

80116\_Auto\_Edited-check.docx

8

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

**Manuscript NO:** 80116

**Manuscript Type:** MINIREVIEWS

## **Sarcopenia in pancreatic cancer: Effect on patient outcomes**

Choi MH *et al.* Sarcopenia in pancreatic cancer

Moon Hyung Choi, Seung Bae Yoon

3

### **Abstract**

Pancreatic cancer is a challenging disease with an increasing incidence and extremely poor prognosis. The clinical outcomes of pancreatic cancer depend on tumor biology, responses to treatments, and malnutrition or cachexia. Sarcopenia represents a severe catabolic condition defined by the age-related loss of muscle mass and strength and affects as much as 70% of malnourished pancreatic cancer patients. The lumbar skeletal muscle index, defined as the total abdominal muscle area at the L3 vertebral level adjusted by the square of the height, is widely used for assessing sarcopenia in patients with pancreatic cancer. Several studies have suggested that sarcopenia may be a risk factor for perioperative complications and decreased recurrence-free or overall survival in patients with pancreatic cancer undergoing surgery. Sarcopenia could also intensify chemotherapy-induced toxicities and worsen the quality of life and survival in the neoadjuvant or palliative chemotherapy setting. Sarcopenia, not only at the time of diagnosis, but also during treatment, decreases survival in patients with pancreatic cancer. Theoretically, multimodal interventions may improve sarcopenia and clinical outcomes; however, no study has reported positive results. Further prospective studies are needed to confirm the prognostic role of sarcopenia and the effects of multimodal interventions in patients with pancreatic cancer.

**Key Words:** Sarcopenia; Pancreatic cancer; Skeletal muscle; Computed tomography; Outcomes; Survival

Choi MH, Yoon SB. <sup>8</sup> Sarcopenia in pancreatic cancer: Effect on patient outcomes. *World J Gastrointest Oncol* 2022; In press

**Core Tip:** Despite advances in diagnosing and treating pancreatic cancer, the prognosis remains poor. In addition to survival issues, more than half of patients with pancreatic cancer develop cachexia and sarcopenia, resulting in poor adherence to intensive treatments. Here, we introduced computed tomography (CT)-based body composition analysis, which has been mostly used for analyzing sarcopenia in cancer patients, and covered controversial issues regarding the lack of consensus and diagnostic cutoff points. Recent studies analyzing the effect of sarcopenia on pancreatic cancer have summarized each treatment: surgery, neoadjuvant therapy, and palliative chemotherapy. Finally, we suggest recommendations for multimodal interventions for the management of sarcopenia and the design of future studies on CT-based body composition analysis.

## INTRODUCTION

<sup>11</sup> Pancreatic cancer is the fourth leading cause of cancer-related death in both men and women worldwide<sup>[1]</sup>. Although overall cancer mortality continues to decrease in both sexes, the mortality rate of pancreatic cancer is still increasing<sup>[2]</sup>. Further, <sup>33</sup> despite advances in cancer treatment, the 5-year survival rate remains poor at approximately 8%. Less than <sup>16</sup> 20% of patients are in a resectable state and can be treated with curative surgery, and approximately 80% of patients have locally advanced or metastatic disease at the time of diagnosis. As such, efforts have been recently made to improve pancreatic cancer treatment, including advanced surgical techniques, adjuvant chemotherapy, neoadjuvant therapy (NAT), and combination chemotherapy regimens [*e.g.*, <sup>31</sup> folinic acid,

fluorouracil, irinotecan hydrochloride, and oxaliplatin (FOLFIRINOX) and gemcitabine plus nab-paclitaxel (Gem-Nab)]<sup>[3,4]</sup>.

The clinical outcomes of pancreatic cancer not only depend on tumor biology and treatment responses, but are also strongly influenced by the nutrition and performance status of the patients. Before or during treatment, many patients experience early alteration of the metabolic state with rapid weight loss or treatment-related performance deterioration. Therefore, the assessment of nutritional status and performance status is crucial to determine the best treatment modality for extending survival with adequate quality of life.

The assessment of body composition typically refers to the measurement of fat and muscle masses. Sarcopenia is a term used to describe the age-related loss of muscle mass and strength. Beyond the quantification of the muscle mass, the importance of the muscle quality assessed for fat infiltration within the muscle is also emerging. A number of parameters have been analyzed for sarcopenic obesity, such as subcutaneous adipose tissue, visceral adipose tissue, and visceral fat-to-skeletal muscle ratio. Sarcopenia has been proven to be related to the prognosis of various diseases, especially in several types of cancer. A wide range of techniques such as body imaging modalities, including computed tomography (CT) and magnetic resonance imaging, bioimpedance analysis, or anthropometric measures, have been used to assess muscle mass; however, no gold standard diagnostic method for sarcopenia has been established yet<sup>[5]</sup>. Despite its high cost and radiation exposure, CT is the most accessible way to measure the fat and muscle area separately because of the regular follow-up CT examinations for cancer patients<sup>[6]</sup>.

