**Name of Journal: *World Journal of Gastrointestinal Oncology***

**Manuscript NO: 46048**

**Manuscript Type: MINIREVIEWS**

**Sarcopenia in pancreatic cancer – effects on surgical outcomes and chemotherapy**

Chan MY & Chok KSH. Sarcopenia in pancreatic cancer

**Miu Yee Chan, Kenneth Siu Ho Chok**

**Miu Yee Chan,** Department of Surgery, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, China

**Kenneth Siu Ho Chok,** Department of Surgery and State Key Laboratory for Liver Research, The University of Hong Kong, Hong Kong, China

**ORCID number:** Miu Yee Chan (0000-0001-5527-1471); Kenneth Siu Ho Chok (0000-0001-7921-3807).

**Author contributions:** Chan MY performed the literature review and drafted the manuscript; Chok KSH was responsible for the concept and supervision of the study and final approval of the manuscript.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Corresponding author: Kenneth Siu Ho Chok, FRCS (Ed), Associate Professor,** Department of Surgery and State Key Laboratory for Liver Research, The University of Hong Kong, 102 Pok Fu Lam Road, Hong Kong, China. Chok6275@hku.hk

**Telephone:** +852-22553025

**Received:** January 26, 2019

**Peer-review started:** January 28, 2019

**First decision:** April 15, 2019

**Revised:** April 23, 2019

**Accepted:** May 21, 2019

**Article in press:** May 22, 2019

**Published online:** July 15, 2019

**Abstract**

Sarcopenia is found in up to 65% of pancreatic cancer patients. The definition and diagnostic methods for sarcopenia have changed over the years, and the measurement of skeletal muscle mass with cross-sectional imaging has become the most popular way of assessment, although the parameters measured vary among different studies. It is still debatable that there is an association between sarcopenia and postoperative pancreatic fistula, but most studies showed a higher risk in patients with sarcopenic obesity. Long-term survival is worse in sarcopenic patients, as shown by meta-analysis. Sarcopenia is also associated with decreased survival and higher toxicity in patients receiving chemotherapy, and chemotherapy also tends to potentiate sarcopenia. Treatment for sarcopenia still remains an area for research, although oral supplements, nutritional modifications and exercise training have been shown to improve sarcopenia.

**Key words:** Sarcopenia; Pancreatic cancer; Clinical outcomes; Surgical outcomes; Chemotherapy; Radiotherapy

**© The Author(s) 2019.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Sarcopenia is a common condition found in pancreatic cancer patients. There is growing evidence showing that sarcopenia is associated with worse survival outcomes. This article summarizes the current evidence for the definition and diagnosis of sarcopenia, as well as its relationship with surgical outcomes, survival and chemotherapy.

**Citation:** Chan MY, Chok KSH. Sarcopenia in pancreatic cancer – effects on surgical outcomes and chemotherapy. *World J Gastrointest Oncol* 2019; 11(7): 527-537

**URL:** https://www.wjgnet.com/1948-5204/full/v11/i7/527.htm

**DOI:** https://dx.doi.org/10.4251/wjgo.v11.i7.527

**INTRODUCTION**

The topic of sarcopenia in pancreatic cancer has come under the spotlight in the past decade. With the updates on several consensus statements, including those from the Asian Working Group for Sarcopenia in 2016[[1](#_ENREF_1)] and European Working Group on Sarcopenia in Older People (EWGSOP) in 2018[[2](#_ENREF_2)], it is now known that sarcopenia is a condition that not only relates to age but is also affected by multiple factors, such as systemic inflammation, physical inactivity, and inadequate intake. The relationship between pancreatic cancer and cachexia has long been recognized, but it is only in the last decade that researchers have started to understand the importance of sarcopenia.

Pancreatic cancer is one of the most deadly malignancies worldwide, with a 5-year survival of only about 5%, despite numerous efforts to improve various therapeutic strategies over the decades[[3](#_ENREF_3)]. It has become the third leading cause of cancer-related deaths in the United States and is projected to become the second by 2030[[4](#_ENREF_4)]. Among pancreatic cancer patients, those who have undergone resection have much better survival rates than those who are unresectable[[5](#_ENREF_5)]. Unfortunately, less than one-fifth of patients with this malignancy are considered resectable[[3](#_ENREF_3)]. The low resection rate is due to unfavorable tumor stage and location and also to comorbidities and poor functional performance of patients[[6](#_ENREF_6)]. In pancreatic cancer patients, poor oral intake, altered metabolism due to malignancy, and malabsorption because of obstruction or exocrine insufficiency can all come into play at the same time and contribute to both cachexia and sarcopenia[[7](#_ENREF_7)]. These in turn worsen the patients’ performance status and their suitability for surgery.

In various studies, the prevalence of sarcopenia in pancreatic cancer patients ranges from 30% to 65%[[8-10](#_ENREF_8)]. The wide variation is likely due to the heterogeneous groups of patients, difference in disease stage, and different methods of measuring sarcopenia[[1](#_ENREF_1),[7](#_ENREF_7),[11](#_ENREF_11)]. Despite these variations, it has been repeatedly shown that sarcopenia patients are more likely to have poorer outcomes[[12-14](#_ENREF_12)]. This article aims to examine the current evidence on sarcopenia, as well as its impact on the management of patients with pancreatic ductal adenocarcinoma.

**DEFINITION OF SARCOPENIA**

# Since the term “sarcopenia” was coined by Rosenberg[[15](#_ENREF_15)] in 1997, remarkable progress has been made in understanding this condition and its relationship with malignancies and surgery. Instead of merely detecting the decline in muscle mass, EWGSOP redefined the condition in 2010 as the syndrome characterized by progressive and generalized loss of both skeletal muscle mass and quality (strength or performance) with a risk of adverse outcomes[[16](#_ENREF_16)]. In the latest consensus by EWGSOP in 2018[[2](#_ENREF_2)], muscle strength has come to the forefront in the diagnosis. From the evolution of the definition, it is clear that more emphasis has been put on muscle quality over quantity over the years. Similar definitions have been put forward by other groups, including the International Working Group on Sarcopenia[[17](#_ENREF_17)], the European Society for Clinical Nutrition and Metabolism (ESPEN) Special Interest Group[[18](#_ENREF_18)], the Society of Sarcopenia, Cachexia and Wasting Disorders[[19](#_ENREF_19)], and the Asian Working Group for Sarcopenia[[20](#_ENREF_20)]. According to these definitions, the assessment of both muscle quantity and muscle quality is required when diagnosing sarcopenia (Table 1).

**ASSESSMENT OF SARCOPENIA IN PANCREATIC CANCER PATIENTS**

Despite the relatively unified definition from different consensus groups, there is a wide array of assessment tools for sarcopenia. Each tool differs in applicability in research settings, clinical settings and primary care settings. Since different studies utilized different tools for assessment and there is no unified cut-off value, the interpretation and comparison of results across different studies is particularly difficult.

