface, which is time consuming. Very few studies have used or investigated the reproducibility of automated methods applied to MRI (Borga, 2018). This is most likely due to the fact that MRI is not used in a quantitative way because, unlike HU on CT imaging, the intensity levels on MRI are expressed in arbitrary units and are not correlated to tissue composition.

A single-muscle approach to muscle mass quantification using cross-sectional analysis (surface and/or density) of the psoas muscle on abdominal CT and of the pectoralis muscle on thoracic CT in patients who do not undergo abdominal CT (e.g. osteosarcomas and head and neck cancers) has been proposed (Go et al., 2017; Y. S. Kim, Kim, Kang, Ahn, & Kim, 2017). However, these single-muscle, simplified approaches, which hypothesized that one muscle may be representative of total skeletal mass have not been validated by any expert group (Bahat et al., 2016; Baracos, 2017; Cesari et al., 2012). Automated total muscle segmentation on CT imaging has been suggested as an alternative, more accurate method to improve body composition quantification availability and routine application (Baracos, 2017; Popuri, Cobzas, Esfandiari, Baracos, & Jägersand, 2016).

Assessment of muscle quality may provide prognostic information beyond quantity estimation (Sami Antoun et al., 2013; Looijaard et al., 2016; Martin et al., 2013). Skeletal muscle lipid content has been associated with muscle quality i.e., high-lipid content being correlated with poor muscle quality. It can be assessed by measuring muscle density on CT imaging, as the latter decreases with lipid infiltration (Heymsfield, 2008). Goodpaster et al. showed that muscle density in elderly patients can account for differences in muscle strength not explained by muscle quantity (Goodpaster, Kelley, Thaete, He, & Ross, 2000). This however was not confirmed by another study of healthy adults (Weeks, Gerrits, Horan, & Beck, 2016). Similarly to TMA estimation, there is no consensus for important technical aspects of CT acquisition such as contrast enhancement, slice thickness, and tube potential influence, which significantly impact HU density values of the muscle. Further research is needed for the standardization of image acquisition and protocols of analysis.

In summary, cancer-related sarcopenia and body composition can be estimated by simple anthropometric values (weight loss and BMI) and L3 SMI using CT or MRI, with CT being the most commonly used modality in clinical practice and oncology research (Kazemi-Bajestani, Mazurak, & Baracos, 2016) (Table 3). Indeed, CT is routinely performed for diagnosis, treatment evaluation, and follow-up in oncological care and TMA assessment. In addition, it can be performed on the same imaging exam without requiring an additional procedure. However, in the foreseeable future, with the development of artificial intelligence, the next gold standard for body composition assessment will most likely rely on 3D body-scanning with automated scoring systems (Cornet et al., 2015; Fang, Berg, Cheng, & Shen, 2018).

2.3. Unsolved questions including cut-off issues

A major unsolved issue in sarcopenia evaluation is the question of the best cut-off value for sarcopenia definition. Sarcopenia is more often considered in a binary fashion for research purposes in the literature, patients being classified as either "sarcopenic" or "non-sarcopenic". Several cut-offs have been proposed (Cornet et al., 2015; Cruz-Jentoft, Baeyens, et al., 2010) for sarcopenia diagnosis, yielding broad variations in sarcopenia prevalence (Bijlsma et al., 2013). The first available cut-off values specific to patients with cancer were published by Prado et al. reporting on a population of obese Canadian patients with respiratory and gastrointestinal tract cancers (Prado et al., 2008). They defined cut-off value of 52.4 cm^2/m^2 in men and 38.5 cm^2/m^2 in women associated with mortality. Mourtzakis et al. showed that CT-based muscle analysis at L3 was strongly related to appendicular skeletal mass measured with DXA (Mourtzakis et al., 2008). They generated corresponding CT cut-off values of 55.4 cm^2/m^2 in men and 38.9 cm^2/m^2 in women using established DXA cut-off values (7.26 kg/m^2 and 5.45 kg/m^2, respectively). In 2011, an international panel of cachexia experts established a new diagnostic criterion for cancer cachexia, using both anthropometric measures and SMI based on cut-off values of 55 cm^2/m^2 in men and 39 cm^2/m^2 in women by CT imaging (Fearon et al., 2011). Following, Martin et al. proposed SMI thresholds for sarcopenia in non-obese Caucasians according to sex and BMI (Martin et al., 2013) based on optimal stratification of SMI and survival; selected cut-off values were 43 and 53 cm^2/m^2 in men with a BMI < and > 25 kg/m^2, respectively, and 41 cm^2/m^2 in women. Several further studies have demonstrated predictive value for toxicity (Sjøblom et al., 2015; Srdic et al., 2016; Stene et al., 2015; B. H. L. Tan et al., 2015), post-surgery complications (Lieffers, Bathe, Fassbender, Winget, & Baracos, 2012; P. Peng et al., 2012; Reisinger et al., 2015), and survival (M. H. Choi, Oh, Lee, Oh, & Won, 2018; Lee et al., 2018) using these thresholds (Table 2).

Table 2
Correlation of sarcopenia with clinical outcomes according to different cut-offs measured by computed tomography at the third lumbar vertebrae.

Cut-offs	Study	N	Cancer type/Stage	Country/Ethnicity	Overweight/Obese	Correlation
SMI ≤ 52.4 cm^2/m^2 for men	(Parsons, Tsimberidou, et al., 2012)	48	Mostly colorectal Metastatic	USA	27% obese 17% overweight	No association with toxicity or survival
SMI ≤ 38.5 cm^2/m^2 for women	(Prado et al., 2008)	2115	Respiratory or gastrointestinal cancers All stages	Canada	15% obese	Association with poorer status functional status and worst survival
	(Parsons, Baracos, et al., 2012)	114	Mixed Advanced	Canada Including: Caucasian 81% Hispanic 9% African-American 8% Other 2%	63% overweight	Association with survival for patients ≤65 years
	(Del Fabbro et al., 2012)	129	Breast cancer Nonmetastatic	USA Including: White 60% Hispanic 17% Asian 10% African-American 13%	39% obese 26% overweight	Association with survival
	(Prado et al., 2009)	55	Breast cancer Metastatic	Canada	Not specified	Association with toxicity and time to tumor progression
	(Arrieta et al., 2015)	84	NSCLC Metastatic	Canada	Not specified	No association with toxicity
	(Anandavadivelan et al., 2016)	72	Oesophageal cancer Localized	Sweden	57% overweight/obese	Association with toxicity
	(B. H. L. Tan et al., 2015)	89	Oesophago-gastric cancer Localized	United Kingdom	Not specified	Association with toxicity and survival

(continued on next page)

Table 2 (*continued*)

Cut-offs	Study	N	Cancer type/Stage	Country/Ethnicity	Overweight/Obese	Correlation
	(Benjamin H. L. Tan, Birdsell, Martin, Baracos, & Fearon, 2009)	111	Pancreatic cancer Metastatic	Canada	39.6% overweight/obese	Association with survival
	(Voron et al., 2015)	109	Hepatocellular carcinoma	France	42.2% overweight	
	Non metastatic	12.-8%	Association with survival	obese		
	(Kamachi et al., 2016)	92	Hepatocellular carcinoma Non metastatic	Japan	19.6% overweight 1.1% obese	Association with tumor recurrence
	(Dalal et al., 2012)	41	Pancreatic cancer 37% obese	USA Including: Caucasians 95%	59% overweight	Association with survival only in obese patients
Locally advanced SMI ≤ 43 cm^2/m^2 for men with a BMI under 25 SMI ≤ 53 cm^2/m^2 for men with a BMI above 25	(Daly et al., 2017)	84	Melanoma Metastatic	Ireland	21% obese 45% overweight	Association with toxicity
SMI ≤ 41 cm^2/m^2 for women	(Cushen et al., 2016)	63	Prostate Metastatic	Ireland	40% overweight 36% obese	No association with survival
	(Fukushima et al., 2016)	92	Renal cell carcinoma Metastatic	Japan	27% overweight/obese	Association with survival
	(Fukushima, Yokoyama, Nakanishi, Tobisu, & Koga, 2015)	88	Urothelial carcinoma Metastatic	Japan	Not specified	Association with survival
	(Shachar, Deal, Weinberg, Nyrop, et al., 2017)	40	Breast cancer Metastatic	USA	Not specified	Association with toxicity
	(Palmela et al., 2017)	48	Gastric cancer Locally advanced	Portugal	38% overweight 2% obese	Association with survival and toxicity
	(Tegels et al., 2015)	152	Gastric cancer Localized	Netherlands	Not specified	No association with survival and postoperative complications
	(Meza-Junco et al., 2013)	116	Hepatocellular carcinoma Localized and metastatic	Canada Including: White 76% Oriental 10% Asian Indian 4% Arabian 3% Other 7%	41% overweight 30% obese	Association with survival
SMI ≤ 55 cm^2/m^2 for men SMI ≤ 39 cm^2/m^2 for women	(Camus et al., 2014)	80	Diffuse large B-cell lymphoma (DLBCL)	France	38% obese/overweight	Association with survival
	(Lanic et al., 2014)	82	Diffuse large B-cell lymphoma (DLBCL)	France	39% obese/overweight	Association with survival
	(Srdic et al., 2016)	100	NSCLC Locally advanced and metastatic	Croatia Including: Caucasians 100%	26% overweight 14% obese	Association with survival and toxicity
	(Sharma, Zargar-Shoshtari, Caracciolo, Richard, et al., 2015)	43	Penile Locally advanced	USA	Not specified	Association with postoperative complications
	(E. Y. Kim et al., 2015)	149	Small cell lung cancer	Korea	21% overweight 20% obese	Association with survival
	(Nault et al., 2015)	52	Hepatocellular carcinoma Advanced	France	38% overweight 12% obese	Association with toxicity
	(Mir, Coriat, Boudou-Rouquette, et al., 2012)	18	Hepatocellular carcinoma Advanced	France	22.2% overweight 11.1% obese	Association with survival
	(Barret et al., 2014)	51	Colorectal cancer Metastatic	France	41.2% overweight 3.9% obese	Association with toxicity
	(Huillard et al., 2013)	61	Renal cancer Metastatic	France	26.2% overweight 21.3% obese	Association with toxicity
SMI ≤ 52 cm^2/m^2 for men SMI ≤ 39.5 cm^2/m^2 for women	(Levolger et al., 2015)	99	Hepatocellular carcinoma Non metastatic	Netherlands	36.7% overweight 15.6% obese	Association with survival and postoperative complications
SMI ≤ 43.7 cm^2/m^2 for men SMI ≤ 41.1 cm^2/m^2 for women	(van Vledder et al., 2012)	196	Colorectal cancer Metastatic	Netherlands	Not specified	Association with tumor recurrence and survival
SMI < 43.2 cm^2/m^2	(Wendrich et al., 2017)	132	Head and neck Locally advanced	Netherlands	Not specified	Association with toxicity
SMI ≤ 47.1 cm^2/m^2 for men SMI ≤ 34.4 cm^2/m^2 for women	(N. Nakamura et al., 2015)	207	Diffuse large B-cell lymphoma (DLBCL)	Japan	Not specified	Association with survival
SMI ≤ 42.2 cm^2/m^2 for men SMI ≤ 33.9 cm^2/m^2 for women	(Y. Choi et al., 2015)	484	Pancreatic cancer Advanced	Korea	11.6% overweight/obese	Association with survival
SMI ≤ 36 cm^2/m^2 for men SMI ≤ 29 cm^2/m^2 for women	(S.-L. Wang et al., 2016)	255	Gastric cancer Localized	China	Not specified	Association with postoperative complications
	(Huang et al., 2015)	142	Colorectal cancer Localized	China	Not specified	Association with postoperative complications

However, normal amounts of muscle and adipose tissues depend on demographic factors such as age (McCormick & Vasilaki, 2018) and ethnicity (Wells, 2012). It seems that sarcopenia is less prevalent among African-American (Parsons, Baracos, Dhillon, Hong, & Kurzrock, 2012) and Asian patients (Lau, Lynn, Woo, Kwok, & Melton, 2005) as compared to Caucasians. Therefore, these cut-offs may not be optimal for all patients and may be refined depending on type and stage of the cancer, sex, age, and ethnicity.

Nevertheless, rather than classifying a patient dichotomically as sarcopenic vs. non-sarcopenic based on a cut-off value, imaging biomarkers like SMI may be considered as continuous variables as suggested by Voron et al. (Voron et al., 2015). In such way, these may be used as the next reference for chemotherapy dosing calculation. This approach is already being tested with promising results (Baracos & Arribas, 2018; Iannessi, Beaumont, Hebert, Dittlot, & Falewee, 2018).

3. Sarcopenia prevalence and prognostic value

Sarcopenia has been reported across all cancer types. Prevalence rates according to primary tumor location and stage are displayed in Table 3. Most studies reported sarcopenia rates above 50% using L3 CT scan, particularly at advanced stages and in pancreatic, lung, bladder, and hematological malignancies. Noticeably, heterogeneity in prevalence rates is observed within single cancer types due to different cut-offs used to define sarcopenia and factors (e.g., clinical stage, ethnicity, age, cancer treatment).

Several studies investigated the prognostic value of sarcopenia in cancer patients. In a meta-analysis of patients with solid tumors a significant association between sarcopenia and shorter overall survival (OS; overall HR = 1.51, $p < .001$) has been reported, both for advanced and localized stages (Shachar, Williams, Muss, & Nishijima, 2016). However, a recent study suggested that survival may not be different for combined muscle and fat loss compared to fat-only loss in patients with advanced pancreatic cancer (Kays et al., 2018). Besides, a higher risk of post-surgical complications has been identified in several cancers, especially infectious complications following surgery for gastrointestinal (Ida et al., 2015; Krell et al., 2013; Lieffers et al., 2012; P. Peng et al., 2012; Takagi et al., 2017; Zhuang et al., 2016) and lung cancers (Miller et al., 2018; R. Nakamura et al., 2018). Finally, loss of skeletal muscle mass during chemotherapy has also been described as a negative prognostic factor (Daly et al., 2018).

Overall, several studies evaluating body composition using various modalities have consistently reported that sarcopenia is a strong prognostic indicator for localized and advanced cancers.

4. Sarcopenia and toxicity of anticancer treatments

In addition to its prognostic value, sarcopenia is a predictive factor of anticancer drug toxicity and may be more relevant for drug dose calculation than the "classical" body surface area or flat-fixed dosing. Anticancer drugs display various pharmacokinetics (PK) properties but share a narrow therapeutic index. Serious adverse events that may

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 × mass (kg) − 0.15 × age (years))] × mass (kg) + 73.2 which is divided by square of height (m^2).
Female; [(69.8–0.26 × mass (kg) − 0.12 × age (years))] × mass (kg) + 73.2 which is divided by square of height (m^2).

result in toxic death are common in this setting. Furthermore, specific cancer patient populations may exhibit vulnerabilities due to age and comorbidities. Identifying factors that can explain individual variations in treatment efficacy and toxicity is a new challenge of modern oncology. Performance status (PS) has a strong prognostic value (Atkinson et al., 2015) and is predictive of anticancer treatment-related acute toxicity (Sargent et al., 2009). However, PS evaluation is only semi-quantitative and is subjected to inter-observer variability. Thus, additional parameters are needed for the risk assessment of anticancer treatments. Other studies have investigated whether wide variations in body composition could be associated with morbidity in cancer patients. In recent years a large interest has grown in muscle mass due to the development of muscle mass assessments by CT.

We performed systematic search on PubMed using MeSH terms "Neoplasms AND (Sarcopenia OR Body composition OR Malnutrition OR Cachexia) AND Toxicity". Forty-two studies that focused on sarcopenia and toxicity of anticancer treatments were selected (Fig. 3).

4.1. Chemotherapy

In total, among 32 studies that investigated the association between sarcopenia and chemotherapy toxicity, 24 showed a significant association between sarcopenia and chemotherapy toxicity (Table 4). Although most of the studies were conducted retrospectively and with a small number of patients ($n < 100$), this correlation was found consistently across studies regardless of the time of assessment (i.e., early, within the first months of chemotherapy, or later), the tumor type and stage (i.e., from localized/curative to the metastatic/palliative setting), and the chemotherapy regimen. For example, Prado et al. (Prado et al., 2009) evaluated prospectively the tolerance of capecitabine in 55 patients with metastatic breast cancer after the first treatment cycle. Toxicities occurred in 50% of sarcopenic patients vs. 20% of non-sarcopenic patients ($p = .03$). Sarcopenia was also a predictive factor of toxicity in apparently fit patients (i.e., PS 0–1) such as those treated in phase I trials (Cousin et al., 2014). Indeed, Cousin et al. studied body composition in 93 phase I patients and showed that low SMI was the only factor associated with severe toxicity (Cousin et al., 2014).

Body composition in cancer patients can also be evaluated through renal function assessments in cancer patients. In daily practice, Glomerular Filtration Rate (GFR) is evaluated using the Cockcroft–Gault, Chronic Kidney Disease - Epidemiology Collaboration (CKD-EPI), and Modification of diet in renal disease (MDRD) formulas, which are derived from serum creatinine (Cr) level; this latter is influenced by the total muscle mass (Perrone, Madias, & Levey, 1992). In sarcopenic patients, reduced muscle mass may result in apparently low Cr level and overestimation of renal function by these formulas. Serum cystatin C

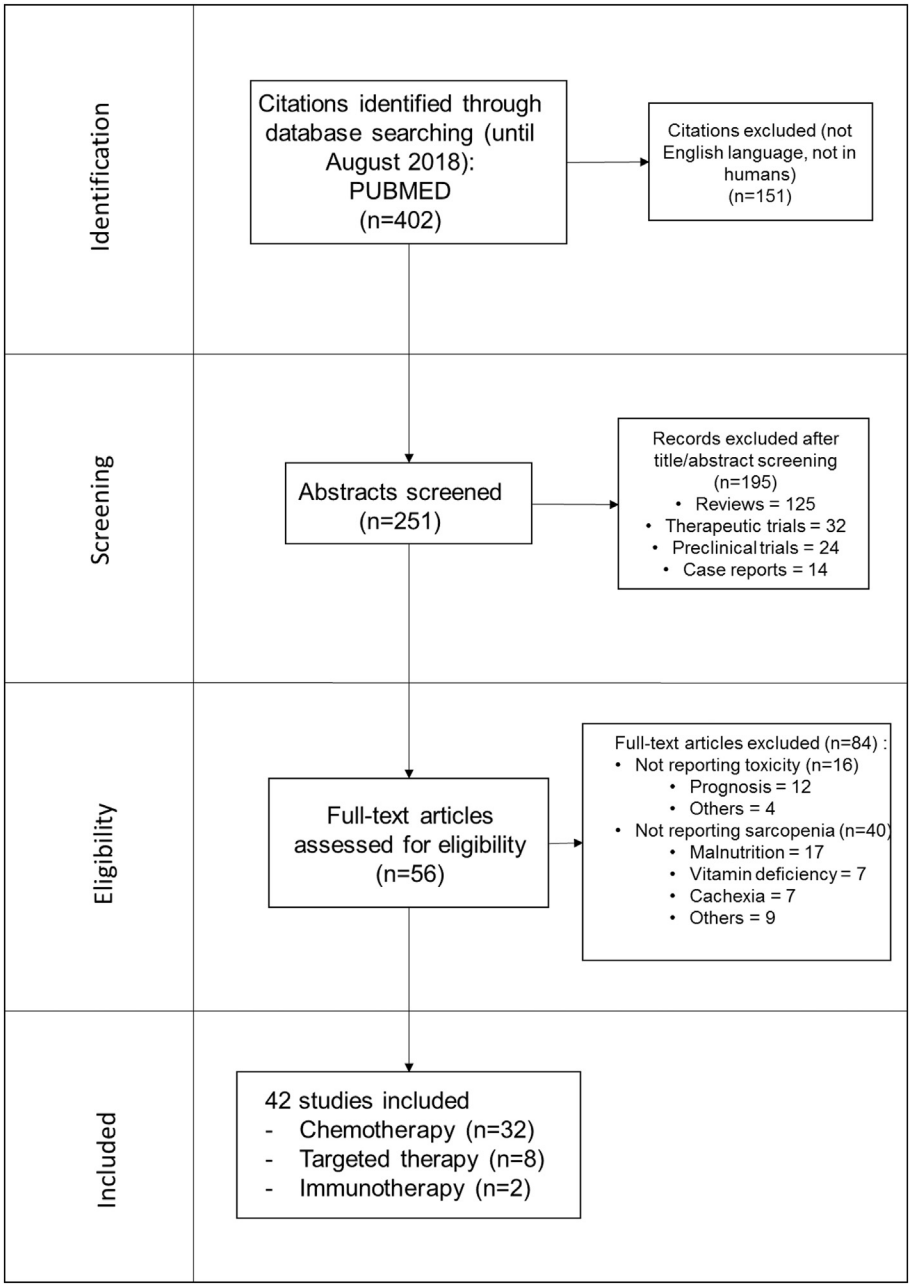

Fig. 3. Flowchart of selected studies for sarcopenia and anticancer treatment toxicity.

(CysC) is an alternative marker of GFR, independent from muscle mass (Baxmann et al., 2008; Rule, Bergstralh, Slezak, Bergert, & Larson, 2006). Thus, CysC appears as a better alternative for assessing renal function in patients with low muscle mass. The Cr/CysC ratio can be used as a quantitative surrogate marker of muscle mass (Tetsuka, Morita, Ikeguchi, & Nakano, 2013). In a study including 25 patients with non-small cell lung cancer (NSCLC) (Suzuki et al., 2015), a significant difference was noted in the Cr/CysC ratios of patients exhibiting moderate (grade 1–2) vs. severe (grade 3–4) toxicities (mean ratios: 0.84 vs. 0.70, respectively; $p < .05$). Similar results were found in a prospective study of ovarian cancer patients treated with carboplatin (Bretagne et al., 2017). Moreover, renal failure from the early stages exacerbates sarcopenia, explaining the frequent overlap between these two conditions (de Souza et al., 2017).