This study aimed to describe a method to assess body composition using CT images and the role of sarcopenia in the management and prognosis of pancreatic cancer.

### **CT-BASED BODY COMPOSITION ANALYSIS**

Various methods have been introduced for CT-based body composition analysis. The total abdominal muscle area, including the entire abdominal wall and back muscle, is

commonly measured on CT images. Muscle area can be measured on one axial slice, or muscle volume can be measured on several consecutive slices. Among the many different landmarks, the level of the transverse processes of the L3 vertebra is generally used. Measurement of the psoas muscle area is a simple method, and the psoas muscle area has been proven to be highly correlated with the total abdominal muscle area.

Thresholds of CT attenuation can affect the muscle area, as they determine the pixels that contain muscles other than other tissues. If the threshold range is wider, more pixels are selected as the muscle area, leading to a larger muscle area. The use of intravenous contrast or slice thickness can affect body composition data<sup>[7]</sup>. The phase of CT acquisition (*e.g.*, arterial or portal) also affects the assessment of the skeletal muscle area because the contrast agent increases tissue attenuation. Therefore, the consistent use of certain thresholds and a particular phase of CT is important to obtain reliable results. In addition, CT acquisition parameters should be reported together with body composition data using CT. As body habitus affects muscle mass, several methods are used to adjust the body habitus using the square of height and body weight. The most commonly used index is the skeletal muscle index, which is calculated as muscle area/height squared (cm<sup>2</sup>/m<sup>2</sup>). In pancreatic cancer, the lumbar skeletal muscle index (LSMI) (cm<sup>2</sup>/m<sup>2</sup>), defined as the total abdominal muscle area at the L3 vertebral level adjusted by the height square, is commonly used. Additionally, the mean density of the muscle reflecting the amount of intervening fat in the muscle may be related to muscle quality.

## **PANCREATIC CANCER AND SARCOPENIA**

There is a lack of consensus regarding the definition of sarcopenia in patients with pancreatic cancer. Among the many definitions of sarcopenia, the cutoff values for sex-specific LSMI suggested by Prado *et al*<sup>[8]</sup> (52.4 cm<sup>2</sup>/m<sup>2</sup> for males and 38.5 cm<sup>2</sup>/m<sup>2</sup> for females) have been widely used in early Western studies<sup>[9-11]</sup>. These sex-specific cutoffs were obtained from the most significant P-value by optimal stratification of mortality in obese cancer patients. In addition, Martin *et al*<sup>[12]</sup> reported a new sex- and body mass

index (BMI)-specific threshold value of sarcopenia applicable to both obese and non-obese cancer patients as follows: <sup>9</sup>  $< 43 \text{ cm}^2/\text{m}^2$  for males with BMI  $< 25 \text{ kg}/\text{m}^2$  or  $< 53 \text{ cm}^2/\text{m}^2$  for males with BMI  $> 25 \text{ kg}/\text{m}^2$  and  $< 41 \text{ cm}^2/\text{m}^2$  for females. This definition of sarcopenia has also been widely used in studies on pancreatic cancer<sup>[13-17]</sup>. However, if the cutoff values based on Western studies are applied to Eastern cancer patients, the prevalence of sarcopenia is increased, with more than two-thirds of males classified as having sarcopenia, and a maldistribution between sexes occurs<sup>[18,19]</sup>. Therefore, many Eastern studies on pancreatic cancer have applied the following criteria <sup>29</sup> based on a consensus report of the Asian Working Group for Sarcopenia<sup>[20]</sup>: <sup>25</sup>  $42 \text{ cm}^2/\text{m}^2$  for males and  $38 \text{ cm}^2/\text{m}^2$  for females<sup>[21-23]</sup>. Because body composition can vary among ethnicities and tumor stages, a few studies have set their own cutoff values based on the lowest sex-specific tertile or quartile of the individual cohorts<sup>[18,24,25]</sup>.

<sup>23</sup> Pretreatment sarcopenia is present in 40%-73% of patients with pancreatic cancer. The incidence of sarcopenia and cancer cachexia is particularly higher in pancreatic cancer than in other malignancies<sup>[26]</sup>, possibly owing to the high activation of host inflammatory response and its catabolic pathways in patients with pancreatic cancer. Pancreatic exocrine insufficiency also contributes to malnutrition and weight loss. Pancreatic enzymes are essential for the degradation and absorption of fat and liposoluble vitamins; thus, deficiency of pancreatic enzymes results in steatorrhea and severe maldigestion<sup>[27]</sup>. Finally, <sup>3</sup> patients with pancreatic cancer can exhibit endocrine insufficiency, usually resulting in pancreatogenic diabetes.