The traditional way to determine appendicular lean muscle mass is dual-energy X-ray absorptiometry[[21-23](#_ENREF_21)]. However, it is less sensitive in evaluating intramuscular fat, which can make up 5%-15% of muscle mass in obese people[[24](#_ENREF_24)]. Other methods such as bioimpedance analysis and urinary metabolites have also been mentioned in the literature[[25](#_ENREF_25)] but are subject to error. As most patients diagnosed with pancreatic cancer would have had cross-sectional imaging such as computed tomography or magnetic resonance imaging, most of the studies used these scanning methods to diagnose sarcopenia. Both computed tomography and magnetic resonance imaging have been shown to be more sensitive to small changes in muscle area than dual-energy X-ray absorptiometry[[23](#_ENREF_23),[26](#_ENREF_26)] and are now considered to be the gold standard for evaluating muscle mass[[27](#_ENREF_27)].

There are a number of measurements that can be taken from cross-sectional imaging. The areas of fat, fat-free and lean muscle can be calculated with the specific Hounsfield unit[[27](#_ENREF_27)] and then converted into whole-body fat mass, fat-free mass and lean muscle mass[[28](#_ENREF_28)]. The most commonly used landmark is the cross-sectional area of muscle at the L3 vertebra, and there are studies showing that the measurement at this level significantly correlates with whole-body muscle mass[[28](#_ENREF_28),[29](#_ENREF_29)]. There are also other measurements such as the cross-sectional area of the psoas muscle[[30](#_ENREF_30)] and the volume of the psoas muscle[[31](#_ENREF_31)], but some researchers opined that these measurements might not be representative enough to be a surrogate marker, as the psoas muscle is a minor muscle[[32](#_ENREF_32)]. It is important to examine which measurement was used in a study, as well as whether the results were adjusted for height, weight or body mass index. As suggested by EWGSOP[[2](#_ENREF_2)] and the ESPEN Special Interest Group[[18](#_ENREF_18)], the cut-off point for the measurements should be more than two standard deviations below the mean reference value of healthy young adults of the same sex and same ethnicity.

As mentioned above, sarcopenia is not only defined by a decrease in muscle mass. As in osteoporosis, where an increase in bone mass does not necessarily translate into a lower fracture risk, an increase in muscle mass does not translate into better physical performance. Physical performance is a combination of many aspects, and muscle quantity is only a small part of it. Other aspects, including muscle quality, strength, power, motor control and coordination all play a part. Therefore, a decline in muscle strength or power should be documented. There are simple methods to assess muscle strength and power, such as handgrip strength with dynamometry and sit-to-stand time[[2](#_ENREF_2),[33](#_ENREF_33)]. According to EWGSOP in 2018[[2](#_ENREF_2)], physical performance should also be assessed by a test such as gait speed, 400-meter walk test, or the short physical performance battery[[34](#_ENREF_34)]. Although there may be certain limitations in these tests, like in patients with mobility problems due to orthopedic or neurological problems, attempts should be made to include these parameters when discussing sarcopenia. However, in the current available studies on pancreatic cancer patients, these parameters were rarely included (Table 1). Therefore, the true prevalence of sarcopenia in the study populations may still be unknown.

**IMPACT OF SARCOPENIA**

Surgical resection remains as the only potentially curative treatment for pancreatic cancer. The evolvement of operative techniques and perioperative care has lowered the perioperative mortality rate to 3%-5% at high-volume centers and the morbidity rate to about 40%[[35](#_ENREF_35)]. Despite the advances in surgery and the combination of chemotherapy and radiotherapy, the median survival after resection and chemotherapy is only around 30 mo, with a 5-year survival rate of around 30%[[36](#_ENREF_36),[37](#_ENREF_37)]. Therefore, there has been ongoing research trying to identify the risk factors for such poor outcomes, and sarcopenia is a factor being investigated.

***Surgery***

**Perioperative outcomes:** A study by Peng *et al*[[14](#_ENREF_14)] in 2012 is one of the earliest studies reporting the relationship between sarcopenia and surgical outcomes of pancreatic cancer. The study included 557 patients who underwent pancreatic surgery for pancreatic cancer, and 139 of them (25.0%) were found to be sarcopenic after measurement of their total psoas area. Sarcopenic and non-sarcopenic patients had no statistically significant difference in hospital stay, intensive care unit stay, or overall morbidity rate. Sarcopenia was not associated with increased hazard of 90-d mortality [hazard ratio [HR] 2.31, 95% confidence interval (CI): 0.78–6.77; *P* = 0.13].

Such discrepancy in results was likely partially due to the different assessment parameters used. It is important to bear this in mind when interpreting results from different studies. For example, Pecorelli *et al*[[38](#_ENREF_38)] reported that sarcopenia, as defined by Prado *et al*[[39](#_ENREF_39)] using total abdominal muscle area (TAMA), was not a significant prognostic factor for 60-d postoperative mortality (*P* = 0.224). However, the ratio of visceral fat area (VFA) to TAMA was found to be a significant predictor for 60-d mortality when the ratio was > 3.2 in multivariable analysis [odds ratio (OR) 6.76, 95%CI: 2.41-18.99; *P* < 0.001]. Similarly in another study by Amini *et al*[[31](#_ENREF_31)], total psoas volume was used instead of total psoas area in patients who underwent curative surgery. With a different assessment tool, they were able to show that sarcopenia was associated with adverse short-term outcomes. While sarcopenia based on total psoas area was not associated with morbidity after operation (OR 1.06, 95%CI: 0.77-1.47; *P* = 0.72), sarcopenia based on total psoas volume was found to be associated with a significantly higher complication risk (OR 1.79, 95%CI: 1.25-2.56; *P* = 0.002) and significantly longer intensive care unit stay (*P* = 0.002).

Meta-analysis by Ratnayake *et al*[[40](#_ENREF_40)] reported that there was no statistical difference in the incidence of delayed gastric emptying (sarcopenic 19% *vs* non-sarcopenic 17%, 95%CI: 0.80-1.29; *P* = 0.895), postoperative bile leakage (sarcopenic 7% *vs* non-sarcopenic 7%, 95%CI: 0.61-1.71; *P* = 0.933), surgical site infection (sarcopenic 17% *vs* non-sarcopenic 22%, 95%CI: 0.75-1.16; *P* = 0.518), or morbidity of Clavien-Dindo grade 3 or above (sarcopenic 30% *vs* non-sarcopenic 24%, 95%CI: 0.86-1.14; *P* = 0.869). The only significant difference was in postoperative hospital stay, which was longer in the sarcopenic group (mean difference 0.73 d, 95%CI: 0.06-1.40; *P* = 0.033). However, some studies in this meta-analysis included patients receiving pancreatic surgery for both benign and malignant conditions, and not all studies used the same parameters to diagnose sarcopenia. Overall, the impact of sarcopenia on short-term surgical outcomes did not seem significant, but further research in this area is needed to have a more definitive answer.