Contrarily, eight studies showed no association between sarcopenia and chemotherapy toxicity (Blauwhoff-Buskermolen et al., 2016; Jung et al., 2015; Miyata et al., 2017; Palmela et al., 2017; Parsons, Tsimberidou, et al., 2012; Rollins et al., 2016; Srdic et al., 2016; Stene et al., 2015; Versteeg et al., 2017). One explanation could be that not all forms of chemotherapy exhibit sarcopenia-dependent toxicity, even if the studies were adequately powered to detect an association. Finally, one study used liver intra-arterial chemotherapy (Parsons, Tsimberidou, et al., 2012), which displays a specific PK profile.

4.2. Targeted therapy

Eight studies investigated the association between sarcopenia and toxicity of targeted therapies with multikinase inhibitors (MKI), mainly antiangiogenics (Table 5). Overall, patients were metastatic in all studies and had infrequent tumor types in all but one study (four studies of renal carcinoma, two studies of hepatocellular carcinoma, and one study of thyroid carcinoma). The association between sarcopenia and toxicity was reported in seven studies. A meta-analysis pooling the results of four studies of metastatic renal cell carcinoma, showed that

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	First cycle	Lower LBM (mean 41.6 vs 56.2 kg) in pts. with toxicity	Yes
				LBM as continuous variable	Retrospective	Correlation of LBM with neutrophil nadir (r = 0.5)	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	Entire length	More grade 3–4 toxicity (57% vs 18%) in sarcopenic pts.	Yes
				SMI < 41 cm^2/m^2	of chemotherapy Retrospective	More toxicity-related hospitalizations (39% vs 0%) in sarcopenic patients	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	More dose reduction in sarcopenic pts. (51.7% vs 29.5%)	Yes
					Retrospective	Higher treatment-related mortality (50.0 vs. 8.4%) in sarcopenic pts. with high NLR	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
Srdic et al., 2016	Metastatic NSCLC	Platinum-based chemotherapy	100	L3 CT scan SMI ≤ 39 cm^2/m^2 for women SMI ≤ 55 cm^2/m^2 for men	First cycle Prospective	No association between sarcopenia and toxicity ≥ grade 2	No p > .05
(B. H. L. Tan et al., 2015)	Localized oesophago-gastric cancer	Neo-adjuvant 5FU cisplatin or capecitabine, epirubicin, cisplatin	89	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	More DLT in sarcopenic pts. (54.5 vs 28.9%)	Yes p = .015
Anandavadivelan et al., 2016	Resectable oesophageal cancer	Neo-adjuvant cisplatin and 5FU	72	L3 CT scan SMI ≤ 38.5 cm^2/m^2 for women SMI ≤ 52.4 cm^2/m^2 for men	First cycle Retrospective	More DLT in sarcopenic pts. with normal BMI but non-significant (OR = 1.60) More DLT in obese sarcopenic pts. (OR = 5.54)	Yes p < .1 p = .04
Murimwa et al., 2017	Locally advanced esophageal cancer	Neo-adjuvant chemoradiation (cisplatin and continuous infusion 5FU)	56	L4 CT scan (psoas muscle) Bottom median SMI	Three first months Retrospective	More acute grade 3/4 toxicity in sarcopenic pts. (OR = 5.78)	Yes p = .004
Miyata et al., 2017	Locally advanced esophageal cancer	Neo-adjuvant (DCF or ACF)	94	BIA Skeletal muscle mass < 90% of the standard	Cycles 1–3 Retrospective	No association between sarcopenia and toxicity	No p > .05
Palmela et al., 2017	Locally advanced gastric cancer	Neo-adjuvant (5FU or capecitabine based chemotherapy)	48	L3 CT scan SMI < 41 cm^2/m^2 in women SMI < 43 cm^2/m^2 in men and < 53 cm^2/m^2 in obese men	Entire length of chemotherapy Retrospective	More treatment termination in sarcopenic pts. (OR = 4.23)	Yes p = .05
Rollins et al., 2016	Unresectable	Gemcitabine-based	228	L3 CT scan	Cycles 1–6	No association between sarcopenia	No

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
Chemama et al., 2016	Locally advanced colorectal cancer	5FU + hyperthermic intraperitoneal chemotherapy with oxaliplatin and irinotecan	97	L3 CT scan SMI < 41 cm^2/m^2 for women SMI < 43 cm^2/m^2 for men and < 53 cm^2/m^2 for overweight/obese men	Days 1–30 after surgery Prospective	More toxicity in sarcopenic pts. (OR = 3.97)	Yes p = .005
(Parsons, Tsimberidou, et al., 2012)	Metastatic cancers, mostly colorectal	Hepatic arterial infusion chemotherapy with systemic 5FU bevacizumab	48	L3 CT scan SMI ≤ 38.5 cm^2/m^2 for women SMI ≤ 52.4 cm^2/m^2 for men	Not specified Retrospective	No association between sarcopenia and grade 3–4 toxicity	No p > .05
Cushen et al., 2016	Metastatic castrate-resistant prostate cancer	Docetaxel	63	L3 CT scan SMI < 43 cm^2/m^2 in men SMI < 53 cm^2/m^2 in obese men	Cycles 1–3 Retrospective	Lower SMI in pts. with neutropenia grade 1–2 (46.5 cm^2/m^2 vs. 51.2 cm^2/m^2)	Yes p = .005 p = .044
Carla M. M. Prado et al., 2014	Advanced or metastatic ovarian cancer	Pegylated liposomal doxorubicin Trabectedin	74	L3 CT scan LBM as continuous variable	First cycle Retrospective	Lower ratio of fat mass/LBM (0.54 vs 0.63) in overweight/obese pts. with toxicity	Yes p = .006
Stanisavljevic & Marisavljevic, 2010	Non-Hodgkin's lymphoma	R-CHOP (rituximab, cyclophosphamide, vincristine, prednisolone)	30	BIA LBM as continuous variable	Cycles 1–6 Prospective	Higher dose/kg LBM of cyclophosphamide (27.2 vs 22.9 mg/kg) and doxorubicin (1.71 vs 1.5 mg/kg) in pts. with hematological toxicity	Yes p < .05
Sucak et al., 2012	Hematologic malignancies	Busulfan-cyclophosphamide	71	LBM: Cunningham formula* LBM ≤ 14.5 kg/m^2 LBM ≤ 16.6 kg/m^2 for men	Not specified Retrospective	Lower LBM (median 17 kg/m^2 vs 18.59 kg/m^2) in patients with cardiac toxicity and emesis.	Yes p = .001

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Table 4 (*continued*)

Study	Tumor type	Treatment	N	Sarcopenia evaluation	Toxicity assessment	Main results	Significant association
Cousin et al., 2014	Diverse tumor types	Phase I drugs	93	L3 CT scan SMI below sex-adjusted median	First cycle Prospective	More severe toxicity (25.5 vs 6.5%) in sarcopenic pts	Yes p = .02
Bretagne et al., 2017	Diverse tumor types	Carboplatin alone or with paclitaxel	24	Cr/CysC ratio as continuous variable	Entire length of chemotherapy Prospective	Higher Cr/CysC ratio (1.3 vs 1.0) in pts. with severe thrombocytopenia	Yes p = .006
Versteeg et al., 2017	Diverse tumor types	Not specified	103	L3 CT scan SMI ≤ 38.9 cm^2/m^2 for women SMI ≤ 55.4 cm^2/m^2 for men	Entire length of chemotherapy Prospective	No association between sarcopenia and toxicity	No p = .29

Abbreviations: 5FU: 5-fluorouracil, ACF: 5FU, cisplatin, and adriamycin, BIA: bioelectrical impedance analysis, Cr: creatinine, CMF: cyclophosphamide, methotrexate, and 5FU, CysC: cystatin C, DCF: 5FU, cisplatin, and docetaxel, FOLFOX: 5FU, folinic acid, and oxaliplatin, L3 CT scan: computed tomography at the third lumbar vertebra level, LBM: lean body mass, N: number of patients included in the study, NLR: neutrophil lymphocyte ratio, Pts: patients, SCLC: small cell lung cancer, SMI: skeletal muscle index, OR: odds ratio.
* Male; [(79.5–0.24 × mass (kg) − 0.15 × age (years))] × mass (kg) + 73.2 which is divided by square of height (m^2).
Female; [(69.8–0.26 × mass (kg) − 0.12 × age (years))] × mass (kg) + 73.2 which is divided by square of height (m^2).

dose-limiting toxicities (DLT) of antiangiogenic drugs were more frequent in patients with low SMI (p = .03) (Vrieling et al., 2016). As observed with chemotherapy, increased toxicity in sarcopenic patients was observed from the first cycle of treatment (Huillard et al., 2013) and was associated with high serum concentration of MKI (Massicotte et al., 2013; Mir, Coriat, Blanchet, et al., 2012). In one study of NSCLC patients treated with afatinib (Arrieta et al., 2015), sarcopenia was not found predictive of toxicity using sex-specific cut-offs defined by Prado et al. (Prado et al., 2008) and low LBM and malnutrition were associated with severe gastro-intestinal toxicity and DLT.

4.3. Immunotherapy

In recent years, immune checkpoint blockade inhibitors have opened new opportunities in cancer therapy. They have markedly improved the clinical outcomes in several cancers, including metastatic melanoma (Hodi et al., 2010; Robert et al., 2014), renal cancer (Motzer et al., 2018), and lung cancer (Reck et al., 2016). Severe immune-related adverse events occurred in 10%–20% of patients treated with single-agent immune checkpoint inhibitor (Brahmer et al., 2015; Hodi et al., 2010; Motzer, Escudier, et al., 2015). Predictive factors of toxicity are still poorly known. Unlike for chemotherapy, the use of DLT for immune therapies, and more broadly for monoclonal antibodies (mAb), is inappropriate. Indeed, no maximum tolerated dose was found in phase I trials with bevacizumab (Gordon et al., 2001), rituximab (Ghielmini, 2005), cetuximab, pembrolizumab (Sachs, Mayawala, Gadamsetty, Kang, & de Alwis, 2016), and nivolumab (S. Agrawal, Feng, Roy, Kollia, & Lestini, 2016). Several dosing schemes have been developed based on weight (dose in mg/kg) or flat doses. The Food and Drug Administration (FDA) concluded that response/toxicity of nivolumab is not related to dose/exposure and shifted from body weight dosing (i.e. 3 mg/kg) to fixed dosing (240 mg) (www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm520871.htm). However, the rate of severe toxicities seems to increase with ipilimumab

Table 5
Sarcopenia and targeted therapy toxicity.

Study	Tumor type	Treatment	N	Sarcopenia evaluation	Toxicity assessment	Main results	Significant association
Massicotte et al., 2013	Metastatic medullary thyroid carcinoma	Vandetanib	33	L3 CT scan SMI as continuous variable	Not specified Prospective	Lower SMI (37.2 vs 44.3 cm^2/m^2) in pts. with DLT	Yes p = .003
Arrieta et al., 2015	Metastatic NSCLC	Afatinib	84	L3 CT scan SMI ≤ 38.5 cm^2/m^2 for women SMI ≤ 52.4 cm^2/m^2 for men LBM as continuous variable	First 4 months Prospective	No association between sarcopenia and severe toxicity More DLT in pts. with low LBM and BMI < 25 kg/m^2 (71.4 vs 18.8%)	Yes p = .0017
Mir et al., 2012	Advanced hepatocellular carcinoma	Sorafenib	40	L3 CT scan SMI ≤ 38.9 cm^2/m^2 for women SMI ≤ 55.4 cm^2/m^2 for men	First month Retrospective	More DLT in sarcopenic pts. (82 vs 31%)	Yes p = .005
Nault et al., 2015	Advanced hepatocellular carcinoma	Sorafenib or brivatinib	52	L3 CT scan SMI ≤ 39 cm^2/m^2 for women SMI ≤ 55 cm^2/m^2 for men	Not specified Retrospective	More hand–foot syndrome in sarcopenic pts. (OR = 9.16)	Yes p = .049
Huillard et al., 2013	Metastatic renal cancer	Sunitinib	61	L3 CT scan SMI ≤ 38.9 cm^2/m^2 for women SMI ≤ 55.4 cm^2/m^2 for men	First cycle Retrospective	More DLT in sarcopenic pts. (50 vs 19.5%)	Yes p = .01
Cushen et al., 2017	Metastatic renal cancer	Sunitinib	55	L3 CT scan SMI ≤ 38.9 cm^2/m^2 for women SMI ≤ 55.4 cm^2/m^2 for men	After 4 cycles Retrospective	Lower SMI in pts. with DLT (51.7 vs 59.4 cm^2/m^2)	Yes p = .01
Ishihara et al., 2016	Metastatic renal cancer	Sunitinib	71	L3 CT scan SMI < 41 cm^2/m^2 for women SMI < 43 cm^2/m^2 for men and < 53 cm^2/m^2 for overweight/obese men	Cycle 1–6 Retrospective	No association between sarcopenia and toxicity	No p = .157
Antoun et al., 2010	Metastatic renal cancer	Sorafenib	84	L3 CT scan SMI ≤ 38.9 cm^2/m^2 for women SMI ≤ 55.4 cm^2/m^2 for men	Not specified Retrospective	More DLT in sarcopenic pts. (41 vs 13%)	Yes p = .03

dose. In a retrospective study of exposure-response analysis in advanced melanoma patients, Feng et al. (Feng et al., 2013) showed that the occurrence of grade 3–4 immune-related adverse events was related to ipilimumab dose, with 3%, 13%, and 24% of patients developing severe toxicities when treated with 0.3 mg/kg, 3 mg/kg, and 10 mg/kg ipilimumab, respectively. Interestingly, no DLT was observed with tremelimumab despite a similar toxicity profile to ipilimumab (Camacho et al., 2009). A study of 84 patients with metastatic melanoma (Daly et al., 2017) treated with ipilimumab showed that sarcopenic patients developed higher grade adverse events than non-sarcopenic patients (OR = 5.34, p = .033). Similar results were observed in 68 metastatic melanoma patients treated with nivolumab and pembrolizumab (Heidelberger et al., 2017). However, it is hard to discern differences between a direct PK link and a consequence of increased frailty and susceptibility to treatment complications in sarcopenic patients in this setting.

4.4. Summary and discussion

Overall, this literature review shows that sarcopenic patients exhibit high rates of toxicity and highlights the role of body composition in the risk assessment of anticancer treatment in this setting. However, several questions remain unsolved due to methodological limitations and heterogeneity across reviewed studies. Reporting biases favoring positive over negative studies may have affected the validity of evidence. In addition, most of these studies included limited numbers of patients, with no preliminary estimation of sample size for statistical analysis. Besides, the evaluation of toxicities varied from one study to another: some studies considered all DLT, while other only analyzed some specific toxicities such as hematologic adverse events. The duration of toxicity evaluation ranged from the first cycle only to the entire length of treatment. Moreover, for a single tumor location, the thresholds and techniques used to detect sarcopenia differed between studies. Finally, although several studies using the SMI cut-offs defined for survival by Prado et al. showed a positive correlation between sarcopenia and toxicity, it is not certain that these are the best suited for toxicity (Table 2). As it was achieved for prognosis, it would be relevant to conduct a meta-analysis of studies dedicated to toxicity.

5. The pharmacology of sarcopenia

Several hypotheses can be raised to explain the association between cancer-related sarcopenia and toxicity. Evidence has accumulated during the last decade unravelling the “pharmacology” of sarcopenia. We will below develop the main hypotheses through PK and pharmacodynamics.

5.1. Pharmacokinetics

The PK hypothesis assumes that toxicity may be explained by overexposure of anticancer drugs in sarcopenic patients. From a pharmacological perspective, sarcopenia increases drug exposure and several studies showed correlation between LBM, drug exposure, and toxicity (Ali et al., 2016; Arrieta et al., 2015; Prado et al., 2007, 2014, 2011; Sjøblom et al., 2017, 2015; Stanisavljevic & Marisavljevic, 2010; Sucak et al., 2012). Regarding mAb (e.g. immune therapies and some of targeted therapies), no data was published so far on sarcopenia and PK. However, mAb are a category of drugs known for larger therapeutic index than cytotoxic chemotherapies or MKI. For instance, no DLT were observed for the highest doses of anti-programmed-death-1 (PD-1)/anti-programmed-death-ligand-1 (PD-L1) antibodies in phase I and II trials (Motzer, Rini, et al., 2015; Robert et al., 2014).

5.1.1. Absorption changes

It has been suggested in animal models that cancer-induced cachexia is associated with a gut barrier dysfunction due to microbiota dysbiosis and increased intestinal permeability (Klein, Petschow, Shaw, & Weaver, 2013), possibly leading to overexposure to drugs that are taken orally. The same mechanisms may exist in sarcopenia, but no studies have been conducted to confirm this hypothesis in specific models. This issue would be most pertinent when the drug in question is not typically well-absorbed orally. Absorption of drugs that are intended to be taken with meals may be compromised in patients with low oral intakes.

Obese sarcopenic patients have higher fat-to-lean-mass ratios than obese non-sarcopenic patients. This may explain an overexposure to targeted subcutaneous therapies (i.e. trastuzumab) through an increase in (highly vascularized) fat tissue and subcutaneous blood flow. Studies supporting this hypothesis are warranted. Similarly, no studies have been conducted to assess whether intramuscular fat deposits in obese sarcopenic patients alter absorption of intramuscular lipophilic injection drugs (i.e., decapeptyl, fulvestrant). In contrast, drugs with intravenous administration route are not affected by absorption changes.

5.1.2. Distribution changes

Changes in tissue relative proportion are likely to alter PK. Body composition is described as a two compartments model consisting of FM and LBM. LBM is defined as the sum of cellular mass and non-fatty intercellular connective tissue including tendons, ligaments, and bone (Ronenn Roubenoff & Kehayias, 2009). Indeed, muscle mass, being part of LBM, acts as a diffusion compartment for cancer treatments. Thus, decreased LBM in sarcopenia may lead to increased plasma levels of anticancer drugs. Five studies showed that toxicities were increased for higher doses of chemotherapies per kilogram of LBM (Ali et al., 2016; Prado et al., 2007; Sjøblom et al., 2017, 2015; Stanisavljevic & Marisavljevic, 2010). Other chemotherapy and MKI studies showed increased toxicity in women (Arrieta et al., 2015; Huillard et al., 2013; Prado et al., 2007; Sloan et al., 2002). The most likely explanation is that LBM is lower in women compared to men of the same age (Bredella, 2017), resulting in higher exposure to these drugs. Indeed, BSA, which is used for chemotherapy prescription, does not properly reflect the relative proportion of LBM and FM that are usually higher in men and women, respectively, in body composition (Gusella, Toso, Ferrazzi, Ferrari, & Padrini, 2002). Distribution volumes of mAb are low (i.e only extracellular fluids and blood plasma) due to their high hydrophilicity and size (Keizer, Huitema, Schellens, & Beijnen, 2010). As a result, they are less affected by body composition since changes in blood volume are less than proportional with the change in body weight (Boer, 1984). Several studies based on population PK showed that fixed dosing of mAb is more relevant that body weight dosing since it reduces interpatient variability (Hendrikx et al., 2017).

Besides distribution volumes, cancer-related sarcopenia could also be linked to overexposure through its association with hypoalbuminemia (Visser et al., 2005). Plasmatic free fraction increases for highly albumin-bound drugs (e.g. carboplatin, etoposide, cisplatin, docetaxel, paclitaxel, irinotecan) in patients with hypoalbuminemia. In a prospective cohort of 100 patients with NSCLC (Srdic et al., 2016), albumin concentration was established as a predictive factor for both chemotherapy toxicity and survival. This finding was confirmed in other studies of NSCLC (Arrieta et al., 2010; X. Wang et al., 2014).

5.1.3. Metabolic and clearance changes

Another explanation for overexposure in sarcopenic patients may be decreased activity of liver cytochromes (CYP) that are involved in metabolism of numerous anticancer drugs. In a PK study conducted to evaluate liver metabolism in rats affected by cancer-induced cachexia (Cvan Trobec et al., 2015), midazolam and propranolol clearances were used as reliable markers of CYP3A4 (Rogers, Rocci, Haughey, & Bertino, 2003) and CYP2D6 (Pirttiaho et al., 1980) activities. In the cachectic setting, midazolam and propranolol clearances decreased by 80%, leading to higher drug concentrations. Cancer-related inflammation, which is associated with sarcopenia, leads to decreased expression of liver

CYP450 (Charles et al., 2006). Beside cytochromes, other enzymes are involved in drug metabolism and may be modulated by nutritional status and cancer-related sarcopenia. An experimental study in rats showed that protein uptake impacted 5-fluorouracil (5-FU) toxicity, with 85% mortality in rats fed with low-protein diet vs. 12% with high-protein diet (Davis, Lenkinski, Shinkwin, Kressel, & Daly, 1993). The group of protein-deficient rats showed decreased activity of dihydropyrimidine dehydrogenase, the key enzyme of 5-FU catabolism. Conversely, a high-protein diet was associated with decreased 5-FU toxicity (Flanigen-Roat, Milholland, & Ip, 1985).

In addition, through the reduction of liver enzyme activity, sarcopenia is associated with a lower clearance for drugs which elimination relies on liver metabolism (characterized by low extraction ratio), including anthracyclines (Ballet, Vrignaud, Robert, Rey, & Poupon, 1987). In a study of 24 breast cancer patients, Prado et al. (Prado et al., 2011) showed a correlation between LBM and epirubicin clearance. Similar results were found in two other studies including adults and children treated with doxorubicin (Thompson et al., 2009; Wong et al., 2014). Cancer-related inflammation could be a confounding factor by downregulating CYP450 activity and thus detoxification of most of antineoplastic agents (Christmas, 2015). Nevertheless, the epirubicin study of Prado et al. included only localized and operated breast cancer cases for which a systemic inflammation level is low, suggesting that sarcopenia may also have a direct, inflammation-independent effect on drug metabolism (Prado et al., 2011). For most MKI, exposure is mainly dependent on liver clearance and LBM was shown to be a good PK predictor. In a study of 40 hepatocellular carcinoma patients treated with sorafenib, median area under the curve (AUC) of sorafenib was twice higher in sarcopenic than in non-sarcopenic patients (Mir, Coriat, Blanchet, et al., 2012). Similar results were found in medullary thyroid cancer patients treated with vandetanib (Massicotte et al., 2013). Moreover, clearance of mAb differs from MKI and does not rely on liver elimination. Indeed, they are primarily eliminated through intracellular degradation after binding to the target, which is fast and saturable, and to a lesser extent through proteolytic catabolism, a non-specific immunoglobulin G pathway, which is slow and linear (Keizer et al., 2010). As a result, mAb clearance is not related to body weight, but to their affinity, tumor burden, and target expression levels. Overall, except mAb, changes in drug metabolism in sarcopenic patients are related to liver function with an overlap with malnutrition and inflammation.

