Postprint of Research Advances on Sarcopenic Obesity in Cancer

Authors: Peng Lei, Zhu Kexiang, Zhu Kexiang

Date: 2023-07-05T00:00:00+00:00

Abstract

With the increasing number of obese and elderly population subgroups worldwide, sarcopenic obesity is emerging as a factor associated with higher risks of adverse events and outcomes in multiple clinical settings, including cancer. However, there is currently a lack of consensus regarding the definition and diagnostic criteria for sarcopenic obesity, and its interplay with cancer requires further elucidation. This article systematically and comprehensively reviews the relevant definitions and diagnostic methods of sarcopenic obesity, elaborates on its specific clinical impact on cancer patients, including effects on surgical and chemotherapy patients, and briefly outlines the main prevention and treatment strategies. Based on the summarized literature, this article concludes that sarcopenic obesity has a relatively high incidence among cancer patients, but its definition and diagnostic criteria remain controversial. Sarcopenic obesity is an independent predictor of cancer prognosis and holds significant clinical utility.

Full Text

Preamble

Research Progress of Sarcopenic Obesity in Cancer

PENG Lei[1], ZHU Kexiang[2]*
[1]The First Clinical College of Medicine, Lanzhou University, Lanzhou 730000, China
[2]Department of General Surgery, the First Hospital of Lanzhou University, Lanzhou 730000, China
*Corresponding author: ZHU Kexiang, Associate Professor; E-mail: flexzhu6910@163.com

Abstract: As the number of obese and elderly individuals increases worldwide, sarcopenic obesity is increasingly associated with a higher risk of adverse events and outcomes in multiple clinical situations, including cancer. However, there

is a lack of unified definition and diagnostic criteria for sarcopenic obesity, and the interaction between sarcopenic obesity and cancer needs to be further clarified. This paper systematically and comprehensively summarizes the relevant definitions and diagnostic methods of sarcopenic obesity, discusses its clinical impact on cancer patients in detail—including the effects on patients undergoing surgery and chemotherapy—and briefly describes the main prevention and treatment strategies. This review concludes that the incidence of sarcopenic obesity is high in cancer patients, but its definition and diagnostic criteria remain controversial. Sarcopenic obesity is an independent predictor of cancer prognosis with important clinical application value.

Key words: Neoplasms; Sarcopenia; Obesity; Sarcopenic obesity; Prognosis; Review

---

Cancer represents a major global healthcare challenge. In China, the 5-year survival rate for cancer is only 40.5%, posing a serious threat to public health and imposing a heavy burden on societal development [1]. Although cancer treatments, particularly immunotherapy and adjuvant chemotherapy, have been optimized in recent years, the prognosis for cancer patients remains discouraging. Treatment-related adverse events (AEs), chemotherapy toxicity, and postoperative complications can lead to decreased quality of life [2]. Therefore, identifying novel prognostic factors is crucial for improving cancer treatment and patient outcomes.

Sarcopenia is a debilitating condition characterized by the loss of muscle mass, strength, and function, leading to impaired functional capacity and physical performance. It is highly prevalent among cancer patients [3] and has been reported to be associated with increased chemotherapy toxicity and poor prognosis in several malignancies, including gastric cancer, particularly in patients with concurrent obesity [4]. As obesity has become a global epidemic, its combination with sarcopenia has gained increasing relevance. Recently, the novel concept of sarcopenic obesity (SO) has been proposed, defined as the coexistence of sarcopenia and obesity—what Roubenoff described as the "convergence of two epidemics"[5]. Accumulating evidence suggests that SO may indicate poor prognosis in cancer patients and serves as a predictive factor for chemotherapy toxicity and postoperative complications [6-7]. SO is also closely associated with metabolic syndrome, conferring a higher risk of metabolic disorders and mortality compared with either obesity or sarcopenia alone [8]. Indeed, negative clinical outcomes associated with sarcopenic obesity include increased risks of dose-limiting toxicity, surgical complications, physical disability, and shorter survival [9]. In February 2022, expert members of the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) systematically evaluated SO-related research and jointly published the "Consensus on the Definition and Diagnostic Criteria for Sarcopenic Obesity" [10]. This review aims to provide an overview of recent advances in the definition, mechanisms, clinical relevance to cancer, and preven-

tion of SO.

Literature Search Strategy: We searched PubMed, Medline, and Web of Science using the English keywords "cancer/carcinoma," "sarcopenia," "obesity," "sarcopenic obesity," and "prognosis," and searched CNKI, Wanfang Data, and SinoMed using the Chinese keywords "癌症"(cancer), "肌肉减少症"(sarcopenia), "肥胖" (obesity), "肌肉减少性肥胖" (sarcopenic obesity), and "预后" (prognosis). The search timeframe was from database inception to February 10, 2023. Inclusion criteria: published literature, with priority given to high-quality journal articles. Exclusion criteria: (1) articles with insufficient data, duplicate publications, or unavailable full text; (2) articles of poor quality.