**Postoperative pancreatic fistula:** Postoperative pancreatic fistula (POPF) is one of the most concerning complications in patients undergoing pancreatic surgery. There were a number of studies that examined the relationship between sarcopenia and pancreatic fistula. Nishida *et al*[[41](#_ENREF_41)] measured the skeletal muscle index [skeletal muscle area at L3/(body height)2] of 266 patients who underwent pancreatoduodenectomy. A total of 61.3% of patients had pancreatic malignancy. The authors reported a significantly higher rate of major complications (Clavien-Dindo grade 3 and above) and, specifically, a higher rate of POPF (sarcopenic 22.0% *vs* non-sarcopenic 10.4%; *P* = 0.011) in sarcopenia patients. Sarcopenia was also a significant independent risk factor for clinically relevant POPF (OR 2.869, 95%CI: 1.329-6.197; *P* = 0.007) in multivariate analysis taking into account factors including body mass index, presence of pancreatic tumor, portal vein or superior mesenteric vein resection, diameter of the pancreatic duct, and consistency of the pancreas.

In the study by Pecorelli *et al*[[38](#_ENREF_38)] in 2016, 202 patients who underwent pancreatoduodenectomy were included. The VFA and TAMA at L3 on computed tomography were measured. A high VFA-to-TAMA ratio was associated with 60-d mortality by multivariate analysis (OR 6.76, 95%CI: 2.41-18.99; *P* < 0.001). Only a large VFA, but not TAMA or VFA-to-TAMA ratio, was associated with POPF (OR 4.05, 95%CI: 1.85-8.84; *P* < 0.001). Although a relationship between TAMA and POPF could not be identified, a VFA-to-TAMA ratio > 3.2 was shown to be predictive of a higher mortality risk (OR 6.33, 95%CI: 1.37-29.21; *P* = 0.018) in the subgroup of patients with major complications.

In the meta-analysis by Ratnayake *et al*[[40](#_ENREF_40)], which included 13 studies involving 3608 patients, six studies reported on POPF. There was no difference in the incidence of POPF between the sarcopenic and non-sarcopenic groups [risk ratio (RR) 1.05, 95%CI: 0.68-1.61; *P* = 0.843]. Two of these studies reported on patients with sarcopenic obesity. Yamane *et al*[[42](#_ENREF_42)] analyzed the ratio of visceral adipose tissue area to skeletal muscle index of 99 patients who underwent pancreaticoduodenectomy. Multivariate analysis showed that a ratio ≥ 2.0 was one of the independent risk factors associated with clinically significant POPF (grade B or C). In another study by Sandini *et al*[[43](#_ENREF_43)], the VFA-to-TAMA ratio was measured in 124 patients. It was reported that the rate of POPF was slightly higher in patients with sarcopenic obesity after pancreaticoduodenectomy, but it did not reach statistical significance (46.7% *vs* 32.3%; *P* = 0.103). This may imply that sarcopenia alone is not associated with POPF, but patients with sarcopenic obesity may have a higher risk of POPF.

**Long-term survival:** In the study by Peng *et al*[[14](#_ENREF_14)] in 2012 cited above, the 3-year survival rates of men (non-sarcopenic 39.2% *vs* sarcopenic 20.3%; *P* < 0.05) and women (non-sarcopenic 40.8% *vs* sarcopenic 26.1%; *P* < 0.05) were both significantly lower in the sarcopenic group. Sarcopenia was found to be associated with 3-year mortality in both univariate (HR 1.68, 95%CI: 1.34-2.11; *P* < 0.001) and multivariate analyses (HR 1.63, 95%CI: 1.28-2.07; *P* < 0.001)[[44](#_ENREF_44)].

Table 2 is a summary of long-term survival outcomes in sarcopenic patients from eight studies. In the study by Amini *et al*[[31](#_ENREF_31)], a low total psoas volume was found to be associated with worse survival (HR 1.72, 95%CI: 1.36-2.19; *P* < 0.001). Similar results were obtained by Okumura *et al*[[45](#_ENREF_45)], who used the total psoas index at umbilical level rather than at L3. Overall survival and disease-free survival were both significantly lower in the sarcopenic group (median overall survival: sarcopenic 17.7 mo *vs* non-sarcopenic 33.2 mo; *P* < 0.001; actual median disease-free survival not available; *P* < 0.001). There were also studies that did not find any significant difference between sarcopenic and non-sarcopenic patients, such as the studies by Joglekar *et al*[[46](#_ENREF_46)] and Van Dijk *et al*[[47](#_ENREF_47)].

Most of the studies in Table 2 used measurements from total psoas area or total psoas index for comparison. However, the cut-off points for sarcopenia varied widely. Some studies, such as the one by Van Dijk *et al*[[47](#_ENREF_47)], did not find any significant results with more commonly used parameters (TAMA) but had significant findings using values derived from computed tomography (radiation attenuation of skeletal muscle). Whether this indicates a low sensitivity of the initial parameter requires further investigation.

Mintziras *et al*[[48](#_ENREF_48)] conducted a meta-analysis including 11 studies of pancreatic cancer and sarcopenia and concluded that the hazard of death was 1.4 times higher in sarcopenic patients (summary adjusted HR 1.35, 95%CI: 1.18-1.54), and the hazard was even higher for patients with sarcopenic obesity (summary adjusted HR 2.01, 95%CI: 1.55-2.61). Nevertheless, studies on both palliative and curative surgeries were included in this meta-analysis. Some studies also included pathologies other than pancreatic cancer.

***The vicious cycle of sarcopenia and chemotherapy***

Most of the available studies on chemotherapy for pancreatic cancer reported a poorer response and worse survival in sarcopenic patients[[49](#_ENREF_49),[50](#_ENREF_50)]. In the study by Dalal *et al*[[9](#_ENREF_9)], patients with inoperable locally advanced pancreatic cancer received bevacizumab in combination with capecitabine and radiation. An increased loss in skeletal muscle index of more than 3.8% was found to be associated with poorer survival (*P* = 0.02). The effect on survival was especially obvious in sarcopenic obesity. Pretreatment sarcopenic obesity was significantly associated with overall survival (*P* = 0.04) in the study by Cooper *et al*[[51](#_ENREF_51)]. Patients with sarcopenia or obesity alone also had a shorter median survival, but the difference did not reach statistical significance. In the retrospective study by Kays *et al*[[49](#_ENREF_49)], six out of 53 patients with advanced pancreatic cancer treated with FOLFIRINOX were found to have sarcopenic obesity. This group of patients had a significantly shorter median overall survival when compared with the rest of the cohort (10.4 mo *vs* 16.1 mo; *P* = 0.04).