## **SURGICAL TREATMENT**

<sup>1</sup> Surgical resection is the only curative treatment option for localized pancreatic cancer. However, pancreatic cancer surgery carries a high risk of perioperative morbidity and recurrence. <sup>2</sup> Therefore, the role of sarcopenia in patients undergoing surgery is a major topic of interest in the field of pancreatic cancer. The main studies that analyzed the effect of sarcopenia on the surgical treatment of pancreatic cancer are summarized in Table 1<sup>[7,9,10,18,19,24,25,28-30]</sup>. In 2012, Peng *et al*<sup>[24]</sup> evaluated 557 patients with pancreatic



cancer who underwent curative resection at the Johns Hopkins University. Sarcopenia stratified by total psoas muscle area increased the 3-year mortality by 63%. A few years later, a study by Amini *et al*<sup>[7]</sup> showed that assessing the psoas muscle volume might be a better method than assessing the psoas muscle area to define sarcopenia. Most subsequent studies have evaluated the total abdominal muscle area instead of the psoas muscle area or volume.

The effect of sarcopenia in the surgical setting has been well-summarized in a recent meta-analysis<sup>[31]</sup>. Bundred *et al*<sup>[31]</sup> analyzed 43 studies assessing body composition in patients with pancreatic cancer before surgery, 30 studies of which assessed body composition using CT. Among these, 10 studies reported the impact of preoperative sarcopenia on post-operative outcomes. Sarcopenia was associated with perioperative mortality [odds ratio (OR): 2.40; 95% confidence interval (CI), 1.19-4.85] and overall survival [hazard ratio (HR): 1.95; 95%CI, 1.54-2.05] but not with overall complications (OR: 0.96; 95%CI, 0.78-1.19). This meta-analysis was limited by the heterogeneity in the methods and cutoff values for assessing sarcopenia in individual studies.

Patients with overweight or obesity and sarcopenia exhibit worse clinical outcomes than those with sarcopenia alone. In many studies, the combination of obesity and sarcopenia was associated with a higher incidence of perioperative complications and lower survival<sup>[9,10,28,30]</sup>. Sarcopenic obesity is a complex syndrome associated with aging and lifestyle changes. Reduced physical activity may result in accelerated muscle loss; decreased energy consumption; and adverse health effects such as hypertension, dyslipidemia, and insulin resistance. Sarcopenia and obesity should be comprehensively considered to stratify patients undergoing pancreatic cancer surgery into risk categories for predicting clinical outcomes.

The amount of skeletal muscle mass has been traditionally used as a criterion to determine sarcopenia. However, some studies reported that a decrease in muscle quality, represented by low skeletal muscle attenuation, also negatively impacts prognosis after pancreatic cancer surgery<sup>[25,29]</sup>. Although the muscle mass remains normal, muscle strength and function may be reduced. In such cases, the deposition of

intramuscular adipose tissue causes reduced muscle density, resulting in a decline in muscle quality. A previous study reported that skeletal muscle density decreased before the reduction in skeletal muscle mass in patients with cancer<sup>[32]</sup>. Thus, efforts should be made to evaluate and monitor muscle quantity and quality closely.

Choi *et al*<sup>[18]</sup> demonstrated that preoperative sarcopenia and post-operative accelerated muscle loss were associated with poor overall survival in pancreatic cancer patients undergoing surgery. Post-operative skeletal muscle changes were assessed based on the difference between the initial and follow-up CT scans at an approximately 60-d interval. Approximately 30% of their patients showed significant muscle loss of more than 10% over 60 d. Given that most patients undergoing pancreatic cancer surgery receive adjuvant chemotherapy, it may be necessary to maintain muscle mass through active nutritional support and rehabilitation exercise after surgery.

### **NEOADJUVANT THERAPY**

In recent years, neoadjuvant therapy (NAT), including neoadjuvant chemotherapy and chemoradiation, has become the standard of care for borderline resectable or locally advanced pancreatic cancers. NAT may increase the rate of margin-negative resections and help clinicians screen patients with progressive disease during NAT who might not benefit from surgery<sup>[33]</sup>. In addition, NAT may be able to treat micrometastases at the time of diagnosis, which can reduce early lymph node or hepatic recurrence after surgery<sup>[34]</sup>. However, because not all patients receiving NAT are eligible for curative surgery and have increased survival, it is imperative to develop biomarkers that can predict responses to NAT. Recent studies that assessed the correlation of body composition with the response to and outcome of NAT in patients with pancreatic cancer are summarized in Table 2<sup>[13-15,35-37]</sup>.

The prevalence of sarcopenia before NAT ranges from 40% to 63%. However, no studies have shown that sarcopenia at the time of diagnosis affects resectability after NAT. Meanwhile, in a recent study by Jin *et al*<sup>[37]</sup> in 2022, sarcopenia before NAT was associated with decreased overall survival and disease-free survival. Among 119



patients, 57 (47.9%) had sarcopenia before NAT. The median overall survival and disease-free survival for sarcopenia patients were 16.6 mo and 10.9 mo, respectively, which were significantly lower than those for non-sarcopenia patients (21.4 mo and 14.0 mo, respectively; all  $P < 0.001$ ). However, because of the retrospective nature of this study, <sup>10</sup> unavoidable biases were associated with variations in the NAT regimens and treatment durations.