5.2. Pharmacodynamics

Alternatively, the PD hypothesis postulates that, independently from PK, sarcopenic patients are more sensitive to treatment and may experience toxicities even in the absence of overdose. This is related to the concept of frailty, which has become increasingly recognized as one of the most important issues in health outcomes and is of particular importance in cancer patients (Kumar Pal, Katheria, & Hurria, 2010). Frailty can be defined as a state of diminished physiologic reserve that results in increased vulnerability to stressors (cancer itself, anticancer treatments) and higher risk of adverse events (complications, dependency, death) (Xue, 2011). Frailty, malnutrition, sarcopenia, and cachexia are overlapping entities. Even if frailty is a phenotype that has been primarily described in older adults (≥ 70 years), similar to sarcopenia, it is also observed in younger patients (Smart et al., 2017) and it is associated with increased risk of postoperative complications, chemotherapy toxicities, disease progression, and death (Ethun et al., 2017). Although the Clinical Frailty Scale (Rockwood et al., 2005) is widely used, there is no standardized scale or cut-off to assess frailty, contributing to variable prevalence rate. In a systematic review including 20 studies and nearly 3000 older cancer patients, the median prevalence of frailty was 42% (range 6%–86%) (Handforth et al., 2015). One explanation is that sarcopenic patients exhibit decreased immunity and slower cell renewal, which results in higher risk of febrile neutropenia and severe mucositis. The association between nutritional status and radiotherapy toxicity (Hill, Kiss, Hodgson, Crowe, & Walsh, 2011) is another argument in favor of the frailty hypothesis since radiation therapy exposure is independent of PK parameters.

6. Sarcopenic obesity: a new entity

Sarcopenic obesity is defined by the association of low muscle mass and obesity (i.e., BMI ≥30 kg/m^2). The growing prevalence of obesity worldwide and the recent gain of interest in cancer-related sarcopenia contributed to identification of a growing number of patients presenting with both the highest ranges of fat mass and the lowest ranges of muscle mass. The mean prevalence of sarcopenic obesity in cancer patients is around 10% (Baracos & Arribas, 2018). However, there is a large variation in prevalence (range 1–27%; Table 3), depending on the methods used for the body composition assessment, the inclusion of sarcopenic overweight patients (i.e. BMI ≥ 25 kg/m^2), and the tumor type and stage. Sarcopenic obesity is observed more frequently in advanced and metastatic tumors than in localized stages (Anandavadivelan, Brismar, Nilsson, Johar, & Martin, 2016; Dalal et al., 2012; Del Fabbro et al., 2012; Heidelberger et al., 2017; Rollins et al., 2016). In comparison to Caucasian patients, the prevalence of sarcopenic obesity seems lower in Asians, probably owing to the low prevalence of obesity in this population (Zhuang et al., 2016).

Sarcopenic obese patients carry the burden of both obesity and sarcopenia, which result in higher health-related risks than any of these conditions alone. Indeed, sarcopenic obesity is associated with shorter survival, worse postoperative outcomes, and increased toxicities of antitumor treatments. Prado et al. (Prado et al., 2008) were first to report an association between sarcopenic obesity and survival in cancer patients. They found that sarcopenic obese patients have poorer functional status and shorter survival compared to those with normal SMI (21.6 vs. 11.3 months respectively, $p < .001$). Moreover, sarcopenic obesity was an independent predictor of poorer survival (HR = 4.2, $p < .0001$) in a multivariate analysis adjusted for age, sex, tumor type, tumor stage, and PS. These findings were confirmed by other studies in different cancer types (Table 2), especially pancreatic cancer (Dalal et al., 2012; Rollins et al., 2016; B. H. L. Tan et al., 2015). Obese cancer patients present with usually poor outcomes, with a U-shaped association between BMI and survival, called the "obesity paradox" (Caan et al., 2017; Valentijn et al., 2013), which may be explained by high prevalence of sarcopenic obesity. In a cohort of 1473 patients with lung or gastrointestinal cancer, Martin et al. (Martin et al., 2013) showed that non-sarcopenic obese patients had longer survival (median OS: 35.6 months, i.e., a doubling of overall median OS: 16.7 months) than sarcopenic and weight-losing obese patients (median OS: 8.5 months). Sarcopenic obesity is also associated with worse short and long-term outcomes after cancer surgery. Several studies reported lower survival rates in obese sarcopenic compared to non-obese non-sarcopenic patients after surgery for bladder (Psutka et al., 2015), colon (Malietzis et al., 2016), hepatocellular (Kobayashi et al., 2017), or gastric cancers (Palmela et al., 2017). Sarcopenic obesity has also been associated with surgical complications such as infections and delayed wound healing. Sarcopenic obese patients have 3 to 6-fold higher risk of developing major postoperative complications than non-sarcopenic patients after gastrectomy for gastric cancer (Lou et al., 2017; Nishigori et al., 2016) and after liver (P. D. Peng et al., 2011) or colorectal resection (Berkel et al., 2018; Malietzis et al., 2016) for colorectal cancer. Additionally, sarcopenic obesity is associated with longer hospital stay (Lou et al., 2017; P. D. Peng et al., 2011) and the higher 30-day readmission rates (Lou et al., 2017). However, in another recent study, no relationship was found between sarcopenia or sarcopenic obesity and postoperative complications (Lodewick et al., 2015).

Several hypotheses can be raised to explain the association between sarcopenic obesity and postoperative complications in cancer patients. Obesity is commonly associated with insulin-resistance, which could

be exacerbated in case of sarcopenia, since skeletal muscle is a major target for insulin-mediated glucose storage (Cleasby, Jamieson, & Atherton, 2016; Srikanthan, Hevener, & Karlamangla, 2010). Moreover, obesity and sarcopenia are both strongly associated with chronic inflammation (Cancello & Clément, 2006; Malietzis et al., 2016; Neves et al., 2016; Reisinger et al., 2015), which could in turn negatively affect the metabolic response and impair the immune response to surgical stress, leading to higher susceptibility to surgical site infections and impaired wound healing (Pierpont et al., 2014). Although the association with chemotherapy toxicity is less documented for sarcopenic obesity than for sarcopenia *per se*, a few recent studies reported an association between sarcopenic obesity and the occurrence of DLT (Table 4). Anandavadivelan et al. reported that sarcopenic obese patients have a 5-fold higher early DLT (during cycle 1) rate after neo-adjuvant therapy for esophageal cancer, compared to non-sarcopenic obese patients (Anandavadivelan et al., 2016). Conversely, high BMI or sarcopenia alone were not associated with a significantly increased risk of DLT. Similar results were found in the neoadjuvant setting in gastric cancer, where all sarcopenic obese patients had to discontinue chemotherapy prematurely due to severe adverse events (Palmela et al., 2017). Heidelberger et al. showed that sarcopenic obese women treated with anti-PD1 checkpoints inhibitors for metastatic melanoma had more frequent early DLT (50% vs. 7.7% in non-sarcopenic obese, $p < .01$) (Heidelberger et al., 2017). In contrast, some authors did not find any association between sarcopenic obesity and the occurrence of DLT (Cushen et al., 2016; Grotenhuis et al., 2016).

In conclusion, sarcopenic obesity has an increased prevalence in oncology and is associated with worse functional status, shorter survival, and higher risk of developing postoperative complications or DLT. This new entity reinforces the importance of body composition measurement in daily oncology practice since muscle loss in sarcopenic obese patients is often hidden by the increased BMI and stable body weight.

7. Therapeutic implications

7.1. Muscle mass-guided dose adjustments in daily practice and clinical trials

From the pharmacological point of view, body composition assessment could be helpful for identifying patients at higher risk of complications and severe toxicity and, as a next step, for adjusting dose administration of anticancer treatments. In recent years, many studies highlighted the relationship between body composition and toxicities of anticancer drugs. However, in clinical practice, dose calculation does not take into account body composition. On the one hand, the doses of chemotherapeutic agents are calculated using BSA, which relies on the fact that blood volume – i.e., distribution volume - is correlated to BSA. The BSA equations are based on weight and height and were validated 100 years ago on nine subjects (Du Bois & Du Bois, 1989). Although several formulas have been proposed for BSA calculation since then, none of them seem to fit all patients correctly (Redlarski, Palkowski, & Krawczuk, 2016). On the other hand, oral targeted therapies are prescribed at a flat dose, regardless of body composition. As mentioned above, sarcopenic patients show increased drug exposure. For prescriptions, dose calculations may be adapted to the type of drug and to the patient body composition. Regarding drugs prescribed for BSA, obese sarcopenic patients are particularly at risk of overdose (La Colla et al., 2007). Indeed, an increase in the distribution volume is expected for lipophilic molecules and thus extending their elimination half-lives (Baker, Grochow, & Donehower, 1995) and requiring a dosage adjustment based on the total body weight. Conversely, low lipophilic molecules have limited diffusion in adipose tissue and can be then adjusted to LBM. On the contrary, for MKI that are prescribed in flat doses, underweight sarcopenic patients (BMI <18.5 kg/m^2) are more prone to drug overexposure since they display low body mass in addition to low LBM. Patients treated with MKI may also benefit from therapeutic drug monitoring (i.e., assessment of circulating levels). Therapeutic drug monitoring of drugs with strong binding to albumin or subject to liver metabolism is also of interest. Following first cycle administration and assessment of early toxicity, dose adaptation for subsequent cycles may be made according to individual tolerance, as previously proposed (Gurney, 1996).

Beyond the aforementioned "frailty" hypothesis, PK changes may explain the increased incidence of DLT in sarcopenic obese patients treated with chemotherapy. For BSA-based prescriptions, such as cytotoxic chemotherapies, sarcopenic obesity results in high absolute doses (due to large BSA/obesity), while drug distribution volume and metabolism are reduced. Indeed, many cytotoxic chemotherapies are hydrophilic, with distribution and metabolism into the LBM compartment, which is very depleted in case of sarcopenia, resulting in overexposure (La Colla et al., 2007) and a higher incidence of DLT. The distribution volume of lipophilic drugs will also be altered due to decreased plasma protein binding in both obesity and sarcopenia (Feldschuh & Enson, 1977; Hunter et al., 2009). In a study of ovarian cancer patients treated with lipophilic drugs such as liposomal doxorubicin and trabectedin toxicity was strongly associated with a higher FM/LBM (reflecting sarcopenia) in obese and overweight patients (Prado et al., 2014). Drug metabolism may be altered not only by muscle depletion, but also by obesity itself. Indeed, the clearance capacity of liver and kidneys does not grow proportionally with total body weight (Young et al., 2009). For instance, Demirovic et al. showed that incorporation of LBM into the Cockcroft-Gault equation provides an accurate estimation of kidney function in obese patients (Demirovic, Pai, & Pai, 2009). Finally, experimental studies in rats with fatty-liver showed that lipid accumulation results in reduced CYP expression and activity (Su, Sefton, & Murray, 1999), which may partially explain excess toxicity in obese patients.

Studies assessing DLT in obese patients should also be considered in relation to the common practice of "dose-capping", i.e., calculating chemotherapy doses with a maximum BSA of 2.0 m^2 for obese individuals (Griggs, Mangu, Anderson, et al., 2012; Pai, 2012). Given that dose capping is done without considering body composition, the dose reduction cannot be optimal and may result in under or overdosing (Hunter et al., 2009). Dose capping leads to overestimation of drug dose in sarcopenic obese patients, and to underestimation in non-sarcopenic obese patients. Dignam et al. showed that obese patients treated with capped doses of adjuvant chemotherapy for colon cancer, generally tolerate more chemotherapy cycles than normal weighted individuals (Dignam et al., 2006). However, obese patients receiving chemotherapy based on unadjusted BSA develop more severe toxicities (Furlanetto et al., 2016). LBM-based prescriptions would then appear as a better approach for determining chemotherapy doses, although further studies are needed for further clarification of the potential benefit from dose modifications in obese sarcopenic patients. An ongoing LEANOX study (NCT03255434) will compare an impact of LBM-based and BSA-based normalization of oxaliplatin-based chemotherapy on the incidence of severe neurotoxicity in stage III colon cancer patients.

For treatment subjected to renal clearance, we recommend calculation of GFR using CysC since GFR formula based on creatinine may overestimate renal function in sarcopenic patients. In addition, the calculation of carboplatin dose relies directly on GFR estimation and CysC may be considered instead of creatinine for this agent (Schmitt et al., 2009). The relevance of CysC and LBM-based dose adjustment for drugs with renal elimination in clinical practice needs to be confirmed by prospective studies evaluating not only safety parameters, but also response rates, progression-free survival, and OS to ensure that dose adjustments will not translate into decreased drug efficacy. A randomized phase II trial of advanced lung cancer (NCT01624051) comparing cisplatin dosing based on LBM or BSA is ongoing.

Finally, it is now possible to monitor immunotherapies (Puszkiel et al., 2017), even if they display a larger therapeutic index for which the usual definition of DLT is inappropriate (Postel-Vinay, 2015). Thus,

our proposal is not to include LBM-based dose adjustment, but only to closely monitor toxicities in sarcopenic patients receiving mAb as these are more vulnerable. If a total body weight is lower than a threshold in which the flat dose was studied, it is necessary to be careful and switch to weight-adjusted dose (i.e., mg/kg).

Given the prognostic and predictive toxicity values of cancer-related sarcopenia, it is preferable in phase I trials to either exclude sarcopenic patients or to perform a subgroup analysis of those patients (i.e., specific cohort or stratification). For malignancies in which sarcopenia is extremely prevalent, it could be argued that including a sarcopenic subanalysis in safety studies is crucial data for determining whether the drug is a generally feasible option for that type of cancer.

7.2. Nutritional interventions, physical activity and drugs targeting muscle loss

Since sarcopenia has a major impact on patient survival and HRQoL, therapeutic interventions aiming at reducing muscle loss (nutritional, physical activity, and pharmacological interventions) have been developed and are prospectively evaluated in randomized controlled clinical trials. It is now acknowledged that this supportive care dimension of oncological management is essential to ensure the success of any anticancer treatment.

7.2.1. Nutritional interventions

A multicenter randomized trial by Cramer et al. evaluating the impact of high-protein oral nutritional supplements during 24 weeks in sarcopenic patients with cancer (Cramer et al., 2016) showed no benefit of nutritional intervention in the severe sarcopenia stage (like in refractory cachexia). In patients with moderate sarcopenia, an improvement was observed only in leg muscle strength with no benefit on muscle mass. Oral solutions enriched with specific amino acids such as glutamine (Ishikawa et al., 2016) and leucine (Deutz et al., 2011) also appeared to improve muscle mass loss in cancer patients. Omega-3 fatty acids such as eicosapentaenoic acid promote muscle synthesis and decrease muscle degradation by downregulating IL-6 and TNF-alpha production via ubiquitin proteasome pathway and by increasing muscle insulin sensitivity (Pappalardo, Almeida, & Ravasco, 2015). Four randomized trials showed a positive effect of eicosapentaenoic acid on LBM (maintenance or increase) despite the lack of survival benefit (Ryan et al., 2009; Mantovani et al., 2008; Sánchez-Lara et al., 2014; Vasson et al., 2014).

Finally, enteral nutrition appears to provide a significantly greater benefit than parenteral route due to the high infectious risk that is associated with this latter (Koretz, Lipman, Klein, & American Gastroenterological Association, 2001; Zaloga, 2006). In terminally ill patients, it is now clear that implementing artificial nutrition brings no benefit to patients in terms of OS and HRQoL (McCann, Hall, & Groth-Juncker, 1994).

However, nutritional interventions alone are ineffective in improving survival. They may be active and essential as a part of multimodal approaches, including combination with exercise.

7.2.2. Physical activity

In cancer patients, adapted physical activity (APA) reduces disease and/or treatment-induced symptoms (including pain, fatigue, and anxiety/depression), improves physical fitness, muscle function, and HRQoL (Buffart, Galvão, Brug, Chinapaw, & Newton, 2014; Cramp & Byron-Daniel, 2012), even in advanced-stage disease (Mustian et al., 2017). On contrary, no drug has shown any benefit in the treatment of cancer-related fatigue (Mücke et al., 2015; Mustian et al., 2017).

A randomized controlled trial reported by Cormie et al. showed that patients with prostate cancer benefit from supervised exercise in terms of muscle mass gain and FM loss, preventing treatment toxicity of androgen-deprivation therapy (Cormie et al., 2015). Similarly, positive results were found in breast cancer premenopausal women during endocrine therapy (Hojan, Milecki, Molińska-Glura, Roszak, & Leszczyński, 2013). Two randomized trials also demonstrated a benefit of supervised APA in breast cancer in the adjuvant setting on physical fitness, fatigue and chemotherapy completion (van Waart et al., 2015), and metabolic syndrome, sarcopenic obesity and circulating biomarkers in overweight/obese patients (Dieli-Conwright et al., 2018), respectively.

Exercise have beneficial effects on tumor outcome (Schmid & Leitzmann, 2014) by modulating various pro-tumoral signaling pathways such as reduced insulin resistance and inflammation (Ashcraft, Peace, Betof, Dewhirst, & Jones, 2016). Besides, combining a high protein diet less than two hours after exercise seems to promote muscle synthesis (Atherton et al., 2010; Pennings et al., 2011). The benefit of physical activity and nutritional interventions for treating sarcopenia in elderly patients by promoting muscle mass, muscle strength, and physical function was confirmed in a meta-analysis reported by Yoshimura et al. (Yoshimura et al., 2017). In cancer patients, the extent of the benefit appears lower because chronic fatigue and a deficient oxidative metabolism are current in advanced stage disease (Argilés, Busquets, López-Soriano, Costelli, & Penna, 2012). In any case, as sarcopenia and fatigue frequently affect patients with metastatic cancer, physical exercise is a promising strategy to improve HRQoL (Focht et al., 2013).

Implementation of an APA program in cancer patients implies a multidisciplinary collaboration between physicians, nurses, dietitians, and the physical activity professionals (Wolin, Schwartz, Matthews, Courneya, & Schmitz, 2012). The APA program should be personalized to the patient characteristics (physical fitness, exercise type preferences, psychological functions, and expectations) and the cancer type and settings (stage, treatments, and tolerance) in order to improve the patient adherence. A combined aerobic exercise and resistance-training program in groups of patients having similar physical capabilities and under the supervision of a physical activity professional seems to be the best setting for exercise intervention efficacy (Cadore & Izquierdo, 2013; Pahor et al., 2014). Besides, cancer patients often present with an elevated basal resting energy expenditure (Jouinot, Vazeille, & Goldwasser, 2018). Given that the APA program is expected to increase energy expenditures, nutritional management is crucial for monitoring and adapting food intakes to ensure that patients meet their nutritional needs. Moreover, the main difficulty is to propose exercise interventions to all patients suffering from sarcopenia, particularly to the most severely deconditioned (i.e., PS ≥ 2) for whom participation in voluntary exercise sessions in hospital can be challenging.

Therefore, there is a need for developing alternative physical-therapy strategies in these severely deconditioned patients. Neuromuscular electrical stimulation (NMES) consists in generating muscle contractions using portable devices connected to surface electrodes. NMES was proven effective to improve muscle mass and function in sarcopenic patients with chronic obstructive pulmonary disease (Maddocks et al., 2016) and has recently been introduced in cancer patients. NMES is safe, does not require the active cooperation of the patient and can be self-administered at home, thereby providing an acceptable physical therapy for patients with advanced cancer and an altered PS and/or a high-symptom burden for whom attendance to hospital-based exercise training is difficult. However, the effectiveness of NMES in cancer patients remains equivocal (Crevenna, Marosi, Schmidinger, & Fialka-Moser, 2006; Maddocks et al., 2013; O'Connor & Caulfield, 2018; Windholz, Swanson, Vanderbyl, & Jagoe, 2014). Conflicting findings from previous clinical studies may be due to methodological limitations (small sample size, timing of intervention, suboptimal adherence) and heterogeneity of NMES protocols. Indeed, the main determinant of the NMES effectiveness is strength produced in response to stimulation (Gondin, Cozzone, & Bendahan, 2011; Maffiuletti, 2010), which has never been monitored in cancer patients. Overall, there is a need for carefully designed studies in order to draw definitive conclusions on the potential benefits of NMES interventions on cancer-related sarcopenia. It is therefore necessary to better

understand the cellular and molecular mechanisms involved in the development of sarcopenia associated with cancer and to propose new complementary and/or alternative therapeutic interventions to APA.

7.2.3. Drugs

7.2.3.1. Hormonal therapy. Testosterone showed a benefit on muscle mass and grip strength in older men (Bakhshi, Elliott, Gentili, Godschalk, & Mulligan, 2000; Ferrando et al., 2002). This improvement is counterbalanced by harmful side effects (i.e., prostate cancer, vascular thrombosis, and sleep apnea) leading to the development of selective androgen receptor modulators that demonstrate a safer therapeutic profile. Enobosarm is a selective androgen receptor modulator tested vs. placebo in 159 pre-cachectic patients with hormone-naive prostate cancer. It showed a significant positive effect on muscle mass ($p = .046$) with a positive impact on HRQoL, but without difference on tumor progression and muscle strength (Dobs et al., 2013). Similar results were observed in a randomized, prospective, double-blinded study of 170 sarcopenic women without cancer (Papanicolaou et al., 2013). These therapies may behave differently in young versus aged individuals.