It has been well reported that chemotherapy for other cancers affects the body composition throughout the treatment course[[52-54](#_ENREF_52)]. It was estimated that patients undergoing chemotherapy for pancreatic cancer experienced a relative muscle loss of 2.9% every 100 d (95%CI: -5.2--0.8; *P* = 0.01)[[55](#_ENREF_55)]. This rate of muscle loss is much greater than that in a healthy adult, who generally loses muscle at a rate of 1%–1.4% per year[[56](#_ENREF_56),[57](#_ENREF_57)]. The muscle-loss effect is especially prominent in the case of neoadjuvant chemotherapy. It was reported that the relative mean difference in loss of muscle mass was 4.5% more in patients receiving neoadjuvant chemotherapy than in those having palliative chemotherapy[[55](#_ENREF_55)]. From this, one may postulate that the effect of muscle loss is not from disease progress alone, but from the chemotherapy as well.

Not only does chemotherapy potentiate sarcopenia, sarcopenia also increases the toxicity of chemotherapy[[58](#_ENREF_58),[59](#_ENREF_59)]. This is likely due to the fact that the dosage of chemotherapy is largely dependent on the patient’s height and weight (*i.e.* body surface area), with the change in body composition factored out[[60-62](#_ENREF_60)]. Patients with sarcopenia tend to receive a higher dose of chemotherapeutic agent for a relatively small lean muscle mass and are thus more likely to suffer toxicity. Such a relationship is not limited to a specific tumor type or chemotherapy. In a phase 1 trial by Cousin *et al*[[63](#_ENREF_63)], a low skeletal muscle index was the only factor associated with dose-limiting toxicity, regardless of cancer type. With a higher incidence of toxicity, there is also a higher incidence of treatment termination and hospitalization. This implies that the current method of dosage calculation still has room for improvement. The optimal way of adjustment for sarcopenia when prescribing chemotherapeutic agents is still an area for further research.

**DISCUSSION**

Assessment of nutritional status of cancer patients has evolved from a simple “eyeballing test” at bedside to sophisticated tests, such as bioelectrical impedance analysis and lean muscle mass calculation from various imaging studies. In order to identify patients with sarcopenia and provide timely intervention, a more proactive approach should be employed. Proper assessment of sarcopenia should be incorporated into the management of pancreatic cancer. Ideally, all patients receiving imaging studies can be screened for sarcopenia, but this requires special software and trained personnel. Even without those sophisticated measures, measurements from simple tests, such as hand grip strength, gait speed and bioelectrical impedance, can be obtained relatively easily in clinical settings.

In spite of all the knowledge of sarcopenia and its relationship with oncology, there is still no optimal treatment to reverse sarcopenia. On the one hand, cancer patients need adequate amounts of protein intake for anabolism, but on the other hand, excessive energy intake may potentiate obesity[[64](#_ENREF_64)]. Sarcopenic obesity has been shown to have a more deleterious effect on outcomes. The endocrine activity of visceral adipose tissue may work synergistically with cancer hormone-like mechanisms and protein wasting[[65](#_ENREF_65)]. Therefore, a careful balance of nutrition intake is crucial in the management of sarcopenia and sarcopenic obesity.

In additional to nutritional modification, exercise intervention is also beneficial in reversing sarcopenia. Resistance training intervention and compound exercise intervention (a blend of aerobic, resistance, flexibility and balance training) have been shown to improve muscle mass and/or physical performance[[11](#_ENREF_11)]. However, these training programs were mainly conducted in community-dwelling elderly people. They would be challenging for cancer patients due to various reasons, including fatigue and cancer-related pain.

With a better understanding of sarcopenia, clinical strategies should be revolutionized to identify and combat the condition once a patient is diagnosed with pancreatic cancer. Screening for sarcopenia in this group of patients should be made a routine practice. They should be referred to respective allied health professionals for early optimization, with reassessment at regular intervals if surgery is pending. A dedicated multidisciplinary team consisting of surgeons, oncologists, nurses, dietitians and physiotherapists will be needed.

To conclude, sarcopenia is prevalent in pancreatic cancer patients and is associated with worse survival outcomes after surgical resection and chemotherapy. In particular, sarcopenic obesity has higher morbidity and mortality risks, including the risk of POPF. The relationship between sarcopenia and other short-term surgical outcomes still remain unclear, as different studies used different cut-off values and diagnostic methods. With the latest guidelines and consensus, it is hoped that more standardized reporting can be used in upcoming studies so that good quality level 1 studies can be conducted.

REFERENCES

1 **Chen LK**, Lee WJ, Peng LN, Liu LK, Arai H, Akishita M; Asian Working Group for Sarcopenia. Recent Advances in Sarcopenia Research in Asia: 2016 Update From the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc* 2016; **17**: 767.e1-767.e7 [PMID: 27372539 DOI: 10.1016/j.jamda.2016.05.016]

2 **Cruz-Jentoft AJ**, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2 . Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019; **48**: 16-31 [PMID: 30312372 DOI: 10.1093/ageing/afy169]

3 **Wolfgang CL**, Herman JM, Laheru DA, Klein AP, Erdek MA, Fishman EK, Hruban RH. Recent progress in pancreatic cancer. *CA Cancer J Clin* 2013; **63**: 318-348 [PMID: 23856911 DOI: 10.3322/caac.21190]

4 **Rahib L**, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014; **74**: 2913-2921 [PMID: 24840647 DOI: 10.1158/0008-5472.CAN-14-0155]

5 **Ducreux M**, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, Seufferlein T, Haustermans K, Van Laethem JL, Conroy T, Arnold D; ESMO Guidelines Committee. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; **26 Suppl 5**: v56-v68 [PMID: 26314780 DOI: 10.1093/annonc/mdv295]

6 **Huang L**, Jansen L, Balavarca Y, Molina-Montes E, Babaei M, van der Geest L, Lemmens V, Van Eycken L, De Schutter H, Johannesen TB, Fristrup CW, Mortensen MB, Primic-Žakelj M, Zadnik V, Becker N, Hackert T, Mägi M, Cassetti T, Sassatelli R, Grützmann R, Merkel S, Gonçalves AF, Bento MJ, Hegyi P, Lakatos G, Szentesi A, Moreau M, van de Velde T, Broeks A, Sant M, Minicozzi P, Mazzaferro V, Real FX, Carrato A, Molero X, Besselink MG, Malats N, Büchler MW, Schrotz-King P, Brenner H. Resection of pancreatic cancer in Europe and USA: an international large-scale study highlighting large variations. *Gut* 2019; **68**: 130-139 [PMID: 29158237 DOI: 10.1136/gutjnl-2017-314828]

7 **Pamoukdjian F**, Bouillet T, Lévy V, Soussan M, Zelek L, Paillaud E. Prevalence and predictive value of pre-therapeutic sarcopenia in cancer patients: A systematic review. *Clin Nutr* 2018; **37**: 1101-1113 [PMID: 28734552 DOI: 10.1016/j.clnu.2017.07.010]

8 **Tan BH**, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res* 2009; **15**: 6973-6979 [PMID: 19887488 DOI: 10.1158/1078-0432.CCR-09-1525]