Several studies have evaluated changes in body composition during NAT and their effect on clinical outcomes<sup>[13,14,35-37]</sup>. In these studies, most patients experienced further depletion of skeletal muscle during NAT, and the degree of skeletal muscle loss correlated with resectability or survival. Sandini *et al*<sup>[13]</sup> reported that patients who underwent resection after NAT had skeletal muscle gain, whereas <sup>17</sup> unresectable patients experienced muscle wasting during NAT. Therefore, skeletal muscle changes must be considered in the setting of NAT, and further efforts should focus on maintaining muscle mass during treatment.

## **PALLIATIVE CHEMOTHERAPY**

<sup>24</sup> Approximately 80% of pancreatic cancer patients are diagnosed at an advanced stage, including locally advanced or metastatic disease. Combination chemotherapy with FOLFIRINOX or Gem-Nab is associated with more prolonged overall survival than gemcitabine monotherapy, with acceptable adverse events<sup>[3,4]</sup>. Currently, these two combination regimens are considered the standard first-line treatments for advanced pancreatic cancer. Therefore, selecting appropriate patients who can tolerate aggressive palliative chemotherapy is crucial. In palliative chemotherapy settings, the occurrence of sarcopenia can be related to exacerbated chemotherapy toxicity, reduced adherence to treatment, or worsened survival.

Several recent studies evaluated the effect of sarcopenia on various clinical outcomes in patients with advanced pancreatic cancer receiving palliative chemotherapy (Table <sup>4</sup> 3)<sup>[11,16,17,21-23,38-40]</sup>. Kim *et al*<sup>[17]</sup> investigated the clinical impact of sarcopenia in <sup>4</sup> 330 patients with metastatic pancreatic cancer who were treated with first-line gemcitabine-

based chemotherapy. All grade  $\geq 3$  toxicities developed at a significantly higher frequency in sarcopenia patients than in non-sarcopenia patients. This result might be explained by the link between body composition and the pharmacokinetics of chemotherapy drugs. In addition, a recent study by Emori *et al*<sup>[23]</sup> in 2022 showed that major adverse events, including hematologic toxicity, occurred more frequently in sarcopenia patients. Remarkably, the grade  $\geq 3$  neutropenia rate was significantly higher in sarcopenia patients than in non-sarcopenia patients (64% vs 40%,  $P = 0.028$ ). Therefore, patients with sarcopenia should be considered for dose modification or aggressive preventive interventions to reduce chemotherapy-related toxicity.

A study by Kurita *et al*<sup>[38]</sup> conducted on 82 pancreatic cancer patients treated with FOLFIRINOX showed that compared with non-sarcopenia patients, sarcopenia patients had a significantly lower median overall survival (11.3 mo vs 17.0 mo) and progression-free survival (3.0 mo vs 6.1 mo). In another study that evaluated 84 patients treated with Gem-Nab, the median overall and progression-free survival were also lower in sarcopenia patients than in non-sarcopenia patients (10.3 mo vs 18.1 mo and 5.0 mo vs 8.0 mo, respectively)<sup>[23]</sup>. Skeletal muscle mass can also be used as a critical prognostic factor in patients receiving second-line FOLFIRINOX chemotherapy for advanced pancreatic cancer<sup>[39]</sup>. In addition, body composition-based patient selection and dose determination may be clinically useful for patients receiving palliative chemotherapy to minimize toxicity and maximize therapeutic benefits.

Some studies have reported the negative impact of accelerated muscle loss during palliative chemotherapy on the clinical outcomes of advanced pancreatic cancer<sup>[16,21]</sup>. Basile *et al*<sup>[16]</sup> reported that early loss of skeletal muscle by more than 10% during the first 3 mo of chemotherapy was significantly associated with poor overall and progression-free survival. In a study by Uemura *et al*<sup>[21]</sup>, patients with a greater decrease in skeletal muscle index ( $\geq 7.9\%$ ) 2 mo after the start of FOLFIRINOX therapy had a shorter survival (10.9 mo) than those who did not (21.0 mo,  $P < 0.01$ ). The management of sarcopenia, not only at the time of diagnosis, but also during palliative chemotherapy, is important in patients with advanced pancreatic cancer.

## LIMITATIONS

There has been heterogeneity among studies regarding the threshold for sarcopenia based on low SMI. The races of study participants, clinical stages, and treatment methods could affect SMI. Therefore, caution is needed when synthesizing or comparing each study. Another limitation of the studies based on CT-assessed sarcopenia relates to the failure to include any functional measurement or patient-reported quality of life. Although the decrease and change of skeletal muscle mass is a major concern for supportive care in pancreatic cancer patients, physical functional assessments and quality of life measures have been highlighted as meaningful outcomes for cancer cachexia research.