Ghrelin is a neurohormone secreted by the stomach that stimulate appetite and muscle anabolism in the hypothalamus (Guillory, Splenser, & Garcia, 2013). Ghrelin analogues such as anamorelin have been developed. >450 cachectic advanced NSCLC patients were randomized to receive anamoreline or placebo for 12 weeks in the ROMANA trials (Currow et al., 2017; Temel et al., 2016). The results were in favor of a muscle mass gain in the experimental arm. However, there was no benefit on muscle strength or on OS. In contrast, there was a significant improvement in HRQoL and OS from 9 to 13 months only in patients with increased muscle mass ($p < .001$). Overall, there is a subgroup of good responders to anamorelin that could benefit from this treatment in terms of survival. Another Japanese study, which enrolled 180 patients, found similar results with an improvement in muscle mass and HRQoL, but with no effect on muscle strength and OS (Takayama et al., 2016).

Vitamin D supplementation reduces the risk of falls in elderly patients (Bischoff-Ferrari et al., 2004) because of its strengthening effects on muscle and bone (Arik & Ulger, 2016). A meta-analysis that included 29 randomized clinical trials found a benefit of vitamin D supplementation on muscle strength, without impact on muscle mass (Beaudart et al., 2014). Even if the benefit seems more important for patients >65 years and deficient in vitamin D, the precise therapeutic role of vitamin D in cancer-related sarcopenia remains to be defined. Considering its favorable tolerance profile, it would be interesting to combine it with other agents for synergistic effect.

7.2.3.2. Other therapies. As mentioned above, pro-inflammatory cytokines (e.g. IL-1, IL-6, TNF-alpha) are involved in muscle wasting in cancer-related sarcopenia. Therefore, counteracting their effects is a relevant strategy to reverse sarcopenia. Infliximab, an anti-TNF agent, has been shown to reverse sarcopenia in inflammatory bowel disease such as Crohn's disease (Subramaniam et al., 2015). However, in a phase II study of 89 patients with pancreatic cancer and cachexia, infliximab failed to significantly improve LBM when compared to placebo (Wiedenmann et al., 2008). Besides TNF, other cytokines may be more attractive targets. Targeting IL-6 with tocilizumab, an anti-IL-6 receptor antibody, was demonstrated to be effective in a patient with lung cancer cachexia by reversing weight loss, inflammation, and altered PS (Ando et al., 2013). Furthermore, blocking IL-1 pathway with MABp1 has led to a statistical increase of LBM ($p = .02$) with limited adverse events in a phase I study of 30 metastatic cancer patients (Hong et al., 2014). Randomized clinical trials are warranted to demonstrate the benefit of targeting IL-6 and IL-1 pathways in cancer-related sarcopenia. As an alternative strategy, antagonization of myostatin pathway by targeting activin type II receptor highlighted the potential therapeutic effects in muscle growth in preclinical models (Lach-Trifilieff et al., 2014; Zhou et al., 2010). Clinically, the same positive results (safely increased LBM and improved physical performance) have been found in two phase I studies in cancer patients treated by antimyostatin mAb. (Jameson et al., 2012; Padhi et al., 2014). However, a recent randomized phase II trial in pancreatic cancer patients showed no clinical benefit of antimyostatin mAb, with decreased progression-free survival and OS in patients treated with LY2495655 (Golan et al., 2018). Other cytokines from the TGFβ family may be alternative drug targets.

Other strategies to reduce muscle loss are currently being explored such as mirtazapine, a noradrenergic and specific serotonergic antidepressant (NCT03254173, NCT03283488), and espindolol, a non-selective beta-blocker (Stewart Coats et al., 2016).

Combining physical activity dietary counseling and drugs in a multimodal strategy is expected to be the most effective approach and therefore is recommended (Fig. 2). In addition, administration of anticancer drugs must be considered in order to reduce tumor burden and inflammation along with the optimal management of their adverse advents in order to limit malnutrition and sarcopenia (Yip et al., 2014; Temel et al., 2010). It is therefore necessary to question the risk benefit ratio of each prescription.

8. Conclusions

Overall, body composition has gained increasing attention in oncology practice and research in recent years due to fact that sarcopenia has been revealed as a prognostic and predictive factor across multiple stages and cancer types and responsible for a significant proportion of cancer-related deaths, increased risk of surgery complications and treatment toxicities, and severe impairment of HRQoL. About 30% of cancer deaths are related to cachexia and sarcopenia (von Haehling & Anker, 2010). Hence, implementing therapeutic strategies to preserve or increase muscle mass in cancer patients, in order to optimize anticancer treatment tolerance and efficacy, is now acknowledged as an essential part of supportive care. Treatment of cancer-related sarcopenia should be multimodal and implemented as early as possible. The assessment of body composition may allow more accurate treatment dose calculation in sarcopenic patients. Prospective studies are needed to evaluate the effect of dose adjustment to LBM for toxicity and for the efficacy outcomes such as response rate and survival. The treatment efficacy may even be improved due to a more favorable toxicity profile and less dose adjustments, leading to a better dose-intensity.

Conflicts of interest

François Goldwasser and Frédéric Pigneur participated in the Fresenius Kabi board of experts.

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References

Abbatecola, A. M., Paolisso, G., Fattoretti, P., Evans, W. J., Fiore, V., Dicioccio, L., & Lattanzio, F. (2011). Discovering pathways of sarcopenia in older adults: a role for insulin resistance on mitochondria dysfunction. *The Journal of Nutrition, Health & Aging 15*(10), 890–895.

Agrawal, A., Suryakumar, G., & Rathor, R. (2018). Role of defective Ca2+ signaling in skeletal muscle weakness: Pharmacological implications. *Journal of Cell Communication and Signaling*.. https://doi.org/10.1007/s12079-018-0477-z.

Agrawal, S., Feng, Y., Roy, A., Kollia, G., & Lestini, B. (2016). Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy. *Journal for ImmunoTherapy of Cancer 4*(1), 72. https://doi.org/10.1186/s40425-016-0177-2.

Agustsson, T., D'souza, M. A., Nowak, G., & Isaksson, B. (2011). Mechanisms for skeletal muscle insulin resistance in patients with pancreatic ductal adenocarcinoma.

Nutrition (Burbank, Los Angeles County, CAL) 27(7–8), 796–801. https://doi.org/10.1016/j.nut.2010.08.022.

Ali, R., Baracos, V. E., Sawyer, M. B., Bianchi, L., Roberts, S., Assenat, E., ... Senesse, P. (2016). Lean body mass as an independent determinant of dose-limiting toxicity and neuropathy in patients with colon cancer treated with FOLFOX regimens. *Cancer Medicine 5*(4), 607–616. https://doi.org/10.1002/cam4.621.

Amini, N., Spolverato, G., Gupta, R., Margonis, G. A., Kim, Y., Wagner, D., ... Pawlik, T. M. (2015). Impact total psoas volume on short- and long-term outcomes in patients undergoing curative resection for pancreatic adenocarcinoma: a new tool to assess sarcopenia. *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract 19*(9), 1593–1602. https://doi.org/10.1007/s11605-015-2835-y.

Anandavadivelan, P., Brismar, T. B., Nilsson, M., Johar, A. M., & Martin, L. (2016). Sarcopenic obesity: A probable risk factor for dose limiting toxicity during neo-adjuvant chemotherapy in oesophageal cancer patients. *Clinical Nutrition (Edinburgh, Scotland) 35*(3), 724–730. https://doi.org/10.1016/j.clnu.2015.05.011.

Ando, K., Takahashi, F., Motojima, S., Nakashima, K., Kaneko, N., Hoshi, K., & Takahashi, K. (2013). Possible role for tocilizumab, an anti-interleukin-6 receptor antibody, in treating cancer cachexia. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 31*(6), e69–e72. https://doi.org/10.1200/JCO.2012.44.2020.

Antoun, S., Baracos, V. E., Birdsell, L., Escudier, B., & Sawyer, M. B. (2010). Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. *Annals of Oncology: Official Journal of the European Society for Medical Oncology 21*(8), 1594–1598. https://doi.org/10.1093/annonc/mdp605.

Antoun, S., Lanoy, E., Iacovelli, R., Albiges-Sauvin, L., Loriot, Y., Merad-Taoufik, M., ... Escudier, B. (2013). Skeletal muscle density predicts prognosis in patients with metastatic renal cell carcinoma treated with targeted therapies. *Cancer 119*(18), 3377–3384. https://doi.org/10.1002/cncr.28218.

Argilés, J. M., Busquets, S., López-Soriano, F. J., Costelli, P., & Penna, F. (2012). Are there any benefits of exercise training in cancer cachexia. *Journal of Cachexia, Sarcopenia and Muscle 3*(2), 73–76. https://doi.org/10.1007/s13539-012-0067-5.

Argilés, J. M., Campos, N., Lopez-Pedrosa, J. M., Rueda, R., & Rodriguez-Mañas, L. (2016). Skeletal muscle regulates metabolism via interorgan crosstalk: Roles in health and disease. *Journal of the American Medical Directors Association 17*(9), 789–796. https://doi.org/10.1016/j.jamda.2016.04.019.

Arik, G., & Ulger, Z. (2016). Vitamin D in sarcopenia: Understanding its role in pathogenesis, prevention and treatment. *European Geriatric Medicine 7*(3), 207–213. https://doi.org/10.1016/j.eurger.2015.12.001.

Arrieta, O., De la Torre-Vallejo, M., López-Macías, D., Orta, D., Turcott, J., Macedo-Pérez, E. -O., ... Baracos, V. E. (2015). Nutritional status, body surface, and low lean body mass/body mass index are related to dose reduction and severe gastrointestinal toxicity induced by afatinib in patients with non-small cell lung cancer. *The Oncologist 20*(8), 967–974. https://doi.org/10.1634/theoncologist.2015-0058.

Arrieta, O., Michel Ortega, R. M., Villanueva-Rodríguez, G., Serna-Thomé, M. G., Flores-Estrada, D., Diaz-Romero, C., ... Sánchez-Lara, K. (2010). Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: a prospective study. *BMC Cancer 10*, 50. https://doi.org/10.1186/1471-2407-10-50.

Ashcraft, K. A., Peace, R. M., Betof, A. S., Dewhirst, M. W., & Jones, L. W. (2016). Efficacy and mechanisms of aerobic exercise on cancer initiation, progression, and metastasis: A critical systematic review of in vivo preclinical data. *Cancer Research 76*(14), 4032–4050. https://doi.org/10.1158/0008-5472.CAN-16-0887.

Atherton, P. J., Etheridge, T., Watt, P. W., Wilkinson, D., Selby, A., Rankin, D., ... Rennie, M. J. (2010). Muscle full effect after oral protein: time-dependent concordance and discordance between human muscle protein synthesis and mTORC1 signaling. *The American Journal of Clinical Nutrition 92*(5), 1080–1088. https://doi.org/10.3945/ajcn.2010.29819.

Atkinson, T. M., Andreotti, C. F., Roberts, K. E., Saracino, R. M., Hernandez, M., & Basch, E. (2015). The level of association between functional performance status measures and patient-reported outcomes in cancer patients: a systematic review. *Supportive Care in Cancer 23*(12), 3645–3652. https://doi.org/10.1007/s00520-015-2923-2.

Awad, S., Tan, B. H., Cui, H., Bhalla, A., Fearon, K. C. H., Parsons, S. L., ... Lobo, D. N. (2012). Marked changes in body composition following neoadjuvant chemotherapy for oesophagogastric cancer. *Clinical Nutrition (Edinburgh, Scotland) 31*(1), 74–77. https://doi.org/10.1016/j.clnu.2011.08.008.

Bahat, G., Tufan, A., Tufan, F., Kilic, C., Akpinar, T. S., Kose, M., ... Cruz-Jentoft, A. J. (2016). Cut-off points to identify sarcopenia according to European Working Group on Sarcopenia in Older People (EWGSOP) definition. *Clinical Nutrition (Edinburgh, Scotland) 35*(6), 1557–1563. https://doi.org/10.1016/j.clnu.2016.02.002.

Baker, S. D., Grochow, L. B., & Donehower, R. C. (1995). Should anticancer drug doses be adjusted in the obese patient. *Journal of the National Cancer Institute 87*(5), 333–334.

Bakhshi, V., Elliott, M., Gentili, A., Godschalk, M., & Mulligan, T. (2000). Testosterone improves rehabilitation outcomes in ill older men. *Journal of the American Geriatrics Society 48*(5), 550–553.

Ballet, F., Vrignaud, P., Robert, J., Rey, C., & Poupon, R. (1987). Hepatic extraction, metabolism and biliary excretion of doxorubicin in the isolated perfused rat liver. *Cancer Chemotherapy and Pharmacology 19*(3), 240–245.

Bano, G., Trevisan, C., Carraro, S., Solmi, M., Luchini, C., Stubbs, B., ... Veronese, N. (2017). Inflammation and sarcopenia: A systematic review and meta-analysis. *Maturitas 96*, 10–15. https://doi.org/10.1016/j.maturitas.2016.11.006.

Baracos, V. E. (2017). Psoas as a sentinel muscle for sarcopenia: a flawed premise. *Journal of Cachexia, Sarcopenia and Muscle 8*(4), 527–528. https://doi.org/10.1002/jcsm.12221.

Baracos, V. E., & Arribas, L. (2018). Sarcopenic obesity: Hidden muscle wasting and its impact for survival and complications of cancer therapy. *Annals of Oncology*. https://doi.org/10.1093/annonc/mdx810.

Baracos, V. E., Reiman, T., Mourtzakis, M., Gioulbasanis, I., & Antoun, S. (2010). Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. *The American Journal of Clinical Nutrition 91*(4), 1133S–1137S. https://doi.org/10.3945/ajcn.2010.28608C.

Barret, M., Antoun, S., Dalban, C., Malka, D., Mansourbakht, T., Zaanan, A., ... Taieb, J. (2014). Sarcopenia is linked to treatment toxicity in patients with metastatic colorectal cancer. *Nutrition and Cancer 66*(4), 583–589. https://doi.org/10.1080/01635581.2014.894103.

Baumgartner, R. N., Koehler, K. M., Gallagher, D., Romero, L., Heymsfield, S. B., Ross, R. R., ... Lindeman, R. D. (1998). Epidemiology of sarcopenia among the elderly in New Mexico. *American Journal of Epidemiology 147*(8), 755–763.

Baxmann, A. C., Ahmed, M. S., Marques, N. C., Menon, V. B., Pereira, A. B., Kirsztajn, G. M., & Heilberg, I. P. (2008). Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. *Clinical Journal of the American Society of Nephrology: CJASN 3*(2), 348–354. https://doi.org/10.2215/CJN.02870707.

Beaudart, C., Buckinx, F., Rabenda, V., Gillain, S., Cavalier, E., Slomian, J., ... Bruyère, O. (2014). The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. *The Journal of Clinical Endocrinology and Metabolism 99*(11), 4336–4345. https://doi.org/10.1210/jc.2014-1742.

Berkel, A. E. M., Klaase, J. M., de Graaff, F., Brusse-Keizer, M. G. J., Bongers, B. C., & van Meeteren, N. L. U. (2018). Patient's skeletal muscle radiation attenuation and sarcopenic obesity are associated with postoperative morbidity after neoadjuvant chemoradiation and resection for rectal cancer. *Digestive Surgery*, 1–8. https://doi.org/10.1159/000490069.

Bijlsma, A. Y., Meskers, C. G. M., Ling, C. H. Y., Narici, M., Kurrle, S. E., Cameron, I. D., ... Maier, A. B. (2013). Defining sarcopenia: the impact of different diagnostic criteria on the prevalence of sarcopenia in a large middle aged cohort. *Age (Dordrecht, Netherlands) 35*(3), 871–881. https://doi.org/10.1007/s11357-012-9384-z.

Bischoff-Ferrari, H. A., Dawson-Hughes, B., Willett, W. C., Staehelin, H. B., Bazemore, M. G., Zee, R. Y., & Wong, J. B. (2004). Effect of Vitamin D on falls: a meta-analysis. *JAMA 291*(16), 1999–2006. https://doi.org/10.1001/jama.291.16.1999.

Blauwhoff-Buskermolen, S., Versteeg, K. S., de van der Schueren, M. A. E., den Braver, N. R., Berkhof, J., Langius, J. A. E., & Verheul, H. M. W. (2016). Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. *Journal of Clinical Oncology 34*(12), 1339–1344. https://doi.org/10.1200/JCO.2015.63.6043.

Boer, P. (1984). Estimated lean body mass as an index for normalization of body fluid volumes in humans. *The American Journal of Physiology 247*(4 Pt 2), F632–F636. https://doi.org/10.1152/ajprenal.1984.247.4.F632.

Bonekamp, S., Ghosh, P., Crawford, S., Solga, S. F., Horska, A., Brancati, F. L., ... Clark, J. M. (2008). Quantitative comparison and evaluation of software packages for assessment of abdominal adipose tissue distribution by magnetic resonance imaging. *International Journal of Obesity 32*(1), 100–111. https://doi.org/10.1038/sj.ijo.0803696.

Borga, M. (2018). MRI adipose tissue and muscle composition analysis-a review of automation techniques. *The British Journal of Radiology 91*(1089), 20180252. https://doi.org/10.1259/bjr.20180252.

Bozzetti, F. (2017). Forcing the vicious circle: Sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. *Annals of Oncology: Official Journal of the European Society for Medical Oncology 28*(9), 2107–2118. https://doi.org/10.1093/annonc/mdx271.

Brahmer, J., Reckamp, K. L., Baas, P., Crinò, L., Eberhardt, W. E. E., Poddubskaya, E., ... Spigel, D. R. (2015). Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. *New England Journal of Medicine 373*(2), 123–135. https://doi.org/10.1056/NEJMoa1504627.

Bredella, M. A. (2017). Sex differences in body composition. *Advances in Experimental Medicine and Biology 1043*, 9–27. https://doi.org/10.1007/978-3-319-70178-3_2.

Bretagne, M., Jouinot, A., Durand, J. P., Huillard, O., Boudou Rouquette, P., Tlemsani, C.,, ... Alexandre, J. (2017). Estimation of glomerular filtration rate in cancer patients with abnormal body composition and relation with carboplatin toxicity. *Cancer Chemotherapy and Pharmacology*. https://doi.org/10.1007/s00280-017-3326-5.

Broughman, J. R., Williams, G. R., Deal, A. M., Yu, H., Nyrop, K. A., Alston, S. M., ... Muss, H. B. (2015). Prevalence of sarcopenia in older patients with colorectal cancer. *Journal of Geriatric Oncology 6*(6), 442–445. https://doi.org/10.1016/j.jgo.2015.08.005.

Buffart, L. M., Galvão, D. A., Brug, J., Chinapaw, M. J. M., & Newton, R. U. (2014). Evidence-based physical activity guidelines for cancer survivors: current guidelines, knowledge gaps and future research directions. *Cancer Treatment Reviews 40*(2), 327–340. https://doi.org/10.1016/j.ctrv.2013.06.007.

Bulow, J., Ulijaszek, S. J., & Holm, L. (2018). Rejuvenation of the term sarcopenia. *Journal of Applied Physiology (Bethesda, Md.: 1985)*. https://doi.org/10.1152/japplphysiol.00400.2018.

Caan, B. J., Meyerhardt, J. A., Kroenke, C. H., Alexeeff, S., Xiao, J., Weltzien, E., ... Prado, C. M. (2017). Explaining the obesity paradox: The association between body composition and colorectal cancer survival (C-SCANS Study). *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 26*(7), 1008–1015. https://doi.org/10.1158/1055-9965.EPI-17-0200.

Cadore, E. L., & Izquierdo, M. (2013). New strategies for the concurrent strength-, power-, and endurance-training prescription in elderly individuals. *Journal of the American*

Medical Directors Association 14(8), 623–624. https://doi.org/10.1016/j.jamda.2013.04.008.

Camacho, L. H., Antonia, S., Sosman, J., Kirkwood, J. M., Gajewski, T. F., Redman, B., ... Ribas, A. (2009). Phase I/II trial of tremelimumab in patients with metastatic melanoma. *Journal of Clinical Oncology 27*(7), 1075–1081. https://doi.org/10.1200/JCO.2008.19.2435.

Camus, V., Lanic, H., Kraut, J., Modzelewski, R., Clatot, F., Picquenot, J. M., ... Jardin, F. (2014). Prognostic impact of fat tissue loss and cachexia assessed by computed tomography scan in elderly patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *European Journal of Haematology 93*(1), 9–18. https://doi.org/10.1111/ejh.12285.

Cancello, R., & Clément, K. (2006). Is obesity an inflammatory illness? Role of low-grade inflammation and macrophage infiltration in human white adipose tissue. *BJOG: An International Journal of Obstetrics and Gynaecology 113*(10), 1141–1147. https://doi.org/10.1111/j.1471-0528.2006.01004.x.

Cesari, M., Fielding, R. A., Pahor, M., Goodpaster, B., Hellerstein, M., van Kan, G. A., ... International Working Group on Sarcopenia (2012). Biomarkers of sarcopenia in clinical trials-recommendations from the International Working Group on Sarcopenia. *Journal of Cachexia, Sarcopenia and Muscle 3*(3), 181–190. https://doi.org/10.1007/s13539-012-0078-2.

Cespedes Feliciano, E. M., Lee, V. S., Prado, C. M., Meyerhardt, J. A., Alexeeff, S., Kroenke, C. H., ... Caan, B. J. (2017). Muscle mass at the time of diagnosis of nonmetastatic colon cancer and early discontinuation of chemotherapy, delays, and dose reductions on adjuvant FOLFOX: The C-SCANS study. *Cancer 123*(24), 4868–4877. https://doi.org/10.1002/cncr.30950.

Charles, K. A., Rivory, L. P., Brown, S. L., Liddle, C., Clarke, S. J., & Robertson, G. R. (2006). Transcriptional repression of hepatic cytochrome P450 3A4 gene in the presence of cancer. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 12*(24), 7492–7497. https://doi.org/10.1158/1078-0432.CCR-06-0023.

Chemama, S., Bayar, M. A., Lanoy, E., Ammari, S., Stoclin, A., Goéré, D., ... Antoun, S. (2016). Sarcopenia is associated with chemotherapy toxicity in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal cancer. *Annals of Surgical Oncology 23*(12), 3891–3898. https://doi.org/10.1245/s10434-016-5360-7.