1 Definition and Diagnostic Criteria for Sarcopenic Obesity

According to the "Consensus on the Definition and Diagnostic Criteria for Sarcopenic Obesity" published by ESPEN and EASO, SO is defined as a clinical and functional disease characterized by the coexistence of sarcopenia and obesity, featuring high fat content, reduced skeletal muscle mass, and low skeletal muscle function [10]. Although both conditions are known to affect cancer patient prognosis and significant metabolic disorders, controversy remains regarding the extent to which their combination produces synergistic effects and whether SO itself can be considered a syndrome. Furthermore, there are currently no unified diagnostic standards or cutoff values [11].

Body composition analysis is crucial for evaluating and diagnosing SO. Multiple techniques have been developed, including bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI) [12]. While DXA and BIA are considered gold standards for assessing muscle mass, their high cost limits clinical applicability. CT, however, is widely used for cancer diagnosis and staging and enables direct analysis of body composition without requiring patients to undergo additional radiation exposure or examination time [13]. Consequently, CT-based body composition analysis has been widely applied in SO and cancer research. Studies have shown that total skeletal muscle area and visceral fat area on a single CT slice at the third lumbar vertebra (L3) strongly correlate with whole-body skeletal muscle and adipose tissue areas. Therefore, CT images at the L3 level are commonly used to objectively measure muscle and adipose tissue areas for SO evaluation and diagnosis [14].

Although CT-based body composition analysis has advanced considerably, no unified diagnostic standard for SO exists. Current literature employs two main approaches. The first involves independently defining sarcopenia and obesity, with SO diagnosed when both conditions coexist [15]. Based on previous research, total skeletal muscle area at the L3 level (TAMA) is calculated from patient CT images, and the skeletal muscle index (SMI) is derived by dividing TAMA by height squared to assess sarcopenia [16]. Due to significant sex differences in body composition, sex-specific SMI cutoff values for sarcopenia have

been proposed (Western populations: 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women [16]; Asian populations: 36.2 cm^2/m^2 for men and 29.6 cm^2/m^2 for women [17]). Obesity cutoff values also vary, with most studies defining obesity as BMI $>$ 25 kg/m^2 [18], while some use BMI $>$ 30 kg/m^2 [19]. Additionally, certain studies have defined their own cutoff values [8].

The second diagnostic approach uses the ratio of visceral fat area (VFA) to TAMA at the L3 level as a single metric for SO diagnosis. This ratio emphasizes disproportionate visceral fat content relative to muscle mass without considering total body mass [7,19]. Although no methodological consensus exists for fat mass measurement, BMI demonstrates weaker associations with long-term outcomes and prognosis compared with high fat mass (visceral obesity) in cancer patients [20]. Consequently, an increasing number of studies have incorporated fat mass or visceral fat mass rather than BMI to define SO in cancer patients [6,21]. Using this method, Jong et al. [19] defined SO as VFA/TAMA $>$ 3.2 and found a 29.6% SO prevalence among 284 pancreatic cancer patients undergoing surgery, with inflammation-associated SO being a strong predictor of postoperative pancreatic fistula (POPF). Another study established a VFA/TAMA cutoff value of 2, defining SO as VFA/TAMA $>$ 2, characterized by high visceral fat content and low muscle utilization, which was associated with postoperative mortality, POPF, and overall survival (OS) in pancreatic cancer patients [22].

Although significant variations in SO diagnosis, definition, and cutoff values across studies substantially limit the analysis, comparison, and interpretation of research findings, most studies have demonstrated that SO is a negative prognostic factor in cancer patients.

2 Interaction Mechanisms Between Sarcopenic Obesity and Cancer

The pathogenesis of SO is complex, encompassing aging, inappropriate lifestyle factors (sedentary behavior, poor diet, lack of exercise), inflammation, acute and chronic diseases, and cancer comorbidities. Concurrently, the dual burden of reduced muscle mass and function combined with fat accumulation can lead to complications such as frailty, disability, metabolic disease, postoperative complications, and chemotherapy dose-limiting toxicity in cancer patients, resulting in poor prognosis [11,23].

The mechanisms underlying the interaction between cancer and SO are not fully understood. Several factors may contribute to progressive alterations in fat metabolism and skeletal muscle, leading to SO in cancer patients, as illustrated in Figure 1 [Figure 1: see original paper].

First, cancer patients often experience inadequate food and nutrient intake, and most patients reduce their physical activity due to cancer, both of which contribute to muscle atrophy [24]. Second, cancer treatments (surgery or chemoradiotherapy) may promote the release of inflammatory cytokines, which not only enhance muscle protein degradation but also reduce synthesis, leading to insulin

and leptin resistance that causes muscle loss while exacerbating fat deposition. Conversely, muscle atrophy and loss further aggravate insulin resistance. Additionally, insulin resistance, muscle loss, and reduced physical activity lead to altered fat metabolism, which in turn affects inflammatory cytokine release [25-26]. Recent studies indicate that cancer and its treatments can cause red blood cell damage resulting in anemia, reducing blood supply to skeletal muscle and thereby causing muscle atrophy and loss [27]. A final potential factor involves various hormonal changes induced by cancer (stress hormones such as glucagon and cortisol, and anabolic hormones including growth hormone and insulin-like growth factor-I), which affect the anabolic and catabolic processes of skeletal muscle and adipose tissue, representing an important contributor to SO development in cancer patients [28]. In summary, the interaction between SO and cancer involves a complex pathophysiological process in which adipose tissue and skeletal muscle interact with tumor tissue at multiple metabolic levels, creating a vicious cycle. SO not only affects overall outcomes by modulating cancer-related metabolic disorders but may also directly promote cancer initiation and progression, ultimately leading to poor patient prognosis.