## FUTURE DIRECTIONS

Since sarcopenia adversely affects the outcomes of patients with pancreatic cancer in surgical or chemotherapy settings, interventions to improve sarcopenia may help increase survival rates. However, studies investigating the impact of nutritional or exercise interventions on survival are immature, and the results are still far from demonstrating their clinical efficacy. A phase II trial on inoperable pancreatic or lung cancer patients reported that multimodal intervention, including polyunsaturated fatty acid nutritional supplements, exercise, and anti-inflammatory medication is feasible and safe<sup>[41]</sup>. In the IMPACT study by Basile *et al*<sup>[16]</sup>, more than half of the patients undergoing FOLFIRINOX chemotherapy were evaluated by a nutritionist and received dietary supplementation. Body weight loss during chemotherapy was the only factor associated with early dietary supplementation; however, nutritional support or intervention did not affect prognosis with respect to overall survival. A "Nutritional Oncology Board" has recently emerged as a good clinical practice tool of routine care for cancer patients<sup>[26]</sup>. Based on the adoption of this system, early nutritional assessment before or during oncological treatment can provide patient-tailored management for preventing or treating sarcopenia.

30 Although there has been increasing interest in the assessment of sarcopenia using CT-based methods, there are some areas to be improved in future studies<sup>[42]</sup>. It is recommended to use validated techniques and appropriate diagnostic criteria based on the study populations<sup>[43]</sup>. For sequential measurements, CT protocols should be controlled, including the timing of image acquisition and amount of contrast agent. It is also recommended to measure various physical performance measures (*e.g.*, gait speed or handgrip strength) as indicators of muscle quality, along with skeletal muscle mass, which reflect muscle quantity. Through the application of artificial intelligence, CT-based body composition analysis, which is a time-consuming process, can be applied to routine clinical practice<sup>[44]</sup>.

## CONCLUSION

6 Sarcopenia has been recognized as a prognostic biomarker in patients with pancreatic cancer receiving surgical or chemotherapy treatments. The CT-based analysis is an objective and useful tool to assess sarcopenia and skeletal muscle changes during treatment. It may be helpful to consider sarcopenia when predicting patient outcomes and to minimize complications. However, whether early nutritional support or exercise improves sarcopenia and clinical outcomes remains unclear. 4 Further prospective studies are necessary to confirm the prognostic role of sarcopenia and the effects of multimodal interventions in patients with pancreatic cancer.

## REFERENCES

- 1 Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* 2022; 72: 7-33 [PMID: 35020204 DOI: 10.3322/caac.21708]
- 2 Carioli G, Malvezzi M, Bertuccio P, Boffetta P, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2021 with focus on pancreatic and female lung cancer. *Ann Oncol* 2021; 32: 478-487 [PMID: 33626377 DOI: 10.1016/j.annonc.2021.01.006]

- 3 **Conroy T**, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]
- 4 **Von Hoff DD**, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691-1703 [PMID: 24131140 DOI: 10.1056/NEJMoa1304369]
- 5 **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]
- 6 **Lee K**, Shin Y, Huh J, Sung YS, Lee IS, Yoon KH, Kim KW. Recent Issues on Body Composition Imaging for Sarcopenia Evaluation. *Korean J Radiol* 2019; **20**: 205-217 [PMID: 30672160 DOI: 10.3348/kjr.2018.0479]
- 7 **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]
- 8 **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]

9 **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]

10 **Gruber ES**, Jomrich G, Tamandl D, Gnant M, Schindl M, Sahora K. Sarcopenia and sarcopenic obesity are independent adverse prognostic factors in resectable pancreatic ductal adenocarcinoma. *PLoS One* 2019; **14**: e0215915 [PMID: 31059520 DOI: 10.1371/journal.pone.0215915]

11 **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]

12 **Martin L**, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, Murphy R, Ghosh S, Sawyer MB, Baracos VE. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 2013; **31**: 1539-1547 [PMID: 23530101 DOI: 10.1200/JCO.2012.45.2722]

13 **Sandini M**, Patino M, Ferrone CR, Alvarez-Pérez CA, Honselmann KC, Paiella S, Catania M, Riva L, Tedesco G, Casolino R, Auriemma A, Salandini MC, Carrara G, Cristel G, Damascelli A, Ippolito D, D'Onofrio M, Lillemoe KD, Bassi C, Braga M, Gianotti L, Sahani D, Fernández-Del Castillo C. Association Between Changes in Body Composition and Neoadjuvant Treatment for Pancreatic Cancer. *JAMA Surg* 2018; **153**: 809-815 [PMID: 29801062 DOI: 10.1001/jamasurg.2018.0979]