Choi, M. H., Oh, S. N., Lee, I. K., Oh, S. T., & Won, D. D. (2018). Sarcopenia is negatively associated with long-term outcomes in locally advanced rectal cancer. *Journal of Cachexia, Sarcopenia and Muscle 9*(1), 53–59. https://doi.org/10.1002/jcsm.12234.

Choi, Y., Oh, D. -Y., Kim, T. -Y., Lee, K. -H., Han, S. -W., Im, S. -A., ... Bang, Y. -J. (2015). Skeletal muscle depletion predicts the prognosis of patients with advanced pancreatic cancer undergoing palliative chemotherapy, independent of body mass index. *PLoS One 10*(10), e0139749. https://doi.org/10.1371/journal.pone.0139749.

Christmas, P. (2015). Role of cytochrome P450s in inflammation. *Advances in Pharmacology (San Diego, Calif.) 74*, 163–192. https://doi.org/10.1016/bs.apha.2015.03.005.

Cleasby, M. E., Jamieson, P. M., & Atherton, P. J. (2016). Insulin resistance and sarcopenia: mechanistic links between common co-morbidities. *The Journal of Endocrinology 229*(2), R67–R81. https://doi.org/10.1530/JOE-15-0533.

Cohen, S., Nathan, J. A., & Goldberg, A. L. (2015). Muscle wasting in disease: molecular mechanisms and promising therapies. *Nature Reviews. Drug Discovery 14*(1), 58–74. https://doi.org/10.1038/nrd4467.

Coletti, D. (2018). Chemotherapy-induced muscle wasting: an update. *European Journal of Translational Myology 28*(2), 7587. https://doi.org/10.4081/ejtm.2018.7587.

Cooper, A. B., Slack, R., Fogelman, D., Holmes, H. M., Petzel, M., Parker, N., ... Katz, M. H. G. (2015). Characterization of anthropometric changes that occur during neoadjuvant therapy for potentially resectable pancreatic cancer. *Annals of Surgical Oncology 22*(7), 2416–2423. https://doi.org/10.1245/s10434-014-4285-2.

Corcoran, M. P., Lamon-Fava, S., & Fielding, R. A. (2007). Skeletal muscle lipid deposition and insulin resistance: effect of dietary fatty acids and exercise. *The American Journal of Clinical Nutrition 85*(3), 662–677. https://doi.org/10.1093/ajcn/85.3.662.

Cormie, P., Galvão, D. A., Spry, N., Joseph, D., Chee, R., Taaffe, D. R., ... Newton, R. U. (2015). Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. *BJU International 115*(2), 256–266. https://doi.org/10.1111/bju.12646.

Cornet, M., Lim, C., Salloum, C., Lazzati, A., Compagnon, P., Pascal, G., & Azoulay, D. (2015). Prognostic value of sarcopenia in liver surgery. *Journal of Visceral Surgery 152*(5), 297–304. https://doi.org/10.1016/j.jviscsurg.2015.08.001.

Cousin, S., Hollebecque, A., Koscielny, S., Mir, O., Varga, A., Baracos, V. E., ... Antoun, S. (2014). Low skeletal muscle is associated with toxicity in patients included in phase I trials. *Investigational New Drugs 32*(2), 382–387. https://doi.org/10.1007/s10637-013-0053-6.

Cramer, J. T., Cruz-Jentoft, A. J., Landi, F., Hickson, M., Zamboni, M., Pereira, S. L., ... Mustad, V. A. (2016). Impacts of high-protein oral nutritional supplements among malnourished men and women with sarcopenia: A multicenter, randomized, double-blinded, controlled trial. *Journal of the American Medical Directors Association 17*(11), 1044–1055. https://doi.org/10.1016/j.jamda.2016.08.009.

Cramp, F., & Byron-Daniel, J. (2012). Exercise for the management of cancer-related fatigue in adults. *The Cochrane Database of Systematic Reviews 11*, CD006145. https://doi.org/10.1002/14651858.CD006145.pub3.

Crevenna, R., Marosi, C., Schmidinger, M., & Fialka-Moser, V. (2006). Neuromuscular electrical stimulation for a patient with metastatic lung cancer–a case report. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer 14*(9), 970–973. https://doi.org/10.1007/s00520-006-0033-x.

Cruz-Jentoft, A. J., Baeyens, J. P., Bauer, J. M., Boirie, Y., Cederholm, T., Landi, F., ... European Working Group on Sarcopenia in Older People (2010). Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age and Ageing 39*(4), 412–423. https://doi.org/10.1093/ageing/afq034.

Cruz-Jentoft, A. J., Landi, F., Topinková, E., & Michel, J. -P. (2010). Understanding sarcopenia as a geriatric syndrome. *Current Opinion in Clinical Nutrition and Metabolic Care 13*(1), 1–7. https://doi.org/10.1097/MCO.0b013e328333c1c1.

Currow, D., Temel, J. S., Abernethy, A., Milanowski, J., Friend, J., & Fearon, K. C. (2017). ROMANA 3: a phase 3 safety extension study of anamorelin in advanced non-small-cell lung cancer (NSCLC) patients with cachexia. *Annals of Oncology: Official Journal of the European Society for Medical Oncology 28*(8), 1949–1956. https://doi.org/10.1093/annonc/mdx192.

Cushen, S. J., Power, D. G., Murphy, K. P., McDermott, R., Griffin, B. T., Lim, M., ... Ryan, A. M. (2016). Impact of body composition parameters on clinical outcomes in patients with metastatic castrate-resistant prostate cancer treated with docetaxel. *Clinical Nutrition ESPEN 13*, e39–e45. https://doi.org/10.1016/j.clnesp.2016.04.001.

Cushen, S. J., Power, D. G., Teo, M. Y., MacEneaney, P., Maher, M. M., McDermott, R., ... Ryan, A. M. (2017). Body composition by computed tomography as a predictor of toxicity in patients with renal cell carcinoma treated with sunitinib. *American Journal of Clinical Oncology 40*(1), 47–52. https://doi.org/10.1097/COC.0000000000000061.

Cvan Trobec, K., Kerec Kos, M., Trontelj, J., Grabnar, I., Tschirner, A., Palus, S., ... Lainscak, M. (2015). Influence of cancer cachexia on drug liver metabolism and renal elimination in rats: Drug liver metabolism and renal elimination in cancer cachexia. *Journal of Cachexia, Sarcopenia and Muscle 6*(1), 45–52. https://doi.org/10.1002/jcsm.12012.

Dalal, S., Hui, D., Bidaut, L., Lem, K., Del Fabbro, E., Crane, C., ... Bruera, E. (2012). Relationships among body mass index, longitudinal body composition alterations, and survival in patients with locally advanced pancreatic cancer receiving chemoradiation: A pilot study. *Journal of Pain and Symptom Management 44*(2), 181–191. https://doi.org/10.1016/j.jpainsymman.2011.09.010.

Daly, L. E., Ní Bhuachalla, É. B., Power, D. G., Cushen, S. J., James, K., & Ryan, A. M. (2018). Loss of skeletal muscle during systemic chemotherapy is prognostic of poor survival in patients with foregut cancer. *Journal of Cachexia, Sarcopenia and Muscle 9*(2), 315–325. https://doi.org/10.1002/jcsm.12267.

Daly, L. E., Power, D. G., O'Reilly, Á., Donnellan, P., Cushen, S. J., O'Sullivan, K., ... Ryan, A. M. (2017). The impact of body composition parameters on ipilimumab toxicity and survival in patients with metastatic melanoma. *British Journal of Cancer 116*(3), 310–317. https://doi.org/10.1038/bjc.2016.431.

Damrauer, J. S., Stadler, M. E., Acharyya, S., Baldwin, A. S., Couch, M. E., & Guttridge, D. C. (2018). Chemotherapy-induced muscle wasting: association with NF-κB and cancer cachexia. *European Journal of Translational Myology 28*(2), 7590. https://doi.org/10.4081/ejtm.2018.7590.

Davis, L. E., Lenkinski, R. E., Shinkwin, M. A., Kressel, H. Y., & Daly, J. M. (1993). The effect of dietary protein depletion on hepatic 5-fluorouracil metabolism. *Cancer 72*(12), 3715–3722.

Del Fabbro, E., Parsons, H., Warneke, C. L., Pulivarthi, K., Litton, J. K., Dev, R., ... Bruera, E. (2012). The relationship between body composition and response to neoadjuvant chemotherapy in women with operable breast cancer. *The Oncologist 17*(10), 1240–1245. https://doi.org/10.1634/theoncologist.2012-0169.

Demirovic, J. A., Pai, A. B., & Pai, M. P. (2009). Estimation of creatinine clearance in morbidly obese patients. *American Journal of Health-System Pharmacy: AJHP: Official Journal of the American Society of Health-System Pharmacists 66*(7), 642–648. https://doi.org/10.2146/ajhp080200.

van der Ende, M., Grefte, S., Plas, R., Meijerink, J., Witkamp, R., Keijer, J., & van Norren, K. (2018). Mitochondrial dynamics in cancer-induced cachexia. *Biochimica Et Biophysica Acta*. https://doi.org/10.1016/j.bbcan.2018.07.008.

Deutz, N. E. P., Safar, A., Schutzler, S., Memelink, R., Ferrando, A., Spencer, H., ... Wolfe, R. R. (2011). Muscle protein synthesis in cancer patients can be stimulated with a specially formulated medical food. *Clinical Nutrition (Edinburgh, Scotland) 30*(6), 759–768. https://doi.org/10.1016/j.clnu.2011.05.008.

Dhooge, M., Coriat, R., Mir, O., Perkins, G., Brezault, C., Boudou-Rouquette, P., ... Chaussade, S. (2013). Feasibility of gemcitabine plus oxaliplatin in advanced hepatocellular carcinoma patients with Child-Pugh B cirrhosis. *Oncology 84*(1), 32–38. https://doi.org/10.1159/000342763.

Di Sebastiano, K. M., & Mourtzakis, M. (2012). A critical evaluation of body composition modalities used to assess adipose and skeletal muscle tissue in cancer. *Applied Physiology, Nutrition, and Metabolism 37*(5), 811–821. https://doi.org/10.1139/h2012-079.

Di Sebastiano, K. M., Yang, L., Zbuk, K., Wong, R. K., Chow, T., Koff, D., ... Mourtzakis, M. (2013). Accelerated muscle and adipose tissue loss may predict survival in pancreatic cancer patients: the relationship with diabetes and anaemia. *The British Journal of Nutrition 109*(2), 302–312. https://doi.org/10.1017/S0007114512001067.

Dieli-Conwright, C. M., Courneya, K. S., Demark-Wahnefried, W., Sami, N., Lee, K., Buchanan, T. A., ... Mortimer, J. E. (2018). Effects of aerobic and resistance exercise on metabolic syndrome, sarcopenic obesity, and circulating biomarkers in overweight or obese survivors of breast cancer: A randomized controlled trial. *Journal of Clinical Oncology 36*(9), 875–883. https://doi.org/10.1200/JCO.2017.75.7526.

Dignam, J. J., Polite, B. N., Yothers, G., Raich, P., Colangelo, L., O'Connell, M. J., & Wolmark, N. (2006). Body mass index and outcomes in patients who receive adjuvant chemotherapy for colon cancer. *Journal of the National Cancer Institute 98*(22), 1647–1654. https://doi.org/10.1093/jnci/djj442.

Dixon, W. T. (1984). Simple proton spectroscopic imaging. *Radiology 153*(1), 189–194. https://doi.org/10.1148/radiology.153.1.6089263.

Dobs, A. S., Boccia, R. V., Croot, C. C., Gabrail, N. Y., Dalton, J. T., Hancock, M. L., ... Steiner, M. S. (2013). Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. *The Lancet. Oncology 14*(4), 335–345. https://doi.org/10.1016/S1470-2045(13)70055-X.

Du Bois, D., & Du Bois, E. F. (1989). A formula to estimate the approximate surface area if height and weight be known. 1916 *Nutrition (Burbank, Los Angeles County, Calif.) 5*(5), 303–311 discussion 312–313.

Ellis, K. J. (2001). Selected Body Composition Methods Can Be Used in Field Studies. *The Journal of Nutrition 131*(5), 1589S–1595S. https://doi.org/10.1093/jn/131.5.1589S.

Ethun, C. G., Bilen, M. A., Jani, A. B., Maithel, S. K., Ogan, K., & Master, V. A. (2017). Frailty and cancer: Implications for oncology surgery, medical oncology, and radiation oncology. *CA: A Cancer Journal for Clinicians 67*(5), 362–377. https://doi.org/10.3322/caac.21406.

Ezeoke, C. C., & Morley, J. E. (2015). Pathophysiology of anorexia in the cancer cachexia syndrome. *Journal of Cachexia, Sarcopenia and Muscle 6*(4), 287–302. https://doi.org/10.1002/jcsm.12059.

Fang, H., Berg, E., Cheng, X., & Shen, W. (2018). How to best assess abdominal obesity. *Current Opinion in Clinical Nutrition and Metabolic Care*. https://doi.org/10.1097/MCO.0000000000000485.

Fearon, K., Strasser, F., Anker, S. D., Bosaeus, I., Bruera, E., Fainsinger, R. L., ... Baracos, V. E. (2011). Definition and classification of cancer cachexia: an international consensus. *The Lancet Oncology 12*(5), 489–495. https://doi.org/10.1016/S1470-2045(10)70218-7.

Feldschuh, J., & Enson, Y. (1977). Prediction of the normal blood volume. Relation of blood volume to body habitus. *Circulation 56*(4), 605–612. https://doi.org/10.1161/01.CIR.56.4.605.

Feng, Y., Roy, A., Masson, E., Chen, T. -T., Humphrey, R., & Weber, J. S. (2013). Exposure-response relationships of the efficacy and safety of ipilimumab in patients with advanced melanoma. *Clinical Cancer Research 19*(14), 3977–3986. https://doi.org/10.1158/1078-0432.CCR-12-3243.

Ferrando, A. A., Sheffield-Moore, M., Yeckel, C. W., Gilkison, C., Jiang, J., Achacosa, A., ... Urban, R. J. (2002). Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. *American Journal of Physiology. Endocrinology and Metabolism 282*(3), E601–E607. https://doi.org/10.1152/ajpendo.00362.2001.

Fielding, R. A., Vellas, B., Evans, W. J., Bhasin, S., Morley, J. E., Newman, A. B., ... Zamboni, M. (2011). Sarcopenia: An undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *Journal of the American Medical Directors Association 12*(4), 249–256. https://doi.org/10.1016/j.jamda.2011.01.003.

Flanigen-Roat, D. T., Milholland, R. J., & Ip, M. M. (1985). Effect of a high-protein-low-carbohydrate diet on toxicity and antitumor activity of 5-fluorouracil in mice. *Journal of the National Cancer Institute 74*(3), 705–710.

Focht, B. C., Clinton, S. K., Devor, S. T., Garver, M. J., Lucas, A. R., Thomas-Ahner, J. M., & Grainger, E. (2013). Resistance exercise interventions during and following cancer treatment: a systematic review. *The Journal of Supportive Oncology 11*(2), 45–60.

Fuchs, G., Chretien, Y. R., Mario, J., Do, S., Eikermann, M., Liu, B., ... Fintelmann, F. J. (2018). Quantifying the effect of slice thickness, intravenous contrast and tube current on muscle segmentation: Implications for body composition analysis. *European Radiology 28*(6), 2455–2463. https://doi.org/10.1007/s00330-017-5191-3.

Fujiwara, N., Nakagawa, H., Kudo, Y., Tateishi, R., Taguri, M., Watadani, T., ... Koike, K. (2015). Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. *Journal of Hepatology 63*(1), 131–140. https://doi.org/10.1016/j.jhep.2015.02.031.

Fukushima, H., Nakanishi, Y., Kataoka, M., Tobisu, K., & Koga, F. (2016). Prognostic significance of sarcopenia in patients with metastatic renal cell carcinoma. *The Journal of Urology 195*(1), 26–32. https://doi.org/10.1016/j.juro.2015.08.071.

Fukushima, H., Yokoyama, M., Nakanishi, Y., Tobisu, K., & Koga, F. (2015). Sarcopenia as a prognostic biomarker of advanced urothelial carcinoma. *PLoS One 10*(1), e0115895. https://doi.org/10.1371/journal.pone.0115895.

Furlanetto, J., Eiermann, W., Marmé, F., Reimer, T., Reinisch, M., Schmatloch, S., ... Möbus, V. (2016). Higher rate of severe toxicities in obese patients receiving dose-dense (dd) chemotherapy according to unadjusted body surface area: results of the prospectively randomized GAIN study. *Annals of Oncology: Official Journal of the European Society for Medical Oncology 27*(11), 2053–2059. https://doi.org/10.1093/annonc/mdw315.

Ghielmini, M. (2005). Multimodality therapies and optimal schedule of antibodies: Rituximab in lymphoma as an example. *ASH Education Program Book 2005*(1), 321–328. https://doi.org/10.1182/asheducation-2005.1.321.

Go, S. -I., Park, M. J., Song, H. -N., Kang, M. H., Park, H. J., Jeon, K. N., ... Lee, G. -W. (2016). Sarcopenia and inflammation are independent predictors of survival in male patients newly diagnosed with small cell lung cancer. *Supportive Care in Cancer 24*(5), 2075–2084. https://doi.org/10.1007/s00520-015-2997-x.

Go, S. -I., Park, M. J., Song, H. -N., Kim, H. -G., Kang, M. H., Kang, J. H., ... Lee, G. -W. (2017). A comparison of pectoralis versus lumbar skeletal muscle indices for defining sarcopenia in diffuse large B-cell lymphoma - two are better than one. *Oncotarget 8*(29), 47007–47019. https://doi.org/10.18632/oncotarget.16552.

Golan, T., Geva, R., Richards, D., Madhusudan, S., Lin, B. K., Wang, H. T., ... Stemmer, S. M. (2018). LY2495655, an antimyostatin antibody, in pancreatic cancer: a randomized, phase 2 trial: LY2495655 in patients with stage II-IV pancreatic cancer. *Journal of Cachexia, Sarcopenia and Muscle 9*(5), 871–879. https://doi.org/10.1002/jcsm.12331.

Gondin, J., Cozzone, P. J., & Bendahan, D. (2011). Is high-frequency neuromuscular electrical stimulation a suitable tool for muscle performance improvement in both healthy humans and athletes? *European Journal of Applied Physiology 111*(10), 2473–2487. https://doi.org/10.1007/s00421-011-2101-2.

Gonzalez, M. C., Barbosa-Silva, T. G., & Heymsfield, S. B. (2018). Bioelectrical impedance analysis in the assessment of sarcopenia. *Current Opinion in Clinical Nutrition and Metabolic Care*. https://doi.org/10.1097/MCO.0000000000000496.

Goodpaster, B. H., Kelley, D. E., Thaete, F. L., He, J., & Ross, R. (2000). Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. *Journal of Applied Physiology (Bethesda, MD: 1985) 89*(1), 104–110. https://doi.org/10.1152/jappl.2000.89.1.104.

Gordon, M. S., Margolin, K., Talpaz, M., Sledge, G. W., Holmgren, E., Benjamin, R., ... Adelman, D. (2001). Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 19*(3), 843–850. https://doi.org/10.1200/JCO.2001.19.3.843.

Griggs, J. J., Mangu, P. B., Anderson, H., Balaban, E. P., Dignam, J. J., Hryniuk, W. M., ... American Society of Clinical Oncology (2012). Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 30*(13), 1553–1561. https://doi.org/10.1200/JCO.2011.39.9436.

Griggs, J. J., Mangu, P. B., Temin, S., & Lyman, G. H. (2012). Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Oncology Practice 8*(4), e59–e61. https://doi.org/10.1200/JOP.2012.000623.

Grotenhuis, B. A., Shapiro, J., van Adrichem, S., de Vries, M., Koek, M., Wijnhoven, B. P. L., & van Lanschot, J. J. B. (2016). Sarcopenia/muscle mass is not a prognostic factor for short- and long-term outcome after esophagectomy for cancer. *World Journal of Surgery 40*(11), 2698–2704. https://doi.org/10.1007/s00268-016-3603-1.

Guglielmi, G., Ponti, F., Agostini, M., Amadori, M., Battista, G., & Bazzocchi, A. (2016). The role of DXA in sarcopenia. *Aging Clinical and Experimental Research 28*(6), 1047–1060. https://doi.org/10.1007/s40520-016-0589-3.

Guillory, B., Splenser, A., & Garcia, J. (2013). The role of ghrelin in anorexia-cachexia syndromes. *Vitamins and Hormones 92*, 61–106. https://doi.org/10.1016/B978-0-12-410473-0.00003-9.

Guralnik, J. M., Ferrucci, L., Leveille, S. G., Markides, K. S., Ostir, G. V., Studenski, S., ... Wallace, R. B. (2000). Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 55*(4), M221–M231.

Gurney, H. (1996). Dose calculation of anticancer drugs: a review of the current practice and introduction of an alternative. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 14*(9), 2590–2611. https://doi.org/10.1200/JCO.1996.14.9.2590.

Gusella, M., Toso, S., Ferrazzi, E., Ferrari, M., & Padrini, R. (2002). Relationships between body composition parameters and fluorouracil pharmacokinetics. *British Journal of Clinical Pharmacology 54*(2), 131–139.

von Haehling, S., & Anker, S. D. (2010). Cachexia as a major underestimated and unmet medical need: facts and numbers. *Journal of Cachexia, Sarcopenia and Muscle 1*(1), 1–5. https://doi.org/10.1007/s13539-010-0002-6.

Handforth, C., Clegg, A., Young, C., Simpkins, S., Seymour, M. T., Selby, P. J., & Young, J. (2015). The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Annals of Oncology: Official Journal of the European Society for Medical Oncology 26*(6), 1091–1101. https://doi.org/10.1093/annonc/mdu540.