9 **Dalal S**, Hui D, Bidaut L, Lem K, Del Fabbro E, Crane C, Reyes-Gibby CC, Bedi D, Bruera E. Relationships among body mass index, longitudinal body composition alterations, and survival in patients with locally advanced pancreatic cancer receiving chemoradiation: a pilot study. *J Pain Symptom Manage* 2012; **44**: 181-191 [PMID: 22695045 DOI: 10.1016/j.jpainsymman.2011.09.010]

10 **Ozola Zalite I**, Zykus R, Francisco Gonzalez M, Saygili F, Pukitis A, Gaujoux S, Charnley RM, Lyadov V. Influence of cachexia and sarcopenia on survival in pancreatic ductal adenocarcinoma: a systematic review. *Pancreatology* 2015; **15**: 19-24 [PMID: 25524484 DOI: 10.1016/j.pan.2014.11.006]

11 **Cruz-Jentoft AJ**, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, Chen LK, Fielding RA, Martin FC, Michel JP, Sieber C, Stout JR, Studenski SA, Vellas B, Woo J, Zamboni M, Cederholm T. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). *Age Ageing* 2014; **43**: 748-759 [PMID: 25241753 DOI: 10.1093/ageing/afu115]

12 **Souza Cunha M**, Wiegert EVM, Calixto-Lima L, Oliveira LC. Relationship of nutritional status and inflammation with survival in patients with advanced cancer in palliative care. *Nutrition* 2018; **51-52**: 98-103 [PMID: 29625409 DOI: 10.1016/j.nut.2017.12.004]

13 **Di Sebastiano KM**, Yang L, Zbuk K, Wong RK, Chow T, Koff D, Moran GR, Mourtzakis M. Accelerated muscle and adipose tissue loss may predict survival in pancreatic cancer patients: the relationship with diabetes and anaemia. *Br J Nutr* 2013; **109**: 302-312 [PMID: 23021109 DOI: 10.1017/S0007114512001067]

14 **Peng P**, Hyder O, Firoozmand A, Kneuertz P, Schulick RD, Huang D, Makary M, Hirose K, Edil B, Choti MA, Herman J, Cameron JL, Wolfgang CL, Pawlik TM. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. *J Gastrointest Surg* 2012; **16**: 1478-1486 [PMID: 22692586 DOI: 10.1007/s11605-012-1923-5]

15 **Rosenberg IH**. Sarcopenia: origins and clinical relevance. *J Nutr* 1997; **127**: 990S-991S [PMID: 9164280 DOI: 10.1093/jn/127.5.990S]

16 **Cruz-Jentoft AJ**, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M; European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010; **39**: 412-423 [PMID: 20392703 DOI: 10.1093/ageing/afq034]

17 **Fielding RA**, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, Abellan van Kan G, Andrieu S, Bauer J, Breuille D, Cederholm T, Chandler J, De Meynard C, Donini L, Harris T, Kannt A, Keime Guibert F, Onder G, Papanicolaou D, Rolland Y, Rooks D, Sieber C, Souhami E, Verlaan S, Zamboni M. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *J Am Med Dir Assoc* 2011; **12**: 249-256 [PMID: 21527165 DOI: 10.1016/j.jamda.2011.01.003]

18 **Muscaritoli M**, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, Boirie Y, Bosaeus I, Cederholm T, Costelli P, Fearon KC, Laviano A, Maggio M, Rossi Fanelli F, Schneider SM, Schols A, Sieber CC. 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". *Clin Nutr* 2010; **29**: 154-159 [PMID: 20060626 DOI: 10.1016/j.clnu.2009.12.004]

19 **Morley JE**, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, Cederholm T, Coats AJ, Cummings SR, Evans WJ, Fearon K, Ferrucci L, Fielding RA, Guralnik JM, Harris TB, Inui A, Kalantar-Zadeh K, Kirwan BA, Mantovani G, Muscaritoli M, Newman AB, Rossi-Fanelli F, Rosano GM, Roubenoff R, Schambelan M, Sokol GH, Storer TW, Vellas B, von Haehling S, Yeh SS, Anker SD; Society on Sarcopenia, Cachexia and Wasting Disorders Trialist Workshop. Sarcopenia with limited mobility: an international consensus. *J Am Med Dir Assoc* 2011; **12**: 403-409 [PMID: 21640657 DOI: 10.1016/j.jamda.2011.04.014]

20 **Chen LK**, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, Chou MY, Chen LY, Hsu PS, Krairit O, Lee JS, Lee WJ, Lee Y, Liang CK, Limpawattana P, Lin CS, Peng LN, Satake S, Suzuki T, Won CW, Wu CH, Wu SN, Zhang T, Zeng P, Akishita M, Arai H. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc* 2014; **15**: 95-101 [PMID: 24461239 DOI: 10.1016/j.jamda.2013.11.025]

21 **Heymsfield SB**, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, Pierson RN Jr. Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. *Am J Clin Nutr* 1990; **52**: 214-218 [PMID: 2375286 DOI: 10.1093/ajcn/52.2.214]

22 **Baumgartner RN**, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, Garry PJ, Lindeman RD. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998; **147**: 755-763 [PMID: 9554417 DOI: 10.1093/oxfordjournals.aje.a009520]

23 **Chen Z**, Wang Z, Lohman T, Heymsfield SB, Outwater E, Nicholas JS, Bassford T, LaCroix A, Sherrill D, Punyanitya M, Wu G, Going S. Dual-energy X-ray absorptiometry is a valid tool for assessing skeletal muscle mass in older women. *J Nutr* 2007; **137**: 2775-2780 [PMID: 18029498 DOI: 10.1093/jn/137.12.2775]

24 **Plank LD**. Dual-energy X-ray absorptiometry and body composition. *Curr Opin Clin Nutr Metab Care* 2005; **8**: 305-309 [PMID: 15809534 DOI: 10.1097/01.mco.0000165010.31826.3d]

25 **Heymsfield SB**, Gonzalez MC, Lu J, Jia G, Zheng J. Skeletal muscle mass and quality: evolution of modern measurement concepts in the context of sarcopenia. *Proc Nutr Soc* 2015; **74**: 355-366 [PMID: 25851205 DOI: 10.1017/S0029665115000129]

26 **Delmonico MJ**, Kostek MC, Johns J, Hurley BF, Conway JM. Can dual energy X-ray absorptiometry provide a valid assessment of changes in thigh muscle mass with strength training in older adults? *Eur J Clin Nutr* 2008; **62**: 1372-1378 [PMID: 17684523 DOI: 10.1038/sj.ejcn.1602880]

27 **Beaudart C**, McCloskey E, Bruyère O, Cesari M, Rolland Y, Rizzoli R, Araujo de Carvalho I, Amuthavalli Thiyagarajan J, Bautmans I, Bertière MC, Brandi ML, Al-Daghri NM, Burlet N, Cavalier E, Cerreta F, Cherubini A, Fielding R, Gielen E, Landi F, Petermans J, Reginster JY, Visser M, Kanis J, Cooper C. Sarcopenia in daily practice: assessment and management. *BMC Geriatr* 2016; **16**: 170 [PMID: 27716195 DOI: 10.1186/s12877-016-0349-4]