14 **Griffin OM**, Duggan SN, Ryan R, McDermott R, Geoghegan J, Conlon KC. Characterising the impact of body composition change during neoadjuvant chemotherapy for pancreatic cancer. *Pancreatology* 2019; **19**: 850-857 [PMID: 31362865 DOI: 10.1016/j.pan.2019.07.039]

- 15 **Takeda T**, Sasaki T, Mie T, Furukawa T, Yamada Y, Kasuga A, Matsuyama M, Ozaka M, Sasahira N. The impact of body composition on short-term outcomes of neoadjuvant chemotherapy with gemcitabine plus S-1 in patients with resectable pancreatic cancer. *Jpn J Clin Oncol* 2021; **51**: 604-611 [PMID: 33479765 DOI: 10.1093/jjco/hyaa247]
- 16 **Basile D**, Parnofiello A, Vitale MG, Cortiula F, Gerratana L, Fanotto V, Lisanti C, Pelizzari G, Ongaro E, Bartoletti M, Garattini SK, Andreotti VJ, Bacco A, Iacono D, Bonotto M, Casagrande M, Ermacora P, Puglisi F, Pella N, Fasola G, Aprile G, Cardellino GG. The IMPACT study: early loss of skeletal muscle mass in advanced pancreatic cancer patients. *J Cachexia Sarcopenia Muscle* 2019; **10**: 368-377 [PMID: 30719874 DOI: 10.1002/jcsm.12368]
- 17 **Kim IH**, Choi MH, Lee IS, Hong TH, Lee MA. Clinical significance of skeletal muscle density and sarcopenia in patients with pancreatic cancer undergoing first-line chemotherapy: a retrospective observational study. *BMC Cancer* 2021; **21**: 77 [PMID: 33461517 DOI: 10.1186/s12885-020-07753-w]
- 18 **Choi MH**, Yoon SB, Lee K, Song M, Lee IS, Lee MA, Hong TH, Choi MG. Preoperative sarcopenia and post-operative accelerated muscle loss negatively impact survival after resection of pancreatic cancer. *J Cachexia Sarcopenia Muscle* 2018; **9**: 326-334 [PMID: 29399990 DOI: 10.1002/jcsm.12274]
- 19 **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]
- 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 **Uemura S**, Iwashita T, Ichikawa H, Iwasa Y, Mita N, Shiraki M, Shimizu M. The impact of sarcopenia and decrease in skeletal muscle mass in patients with advanced pancreatic cancer during FOLFIRINOX therapy. *Br J Nutr* 2021; **125**: 1140-1147 [PMID: 32883372 DOI: 10.1017/S0007114520003463]
- 22 **Asama H**, Ueno M, Kobayashi S, Fukushima T, Kawano K, Sano Y, Tanaka S, Nagashima S, Morimoto M, Ohira H, Maeda S. Sarcopenia: Prognostic Value for Unresectable Pancreatic Ductal Adenocarcinoma Patients Treated With Gemcitabine Plus Nab-Paclitaxel. *Pancreas* 2022; **51**: 148-152 [PMID: 35404889 DOI: 10.1097/MPA.0000000000001985]
- 23 **Emori T**, Itonaga M, Ashida R, Tamura T, Kawaji Y, Hatamaru K, Yamashita Y, Shimokawa T, Koike M, Sonomura T, Kawai M, Kitano M. 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. *Pancreatology* 2022; **22**: 277-285 [PMID: 35033425 DOI: 10.1016/j.pan.2021.12.013]
- 24 **Peng P**, Hyder O, Firoozmand A, Kneuert 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]
- 25 **Rom H**, Tamir S, Van Vugt JLA, Berger Y, Perl G, Morgenstern S, Tovar A, Brenner B, Benchimol D, Kashtan H, Sadot E. Sarcopenia as a Predictor of Survival in Patients with Pancreatic Adenocarcinoma After Pancreatectomy. *Ann Surg Oncol* 2022; **29**: 1553-1563 [PMID: 34716836 DOI: 10.1245/s10434-021-10995-y]
- 26 **Rovesti G**, Valoriani F, Rimini M, Bardasi C, Ballarin R, Di Benedetto F, Menozzi R, Dominici M, Spallanzani A. Clinical Implications of Malnutrition in the Management of Patients with Pancreatic Cancer: Introducing the Concept of the Nutritional Oncology Board. *Nutrients* 2021; **13** [PMID: 34684523 DOI: 10.3390/nu13103522]