Harimoto, N., Shirabe, K., Yamashita, Y. -I., Ikegami, T., Yoshizumi, T., Soejima, Y., ... Yamanaka, T. (2013). Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. *The British Journal of Surgery 100*(11), 1523–1530. https://doi.org/10.1002/bjs.9258.

He, W. A., Berardi, E., Cardillo, V. M., Acharyya, S., Aulino, P., Thomas-Ahner, J., ... Guttridge, D. C. (2013). NF-κB-mediated Pax7 dysregulation in the muscle microenvironment promotes cancer cachexia. *The Journal of Clinical Investigation 123*(11), 4821–4835. https://doi.org/10.1172/JCI68523.

Heidelberger, H., François, G., Nora, K., Anne, J., Olivier, H., Pascaline, B. -R., ... Sélim, A. (2017). Sarcopenic overweight is associated with early acute limiting toxicity of anti-PD1 checkpoint inhibitors in melanoma patients. *Investigational New Drugs*.. https://doi.org/10.1007/s10637-017-0464-x.

Hendrikx, J. J. M. A., Haanen, J. B. A. G., Voest, E. E., Schellens, J. H. M., Huitema, A. D. R., & Beijnen, J. H. (2017). Fixed dosing of monoclonal antibodies in oncology. *The Oncologist 22*(10), 1212–1221. https://doi.org/10.1634/theoncologist.2017-0167.

Heymsfield, S. B. (2008). Development of imaging methods to assess adiposity and metabolism. *International Journal of Obesity (2005) 32*(Suppl. 7), S76–S82. https://doi.org/10.1038/ijo.2008.242.

Hill, A., Kiss, N., Hodgson, B., Crowe, T. C., & Walsh, A. D. (2011). Associations between nutritional status, weight loss, radiotherapy treatment toxicity and treatment outcomes in gastrointestinal cancer patients. *Clinical Nutrition (Edinburgh, Scotland) 30*(1), 92–98. https://doi.org/10.1016/j.clnu.2010.07.015.

Hodi, F. S., O'Day, S. J., McDermott, D. F., Weber, R. W., Sosman, J. A., Haanen, J. B., ... Urba, W. J. (2010). Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. *New England Journal of Medicine 363*(8), 711–723. https://doi.org/10.1056/NEJMoa1003466.

Hojan, K., Milecki, P., Molińska-Glura, M., Roszak, A., & Leszczyński, P. (2013). Effect of physical activity on bone strength and body composition in breast cancer premenopausal women during endocrine therapy. *European Journal of Physical and Rehabilitation Medicine 49*(3), 331–339.

Hojman, P., Fjelbye, J., Zerahn, B., Christensen, J. F., Dethlefsen, C., Lonkvist, C. K., ... Gehl, J. (2014). Voluntary exercise prevents cisplatin-induced muscle wasting during chemotherapy in mice. *PLoS One 9*(9), e109030. https://doi.org/10.1371/journal.pone.0109030.

Hong, D. S., Hui, D., Bruera, E., Janku, F., Naing, A., Falchook, G. S., ... Kurzrock, R. (2014). MABp1, a first-in-class true human antibody targeting interleukin-1α in refractory cancers: an open-label, phase 1 dose-escalation and expansion study. *The Lancet. Oncology 15*(6), 656–666. https://doi.org/10.1016/S1470-2045(14)70155-X.

Huang, D. -D., Wang, S. -L., Zhuang, C. -L., Zheng, B. -S., Lu, J. -X., Chen, F. -F., ... Yu, Z. (2015). Sarcopenia, as defined by low muscle mass, strength and physical performance, predicts complications after surgery for colorectal cancer. *Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland 17*(11), O256–O264. https://doi.org/10.1111/codi.13067.

Huillard, O., Mir, O., Peyromaure, M., Tlemsani, C., Giroux, J., Boudou-Rouquette, P., ... Goldwasser, F. (2013). Sarcopenia and body mass index predict sunitinib-induced early dose-limiting toxicities in renal cancer patients. *British Journal of Cancer 108*(5), 1034–1041. https://doi.org/10.1038/bjc.2013.58.

Hunter, R. J., Navo, M. A., Thaker, P. H., Bodurka, D. C., Wolf, J. K., & Smith, J. A. (2009). Dosing chemotherapy in obese patients: actual versus assigned body surface area (BSA). *Cancer Treatment Reviews 35*(1), 69–78. https://doi.org/10.1016/j.ctrv.2008.07.005.

Iannessi, A., Beaumont, H., Hebert, C., Dittlot, C., & Falewee, M. N. (2018). Computer tomography-based body surface area evaluation for drug dosage: Quantitative radiology versus anthropomorphic evaluation. *PLoS One 13*(2), 1–12. https://doi.org/10.1371/journal.pone.0192124.

Ida, S., Watanabe, M., Yoshida, N., Baba, Y., Umezaki, N., Harada, K., ... Baba, H. (2015). Sarcopenia is a predictor of postoperative respiratory complications in patients with esophageal cancer. *Annals of Surgical Oncology 22*(13), 4432–4437. https://doi.org/10.1245/s10434-015-4559-3.

Iritani, S., Imai, K., Takai, K., Hanai, T., Ideta, T., Miyazaki, T., ... Moriwaki, H. (2015). Skeletal muscle depletion is an independent prognostic factor for hepatocellular carcinoma. *Journal of Gastroenterology 50*(3), 323–332. https://doi.org/10.1007/s00535-014-0964-9.

Ishihara, H., Kondo, T., Omae, K., Takagi, T., Iizuka, J., Kobayashi, H., & Tanabe, K. (2016). Sarcopenia and the modified glasgow prognostic score are significant predictors of survival among patients with metastatic renal cell carcinoma who are receiving first-line sunitinib treatment. *Targeted Oncology 11*(5), 605–617. https://doi.org/10.1007/s11523-016-0430-0.

Ishikawa, T., Yasuda, T., Doi, T., Okayama, T., Sakamoto, N., Gen, Y., ... Itoh, Y. (2016). The amino acid-rich elemental diet Elental® preserves lean body mass during chemo- or chemoradiotherapy for esophageal cancer. *Oncology Reports 36*(2), 1093–1100. https://doi.org/10.3892/or.2016.4877.

Jameson, G. S., Von Hoff, D. D., Weiss, G. J., Richards, D. A., Smith, D. A., Becerra, C., ... Lin, B. K. (2012). Safety of the antimyostatin monoclonal antibody LY2495655 in healthy subjects and patients with advanced cancer. *Journal of Clinical Oncology 30*(15_suppl), 2516. https://doi.org/10.1200/jco.2012.30.15_suppl.2516.

Janssen, I., & Ross, R. (2005). Linking age-related changes in skeletal muscle mass and composition with metabolism and disease. *The Journal of Nutrition 9*(6), 408–419 Health & Aging.

Joglekar, S., Asghar, A., Mott, S. L., Johnson, B. E., Button, A. M., Clark, E., & Mezhir, J. J. (2015). Sarcopenia is an independent predictor of complications following pancreatectomy for adenocarcinoma. *Journal of Surgical Oncology 111*(6), 771–775. https://doi.org/10.1002/jso.23862.

Jouinot, A., Vazeille, C., & Goldwasser, F. (2018). Resting energy metabolism and anticancer treatments. *Current Opinion in Clinical Nutrition and Metabolic Care 21*(3), 145–151. https://doi.org/10.1097/MCO.0000000000000457.

Jung, H. -W., Kim, J. W., Kim, J. -Y., Kim, S. -W., Yang, H. K., Lee, J. W., ... Kim, J. H. (2015). Effect of muscle mass on toxicity and survival in patients with colon cancer undergoing adjuvant chemotherapy. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer 23*(3), 687–694. https://doi.org/10.1007/s00520-014-2418-6.

Kamachi, S., Mizuta, T., Otsuka, T., Nakashita, S., Ide, Y., Miyoshi, A., ... Anzai, K. (2016). Sarcopenia is a risk factor for the recurrence of hepatocellular carcinoma after curative treatment. *Hepatology Research: The Official Journal of the Japan Society of Hepatology 46*(2), 201–208. https://doi.org/10.1111/hepr.12562.

Kays, J. K., Shahda, S., Stanley, M., Bell, T. M., O'Neill, B. H., Kohli, M. D., ... Zimmers, T. A. (2018). Three cachexia phenotypes and the impact of fat-only loss on survival in FOLFIRINOX therapy for pancreatic cancer. *Journal of Cachexia, Sarcopenia and Muscle*. https://doi.org/10.1002/jcsm.12307.

Kazemi-Bajestani, S. M. R., Mazurak, V. C., & Baracos, V. (2016). Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. *Seminars in Cell & Developmental Biology 54*, 2–10. https://doi.org/10.1016/j.semcdb.2015.09.001.

Keizer, R. J., Huitema, A. D. R., Schellens, J. H. M., & Beijnen, J. H. (2010). Clinical pharmacokinetics of therapeutic monoclonal antibodies. *Clinical Pharmacokinetics 49*(8), 493–507. https://doi.org/10.2165/11531280-000000000-00000.

Kilgour, R. D., Vigano, A., Trutschnigg, B., Lucar, E., Borod, M., & Morais, J. A. (2013). Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer 21*(12), 3261–3270. https://doi.org/10.1007/s00520-013-1894-4.

Kim, E. Y., Kim, Y. S., Park, I., Ahn, H. K., Cho, E. K., & Jeong, Y. M. (2015). Prognostic Significance of CT-Determined Sarcopenia in Patients with Small-Cell Lung Cancer. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 10*(12), 1795–1799. https://doi.org/10.1097/JTO.0000000000000690.

Kim, Y. S., Kim, E. Y., Kang, S. M., Ahn, H. K., & Kim, H. S. (2017). Single cross-sectional area of pectoralis muscle by computed tomography - correlation with bioelectrical impedance based skeletal muscle mass in healthy subjects. *Clinical Physiology and Functional Imaging 37*(5), 507–511. https://doi.org/10.1111/cpf.12333.

Klein, G. L., Petschow, B. W., Shaw, A. L., & Weaver, E. (2013). Gut barrier dysfunction and microbial translocation in cancer cachexia: a new therapeutic target. *Current Opinion in Supportive and Palliative Care 7*(4), 361–367. https://doi.org/10.1097/SPC.0000000000000017.

Kobayashi, A., Kaido, T., Hamaguchi, Y., Okumura, S., Shirai, H., Yao, S., ... Uemoto, S. (2017). Impact of Sarcopenic Obesity on Outcomes in Patients Undergoing Hepatectomy for Hepatocellular Carcinoma. *Annals of Surgery*. https://doi.org/10.1097/SLA.0000000000002555.

Koretz, R. L., Lipman, T. O., Klein, S., & American Gastroenterological Association (2001). AGA technical review on parenteral nutrition Gastroenterology *121*(4), 970–1001.

Krell, R. W., Kaul, D. R., Martin, A. R., Englesbe, M. J., Sonnenday, C. J., Cai, S., & Malani, P. N. (2013). Association between sarcopenia and the risk of serious infection among adults undergoing liver transplantation. *Liver Transplantation: Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 19*(12), 1396–1402. https://doi.org/10.1002/lt.23752.

Kumar Pal, S., Katheria, V., & Hurria, A. (2010). Evaluating the older patient with cancer: Understanding frailty and the geriatric assessment. *CA: A Cancer Journal for Clinicians 60*(2), 120–132. https://doi.org/10.3322/caac.20059.

La Colla, L., La Colla, G., Albertin, A., Poli, D., Baruffaldi Preis, F. W., & Mangano, A. (2007). The use of propofol and remifentanil for the anaesthetic management of a super-obese patient. *Anaesthesia 62*(8), 842–845. https://doi.org/10.1111/j.1365-2044.2007.05102.x.

Lach-Trifilieff, E., Minetti, G. C., Sheppard, K., Ibebunjo, C., Feige, J. N., Hartmann, S., ... Glass, D. J. (2014). An antibody blocking activin type II receptors induces strong skeletal muscle hypertrophy and protects from atrophy. *Molecular and Cellular Biology 34*(4), 606–618. https://doi.org/10.1128/MCB.01307-13.

Lanic, H., Kraut-Tauzia, J., Modzelewski, R., Clatot, F., Mareschal, S., Picquenot, J. M., ... Jardin, F. (2014). Sarcopenia is an independent prognostic factor in elderly patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Leukemia & Lymphoma 55*(4), 817–823. https://doi.org/10.3109/10428194.2013.816421.

Lau, E. M. C., Lynn, H. S. H., Woo, J. W., Kwok, T. C. Y., & Melton, L. J. (2005). Prevalence of and risk factors for sarcopenia in elderly Chinese men and women. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 60*(2), 213–216.

Lee, J., Chang, C. -L., Lin, J. -B., Wu, M. -H., Sun, F. -J., Jan, Y. -T., ... Chen, Y. -J. (2018). Skeletal Muscle Loss is an imaging biomarker of outcome after definitive chemoradiotherapy for locally advanced cervical cancer. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*. https://doi.org/10.1158/1078-0432.CCR-18-0788.

Leenders, M., Verdijk, L. B., van der Hoeven, L., Adam, J. J., van Kranenburg, J., Nilwik, R., & van Loon, L. J. C. (2013). Patients with type 2 diabetes show a greater decline in muscle mass, muscle strength, and functional capacity with aging. *Journal of the American Medical Directors Association 14*(8), 585–592. https://doi.org/10.1016/j.jamda.2013.02.006.

Levolger, S., van Vledder, M. G., Muslem, R., Koek, M., Niessen, W. J., de Man, R. A., ... Ijzermans, J. N. M. (2015). Sarcopenia impairs survival in patients with potentially curable hepatocellular carcinoma. *Journal of Surgical Oncology 112*(2), 208–213. https://doi.org/10.1002/jso.23976.

Lieffers, J. R., Bathe, O. F., Fassbender, K., Winget, M., & Baracos, V. E. (2012). Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. *British Journal of Cancer 107*(6), 931–936. https://doi.org/10.1038/bjc.2012.350.

Lodewick, T. M., van Nijnatten, T. J. A., van Dam, R. M., van Mierlo, K., Dello, S. A. W. G., Neumann, U. P., ... Dejong, C. H. C. (2015). Are sarcopenia, obesity and sarcopenic obesity predictive of outcome in patients with colorectal liver metastases? *HPB: The Official Journal of the International Hepato Pancreato Biliary Association 17*(5), 438–446. https://doi.org/10.1111/hpb.12373.

Looijaard, W. G. P. M., Dekker, I. M., Stapel, S. N., Girbes, A. R. J., Twisk, J. W. R., Oudemans-van Straaten, H. M., & Weijs, P. J. M. (2016). Skeletal muscle quality as assessed by CT-derived skeletal muscle density is associated with 6-month mortality in mechanically ventilated critically ill patients. *Critical Care (London, England) 20*(1), 386. https://doi.org/10.1186/s13054-016-1563-3.

Lou, N., Chi, C. -H., Chen, X. -D., Zhou, C. -J., Wang, S. -L., Zhuang, C. -L., & Shen, X. (2017). Sarcopenia in overweight and obese patients is a predictive factor for postoperative complication in gastric cancer: A prospective study. *European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 43*(1), 188–195. https://doi.org/10.1016/j.ejso.2016.09.006.

Maddocks, M., Halliday, V., Chauhan, A., Taylor, V., Nelson, A., Sampson, C., ... Wilcock, A. (2013). Neuromuscular electrical stimulation of the quadriceps in patients with non-small cell lung cancer receiving palliative chemotherapy: a randomized phase II study. *PLoS One 8*(12), e86059. https://doi.org/10.1371/journal.pone.0086059.

Maddocks, M., Nolan, C. M., Man, W. D. -C., Polkey, M. I., Hart, N., Gao, W., ... Higginson, I. J. (2016). Neuromuscular electrical stimulation to improve exercise capacity in patients with severe COPD: a randomised double-blind, placebo-controlled trial. *The Lancet. Respiratory Medicine 4*(1), 27–36. https://doi.org/10.1016/S2213-2600(15)00503-2.

Maffiuletti, N. A. (2010). Physiological and methodological considerations for the use of neuromuscular electrical stimulation. *European Journal of Applied Physiology 110*(2), 223–234. https://doi.org/10.1007/s00421-010-1502-y.

Malietzis, G., Currie, A. C., Athanasiou, T., Johns, N., Anyamene, N., Glynne-Jones, R., ... Jenkins, J. T. (2016). Influence of body composition profile on outcomes following colorectal cancer surgery. *The British Journal of Surgery 103*(5), 572–580. https://doi.org/10.1002/bjs.10075.

Mann, G. E., Yudilevich, D. L., & Sobrevia, L. (2003). Regulation of amino acid and glucose transporters in endothelial and smooth muscle cells. *Physiological Reviews 83*(1), 183–252. https://doi.org/10.1152/physrev.00022.2002.

Mantovani, G., Macciò, A., Madeddu, C., Gramignano, G., Serpe, R., Massa, E., ... Floris, C. (2008). Randomized phase III clinical trial of five different arms of treatment for patients with cancer cachexia: interim results. *Nutrition (Burbank, Los Angeles County, Calif.) 24*(4), 305–313. https://doi.org/10.1016/j.nut.2007.12.010.

Martin, L., Birdsell, L., Macdonald, N., Reiman, T., Clandinin, M. T., McCargar, L. J., ... Baracos, V. E. (2013). Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 31*(12), 1539–1547. https://doi.org/10.1200/JCO.2012.45.2722.

Massicotte, M. -H., Borget, I., Broutin, S., Baracos, V. E., Leboulleux, S., Baudin, E., ... Antoun, S. (2013). Body composition variation and impact of low skeletal muscle mass in patients with advanced medullary thyroid carcinoma treated with vandetanib: Results