28 **Mourtzakis M**, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* 2008; **33**: 997-1006 [PMID: 18923576 DOI: 10.1139/H08-075]

29 **Fearon K**, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S, Baracos VE. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011; **12**: 489-495 [PMID: 21296615 DOI: 10.1016/S1470-2045(10)70218-7]

30 **Hanaoka M**, Yasuno M, Ishiguro M, Yamauchi S, Kikuchi A, Tokura M, Ishikawa T, Nakatani E, Uetake H. Morphologic change of the psoas muscle as a surrogate marker of sarcopenia and predictor of complications after colorectal cancer surgery. *Int J Colorectal Dis* 2017; **32**: 847-856 [PMID: 28190101 DOI: 10.1007/s00384-017-2773-0]

31 **Amini N**, Spolverato G, Gupta R, Margonis GA, Kim Y, Wagner D, Rezaee N, Weiss MJ, Wolfgang CL, Makary MM, Kamel IR, Pawlik TM. Impact Total Psoas Volume on Short- and Long-Term Outcomes in Patients Undergoing Curative Resection for Pancreatic Adenocarcinoma: a New Tool to Assess Sarcopenia. *J Gastrointest Surg* 2015; **19**: 1593-1602 [PMID: 25925237 DOI: 10.1007/s11605-015-2835-y]

32 **Rutten IJG**, Ubachs J, Kruitwagen RFPM, Beets-Tan RGH, Olde Damink SWM, Van Gorp T. Psoas muscle area is not representative of total skeletal muscle area in the assessment of sarcopenia in ovarian cancer. *J Cachexia Sarcopenia Muscle* 2017; **8**: 630-638 [PMID: 28513088 DOI: 10.1002/jcsm.12180]

33 **Cooper C**, Fielding R, Visser M, van Loon LJ, Rolland Y, Orwoll E, Reid K, Boonen S, Dere W, Epstein S, Mitlak B, Tsouderos Y, Sayer AA, Rizzoli R, Reginster JY, Kanis JA. Tools in the assessment of sarcopenia. *Calcif Tissue Int* 2013; **93**: 201-210 [PMID: 23842964 DOI: 10.1007/s00223-013-9757-z]

34 **Guralnik JM**, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994; **49**: M85-M94 [PMID: 8126356 DOI: 10.1093/geronj/49.2.M85]

35 **Hartwig W**, Werner J, Jäger D, Debus J, Büchler MW. Improvement of surgical results for pancreatic cancer. *Lancet Oncol* 2013; **14**: e476-e485 [PMID: 24079875 DOI: 10.1016/S1470-2045(13)70172-4]

36 **Neoptolemos JP**, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, Faluyi O, O'Reilly DA, Cunningham D, Wadsley J, Darby S, Meyer T, Gillmore R, Anthoney A, Lind P, Glimelius B, Falk S, Izbicki JR, Middleton GW, Cummins S, Ross PJ, Wasan H, McDonald A, Crosby T, Ma YT, Patel K, Sherriff D, Soomal R, Borg D, Sothi S, Hammel P, Hackert T, Jackson R, Büchler MW; European Study Group for Pancreatic Cancer. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017; **389**: 1011-1024 [PMID: 28129987 DOI: 10.1016/S0140-6736(16)32409-6]

37 **Strobel O**, Neoptolemos J, Jäger D, Büchler MW. Optimizing the outcomes of pancreatic cancer surgery. *Nat Rev Clin Oncol* 2019; **16**: 11-26 [PMID: 30341417 DOI: 10.1038/s41571-018-0112-1]

38 **Pecorelli N**, Carrara G, De Cobelli F, Cristel G, Damascelli A, Balzano G, Beretta L, Braga M. Effect of sarcopenia and visceral obesity on mortality and pancreatic fistula following pancreatic cancer surgery. *Br J Surg* 2016; **103**: 434-442 [PMID: 26780231 DOI: 10.1002/bjs.10063]

39 **Prado CM**, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, Baracos VE. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 2008; **9**: 629-635 [PMID: 18539529 DOI: 10.1016/S1470-2045(08)70153-0]

40 **Ratnayake CB**, Loveday BP, Shrikhande SV, Windsor JA, Pandanaboyana S. Impact of preoperative sarcopenia on postoperative outcomes following pancreatic resection: A systematic review and meta-analysis. *Pancreatology* 2018; **18**: 996-1004 [PMID: 30287167 DOI: 10.1016/j.pan.2018.09.011]

41 **Nishida Y**, Kato Y, Kudo M, Aizawa H, Okubo S, Takahashi D, Nakayama Y, Kitaguchi K, Gotohda N, Takahashi S, Konishi M. Preoperative Sarcopenia Strongly Influences the Risk of Postoperative Pancreatic Fistula Formation After Pancreaticoduodenectomy. *J Gastrointest Surg* 2016; **20**: 1586-1594 [PMID: 27126054 DOI: 10.1007/s11605-016-3146-7]

42 **Yamane H**, Abe T, Amano H, Hanada K, Minami T, Kobayashi T, Fukuda T, Yonehara S, Nakahara M, Ohdan H, Noriyuki T. Visceral Adipose Tissue and Skeletal Muscle Index Distribution Predicts Severe Pancreatic Fistula Development After Pancreaticoduodenectomy. *Anticancer Res* 2018; **38**: 1061-1066 [PMID: 29374741 DOI: 10.21873/anticanres.12323]

43 **Sandini M**, Bernasconi DP, Fior D, Molinelli M, Ippolito D, Nespoli L, Caccialanza R, Gianotti L. A high visceral adipose tissue-to-skeletal muscle ratio as a determinant of major complications after pancreatoduodenectomy for cancer. *Nutrition* 2016; **32**: 1231-1237 [PMID: 27261062 DOI: 10.1016/j.nut.2016.04.002]

44 **Peng PD**, van Vledder MG, Tsai S, de Jong MC, Makary M, Ng J, Edil BH, Wolfgang CL, Schulick RD, Choti MA, Kamel I, Pawlik TM. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. *HPB (Oxford)* 2011; **13**: 439-446 [PMID: 21689226 DOI: 10.1111/j.1477-2574.2011.00301.x]

45 **Okumura S**, Kaido T, Hamaguchi Y, Fujimoto Y, Masui T, Mizumoto M, Hammad A, Mori A, Takaori K, Uemoto S. Impact of preoperative quality as well as quantity of skeletal muscle on survival after resection of pancreatic cancer. *Surgery* 2015; **157**: 1088-1098 [PMID: 25799468 DOI: 10.1016/j.surg.2015.02.002]