3 Clinical Impact of Sarcopenic Obesity on Cancer Patients

Obesity alone exerts numerous negative effects on cancer [29]. Concurrently, sarcopenia also increases systemic inflammation in cancer patients, thereby reducing OS and increasing postoperative complication rates [30]. Due to the combined burden of sarcopenia and obesity, SO has an even worse impact on health outcomes, potentially exerting cumulative effects [9]. Studies show that sarcopenic obese individuals have significantly higher risks of frailty and disability than non-obese individuals with similar muscle alterations [31]. This may appear contradictory to the so-called "obesity paradox," but it indicates that when obesity combines with sarcopenia, obesity does not protect against chronic disease-related mortality or improve cancer patient prognosis. Instead, SO predominantly exerts negative clinical effects on cancer patients [15]. In multiple cancer types, SO significantly impacts postoperative complications, chemotherapy toxicity, and overall survival.

3.1 Impact on Postoperative Complications

Complete surgical resection is the only curative method for prolonging survival in cancer patients. However, cancer surgeries often involve significant trauma, and postoperative complication rates are high, which may lead to escalated postoperative care (e.g., reoperation, transfer to intensive care unit) and can even be life-threatening in severe cases [32]. Recent evidence increasingly demonstrates that body composition can predict clinical outcomes in patients undergoing surgery, and these assessments are more accurate than overall changes in body weight or BMI. For example, SO has higher predictive value for postoperative complications in pancreatic cancer, as the endocrine activity of adipose tissue and reduced skeletal muscle mass and function may synergize with cancer

hormone-like mechanisms to promote inflammation and protein wasting, thereby affecting the occurrence of postoperative complications and patient prognosis [33].

Similar to sarcopenia, increased obesity, particularly elevated VFA, leads to production and secretion of pro-inflammatory adipocytokines such as leptin, tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which are involved in immune response modulation [34]. During the postoperative period, pro-inflammatory adipocytokines weaken the immune system and delay wound healing, thereby increasing the risk of postoperative complications. Moreover, skeletal muscle loss combined with increased VFA leads to chronic inflammation and insulin resistance, a key component of metabolic syndrome, which is a marker of the surgical stress response—this may explain its negative impact on surgical outcomes [6,35].

An increasing number of studies have confirmed the negative prognostic impact of SO in cancer patients and its effectiveness as a predictor of major postoperative complications [6-7,22]. Pecorelli et al. [7] analyzed 202 patients undergoing pancreatic surgery and found that SO (VFA/TAMA $>$ 3.2) was significantly associated with postoperative mortality and pancreatic fistula risk. Yamane et al. [22] also observed a significantly higher incidence of ISGPF Grade B/C pancreatic fistula in SO patients compared with non-SO patients. A retrospective analysis of 124 pancreatic cancer patients by Sandini et al. [6] similarly confirmed the predictive value of SO for major surgical complication risk: in multivariate analysis, the ratio between VFA and TAMA was the strongest predictor of major complications, with an odds ratio of 3.20.

3.2 Impact on Chemotherapy Toxicity

In recent years, increasing research interest has focused on body composition analysis as a promising simple method to identify chemotherapy toxicity in cancer patients. Chemotherapy dosing is typically determined by body surface area calculated from height and weight, a method that considers only these parameters while ignoring the relative quantity and distribution of muscle and adipose tissue—a significant limitation, as SO can mask skeletal muscle atrophy and loss, leading to greater chemotherapy toxicity and potentially severe adverse reactions [36-37]. Multiple studies have demonstrated that chemotherapy can alter body composition, reduce skeletal muscle mass and function, and promote SO development, thereby significantly impacting chemotherapy tolerance and potentially generating more adverse effects [37-38]. Prado et al. [39] showed that sarcopenia was an important predictor of dose-limiting toxicity in colon cancer patients treated with 5-fluorouracil and leucovorin. A study by Kurita et al. [36] on FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, and fluorouracil) treatment for pancreatic cancer revealed that SO was associated with increased risk of high-grade hematological toxicity. Therefore, for cancer patients with SO, it is advisable to appropriately reduce chemotherapy drug dosage to decrease toxicity and related adverse events.

Cousin et al. [37] demonstrated in a Phase I trial that low SMI was associated with dose-limiting toxicity across cancer types. A recent meta-analysis also reported associations between body composition values and chemotherapy-related toxicity, revealing significant relationships between skeletal muscle loss and hematological toxicity as well as chemotherapy discontinuation or cycle reduction [40]. Moreover, research shows that cancer patients with SO have higher risks of treatment-related toxicity and mortality [41]. Therefore, calculating chemotherapy doses based on body composition parameters such as skeletal muscle and adipose tissue, rather than conventional anthropometric methods, may effectively reduce treatment toxicity. Youn et al. [42] found that this dosing approach could predict treatment toxicity, particularly peripheral neuropathy, in metastatic pancreatic cancer patients receiving gemcitabine plus nab-paclitaxel.