from a placebo-controlled study. *The Journal of Clinical Endocrinology & Metabolism 98* (6), 2401–2408. https://doi.org/10.1210/jc.2013-1115.
Mayers, J. R., Torrence, M. E., Danai, L. V., Papagiannakopoulos, T., Davidson, S. M., Bauer, M. R., ... Vander Heiden, M. G. (2016). Tissue of origin dictates branched-chain amino acid metabolism in mutant Kras-driven cancers. *Science (New York, N.Y.) 353*(6304), 1161–1165. https://doi.org/10.1126/science.aaf5171.
Mayers, J. R., Wu, C., Clish, C. B., Kraft, P., Torrence, M. E., Fiske, B. P., ... Wolpin, B. M. (2014). Elevation of circulating branched-chain amino acids is an early event in human pancreatic adenocarcinoma development. *Nature Medicine 20*(10), 1193–1198. https://doi.org/10.1038/nm.3686.
McCann, R. M., Hall, W. J., & Groth-Juncker, A. (1994). Comfort care for terminally ill patients. The appropriate use of nutrition and hydration. *JAMA 272*(16), 1263–1266.
McCormick, R., & Vasilaki, A. (2018). Age-related changes in skeletal muscle: changes to life-style as a therapy. *Biogerontology*. https://doi.org/10.1007/s10522-018-9775-3.
Meza-Junco, J., Montano-Loza, A. J., Baracos, V. E., Prado, C. M. M., Bain, V. G., Beaumont, C., ... Sawyer, M. B. (2013). Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. *Journal of Clinical Gastroenterology 47* (10), 861–870. https://doi.org/10.1097/MCG.0b013e318293a825.
Miller, J. A., Harris, K., Roche, C., Dhillon, S., Battoo, A., Demmy, T., ... Yendamuri, S. (2018). Sarcopenia is a predictor of outcomes after lobectomy. *Journal of Thoracic Disease 10* (1), 432–440. https://doi.org/10.21037/jtd.2017.12.39.
Mir, O., Coriat, R., Blanchet, B., Durand, J. -P., Boudou-Rouquette, P., Michels, J., ... Goldwasser, F. (2012). Sarcopenia predicts early dose-limiting toxicities and pharmacokinetics of sorafenib in patients with hepatocellular carcinoma. *PLoS One 7*(5), e37563. https://doi.org/10.1371/journal.pone.0037563.
Mir, O., Coriat, R., Boudou-Rouquette, P., Ropert, S., Durand, J. -P., Cessot, A., ... Goldwasser, F. (2012). Gemcitabine and oxaliplatin as second-line treatment in patients with hepatocellular carcinoma pre-treated with sorafenib. *Medical Oncology (Northwood, London, England) 29*(4), 2793–2799. https://doi.org/10.1007/s12032-012-0208-x.
Mitsiopoulos, N., Baumgartner, R. N., Heymsfield, S. B., Lyons, W., Gallagher, D., & Ross, R. (1998). Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *Journal of Applied Physiology (Bethesda, MD: 1985) 85*(1), 115–122. https://doi.org/10.1152/jappl.1998.85.1.115.
Miyamoto, Y., Baba, Y., Sakamoto, Y., Ohuchi, M., Tokunaga, R., Kurashige, J., ... Baba, H. (2015). Sarcopenia is a Negative Prognostic Factor After Curative Resection of Colorectal Cancer. *Annals of Surgical Oncology 22*(8), 2663–2668. https://doi.org/10.1245/s10434-014-4281-6.
Miyata, H., Sugimura, K., Motoori, M., Fujiwara, Y., Omori, T., Yanagimoto, Y., ... Yano, M. (2017). Clinical assessment of sarcopenia and changes in body composition during neoadjuvant chemotherapy for esophageal cancer. *Anticancer Research 37*(6), 3053–3059. https://doi.org/10.21873/anticanres.11660.
Morishita, S., Kaida, K., Tanaka, T., Itani, Y., Ikegame, K., Okada, M., ... Domen, K. (2012). Prevalence of sarcopenia and relevance of body composition, physiological function, fatigue, and health-related quality of life in patients before allogeneic hematopoietic stem cell transplantation. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer 20*(12), 3161–3168. https://doi.org/10.1007/s00520-012-1460-5.
Morley, J. E., Argiles, J. M., Evans, W. J., Bhasin, S., Cella, D., Deutz, N. E. P., ... Anker, S. D. (2010). Nutritional recommendations for the management of sarcopenia. *Journal of the American Medical Directors Association 11*(6), 391–396. https://doi.org/10.1016/j.jamda.2010.04.014.
Morley, J. E., Malmstrom, T. K., Rodriguez-Mañas, L., & Sinclair, A. J. (2014). Frailty, sarcopenia and diabetes. *Journal of the American Medical Directors Association 15* (12), 853–859. https://doi.org/10.1016/j.jamda.2014.10.001.
Morsbach, F., Zhang, Y. -H., Nowik, P., Martin, L., Lindqvist, C., Svensson, A., & Brismar, T. B. (2018). Influence of tube potential on CT body composition analysis. *Nutrition (Burbank, Los Angeles County, Calif.) 53*, 9–13. https://doi.org/10.1016/j.nut.2017.12.016.
Motzer, R. J., Escudier, B., McDermott, D. F., George, S., Hammers, H. J., Srinivas, S., & CheckMate 025 Investigators, ... (2015). Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *The New England Journal of Medicine 373*(19), 1803–1813. https://doi.org/10.1056/NEJMoa1510665.
Motzer, R. J., Rini, B. I., McDermott, D. F., Redman, B. G., Kuzel, T. M., Harrison, M. R., ... Hammers, H. J. (2015). Nivolumab for metastatic renal cell carcinoma: Results of a randomized phase II trial. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 33*(13), 1430–1437. https://doi.org/10.1200/JCO.2014.59.0703.
Motzer, R. J., Tannir, N. M., McDermott, D. F., Arén Frontera, O., Melichar, B., Choueiri, T., ... Escudier, B. (2018). Nivolumab plus Ipilimumab versus sunitinib in advanced renal-cell carcinoma. *New England Journal of Medicine 378*(14), 1277–1290. https://doi.org/10.1056/NEJMoa1712126.
Mourtzakis, M., Prado, C. M. M., Lieffers, J. R., Reiman, T., McCargar, L. J., & Baracos, V. E. (2008). A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Applied Physiology, Nutrition, and Metabolism 33*(5), 997–1006. https://doi.org/10.1139/H08-075.
Mücke, M., Mochamat, C. H., Peuckmann-Post, V., Minton, O., Stone, P., ... Radbruch, L. (2015). Pharmacological treatments for fatigue associated with palliative care. *The Cochrane Database of Systematic Reviews 5*, CD006788. https://doi.org/10.1002/14651858.CD006788.pub3.
Murimwa, G. Z., Venkat, P. S., Jin, W., Leuthold, S., Latifi, K., Almhanna, K., ... Frakes, J. M. (2017). Impact of sarcopenia on outcomes of locally advanced esophageal cancer patients treated with neoadjuvant chemoradiation followed by surgery. *Journal of Gastrointestinal Oncology 8*(5), 808–815. https://doi.org/10.21037/jgo.2017.06.11.
Muscaritoli, M., Anker, S. D., Argilés, J., Aversa, Z., Bauer, J. M., Biolo, G., ... Sieber, C. C. (2010). Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics.". *Clinical Nutrition (Edinburgh, Scotland) 29*(2), 154–159. https://doi.org/10.1016/j.clnu.2009.12.004.
Mustian, K. M., Alfano, C. M., Heckler, C., Kleckner, A. S., Kleckner, I. R., Leach, C. R., ... Miller, S. M. (2017). Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: A meta-analysis. *JAMA Oncology 3*(7), 961–968. https://doi.org/10.1001/jamaoncol.2016.6914.
Nakamura, N., Hara, T., Shibata, Y., Matsumoto, T., Nakamura, H., Ninomiya, S., ... Tsurumi, H. (2015). Sarcopenia is an independent prognostic factor in male patients with diffuse large B-cell lymphoma. *Annals of Hematology 94*(12), 2043–2053. https://doi.org/10.1007/s00277-015-2499-4.
Nakamura, R., Inage, Y., Tobita, R., Yoneyama, S., Numata, T., Ota, K., ... Terashima, T. (2018). Sarcopenia in resected NSCLC: Effect on postoperative outcomes. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 13*(7), 895–903. https://doi.org/10.1016/j.jtho.2018.04.035.
Narsale, A. A., & Carson, J. A. (2014). Role of interleukin-6 in cachexia: therapeutic implications. *Current Opinion in Supportive and Palliative Care 8*(4), 321–327. https://doi.org/10.1097/SPC.0000000000000091.
Nault, J. -C., Pigneur, F., Nelson, A. C., Costentin, C., Tselikas, L., Katsahian, S., ... Decaens, T. (2015). Visceral fat area predicts survival in patients with advanced hepatocellular carcinoma treated with tyrosine kinase inhibitors. *Digestive and Liver Disease 47* (10), 869–876. https://doi.org/10.1016/j.dld.2015.07.001.
Neves, R. X., Rosa-Neto, J. C., Yamashita, A. S., Matos-Neto, E. M., Riccardi, D. M. R., Lira, F. S., ... Seelaender, M. (2016). White adipose tissue cells and the progression of cachexia: Inflammatory pathways. *Journal of Cachexia, Sarcopenia and Muscle 7*(2), 193–203. https://doi.org/10.1002/jcsm.12041.
Nishigori, T., Tsunoda, S., Okabe, H., Tanaka, E., Hisamori, S., Hosogi, H., ... Sakai, Y. (2016). Impact of sarcopenic obesity on surgical site infection after laparoscopic total gastrectomy. *Annals of Surgical Oncology 23*, 524–531. https://doi.org/10.1245/s10434-016-5385-y Suppl 4.
O'Connor, D., & Caulfield, B. (2018). *The application of neuromuscular electrical stimulation (NMES) in cancer rehabilitation: current prescription, pitfalls, and future directions Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer . https://doi.org/10.1007/s00520-018-4269-z.*
Owusu, C., Margevicius, S., Schluchter, M., Koroukian, S. M., & Berger, N. A. (2017). Short physical performance battery, usual gait speed, grip strength and vulnerable elders survey each predict functional decline among older women with breast cancer. *Journal of Geriatric Oncology 8*(5), 356–362. https://doi.org/10.1016/j.jgo.2017.07.004.
Öztürk, Z. A., Kul, S., Türkbeyler, İ. H., Sayıner, Z. A., & Abiyev, A. (2018). Is increased neutrophil lymphocyte ratio remarking the inflammation in sarcopenia? *Experimental Gerontology 110*, 223–229. https://doi.org/10.1016/j.exger.2018.06.013.
Padhi, D., Higano, C. S., Shore, N. D., Sieber, P., Rasmussen, E., & Smith, M. R. (2014). Pharmacological inhibition of myostatin and changes in lean body mass and lower extremity muscle size in patients receiving androgen deprivation therapy for prostate cancer. *The Journal of Clinical Endocrinology and Metabolism 99*(10), E1967–E1975. https://doi.org/10.1210/jc.2014-1271.
Pahor, M., Guralnik, J. M., Ambrosius, W. T., Blair, S., Bonds, D. E., Church, T. S., ... LIFE study investigators (2014). Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA 311*(23), 2387–2396. https://doi.org/10.1001/jama.2014.5616.
Pai, M. P. (2012). Drug dosing based on weight and body surface area: mathematical assumptions and limitations in obese adults. *Pharmacotherapy 32*(9), 856–868. https://doi.org/10.1002/j.1875-9114.2012.01108.x.
Palmela, C., Velho, S., Agostinho, L., Branco, F., Santos, M., Santos, M. P. C., ... Baracos, V. E. (2017). Body composition as a prognostic factor of neoadjuvant chemotherapy toxicity and outcome in patients with locally advanced gastric cancer. *Journal of Gastric Cancer 17*(1), 74–87. https://doi.org/10.5230/jgc.2017.17.e8.
Papanicolaou, D. A., Ather, S. N., Zhu, H., Zhou, Y., Lutkiewicz, J., Scott, B. B., & Chandler, J. (2013). A phase IIA randomized, placebo-controlled clinical trial to study the efficacy and safety of the selective androgen receptor modulator (SARM), MK-0773 in female participants with sarcopenia. *The Journal of Nutrition, Health & Aging 17*(6), 533–543. https://doi.org/10.1007/s12603-013-0335-x.
Pappalardo, G., Almeida, A., & Ravasco, P. (2015). Eicosapentaenoic acid in cancer improves body composition and modulates metabolism. *Nutrition (Burbank, Los Angeles County, Calif.) 31*(4), 549–555. https://doi.org/10.1016/j.nut.2014.12.002.
Parajuli, P., Kumar, S., Loumaye, A., Singh, P., Eragamreddy, S., Nguyen, T. L., ... Atfi, A. (2018). Twist1 activation in muscle progenitor cells causes muscle loss akin to cancer cachexia. *Developmental Cell 45*(6), 712–725 e6 https://doi.org/10.1016/j.devcel.2018.05.026.
Park, S. W., Goodpaster, B. H., Strotmeyer, E. S., Kuller, L. H., Broudeau, R., Kammerer, C., ... Health, Aging, and Body Composition Study (2007). Accelerated loss of skeletal muscle strength in older adults with type 2 diabetes: the health, aging, and body composition study. *Diabetes Care 30*(6), 1507–1512. https://doi.org/10.2337/dc06-2537.
Parsons, H. A., Baracos, V. E., Dhillon, N., Hong, D. S., & Kurzrock, R. (2012). Body composition, symptoms, and survival in advanced cancer patients referred to a phase I service. *PLoS One 7*(1), e29330. https://doi.org/10.1371/journal.pone.0029330.
Parsons, H. A., Tsimberidou, A. M., Pontikos, M., Fu, S., Hong, D., Wen, S., ... Kurzrock, R. (2012). Evaluation of the clinical relevance of body composition parameters in patients with cancer metastatic to the liver treated with hepatic arterial infusion chemotherapy. *Nutrition and Cancer 64*(2), 206–217.
Peng, P., Hyder, O., Firoozmand, A., Kneuertz, P., Schulick, R. D., Huang, D., ... Pawlik, T. M. (2012). Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract 16*(8), 1478–1486. https://doi.org/10.1007/s11605-012-1923-5.

Peng, P. D., van Vledder, M. G., Tsai, S., de Jong, M. C., Makary, M., Ng, J., ... Pawlik, T. M. (2011). Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. *HPB: The Official Journal of the International Hepato Pancreato Biliary Association 13*(7), 439–446. https://doi.org/10.1111/j.1477-2574.2011.00301.x.

Pennings, B., Koopman, R., Beelen, M., Senden, J. M. G., Saris, W. H. M., & van Loon, L. J. C. (2011). Exercising before protein intake allows for greater use of dietary protein-derived amino acids for de novo muscle protein synthesis in both young and elderly men. *The American Journal of Clinical Nutrition 93*(2), 322–331. https://doi.org/10.3945/ajcn.2010.29649.

Perrone, R. D., Madias, N. E., & Levey, A. S. (1992). Serum creatinine as an index of renal function: New insights into old concepts. *Clinical Chemistry 38*(10), 1933–1953.

Pierpont, Y. N., Dinh, T. P., Salas, R. E., Johnson, E. L., Wright, T. G., Robson, M. C., & Payne, W. G. (2014). Obesity and surgical wound healing: A current review. *ISRN Obesity 2014*. https://doi.org/10.1155/2014/638936.

Pirttiaho, H. I., Sotaniemi, E. A., Pelkonen, R. O., Pitkänen, U., Anttila, M., & Sundqvist, H. (1980). Roles of hepatic blood flow and enzyme activity in the kinetics of propranolol and sotalol. *British Journal of Clinical Pharmacology 9*(4), 399–405.

Popuri, K., Cobzas, D., Esfandiari, N., Baracos, V., & Jägersand, M. (2016). Body composition assessment in axial CT images using FEM-based automatic segmentation of skeletal muscle. *IEEE Transactions on Medical Imaging 35*(2), 512–520. https://doi.org/10.1109/TMI.2015.2479252.

Postel-Vinay, S. (2015). Redefining dose-limiting toxicity. *Clinical Advances in Hematology & Oncology: H&O 13*(2), 87–89.

Prado, C. M. M., Baracos, V. E., McCargar, L. J., Mourtzakis, M., Mulder, K. E., Reiman, T., & Sawyer, M. B. (2007). Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 13*(11), 3264–3268. https://doi.org/10.1158/1078-0432.CCR-06-3067.

Prado, C. M. M., Baracos, V. E., McCargar, L. J., Reiman, T., Mourtzakis, M., Tonkin, K., ... Sawyer, M. B. (2009). Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 15*(8), 2920–2926. https://doi.org/10.1158/1078-0432.CCR-08-2242.

Prado, C. M. M., Baracos, V. E., Xiao, J., Birdsell, L., Stuyckens, K., Park, Y. C., ... Sawyer, M. B. (2014). The association between body composition and toxicities from the combination of Doxil and trabectedin in patients with advanced relapsed ovarian cancer. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme 39*(6), 693–698. https://doi.org/10.1139/apnm-2013-0403.

Prado, C. M. M., & Heymsfield, S. B. (2014). Lean tissue imaging: a new era for nutritional assessment and intervention. *JPEN. Journal of Parenteral and Enteral Nutrition 38*(8), 940–953. https://doi.org/10.1177/0148607114550189.

Prado, C. M. M., Lieffers, J. R., McCargar, L. J., Reiman, T., Sawyer, M. B., Martin, L., & Baracos, V. E. (2008). Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *The Lancet. Oncology 9*(7), 629–635. https://doi.org/10.1016/S1470-2045(08)70153-0.

Prado, C. M. M., Lima, I. S. F., Baracos, V. E., Bies, R. R., McCargar, L. J., Reiman, T., ... Sawyer, M. B. (2011). An exploratory study of body composition as a determinant of epirubicin pharmacokinetics and toxicity. *Cancer Chemotherapy and Pharmacology 67*(1), 93–101. https://doi.org/10.1007/s00280-010-1288-y.

Psutka, S. P., Boorjian, S. A., Moynagh, M. R., Schmit, G. D., Costello, B. A., Thompson, R. H., ... Tollefson, M. K. (2016). Decreased skeletal muscle mass is associated with an increased risk of mortality after radical nephrectomy for localized renal cell cancer. *The Journal of Urology 195*(2), 270–276. https://doi.org/10.1016/j.juro.2015.08.072.

Psutka, S. P., Boorjian, S. A., Moynagh, M. R., Schmit, G. D., Frank, I., Carrasco, A., ... Tollefson, M. K. (2015). Mortality after radical cystectomy: impact of obesity versus adiposity after adjusting for skeletal muscle wasting. *The Journal of Urology 193*(5), 1507–1513. https://doi.org/10.1016/j.juro.2014.11.088.

Puszkiel, A., Noé, G., Boudou-Rouquette, P., Cossec, C. L., Arrondeau, J., Giraud, J. -S., ... Blanchet, B. (2017). Development and validation of an ELISA method for the quantification of nivolumab in plasma from non-small-cell lung cancer patients. *Journal of Pharmaceutical and Biomedical Analysis 139*, 30–36. https://doi.org/10.1016/j.jpba.2017.02.041.

Reck, M., Rodríguez-Abreu, D., Robinson, A. G., Hui, R., Csőszi, T., Fülöp, A., ... Brahmer, J. R. (2016). Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. *New England Journal of Medicine 375*(19), 1823–1833. https://doi.org/10.1056/NEJMoa1606774.

Redlarski, G., Palkowski, A., & Krawczuk, M. (2016). Body surface area formulae: an alarming ambiguity. *Scientific Reports 6*, 27966. https://doi.org/10.1038/srep27966.

Reisinger, K. W., van Vugt, J. L. A., Tegels, J. J. W., Snijders, C., Hulsewé, K. W. E., Hoofwijk, A. G. M., ... Poeze, M. (2015). Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. *Annals of Surgery 261*(2), 345–352. https://doi.org/10.1097/SLA.0000000000000628.

Robert, C., Ribas, A., Wolchok, J. D., Hodi, F. S., Hamid, O., Kefford, R., ... Daud, A. (2014). Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *The Lancet 384*(9948), 1109–1117. https://doi.org/10.1016/S0140-6736(14)60958-2.

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D. B., McDowell, I., & Mitnitski, A. (2005). A global clinical measure of fitness and frailty in elderly people. *CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne 173*(5), 489–495. https://doi.org/10.1503/cmaj.050051.

Rogers, J. F., Rocci, M. L., Haughey, D. B., & Bertino, J. S. (2003). An evaluation of the suitability of intravenous midazolam as an in vivo marker for hepatic cytochrome P4503A activity. *Clinical Pharmacology and Therapeutics 73*(3), 153–158. https://doi.org/10.1067/mcp.2003.23.

Rollins, K. E., Tewari, N., Ackner, A., Awwad, A., Madhusudan, S., Macdonald, I. A., ... Lobo, D. N. (2016). The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma. *Clinical Nutrition (Edinburgh, Scotland) 35*(5), 1103–1109. https://doi.org/10.1016/j.clnu.2015.08.005.

Rosenberg, I. H. (1989). Summary comments. *The American Journal of Clinical Nutrition 50*(5), 1231–1233. https://doi.org/10.1093/ajcn/50.5.1231.

Rosenberg, I. H. (1997). Sarcopenia: origins and clinical relevance. *The Journal of Nutrition 127*(5 Suppl), 990S–991S. https://doi.org/10.1093/jn/127.5.990S.

Roubenoff, R. (2000). Sarcopenia: A major modifiable cause of frailty in the elderly. *The Journal of Nutrition, Health & Aging 4*(3), 140–142.

Roubenoff, R., & Kehayias, J. J. (2009). The meaning and measurement of lean body mass. *Nutrition Reviews 49*(6), 163–175. https://doi.org/10.1111/j.1753-4887.1991.tb03013.x.

Rule, A. D., Bergstralh, E. J., Slezak, J. M., Bergert, J., & Larson, T. S. (2006). Glomerular filtration rate estimated by cystatin C among different clinical presentations. *Kidney International 69*(2), 399–405. https://doi.org/10.1038/sj.ki.5000073.

Ryan, A. M., Reynolds, J. V., Healy, L., Byrne, M., Moore, J., Brannelly, N., ... Flood, P. (2009). Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: Results of a double-blinded randomized controlled trial. *Annals of Surgery 249*(3), 355–363. https://doi.org/10.1097/SLA.0b013e31819a4789.

Sachs, J. R., Mayawala, K., Gadamsetty, S., Kang, S. P., & de Alwis, D. P. (2016). Optimal Dosing for Targeted Therapies in Oncology: Drug Development Cases Leading by Example. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 22*(6), 1318–1324. https://doi.org/10.1158/1078-0432.CCR-15-1295.

Sakai, H., Sagara, A., Arakawa, K., Sugiyama, R., Hirosaki, A., Takase, K., ... Narita, M. (2014). Mechanisms of cisplatin-induced muscle atrophy. *Toxicology and Applied Pharmacology 278*(2), 190–199. https://doi.org/10.1016/j.taap.2014.05.001.

Sánchez-Lara, K., Turcott, J. G., Juárez-Hernández, E., Nuñez-Valencia, C., Villanueva, G., Guevara, P., ... Arrieta, O. (2014). Effects of an oral nutritional supplement containing eicosapentaenoic acid on nutritional and clinical outcomes in patients with advanced non-small cell lung cancer: Randomised trial. *Clinical Nutrition (Edinburgh, Scotland) 33*(6), 1017–1023. https://doi.org/10.1016/j.clnu.2014.03.006.

Sargent, D. J., Köhne, C. H., Sanoff, H. K., Bot, B. M., Seymour, M. T., de Gramont, A., ... Goldberg, R. M. (2009). Pooled safety and efficacy analysis examining the effect of performance status on outcomes in nine first-line treatment trials using individual data from patients with metastatic colorectal cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 27*(12), 1948–1955. https://doi.org/10.1200/JCO.2008.20.2879.

Schaap, L. A., Pluijm, S. M. F., Deeg, D. J. H., & Visser, M. (2006). Inflammatory markers and loss of muscle mass (sarcopenia) and strength. *The American Journal of Medicine 119*(6), 526 .e9–17 https://doi.org/10.1016/j.amjmed.2005.10.049.

Schmid, D., & Leitzmann, M. F. (2014). Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. *Annals of Oncology: Official Journal of the European Society for Medical Oncology 25*(7), 1293–1311. https://doi.org/10.1093/annonc/mdu012.

Schmitt, A., Gladieff, L., Lansiaux, A., Bobin-Dubigeon, C., Etienne-Grimaldi, M. -C., Boisdron-Celle, M., ... Chatelut, E. (2009). A universal formula based on cystatin C to perform individual dosing of carboplatin in normal weight, underweight, and obese patients. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 15*(10), 3633–3639. https://doi.org/10.1158/1078-0432.CCR-09-0017.

Segatto, M., Fittipaldi, R., Pin, F., Sartori, R., Dae Ko, K., Zare, H., ... Caretti, G. (2017). Epigenetic targeting of bromodomain protein BRD4 counteracts cancer cachexia and prolongs survival. *Nature Communications 8*. https://doi.org/10.1038/s41467-017-01645-7.

Shachar, S. S., Deal, A. M., Weinberg, M., Nyrop, K. A., Williams, G. R., Nishijima, T. F., ... Muss, H. B. (2017). Skeletal muscle measures as predictors of toxicity, hospitalization, and survival in patients with metastatic breast cancer receiving taxane-based chemotherapy. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 23*(3), 658–665. https://doi.org/10.1158/1078-0432.CCR-16-0940.

Shachar, S. S., Deal, A. M., Weinberg, M., Williams, G. R., Nyrop, K. A., Popuri, K., ... Muss, H. B. (2017). Body composition as a predictor of toxicity in patients receiving anthracycline and taxane-based chemotherapy for early-stage breast cancer. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 23*(14), 3537–3543. https://doi.org/10.1158/1078-0432.CCR-16-2266.

Shachar, S. S., Williams, G. R., Muss, H. B., & Nishijima, T. F. (2016). Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. *European Journal of Cancer 57*, 58–67. https://doi.org/10.1016/j.ejca.2015.12.030.

Sharma, P., Zargar-Shoshtari, K., Caracciolo, J. T., Fishman, M., Poch, M. A., Pow-Sang, J., ... Spiess, P. E. (2015). Sarcopenia as a predictor of overall survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. *Urologic Oncology 33*(8), 339 .e17–23 https://doi.org/10.1016/j.urolonc.2015.01.011.