46 **Joglekar S**, Asghar A, Mott SL, Johnson BE, Button AM, Clark E, Mezhir JJ. Sarcopenia is an independent predictor of complications following pancreatectomy for adenocarcinoma. *J Surg Oncol* 2015; **111**: 771-775 [PMID: 25556324 DOI: 10.1002/jso.23862]

47 **van Dijk DP**, Bakens MJ, Coolsen MM, Rensen SS, van Dam RM, Bours MJ, Weijenberg MP, Dejong CH, Olde Damink SW. Low skeletal muscle radiation attenuation and visceral adiposity are associated with overall survival and surgical site infections in patients with pancreatic cancer. *J Cachexia Sarcopenia Muscle* 2017; **8**: 317-326 [PMID: 27897432 DOI: 10.1002/jcsm.12155]

48 **Mintziras I**, Miligkos M, Wächter S, Manoharan J, Maurer E, Bartsch DK. Sarcopenia and sarcopenic obesity are significantly associated with poorer overall survival in patients with pancreatic cancer: Systematic review and meta-analysis. *Int J Surg* 2018; **59**: 19-26 [PMID: 30266663 DOI: 10.1016/j.ijsu.2018.09.014]

49 **Kays JK**, Shahda S, Stanley M, Bell TM, O'Neill BH, Kohli MD, Couch ME, Koniaris LG, Zimmers TA. Three cachexia phenotypes and the impact of fat-only loss on survival in FOLFIRINOX therapy for pancreatic cancer. *J Cachexia Sarcopenia Muscle* 2018; **9**: 673-684 [PMID: 29978562 DOI: 10.1002/jcsm.12307]

50 **Kurita Y**, Kobayashi N, Tokuhisa M, Goto A, Kubota K, Endo I, Nakajima A, Ichikawa Y. Sarcopenia is a reliable prognostic factor in patients with advanced pancreatic cancer receiving FOLFIRINOX chemotherapy. *Pancreatology* 2019; **19**: 127-135 [PMID: 30473464 DOI: 10.1016/j.pan.2018.11.001]

51 **Cooper AB**, Slack R, Fogelman D, Holmes HM, Petzel M, Parker N, Balachandran A, Garg N, Ngo-Huang A, Varadhachary G, Evans DB, Lee JE, Aloia T, Conrad C, Vauthey JN, Fleming JB, Katz MH. Characterization of Anthropometric Changes that Occur During Neoadjuvant Therapy for Potentially Resectable Pancreatic Cancer. *Ann Surg Oncol* 2015; **22**: 2416-2423 [PMID: 25519927 DOI: 10.1245/s10434-014-4285-2]

52 **Freedman RJ**, Aziz N, Albanes D, Hartman T, Danforth D, Hill S, Sebring N, Reynolds JC, Yanovski JA. Weight and body composition changes during and after adjuvant chemotherapy in women with breast cancer. *J Clin Endocrinol Metab* 2004; **89**: 2248-2253 [PMID: 15126549 DOI: 10.1210/jc.2003-031874]

53 **Yip C**, Goh V, Davies A, Gossage J, Mitchell-Hay R, Hynes O, Maisey N, Ross P, Gaya A, Landau DB, Cook GJ, Griffin N, Mason R. Assessment of sarcopenia and changes in body composition after neoadjuvant chemotherapy and associations with clinical outcomes in oesophageal cancer. *Eur Radiol* 2014; **24**: 998-1005 [PMID: 24535076 DOI: 10.1007/s00330-014-3110-4]

54 **Davis MP**, Panikkar R. Sarcopenia associated with chemotherapy and targeted agents for cancer therapy. *Ann Palliat Med* 2019; **8**: 86-101 [PMID: 30525762 DOI: 10.21037/apm.2018.08.02]

55 **Daly LE**, Ní Bhuachalla ÉB, Power DG, Cushen SJ, James K, Ryan AM. Loss of skeletal muscle during systemic chemotherapy is prognostic of poor survival in patients with foregut cancer. *J Cachexia Sarcopenia Muscle* 2018; **9**: 315-325 [PMID: 29318756 DOI: 10.1002/jcsm.12267]

56 **Frontera WR**, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R. Aging of skeletal muscle: a 12-yr longitudinal study. *J Appl Physiol (1985)* 2000; **88**: 1321-1326 [PMID: 10749826 DOI: 10.1152/jappl.2000.88.4.1321]

57 **Goodpaster BH**, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, Simonsick EM, Tylavsky FA, Visser M, Newman AB. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci* 2006; **61**: 1059-1064 [PMID: 17077199 DOI: 10.1093/gerona/61.10.1059]

58 **Sjøblom B**, Grønberg BH, Benth JŠ, Baracos VE, Fløtten Ø, Hjermstad MJ, Aass N, Jordhøy M. Low muscle mass is associated with chemotherapy-induced haematological toxicity in advanced non-small cell lung cancer. *Lung Cancer* 2015; **90**: 85-91 [PMID: 26198373 DOI: 10.1016/j.lungcan.2015.07.001]

59 **Tan BH**, Brammer K, Randhawa N, Welch NT, Parsons SL, James EJ, Catton JA. Sarcopenia is associated with toxicity in patients undergoing neo-adjuvant chemotherapy for oesophago-gastric cancer. *Eur J Surg Oncol* 2015; **41**: 333-338 [PMID: 25498359 DOI: 10.1016/j.ejso.2014.11.040]

60 **Gusella M**, Toso S, Ferrazzi E, Ferrari M, Padrini R. Relationships between body composition parameters and fluorouracil pharmacokinetics. *Br J Clin Pharmacol* 2002; **54**: 131-139 [PMID: 12207632 DOI: 10.1046/j.1365-2125.2002.01598.x]

61 **Bozzetti F**. Forcing the vicious circle: sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. *Ann Oncol* 2017; **28**: 2107-2118 [PMID: 28911059 DOI: 10.1093/annonc/mdx271]

62 **Hopkins JJ**, Sawyer MB. A review of body composition and pharmacokinetics in oncology. *Expert Rev Clin Pharmacol* 2017; **10**: 947-956 [PMID: 28649898 DOI: 10.1080/17512433.2017.1347503]

63 **Cousin S**, Hollebecque A, Koscielny S, Mir O, Varga A, Baracos VE, Soria JC, Antoun S. Low skeletal muscle is associated with toxicity in patients included in phase I trials. *Invest New Drugs* 2014; **32**: 382-387 [PMID: 24343673 DOI: 10.1007/s10637-013-0053-6]

64 **Prado CM**, Cushen SJ, Orsso CE, Ryan AM. Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact. *Proc Nutr Soc* 2016; **75**: 188-198 [PMID: 26743210 DOI: 10.1017/S0029665115004279]

65 **Argilés JM**, Busquets S, Stemmler B, López-Soriano FJ. Cachexia and sarcopenia: mechanisms and potential targets for intervention. *Curr Opin Pharmacol* 2015; **22**: 100-106 [PMID: 25974750 DOI: 10.1016/j.coph.2015.04.003]