3.3 Impact of Obesity and Sarcopenia on Cancer Immunotherapy

Immunotherapy aims to harness natural antitumor immune processes by stimulating the immune system to specifically target tumor cells, providing passive or active immunity against cancer [43]. Several types are currently in clinical use and development, including cancer vaccines, adoptive cell transfer therapy, and immune checkpoint blockade. Among these, immune checkpoint blockade is most widely used, with immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen-4 having become treatment options for various cancer types [44-45]. While no studies have yet examined the relationship between SO and immunotherapy efficacy in cancer patients, the individual impacts of obesity and sarcopenia on ICI efficacy have been demonstrated across multiple cancers.

3.3.1 Impact of Obesity on Immunotherapy Efficacy Although obesity is a risk factor for tumor development and is associated with accelerated tumor growth and aggressiveness, it is also linked to improved responses to cancer immunotherapy—a phenomenon known as the "obesity paradox" [46]. The relationship between obesity and cancer immunotherapy largely involves insulin resistance, elevated sex hormones, adipokine secretion regulation, and upregulated PD-1 expression [47]. Given the connection between obesity and the immune system, analyzing obesity' s impact on immune checkpoint therapy has garnered increasing interest in recent years. A retrospective cross-sectional study of 976 advanced cancer patients receiving anti-PD-1/PD-L1 immunotherapy found a significant association between obesity (BMI $\geq$ 25 kg/m^2) and improved clinical outcomes with ICIs. To validate these findings, the research team constructed an obese mouse preclinical model, confirming that T-cell dysfunction in obese mice was partially mediated by the PD-1 axis and driven by leptin, which strengthens the known correlation between the JAK/STAT pathway and immune checkpoint inhibition [48-50]. Another independent study found a linear association between increased BMI and overall survival in NSCLC patients

treated with anti-PD-L1 therapy, particularly showing significantly improved overall survival in patients with BMI $\geq$ 30 kg/m^2 [51].

3.3.2 Impact of Sarcopenia on Immunotherapy Efficacy Sarcopenia, a hallmark of all chronic diseases including cancer, has been highlighted as an important predictor of poor prognosis in cancer patients receiving PD-1 inhibitor immunotherapy. A multicenter real-world study found that sarcopenic NSCLC patients treated with nivolumab had shorter progression-free survival (PFS) and overall survival (OS) compared with non-sarcopenic patients [52]. Recent studies have also reported that sarcopenia is associated with shorter PFS in metastatic melanoma, liver cancer, and gastric cancer patients receiving cancer immunotherapy [53-55]. In summary, sarcopenia is a significant predictor of poor prognosis across multiple advanced cancer types treated with PD-1 blockade.

The relationship between sarcopenia and poor immunotherapy outcomes is currently thought to involve several factors. First, chronic inflammation is a primary cause of sarcopenia and promotes tumor immune escape, such as T-cell exhaustion. Second, certain biomarkers implicated in sarcopenia development (e.g., transforming growth factor-β (TGF-β) and IL-6) weaken tumor responses to immune checkpoint inhibitors [56]. Therefore, measuring sarcopenia may help identify various cancer patient types who can benefit from immunotherapy.

3.4 Impact on Survival

Multiple studies have demonstrated that SO is positively associated with shorter OS in both operable and inoperable cancer patients [7,57]. In a study specifically examining OS, SO was an important predictor of OS in gastrointestinal (gastric cancer, pancreatic cancer, etc.) and respiratory tract cancer patients [58]. Additionally, a retrospective analysis of 465 patients who underwent primary hepatectomy for hepatocellular carcinoma found that SO patients had worse median survival and median recurrence-free survival [59]. A study by Chargi et al. [60] also confirmed that SO is a negative prognostic factor for both OS and disease-free survival.

4 Prevention and Treatment Strategies for Sarcopenic Obesity

Despite the current lack of consensus on definition and diagnostic criteria, mounting evidence globally indicates that SO is an important clinically relevant factor in cancer patients. Chemotherapy dose calculation based on body composition assessment may help reduce treatment-related toxicity and ultimately improve patient prognosis. Moreover, CT image-based body composition assessment can be easily implemented in clinical settings and may help identify cancer patients with poor prognosis, enabling early intervention through nutritional or exercise therapy to reduce skeletal muscle loss and adipose tissue

accumulation, thereby improving clinical outcomes and potentially increasing survival rates.

4.1 Nutritional Therapy

Recently, a clinical trial for cachexia confirmed the importance of nutritional therapy, demonstrating that nutritional supplementation can maintain or increase skeletal muscle mass to improve prognosis and quality of life in cancer patients with SO [61]. Indeed, maintaining adequate nutritional status can help restore muscle mass and function, thereby reducing postoperative morbidity and mortality in cancer patients with SO, representing a potential strategy for SO prevention and treatment. However, scientific evidence and experimental studies on the preventive and therapeutic effects of nutritional therapy for SO remain scarce [62].