- 27 **Vujasinovic M**, Valente R, Del Chiaro M, Permert J, Löhr JM. Pancreatic Exocrine Insufficiency in Pancreatic Cancer. *Nutrients* 2017; **9** [PMID: 28241470 DOI: 10.3390/nu9030183]
- 28 **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]
- 29 **Okumura S**, Kaido T, Hamaguchi Y, Kobayashi A, Shirai H, Yao S, Yagi S, Kamo N, Hatano E, Okajima H, Takaori K, Uemoto S. Visceral Adiposity and Sarcopenic Visceral Obesity are Associated with Poor Prognosis After Resection of Pancreatic Cancer. *Ann Surg Oncol* 2017; **24**: 3732-3740 [PMID: 28871520 DOI: 10.1245/s10434-017-6077-y]
- 30 **Ryu Y**, Shin SH, Kim JH, Jeong WK, Park DJ, Kim N, Heo JS, Choi DW, Han IW. The effects of sarcopenia and sarcopenic obesity after pancreaticoduodenectomy in patients with pancreatic head cancer. *HPB (Oxford)* 2020; **22**: 1782-1792 [PMID: 32354655 DOI: 10.1016/j.hpb.2020.04.004]
- 31 **Bundred J**, Kamarajah SK, Roberts KJ. Body composition assessment and sarcopenia in patients with pancreatic cancer: a systematic review and meta-analysis. *HPB (Oxford)* 2019; **21**: 1603-1612 [PMID: 31266698 DOI: 10.1016/j.hpb.2019.05.018]
- 32 **Hayashi N**, Ando Y, Gyawali B, Shimokata T, Maeda O, Fukaya M, Goto H, Nagino M, Kodera Y. Low skeletal muscle density is associated with poor survival in patients who receive chemotherapy for metastatic gastric cancer. *Oncol Rep* 2016; **35**: 1727-1731 [PMID: 26648321 DOI: 10.3892/or.2015.4475]
- 33 **Gugenheim J**, Crovetto A, Petrucciani N. Neoadjuvant therapy for pancreatic cancer. *Updates Surg* 2022; **74**: 35-42 [PMID: 34628591 DOI: 10.1007/s13304-021-01186-1]
- 34 **Sugimoto M**, Takahashi N, Farnell MB, Smyrk TC, Truty MJ, Nagorney DM, Smoot RL, Chari ST, Carter RE, Kendrick ML. Survival benefit of neoadjuvant therapy in patients with non-metastatic pancreatic ductal adenocarcinoma: A propensity matching and intention-to-treat analysis. *J Surg Oncol* 2019; **120**: 976-984 [PMID: 31452208 DOI: 10.1002/jso.25681]

- 35 **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]
- 36 **Cloyd JM**, Nogueras-González GM, Prakash LR, Petzel MQB, Parker NH, Ngo-Huang AT, Fogelman D, Denbo JW, Garg N, Kim MP, Lee JE, Tzeng CD, Fleming JB, Katz MHG. Anthropometric Changes in Patients with Pancreatic Cancer Undergoing Preoperative Therapy and Pancreatoduodenectomy. *J Gastrointest Surg* 2018; **22**: 703-712 [PMID: 29230694 DOI: 10.1007/s11605-017-3618-4]
- 37 **Jin K**, Tang Y, Wang A, Hu Z, Liu C, Zhou H, Yu X. Body Composition and Response and Outcome of Neoadjuvant Treatment for Pancreatic Cancer. *Nutr Cancer* 2022; **74**: 100-109 [PMID: 33629916 DOI: 10.1080/01635581.2020.1870704]
- 38 **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]
- 39 **Lee HS**, Kim SY, Chung MJ, Park JY, Bang S, Park SW, Song SY. Skeletal Muscle Mass Predicts Poor Prognosis in Patients with Advanced Pancreatic Cancer Undergoing Second-Line FOLFIRINOX Chemotherapy. *Nutr Cancer* 2019; **71**: 1100-1107 [PMID: 30955349 DOI: 10.1080/01635581.2019.1597906]
- 40 **Williet N**, Fovet M, Maoui K, Chevalier C, Maoui M, Le Roy B, Roblin X, Hag B, Phelip JM. A Low Total Psoas Muscle Area Index Is a Strong Prognostic Factor in Metastatic Pancreatic Cancer. *Pancreas* 2021; **50**: 579-586 [PMID: 33939672 DOI: 10.1097/MPA.0000000000001796]
- 41 **Solheim TS**, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, Pettersen CH, Fallon M, Fayers P, Fearon K, Kaasa S. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. *J Cachexia Sarcopenia Muscle* 2017; **8**: 778-788 [PMID: 28614627 DOI: 10.1002/jcsm.12201]



- 42 **Griffin OM**, Bashir Y, O'Connor D, Peakin J, McMahon J, Duggan SN, Geoghegan J, Conlon KC. Measurement of body composition in pancreatic cancer: a systematic review, meta-analysis and recommendations for future study design. *Dig Surg* 2022; Online ahead of print [PMID: 35580571 DOI: 10.1159/000524575]
- 43 **Wu CH**, Chang MC, Lyadov VK, Liang PC, Chen CM, Shih TT, Chang YT. Comparing Western and Eastern criteria for sarcopenia and their association with survival in patients with pancreatic cancer. *Clin Nutr* 2019; **38**: 862-869 [PMID: 29503056 DOI: 10.1016/j.clnu.2018.02.016]
- 44 **Hsu TH**, Schawkat K, Berkowitz SJ, Wei JL, Makoyeva A, Legare K, DeCicco C, Paez SN, Wu JSH, Szolovits P, Kikinis R, Moser AJ, Goehler A. Artificial intelligence to assess body composition on routine abdominal CT scans and predict mortality in pancreatic cancer- A recipe for your local application. *Eur J Radiol* 2021; **142**: 109834 [PMID: 34252866 DOI: 10.1016/j.ejrad.2021.109834]