66 **Onesti JK**, Wright GP, Kenning SE, Tierney MT, Davis AT, Doherty MG, Chung MH. Sarcopenia and survival in patients undergoing pancreatic resection. *Pancreatology* 2016; **16**: 284-289 [PMID: 26876798 DOI: 10.1016/j.pan.2016.01.009]

67 **Ninomiya G**, Fujii T, Yamada S, Yabusaki N, Suzuki K, Iwata N, Kanda M, Hayashi M, Tanaka C, Nakayama G, Sugimoto H, Koike M, Fujiwara M, Kodera Y. Clinical impact of sarcopenia on prognosis in pancreatic ductal adenocarcinoma: A retrospective cohort study. *Int J Surg* 2017; **39**: 45-51 [PMID: 28110029 DOI: 10.1016/j.ijsu.2017.01.075]

68 **Sugimoto M**, Farnell MB, Nagorney DM, Kendrick ML, Truty MJ, Smoot RL, Chari ST, Moynagh MR, Petersen GM, Carter RE, Takahashi N. Decreased Skeletal Muscle Volume Is a Predictive Factor for Poorer Survival in Patients Undergoing Surgical Resection for Pancreatic Ductal Adenocarcinoma. *J Gastrointest Surg* 2018; **22**: 831-839 [PMID: 29392613 DOI: 10.1007/s11605-018-3695-z]

**P-Reviewer:** Huang L, Karamouzis MV **S-Editor:** Ji FF **L-Editor:** Filipodia **E-Editor:** Xing YX

**Specialty type:** Oncology

**Country of origin:** China

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

Table 1 Diagnostic criteria for sarcopenia by various working groups

|  |  |  |
| --- | --- | --- |
|  | Criteria | Remarks |
| European Working Group on Sarcopenia in Older People, 2010[[16](#_ENREF_16)] | 1 Low muscle strength  2 Low muscle quantity or quality  3 Low physical performance | Probable sarcopenia is identified by Criterion 1  Diagnosis is confirmed by additional documentation of Criterion 2  Sarcopenia is considered severe if all 3 criteria are met |
| ESPEN Special Interest Group, 2010[[18](#_ENREF_18)] | 1 Low muscle mass  2 Walking speed < 0.8 m/s in the 4-min test or reduced performance in functional test | Cut-off point should be more than 2 standard deviations below mean value of reference population using young adults of the same sex and ethnic background  Functional test can be any test used for comprehensive geriatric assessment  Both criteria should be present |
| International Working Group on Sarcopenia, 2011[[17](#_ENREF_17)] | 1 Gait speed < 1 m/s  2 Lean mass less than the 20th percentile of values for healthy young adults | Both criteria should be present |
| European Working Group on Sarcopenia in Older People, 2018 [[2](#_ENREF_2)] | 1 Low muscle mass  2 Low muscle strength  3 Low physical performance | Cut-off point should be more than 2 standard deviations below mean value of reference population using healthy young adults of the same ethnic background  Diagnosis is based on documentation of Criterion 1 plus Criterion 2 or Criterion 3 |
| Society of Sarcopenia, Cachexia and Wasting Disorders, 2011[[19](#_ENREF_19)] | 1 Walking speed ≤ 1 m/s or < 400 m during 6-min walk  2 Lean appendicular mass corrected for height squared of more than 2 standard deviations below healthy adults of 20–30 years old of the same ethnic group | Both criteria should be present |

Table 2 Summary of long-term survival outcomes in sarcopenic patients in eight studies

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **No. of patients** | **Indication** | **Operation** | **Assessment of sarcopenia** | **Cut-off points for sarcopenia** | **Outcomes** | | ***P* value** |
| Peng *et al*[[14](#_ENREF_14)], 2012 | 557 | Pancreatic cancer | PD and DP | Total psoas index | Lowest quartile of the study cohort | 3-yr survival, male | Sarcopenic: 20.3%  Non-sarcopenic: 39.2% | < 0.05 |
| 3-yr survival, female | Sarcopenic: 26.1%  Non-sarcopenic: 40.8% | < 0.05 |
| Amini *et al*[[31](#_ENREF_31)], 2015 | 763 | Pancreatic adenocarcinoma | PD, DP and TP | Total psoas volume (adjusted for height),total psoas index | Cut-off value from Peng *et al*[[14](#_ENREF_14)] | OS | Sarcopenia as independent risk factor  UV: HR 1.72, 95%CI: 1.36–2.19  MV: HR 1.11, 95%CI: 1.11–1.91 | < 0.001  0.006 |
| Joglekar *et al*[[46](#_ENREF_46)], 2015 | 180 | Pancreatic adenocarcinoma | PD and DP | Total psoas index | Lowest quartile of the study cohort | OS | No significant difference | 0.44 |
| Okumura *et al*[[45](#_ENREF_45)], 2015 | 230 | Pancreatic adenocarcinoma | PD, DP and TP | Total psoas index (measured at umbilical level) | Calculated from receiver-operating characteristic curves | Median OS | Sarcopenic: 17.7 mo  Non-sarcopenic: 33.2 mo | < 0.001 |
| DFS | Significantly shorter survival in sarcopenic group | < 0.001 |
| Onesti *et al*[[66](#_ENREF_66)], 2016 | 270 | Both benign and malignant conditions | PD, DP, central and TP | Total psoas area | Lowest tertile of the study cohort | OS | Significantly worse survival for sarcopenic group in females only | 0.005 |
| Ninomiya *et al*[[67](#_ENREF_67)], 2017 | 265 | Pancreatic adenocarcinoma | PD, DP and TP | Total abdominal muscle area (adjusted for height) | Cut-off value from Prado *et al*[[39](#_ENREF_39)] | Median OS | Sarcopenic: 23.7 mo  Non-sarcopenic: 25.8 mo | 0.185 |
| Van Dijk *et al*[[47](#_ENREF_47)], 2017 | 199 | Cancer of pancreatic head, ampulla, distal bile duct or duodenum | PD | Total abdominal muscle area (adjusted for height), radiation attenuation of skeletal muscle at L3 | Lowest tertile of the study cohort | Median OS | No difference when total abdominal muscle area was compared | Not reported |
| Significantly shorter survival in patients with low radiation attenuation | 0.008 |
| Sugimoto *et al*[[68](#_ENREF_68)], 2018 | 323 | Pancreatic adenocarcinoma | PD, DP and TP | Total abdominal muscle area (adjusted for height) | Cut-off value from Fearon *et al*[[29](#_ENREF_29)] | OS | No significant difference | 0.412 |
| DFS | No significant difference | 0.390 |
| Lowest quartile from study cohort | OS | No significant difference | 0.075 |
| DFS | No significant difference | 0.172 |

PD: Pancreaticoduodenectomy; DP: Distal pancreatectomy; TP: Total pancreatectomy; OS: Overall survival; DFS: Disease-free survival; UV: Univariate analysis; HR: Hazard ratio; CI: Confidence interval; MV: Multivariate analysis.