A randomized controlled trial showed that adequate nutritional support (whey protein, vitamin D, and calcium) was associated with improved muscle mass and function in community-dwelling older men [63]. A recent review by Prado et al. [64] also discussed the role of nutritional therapy in preventing and reversing sarcopenia in cancer patients, an approach that may also be applicable to SO. Research has demonstrated that cancer patients retain adequate anabolic potential for muscle protein synthesis, and protein intake timing affects muscle protein synthesis: a study in young adults found that constant protein intake throughout the day enhanced daily muscle protein synthesis compared with uneven protein distribution [65]. Although nutritional therapy appears potentially associated with improved clinical outcomes in SO patients, no interventional studies have been conducted, and specific evidence is lacking.

4.2 Exercise Therapy

In addition to nutritional intervention, exercise therapy may be a key strategy for reversing SO. Resistance training and general exercise interventions (including aerobic, flexibility, and balance training) have been shown to improve muscle mass and function while reducing adipose tissue accumulation, thereby mitigating some negative effects of SO in cancer patients [66]. Although exercise therapy may be challenging for cancer patients due to various factors (including fatigue and cancer-related pain), growing evidence emphasizes the benefits of exercise training in restoring skeletal muscle mass and function and reducing adipose tissue accumulation in the cancer setting [67]. Therefore, further research should focus on investigating its potential clinical relevance, alone or in combination with nutritional therapy, particularly for cancer patients with SO.

Author Contributions: Peng Lei was responsible for study design, conceptualization, literature collection and organization, and manuscript writing; Zhu Kexiang was responsible for manuscript revision, quality control, and final review and takes overall responsibility for the article; all authors confirmed the final version of the manuscript. This article has no conflicts of interest.

(Received: April 8, 2023; Revised: June 27, 2023)

References

[1] WU C C, LI M N, MENG H B, et al. Analysis of status and countermeasures of cancer incidence and mortality in China[J]. Sci China Life Sci, 2019, 62(5): 640-647. DOI: 10.1007/s11427-

[2] TAKEDA T, SASAKI T, OKAMOTO T, et al. Prognostic impact of osteosarcopenia in patients with advanced pancreatic cancer receiving gemcitabine plus nab-paclitaxel[J]. Pancreatology, 2023, 23(3): 275-282. DOI: 10.1016/j.pan.2023.02.002.

[3] CRUZ-JENTOFT A J, BAHAT G, BAUER J, et al. Sarcopenia: revised European consensus on definition and diagnosis[J]. Age Ageing, 2019, 48(4): 601. DOI: 10.1093/ageing/afz046.

[4] CHAN M Y, CHOK K S H. Sarcopenia in pancreatic cancer - effects on surgical outcomes and chemotherapy[J]. World J Gastrointest Oncol, 2019, 11(7): 527-537. DOI: 10.4251/wjgo.v11.i7.527.

[5] ROUBENOFF R. Excess baggage: sarcopenia, obesity, and cancer outcomes[J]. Lancet Oncol, 2008, 9(7): 605-607. DOI: 10.1016/S1470-2045(08)70160-8.

[6] SANDINI M, BERNASCONI D P, FIOR D, et al. A high visceral adipose tissue-to-skeletal muscle ratio as a determinant of major complications after pancreatoduodenectomy for cancer[J]. Nutrition, 2016, 32(11/12): 1231-1237. DOI: 10.1016/j.nut.2016.04.002.

[7] PECORELLI N, CARRARA G, DE COBELLI F, et al. Effect of sarcopenia and visceral obesity on mortality and pancreatic fistula following pancreatic cancer surgery[J]. Br J Surg, 2016, 103(4): 434-442. DOI: 10.1002/bjs.10063.

[8] KIM Y M, KIM J H, BAIK S J, et al. Sarcopenia and sarcopenic obesity as novel risk factors for gastric carcinogenesis: a health checkup cohort study[J]. Front Oncol, 2019, 9: 1249. DOI: 10.3389/fonc.2019.01249.

[9] CARNEIRO I P, MAZURAK V C, PRADO C M. Clinical implications of sarcopenic obesity in cancer[J]. Curr Oncol Rep, 2016, 18(10): 62. DOI: 10.1007/s11912-016-0546-5.

[10] DONINI L M, BUSETTO L, BISCHOFF S C, et al. Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO consensus statement[J]. Obes Facts, 2022, 15(3): 321-335. DOI: 10.1159/000521241.

[11] BARACOS V E, ARRIBAS L. Sarcopenic obesity: hidden muscle wasting and its impact for survival and complications of cancer therapy[J]. Ann Oncol, 2018, 29(Suppl 2): ii1-9. DOI: 10.1093/annonc/mdx810.

[12] MIJNARENDS D M, MEIJERS J M M, HALFENS R J G, et al. Validity and reliability of tools to measure muscle mass, strength, and physical performance in community-dwelling older people: a systematic review[J]. J Am Med Dir Assoc, 2013, 14(3): 170-178. DOI: 10.1016/j.jamda.2012.10.009.

[13] FARON A, SPRINKART A M, KUETTING D L R, et al. Body composition analysis using CT and MRI: intra-individual intermodal comparison of muscle mass and myosteatosis[J]. Sci Rep, 2020, 10(1): 11765. DOI: 10.1038/s41598-020-68797-3.