Sharma, P., Zargar-Shoshtari, K., Caracciolo, J. T., Richard, G. J., Poch, M. A., Pow-Sang, J., ... Spiess, P. E. (2015). Sarcopenia as a predictor of complications in penile cancer patients undergoing inguinal lymph node dissection. *World Journal of Urology 33*(10), 1585–1592. https://doi.org/10.1007/s00345-014-1471-6.

Shiel, F., Persson, C., Furness, J., Simas, V., Pope, R., Climstein, M., ... Schram, B. (2018). Dual energy X-ray absorptiometry positioning protocols in assessing body composition: A systematic review of the literature. *Journal of Science and Medicine in Sport*. https://doi.org/10.1016/j.jsams.2018.03.005.

Simoneau, J. A., & Kelley, D. E. (1997). Altered glycolytic and oxidative capacities of skeletal muscle contribute to insulin resistance in NIDDM. *Journal of Applied Physiology (Bethesda, MD: 1985) 83*(1), 166–171. https://doi.org/10.1152/jappl.1997.83.1.166.

Sjøblom, B., Benth, J.Š., Grønberg, B. H., Baracos, V. E., Sawyer, M. B., Fløtten, Ø., ... Jordhøy, M. (2017). Drug dose per kilogram lean body mass predicts hematologic toxicity from carboplatin-doublet chemotherapy in advanced non-small-cell lung cancer. *Clinical Lung Cancer 18*(2), e129–e136. https://doi.org/10.1016/j.cllc.2016.09.008.

Sjøblom, B., Grønberg, B. H., Benth, J.Š., Baracos, V. E., Fløtten, Ø., Hjermstad, M. J., ... Jordhøy, M. (2015). Low muscle mass is associated with chemotherapy-induced haematological toxicity in advanced non-small cell lung cancer. *Lung Cancer 90*(1), 85–91. https://doi.org/10.1016/j.lungcan.2015.07.001.

Sloan, J. A., Goldberg, R. M., Sargent, D. J., Vargas-Chanes, D., Nair, S., Cha, S. S., ... Loprinzi, C. L. (2002). Women experience greater toxicity with fluorouracil-based chemotherapy for colorectal cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 20*(6), 1491–1498. https://doi.org/10.1200/JCO.2002.20.6.1491.

Smart, R., Carter, B., McGovern, J., Luckman, S., Connelly, A., Hewitt, J., ... Moug, S. (2017). Frailty exists in younger adults admitted as surgical emergency leading to adverse outcomes. *The Journal of Frailty & Aging 6*(4), 219–223. https://doi.org/10.14283/jfa.2017.28.

de Souza, V. A., Oliveira, D., Barbosa, S. R., Corrêa, J. O. d. A., Colugnati, F. A. B., Mansur, H. N. , ... Bastos, M. G. (2017). Sarcopenia in patients with chronic kidney disease not yet on dialysis: Analysis of the prevalence and associated factors. *PLoS One 12*(4). https://doi.org/10.1371/journal.pone.0176230.

Spotten, L. E., Corish, C. A., Lorton, C. M., Ui Dhuibhir, P. M., O'Donoghue, N. C., O'Connor, B. , & Walsh, T. D. (2017). Subjective and objective taste and smell changes in cancer. *Annals of Oncology: Official Journal of the European Society for Medical Oncology 28*(5), 969–984. https://doi.org/10.1093/annonc/mdx018.

Srdic, D., Plestina, S., Sverko-Peternac, A., Nikolac, N., Simundic, A. -M., & Samarzija, M. (2016). Cancer cachexia, sarcopenia and biochemical markers in patients with advanced non-small cell lung cancer-chemotherapy toxicity and prognostic value. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*.. https://doi.org/10.1007/s00520-016-3287-y.

Srikanthan, P., Hevener, A. L., & Karlamangla, A. S. (2010). Sarcopenia exacerbates obesity-associated insulin resistance and dysglycemia: findings from the National Health and Nutrition Examination Survey III. *PLoS One 5*(5), e10805. https://doi.org/10.1371/journal.pone.0010805.

Stanisavljevic, N. S., & Marisavljevic, D. Z. (2010). Weight and body composition changes during R-CHOP chemotherapy in patients with non-Hodgkin's lymphoma and their impact on dose intensity and toxicity. *Journal of B.U.ON.: Official Journal of the Balkan Union of Oncology 15*(2), 290–296.

Stene, G. B., Helbostad, J. L., Amundsen, T., Sørhaug, S., Hjelde, H., Kaasa, S., & Grønberg, B. H. (2015). Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. *Acta Oncologica 54*(3), 340–348. https://doi.org/10.3109/0284186X.2014.953259.

Stewart Coats, A. J., Ho, G. F., Prabhash, K., von Haehling, S., Tilson, J., Brown, R., ... for and on behalf of the ACT-ONE study group (2016). Espindolol for the treatment and prevention of cachexia in patients with stage III/IV non-small cell lung cancer or colorectal cancer: a randomized, double-blind, placebo-controlled, international multicentre phase II study (the ACT-ONE trial). *Journal of Cachexia, Sarcopenia and Muscle 7*(3), 355–365. https://doi.org/10.1002/jcsm.12126.

Su, G. M., Sefton, R. M., & Murray, M. (1999). Down-regulation of rat hepatic microsomal cytochromes P-450 in microvesicular steatosis induced by orotic acid. *The Journal of Pharmacology and Experimental Therapeutics 291*(3), 953–959.

Subramaniam, K., Fallon, K., Ruut, T., Lane, D., McKay, R., Shadbolt, B., ... Taupin, D. (2015). Infliximab reverses inflammatory muscle wasting (sarcopenia) in Crohn's disease. *Alimentary Pharmacology & Therapeutics 41*(5), 419–428. https://doi.org/10.1111/apt.13058.

Sucak, G. T., Suyanı, E., Baysal, N. A., Altındal, Ş., Çakar, M. K., Akı, Ş. Z., ... Şanlıer, N. (2012). The role of body mass index and other body composition parameters in early post-transplant complications in patients undergoing allogeneic stem cell transplantation with busulfan-cyclophosphamide conditioning. *International Journal of Hematology 95*(1), 95–101. https://doi.org/10.1007/s12185-011-0980-y.

Suzuki, K., Furuse, H., Tsuda, T., Masaki, Y., Okazawa, S., Kambara, K., ... Tobe, K. (2015). Utility of creatinine/cystatin C ratio as a predictive marker for adverse effects of chemotherapy in lung cancer: A retrospective study. *The Journal of International Medical Research 43*(4), 573–582. https://doi.org/10.1177/0300060515579116.

Takagi, K., Yoshida, R., Yagi, T., Umeda, Y., Nobuoka, D., Kuise, T., & Fujiwara, T. (2017). Radiographic sarcopenia predicts postoperative infectious complications in patients undergoing pancreaticoduodenectomy. *BMC Surgery 17*(1), 64. https://doi.org/10.1186/s12893-017-0261-7.

Takayama, K., Atagi, S., Imamura, F., Tanaka, H., Minato, K., Harada, T., ... Watanabe, K. (2016). Quality of life and survival survey of cancer cachexia in advanced non-small cell lung cancer patients-Japan nutrition and QOL survey in patients with advanced non-small cell lung cancer study. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer 24*(8), 3473–3480. https://doi.org/10.1007/s00520-016-3156-8.

Tamandl, D., Paireder, M., Asari, R., Baltzer, P. A., Schoppmann, S. F., & Ba-Ssalamah, A. (2016). Markers of sarcopenia quantified by computed tomography predict adverse long-term outcome in patients with resected oesophageal or gastro-oesophageal junction cancer. *European Radiology 26*(5), 1359–1367. https://doi.org/10.1007/s00330-015-3963-1.

Tan, B. H. L., Brammer, K., Randhawa, N., Welch, N. T., Parsons, S. L., James, E. J., & Catton, J. A. (2015). Sarcopenia is associated with toxicity in patients undergoing neo-adjuvant chemotherapy for oesophago-gastric cancer. *European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 41*(3), 333–338. https://doi.org/10.1016/j.ejso.2014.11.040.

Tan, B. H. L., Birdsell, L. A., Martin, L., Baracos, V. E., & Fearon, K. C. H. (2009). Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 15*(22), 6973–6979. https://doi.org/10.1158/1078-0432.CCR-09-1525.

Tegels, J. J. W., van Vugt, J. L. A., Reisinger, K. W., Hulsewé, K. W. E., Hoofwijk, A. G. M., Derikx, J. P. M., & Stoot, J. H. M. B. (2015). Sarcopenia is highly prevalent in patients undergoing surgery for gastric cancer but not associated with worse outcomes. *Journal of Surgical Oncology 112*(4), 403–407. https://doi.org/10.1002/jso.24015.

Temel, J. S., Abernethy, A. P., Currow, D. C., Friend, J., Duus, E. M., Yan, Y., & Fearon, K. C. (2016). 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. *The Lancet. Oncology 17*(4), 519–531. https://doi.org/10.1016/S1470-2045(15)00558-6.

Temel, J. S., Greer, J. A., Muzikansky, A., Gallagher, E. R., Admane, S., Jackson, V. A., ... Lynch, T. J. (2010). Early palliative care for patients with metastatic non–small-cell lung cancer. *New England Journal of Medicine 363*(8), 733–742. https://doi.org/10.1056/NEJMoa1000678.

Tetsuka, S., Morita, M., Ikeguchi, K., & Nakano, I. (2013). Creatinine/cystatin C ratio as a surrogate marker of residual muscle mass in amyotrophic lateral sclerosis. *Neurology and Clinical Neuroscience 1*(1), 32–37. https://doi.org/10.1002/ncn3.11.

Thompson, P. A., Rosner, G. L., Matthay, K. K., Moore, T. B., Bomgaars, L. R., Ellis, K. J., ... Berg, S. L. (2009). Impact of body composition on pharmacokinetics of doxorubicin in children: A Glaser Pediatric Research Network study. *Cancer Chemotherapy and Pharmacology 64*(2), 243–251. https://doi.org/10.1007/s00280-008-0854-z.

Thoresen, L., Frykholm, G., Lydersen, S., Ulveland, H., Baracos, V., Birdsell, L., & Falkmer, U. (2012). The association of nutritional assessment criteria with health-related quality of life in patients with advanced colorectal carcinoma. *European Journal of Cancer Care 21*(4), 505–516. https://doi.org/10.1111/j.1365-2354.2012.01327.x.

Thoresen, L., Frykholm, G., Lydersen, S., Ulveland, H., Baracos, V., Prado, C. M. M., ... Falkmer, U. (2013). Nutritional status, cachexia and survival in patients with advanced colorectal carcinoma. Different assessment criteria for nutritional status provide unequal results. *Clinical Nutrition (Edinburgh, Scotland) 32*(1), 65–72. https://doi.org/10.1016/j.clnu.2012.05.009.

Valentijn, T. M., Galal, W., Tjeertes, E. K. M., Hoeks, S. E., Verhagen, H. J., & Stolker, R. J. (2013). The obesity paradox in the surgical population. *The Surgeon: Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland 11*(3), 169–176. https://doi.org/10.1016/j.surge.2013.02.003.

Vasson, M. -P., Talvas, J., Perche, O., Dillies, A. -F., Bachmann, P., Pezet, D., ... Bouteloup, C. (2014). Immunonutrition improves functional capacities in head and neck and esophageal cancer patients undergoing radiochemotherapy: A randomized clinical trial. *Clinical Nutrition (Edinburgh, Scotland) 33*(2), 204–210. https://doi.org/10.1016/j.clnu.2013.06.008.

Veni, T., Boyas, S., Beaune, B., Bourgeois, H., Rahmani, A., Landry, S, ... Morel, B. (2018). Handgrip fatiguing exercise can provide objective assessment of cancer-related fatigue: A pilot study. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*. https://doi.org/10.1007/s00520-018-4320-0.

Versteeg, K. S., Blauwhoff-Buskermolen, S., Buffart, L. M., de van der Schueren, M. A. E., Langius, J. A. E., Verheul, H. M. W., ... Konings, I. R. (2017). Higher muscle strength is associated with prolonged survival in older patients with advanced cancer. *The Oncologist*. https://doi.org/10.1634/theoncologist.2017-0193.

Visser, M., Kritchevsky, S. B., Newman, A. B., Goodpaster, B. H., Tylavsky, F. A., Nevitt, M. C., & Harris, T. B. (2005). Lower serum albumin concentration and change in muscle mass: the Health, Aging and Body Composition Study. *The American Journal of Clinical Nutrition 82*(3), 531–537. https://doi.org/10.1093/ajcn/82.3.531.

Visser, M., Pahor, M., Taaffe, D. R., Goodpaster, B. H., Simonsick, E. M., Newman, A. B., ... Harris, T. B. (2002). Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 57*(5), M326–M332.

van Vledder, M. G., Levolger, S., Ayez, N., Verhoef, C., Tran, T. C. K., & Ijzermans, J. N. M. (2012). Body composition and outcome in patients undergoing resection of colorectal liver metastases. *The British Journal of Surgery 99*(4), 550–557. https://doi.org/10.1002/bjs.7823.

Voron, T., Tselikas, L., Pietrasz, D., Pigneur, F., Laurent, A., Compagnon, P., ... Azoulay, D. (2015). Sarcopenia impacts on short- and long-term results of hepatectomy for hepatocellular carcinoma. *Annals of Surgery 261*(6), 1173–1183. https://doi.org/10.1097/SLA.0000000000000743.

Vrieling, A., Kampman, E., Knijnenburg, N. C., Mulders, P. F., Sedelaar, J. P. M., Baracos, V. E., & Kiemeney, L. A. (2016). Body composition in relation to clinical outcomes in renal cell cancer: A systematic review and meta-analysis. *European Urology Focus*. https://doi.org/10.1016/j.euf.2016.11.009.

van Vugt, J. L. A., Braam, H. J., van Oudheusden, T. R., Vestering, A., Bollen, T. L., Wiezer, M. J., ... Boerma, D. (2015). Skeletal muscle depletion is associated with severe postoperative complications in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal cancer. *Annals of Surgical Oncology 22*(11), 3625–3631. https://doi.org/10.1245/s10434-015-4429-z.

van Vugt, J. L. A., Coebergh van den Braak, R. R. J., Schippers, H. J. W., Veen, K. M., Levolger, S., de Bruin, R. W. F., ... Willemsen, F. E. J. A. (2018). Contrast-enhancement influences skeletal muscle density, but not skeletal muscle mass, measurements on computed tomography. *Clinical Nutrition (Edinburgh, Scotland) 37*(5), 1707–1714. https://doi.org/10.1016/j.clnu.2017.07.007.

van Waart, H., Stuiver, M. M., van Harten, W. H., Geleijn, E., Kieffer, J. M., Buffart, L. M., ... Aaronson, N. K. (2015). Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: Results of the PACES randomized clinical trial. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 33*(17), 1918–1927. https://doi.org/10.1200/JCO.2014.59.1081.

Wakefield, L. M., & Hill, C. S. (2013). Beyond TGFβ: Roles of other TGFβ superfamily members in cancer. *Nature Reviews. Cancer 13*(5), 328–341. https://doi.org/10.1038/nrc3500.

Wang, G., Biswas, A. K., Ma, W., Kandpal, M., Coker, C., Grandgenett, P. M., & Acharyya, S. (2018). Metastatic cancers promote cachexia through ZIP14 upregulation in skeletal muscle. *Nature Medicine 24*(6), 770–781. https://doi.org/10.1038/s41591-018-0054-2.

Wang, S. -L., Zhuang, C. -L., Huang, D. -D., Pang, W. -Y., Lou, N., Chen, F. -F., ... Yu, Z. (2016). Sarcopenia adversely impacts postoperative clinical outcomes following gastrectomy in patients with gastric cancer: A prospective study. *Annals of Surgical Oncology 23*(2), 556–564. https://doi.org/10.1245/s10434-015-4887-3.

Wang, X., Han, H., Duan, Q., Khan, U., Hu, Y., & Yao, X. (2014). Changes of serum albumin level and systemic inflammatory response in inoperable non-small cell lung cancer patients after chemotherapy. *Journal of Cancer Research and Therapeutics 10*(4), 1019–1023. https://doi.org/10.4103/0973-1482.137953.

Waning, D. L., Mohammad, K. S., Reiken, S., Xie, W., Andersson, D. C., John, S., ... Guise, T. A. (2015). Excess TGF-β mediates muscle weakness associated with bone metastases in mice. *Nature Medicine 21*(11), 1262–1271. https://doi.org/10.1038/nm.3961.

Weeks, B. K., Gerrits, T. A. J., Horan, S. A., & Beck, B. R. (2016). Muscle size not density predicts variance in muscle strength and neuromuscular performance in healthy adult men and women. *Journal of Strength and Conditioning Research 30*(6), 1577–1584. https://doi.org/10.1519/JSC.0000000000001241.

Wells, J. C. K. (2012). Ethnic variability in adiposity, thrifty phenotypes and cardiometabolic risk: addressing the full range of ethnicity, including those of mixed ethnicity: Ethnicity, body composition and cardiometabolic risk. *Obesity Reviews 13*, 14–29. https://doi.org/10.1111/j.1467-789X.2012.01034.x.

Wendrich, A. W., Swartz, J. E., Bril, S. I., Wegner, I., de Graeff, A., Smid, E. J., ... Pothen, A. J. (2017). Low skeletal muscle mass is a predictive factor for chemotherapy dose-limiting toxicity in patients with locally advanced head and neck cancer. *Oral Oncology 71*, 26–33. https://doi.org/10.1016/j.oraloncology.2017.05.012.

Wiedenmann, B., Malfertheiner, P., Friess, H., Ritch, P., Arseneau, J., Mantovani, G., ... Von Hoff, D. (2008). A multicenter, phase II study of infliximab plus gemcitabine in pancreatic cancer cachexia. *The Journal of Supportive Oncology 6*(1), 18–25.

Wildi, S., Kleeff, J., Maruyama, H., Maurer, C. A., Büchler, M. W., & Korc, M. (2001). Overexpression of activin A in stage IV colorectal cancer. *Gut 49*(3), 409–417.

Windholz, T., Swanson, T., Vanderbyl, B. L., & Jagoe, R. T. (2014). The feasibility and acceptability of neuromuscular electrical stimulation to improve exercise performance in patients with advanced cancer: a pilot study. *BMC Palliative Care 13*, 23. https://doi.org/10.1186/1472-684X-13-23.

Wolin, K. Y., Schwartz, A. L., Matthews, C. E., Courneya, K. S., & Schmitz, K. H. (2012). Implementing the exercise guidelines for cancer survivors. *The Journal of Supportive Oncology 10*(5), 171–177. https://doi.org/10.1016/j.suponc.2012.02.001.

Wong, A. L., Seng, K. Y., Ong, E. M., Wang, L. Z., Oscar, H., Cordero, M. T., ... Lee, S. C. (2014). Body fat composition impacts the hematologic toxicities and pharmacokinetics of doxorubicin in Asian breast cancer patients. *Breast Cancer Research and Treatment 144*(1), 143–152. https://doi.org/10.1007/s10549-014-2843-8.

Xue, Q. -L. (2011). The frailty syndrome: Definition and natural history. *Clinics in Geriatric Medicine 27*(1), 1–15. https://doi.org/10.1016/j.cger.2010.08.009.

Yang, Y. X., Chong, M. S., Lim, W. S., Tay, L., Yew, S., Yeo, A., & Tan, C. H. (2017). Validity of estimating muscle and fat volume from a single MRI section in older adults with sarcopenia and sarcopenic obesity. *Clinical Radiology 72*(5), 427.e9–427.e14. https://doi.org/10.1016/j.crad.2016.12.011.

Yip, C., Goh, V., Davies, A., Gossage, J., Mitchell-Hay, R., Hynes, O., ... Mason, R. (2014). Assessment of sarcopenia and changes in body composition after neoadjuvant chemotherapy and associations with clinical outcomes in oesophageal cancer. *European Radiology 24*(5), 998–1005.

Yoshimura, Y., Wakabayashi, H., Yamada, M., Kim, H., Harada, A., & Arai, H. (2017). Interventions for treating sarcopenia: A systematic review and meta-analysis of randomized controlled studies. *Journal of the American Medical Directors Association 18*(6), 553.e1–553.e16. https://doi.org/10.1016/j.jamda.2017.03.019.

Young, J. F., Luecke, R. H., Pearce, B. A., Lee, T., Ahn, H., Baek, S., ... Taylor, S. J. (2009). Human organ/tissue growth algorithms that include obese individuals and black/white population organ weight similarities from autopsy data. *Journal of Toxicology and Environmental Health, Part A 72*(8), 527–540. https://doi.org/10.1080/15287390802647203.

Zaloga, G. P. (2006). Parenteral nutrition in adult inpatients with functioning gastrointestinal tracts: assessment of outcomes. *Lancet (London, England) 367*(9516), 1101–1111. https://doi.org/10.1016/S0140-6736(06)68307-4.

Zhao, J., Liang, Y., Yin, Q., Liu, S., Wang, Q., Tang, Y., & Cao, C. (2016). Clinical and prognostic significance of serum transforming growth factor-beta1 levels in patients with pancreatic ductal adenocarcinoma. *Brazilian Journal of Medical and Biological Research*(8), 49. https://doi.org/10.1590/1414-431X20165485.

Zhou, X., Wang, J. L., Lu, J., Song, Y., Kwak, K. S., Jiao, Q., ... Han, H. Q. (2010). Reversal of cancer cachexia and muscle wasting by ActRIIB antagonism leads to prolonged survival. *Cell 142*(4), 531–543. https://doi.org/10.1016/j.cell.2010.07.011.

Zhuang, C. -L., Huang, D. -D., Pang, W. -Y., Zhou, C. -J., Wang, S. -L., Lou, N., ... Shen, X. (2016). Sarcopenia is an independent predictor of severe postoperative complications and long-term survival after radical gastrectomy for gastric cancer: Analysis from a large-scale cohort. *Medicine 95*(13), e3164. https://doi.org/10.1097/MD.0000000000003164.