[14] MOURTZAKIS M, PRADO C M M, LIEFFERS J R, et al. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care[J]. Appl Physiol Nutr Metab, 2008, 33(5): 997-1006. DOI: 10.1139/H08-075.

[15] MONTANO-LOZA A J, ANGULO P, MEZA-JUNCO J, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis[J]. J Cachexia Sarcopenia Muscle, 2016, 7(2): 126-135. DOI: 10.1002/jcsm.12039.

[16] PRADO C M M, LIEFFERS J R, MCCARGAR L J, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study[J]. Lancet Oncol, 2008, 9(7): 629-635. DOI: 10.1016/S1470-2045(08)70153-0.

[17] CHO W K, YU J I, PARK H C, et al. Impact of sarcopenia on survival of pancreatic cancer patients treated with concurrent chemoradiotherapy[J]. Tumori, 2021, 107(3): 247-253. DOI: 10.1177/0300891620937795.

[18] SUGAWARA K, YAMASHITA H, OKUMURA Y, et al. Relationships among body composition, muscle strength, and sarcopenia in esophageal squamous cell carcinoma patients[J]. Support Care Cancer, 2020, 28(6): 2797-2803. DOI: 10.1007/s00520-019-05110-7.

[19] JANG M, PARK H W, HUH J, et al. Predictive value of sarcopenia and visceral obesity for postoperative pancreatic fistula after pancreaticoduodenectomy analyzed on clinically acquired CT and MRI[J]. Eur Radiol, 2019, 29(5): 2417-2425. DOI: 10.1007/s00330-018-5790-7.

[20] RICKLES A S, IANNUZZI J C, MIRONOV O, et al. Visceral obesity and colorectal cancer: are we missing the boat with BMI?[J]. J Gastrointest Surg, 2013, 17(1): 133-143; discussion p.143. DOI: 10.1007/s11605-012-2045-9.

[21] KIMURA Y, YAMADA M, OHJI S, et al. Presence of sarcopenic obesity and evaluation of the associated muscle quality in Japanese older men with prostate cancer undergoing androgen deprivation therapy[J]. J Geriatr Oncol, 2019, 10(5): 835-838. DOI: 10.1016/j.jgo.2019.03.017.

[22] YAMANE H, ABE T, AMANO H, et al. Visceral adipose tissue and skeletal muscle index distribution predicts severe pancreatic fistula development after

pancreaticoduodenectomy[J]. Anticancer Res, 2018, 38(2): 1061-1066. DOI: 10.21873/anticanres.12323.

[23] BATSIS J A, VILLAREAL D T. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies[J]. Nat Rev Endocrinol, 2018, 14(9): 513-537. DOI: 10.1038/s41574-018-0062-9.

[24] FACCIORUSSO A, ANTONINO M, MUSCATIELLO N. Sarcopenia represents a negative prognostic factor in pancreatic cancer patients undergoing EUS celiac plexus neurolysis[J]. Endosc Ultrasound, 2020, 9(4): 238-244. DOI: 10.4103/eus.eus_{{{24}}_{{20}}}.

[25] KHAN I M, PERRARD X Y, BRUNNER G, et al. Intermuscular and perimuscular fat expansion in obesity correlates with skeletal muscle T cell and macrophage infiltration and insulin resistance[J]. Int J Obes (Lond), 2015, 39(11): 1607-1618. DOI: 10.1038/ijo.2015.104.

[26] BHULLAR A S, ANOVEROS-BARRERA A, DUNICHAND-HOEDL A, et al. Lipid is heterogeneously distributed in muscle and associates with low radiodensity in cancer patients[J]. J Cachexia Sarcopenia Muscle, 2020, 11(3): 735-747. DOI: 10.1002/jcsm.12533.

[27] MINTZIRAS I, MILIGKOS M, WÄCHTER S, et al. Sarcopenia and sarcopenic obesity are significantly associated with poorer overall survival in patients with pancreatic cancer: systematic review and meta-analysis[J]. Int J Surg, 2018, 59: 19-26. DOI: 10.1016/j.ijsu.2018.09.014.

[28] BIOLO G, CEDERHOLM T, MUSCARITOLI M. Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: from sarcopenic obesity to cachexia[J]. Clin Nutr, 2014, 33(5): 737-748. DOI: 10.1016/j.clnu.2014.03.007.

[29] DOYLE S L, LYSAGHT J, REYNOLDS J V. Obesity and post-operative complications in patients undergoing non-bariatric surgery[J]. Obes Rev, 2010, 11(12): 875-886. DOI: 10.1111/j.1467-789X.2009.00700.x.

[30] REISINGER K W, DERIKX J P M, VAN VUGT J L A, et al. Sarcopenia is associated with an increased inflammatory response to surgery in colorectal cancer[J]. Clin Nutr, 2016, 35(4): 924-927. DOI: 10.1016/j.clnu.2015.07.005.

[31] BEAVERS K M, HSU F C, HOUSTON D K, et al. The role of metabolic syndrome, adiposity, and inflammation in physical performance in the Health ABC Study[J]. J Gerontol A Biol Sci Med Sci, 2013, 68(5): 617-623. DOI: 10.1093/gerona/gls213.

[32] 胰腺癌诊疗规范 (2018 年版) [J]. 中华消化病与影像杂志 (电子版) , 2019, 9(5): 224-240. DOI: 10.3877/cma.j.issn.1674-1935.2019.05.008.

[33] ARGILÉS J M, BUSQUETS S, STEMMLER B, et al. Cachexia and sarcopenia: mechanisms and potential targets for intervention[J]. Curr Opin Pharmacol, 2015, 22: 100-106. DOI: 10.1016/j.coph.2015.04.003.

[34] TILG H, MOSCHEN A R. Adipocytokines: mediators linking adipose tissue, inflammation and immunity[J]. Nat Rev Immunol, 2006, 6(10): 772-783. DOI: 10.1038/nri1937.

[35] SATO H, CARVALHO G, SATO T, et al. The association of preoperative glycemic control, intraoperative insulin sensitivity, and outcomes after cardiac surgery[J]. J Clin Endocrinol Metab, 2010, 95(9): 4338-4344. DOI: 10.1210/jc.2010-0135.

[36] KURITA Y, KOBAYASHI N, TOKUHISA M, et al. Sarcopenia is a reliable prognostic factor in patients with advanced pancreatic cancer receiving FOLFIRINOX chemotherapy[J]. Pancreatology, 2019, 19(1): 127-135. DOI: 10.1016/j.pan.2018.11.001.

[37] COUSIN S, HOLLEBECQUE A, KOSCIELNY S, et al. Low skeletal muscle is associated with toxicity in patients included in phase I trials[J]. Invest New Drugs, 2014, 32(2): 382-387. DOI: 10.1007/s10637-013-0053-6.

[38] YIP C, GOH V, DAVIES A, et al. Assessment of sarcopenia and changes in body composition after neoadjuvant chemotherapy and associations with clinical outcomes in oesophageal cancer[J]. Eur Radiol, 2014, 24(5): 998-1005. DOI: 10.1007/s00330-014-3143-6.

[39] PRADO C M M, BARACOS V E, MCCARGAR L J, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity[J]. Clin Cancer Res, 2007, 13(11): 3264-3268. DOI: 10.1158/1078-0432.CCR-06-3067.

[40] EMORI T, ITONAGA M, ASHIDA R, et al. Impact of sarcopenia on prediction of progression-free survival and overall survival of patients with pancreatic ductal adenocarcinoma receiving first-line gemcitabine and nab-paclitaxel chemotherapy[J]. Pancreatology, 2022, 22(2): 277-285. DOI: 10.1016/j.pan.2021.12.013.

[41] TSAI S. Importance of lean body mass in the oncologic patient[J]. Nutr Clin Pract, 2012, 27(5): 593-598. DOI: 10.1177/0884533612457949.

[42] YOUN S, CHEN A, HA V, et al. An exploratory study of body composition as a predictor of dose-limiting toxicity in metastatic pancreatic cancer treated with gemcitabine plus nab-paclitaxel[J]. Clin Nutr, 2021, 40(8): 4888-4892. DOI: 10.1016/j.clnu.2021.06.026.

[43] BAXEVANIS C N, PEREZ S A, PAPAMICHAIL M. Cancer immunotherapy[J]. Crit Rev Clin Lab Sci, 2009, 46(4): 167-189. DOI: 10.1080/10408360902937809.

[44] YOUSEFI H, YUAN J D, KESHAVARZ-FATHI M, et al. Immunotherapy of cancers comes of age[J]. Expert Rev Clin Immunol, 2017, 13(10): 1001-1015. DOI: 10.1080/1744666X.2017.1366315.

[45] CHENG A L, HSU C, CHAN S L, et al. Challenges of combination therapy

with immune checkpoint inhibitors for hepatocellular carcinoma[J]. J Hepatol, 2020, 72(2): 307-319. DOI: 10.1016/j.jhep.2019.09.025.

[46] PASQUARELLI-DO-NASCIMENTO G, MACHADO S A, DE CARVALHO J M A, et al. Obesity and adipose tissue impact on T-cell response and cancer immune checkpoint blockade therapy[J]. Immunother Adv, 2022, 2(1): ltac015. DOI: 10.1093/immadv/ltac015.

[47] CLOUGHESY T F, MOCHIZUKI A Y, ORPILLA J R, et al. Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma[J]. Nat Med, 2019, 25(3): 477-486. DOI: 10.1038/s41591-018-0337-7.

[48] CORTELLINI A, BERSANELLI M, BUTI S, et al. A multicenter study of body mass index in cancer patients treated with anti-PD-1/PD-L1 immune checkpoint inhibitors: when overweight becomes favorable[J]. J Immunother Cancer, 2019, 7(1): 57. DOI: 10.1186/s40425-019-0527-y.

[49] WANG Z M, AGUILAR E G, LUNA J I, et al. Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade[J]. Nat Med, 2019, 25(1): 141-151. DOI: 10.1038/s41591-018-0221-5.

[50] MULLEN M, GONZALEZ-PEREZ R R. Leptin-induced JAK/STAT signaling and cancer growth[J]. Vaccines, 2016, 4(3): 26. DOI: 10.3390/vaccines4030026.

[51] KICHENADASSE G, MINERS J O, MANGONI A A, et al. Association between body mass index and overall survival with immune checkpoint inhibitor therapy for advanced non-small cell lung cancer[J]. JAMA Oncol, 2020, 6(4): 512-518. DOI: 10.1001/jamaoncol.2019.5241.

[52] CORTELLINI A, BOZZETTI F, PALUMBO P, et al. Weighing the role of skeletal muscle mass and muscle density in cancer patients receiving PD-1/PD-L1 checkpoint inhibitors: a multicenter real-life study[J]. Sci Rep, 2020, 10(1): 1456. DOI: 10.1038/s41598-020-58498-2.

[53] DALY L E, POWER D G, O'REILLY A, et al. The impact of body composition parameters on ipilimumab toxicity and survival in patients with metastatic melanoma[J]. Br J Cancer, 2017, 116(3): 310-317. DOI: 10.1038/bjc.2016.431.

[54] GUO Y S, REN Y Q, WU F H, et al. Prognostic impact of sarcopenia in patients with hepatocellular carcinoma treated with PD-1 inhibitor[J]. Therap Adv Gastroenterol, 2022, 15: 17562848221142417. DOI: 10.1177/17562848221142417.

[55] KANO M, HIHARA J, TOKUMOTO N, et al. Association between skeletal muscle loss and the response to nivolumab immunotherapy in advanced gastric cancer patients[J]. Int J Clin Oncol, 2021, 26(3): 523-531. DOI: 10.1007/s10147-020-01833-4.

[56] SHIROYAMA T, NAGATOMO I, KOYAMA S, et al. Impact of sarcopenia in patients with advanced non-small cell lung cancer treated with PD-1 inhibitors: a preliminary retrospective study[J]. Sci Rep, 2019, 9(1): 2447. DOI: 10.1038/s41598-019-39120-6.

[57] TOZUKA Y, UENO M, KOBAYASHI S, et al. Prognostic significance of sarcopenia as determined by bioelectrical impedance analysis in patients with advanced pancreatic cancer receiving gemcitabine plus nab-paclitaxel: a retrospective study[J]. Oncol Lett, 2022, 24(4): 375. DOI: 10.3892/ol.2022.13495.

[58] LODEWICK T M, VAN NIJNATTEN T J A, VAN DAM R M, et al. Are sarcopenia, obesity and sarcopenic obesity predictive of outcome in patients with colorectal liver metastases?[J]. HPB, 2015, 17(5): 438-446. DOI: 10.1111/hpb.12373.

[59] KOBAYASHI A, KAIDO T, HAMAGUCHI Y, et al. Impact of sarcopenic obesity on outcomes in patients undergoing hepatectomy for hepatocellular carcinoma[J]. Ann Surg, 2019, 269(5): 924-931. DOI: 10.1097/SLA.0000000000002555.

[60] CHARGI N, BRIL S I, SWARTZ J E, et al. Skeletal muscle mass is an imaging biomarker for decreased survival in patients with oropharyngeal squamous cell carcinoma[J]. Oral Oncol, 2020, 101: 104519. DOI: 10.1016/j.oraloncology.2019.104519.

[61] SOLHEIM T S, LAIRD B J A, BALSTAD T R, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer[J]. J Cachexia Sarcopenia Muscle, 2017, 8(5): 778-788. DOI: 10.1002/jcsm.12201.

[62] RICHTER E, DENECKE A, KLAPDOR S, et al. Parenteral nutrition support for patients with pancreatic cancer—improvement of the nutritional status and the therapeutic outcome[J]. Anticancer Res, 2012, 32(5): 2111-2118.

[63] KEMMLER W, KOHL M, FRÖHLICH M, et al. Effects of high-intensity resistance training on osteopenia and sarcopenia parameters in older men with osteosarcopenia-one-year results of the randomized controlled Franconian osteopenia and sarcopenia trial (FrOST)[J]. J Bone Miner Res, 2020, 35(9): 1634-1644. DOI: 10.1002/jbmr.4027.

[64] PRADO C M, PURCELL S A, LAVIANO A. Nutrition interventions to treat low muscle mass in cancer[J]. J Cachexia Sarcopenia Muscle, 2020, 11(2): 366-380. DOI: 10.1002/jcsm.12525.

[65] WITARD O C, WARDLE S L, MACNAUGHTON L S, et al. Protein considerations for optimising skeletal muscle mass in healthy young and older adults[J]. Nutrients, 2016, 8(4): 181. DOI: 10.3390/nu8040181.

[66] FLOREZ BEDOYA C A, CARDOSO A C F, PARKER N, et al. Exercise during preoperative therapy increases tumor vascularity in pancreatic tumor patients[J]. Sci Rep, 2019, 9(1): 13966. DOI: 10.1038/s41598-019-49582-3.

[67] KIRK B, ZANKER J, DUQUE G. Osteosarcopenia: epidemiology, diagnosis, and treatment-facts and numbers[J]. J Cachexia Sarcopenia Muscle, 2020, 11(3): 609-618. DOI: 10.1002/jcsm.12567.

Note: Figure translations are in progress. See original paper for figures.