# 20%

SIMILARITY INDEX

### PRIMARY SOURCES

1	<a href="https://onlinelibrary.wiley.com">onlinelibrary.wiley.com</a> Internet	75 words — 2%
2	<a href="https://bsdwebstorage.blob.core.windows.net">bsdwebstorage.blob.core.windows.net</a> Internet	45 words — 1%
3	<a href="https://www.mdpi.com">www.mdpi.com</a> Internet	44 words — 1%
4	<a href="https://www.researchsquare.com">www.researchsquare.com</a> Internet	35 words — 1%
5	Debora Basile, Carla Corvaja, Riccardo Caccialanza, Giuseppe Aprile. "Sarcopenia", Current Opinion in Supportive and Palliative Care, 2019 Crossref	34 words — 1%
6	<a href="https://www.wjgnet.com">www.wjgnet.com</a> Internet	33 words — 1%
7	<a href="https://jcsn.info">jcsn.info</a> Internet	32 words — 1%
8	<a href="https://f6publishing.blob.core.windows.net">f6publishing.blob.core.windows.net</a> Internet	29 words — 1%
9	Hiroshi Fukushima, Fumitaka Koga. "Impact of sarcopenia in the management of urological cancer	27 words — 1%

---

10 Kaizhou Jin, Yuan Tang, Anqi Wang, Zhiqian Hu, Chen Liu, Haiyang Zhou, Xianjun Yu. "Body Composition and Response and Outcome of Neoadjuvant Treatment for Pancreatic Cancer", Nutrition and Cancer, 2021 26 words — 1%  
Crossref

---

11 [link.springer.com](https://link.springer.com) 26 words — 1%  
Internet

---

12 [www.kjronline.org](https://www.kjronline.org) 22 words — 1%  
Internet

---

13 [www.karger.com](https://www.karger.com) 17 words — < 1%  
Internet

---

14 James Bundred, Sivesh K. Kamarajah, Keith J. Roberts. "Body composition assessment and sarcopenia in patients with pancreatic cancer: a systematic review and meta-analysis", HPB, 2019 15 words — < 1%  
Crossref

---

15 [journals.plos.org](https://journals.plos.org) 15 words — < 1%  
Internet

---

16 [www.antisoma.co.uk](https://www.antisoma.co.uk) 15 words — < 1%  
Internet

---

17 Amanda B. Cooper, Rebecca Slack, David Fogelman, Holly M. Holmes et al. "Characterization of Anthropometric Changes that Occur During Neoadjuvant Therapy for Potentially Resectable Pancreatic Cancer", Annals of Surgical Oncology, 2014 14 words — < 1%  
Crossref

18 Emanuele Rinninella, Marco Cintoni, Pauline Raoul, Carmelo Pozzo et al. "Muscle mass, assessed at diagnosis by L3-CT scan as a prognostic marker of clinical outcomes in patients with gastric cancer: Asystematic review and meta-analysis", Clinical Nutrition, 2019

14 words — < 1%

Crossref

19 studyres.com

Internet

14 words — < 1%

20 www.steadyhealth.com

Internet

14 words — < 1%

21 Yedidya Saiman, Marina Serper. "Frailty and Sarcopenia in Patients Pre- and Post-Liver Transplant", Clinics in Liver Disease, 2020

13 words — < 1%

Crossref

22 Hee Seung Lee, Si Young Kim, Moon Jae Chung, Jeong Youp Park, Seungmin Bang, Seung Woo Park, Si Young Song. "Skeletal Muscle Mass Predicts Poor Prognosis in Patients with Advanced Pancreatic Cancer Undergoing Second-Line FOLFIRINOX Chemotherapy", Nutrition and Cancer, 2019

12 words — < 1%

Crossref

23 "Textbook of Pancreatic Cancer", Springer Science and Business Media LLC, 2021

11 words — < 1%

Crossref

24 Chung-Tzu Hsueh, Julie H Selim, James Y Tsai, Chung-Tsen Hsueh. "Nanovectors for anti-cancer drug delivery in the treatment of advanced pancreatic adenocarcinoma", World Journal of Gastroenterology, 2016

11 words — < 1%

Crossref

25 Taiga Wakabayashi, Masahiro Shinoda, Hideaki Obara, Minoru Kitago et al. "Decreased Incidence of Acute Cellular Rejection in Low Muscle Mass Recipients after Living-Donor Liver Transplantation", Transplantation Proceedings, 2018

11 words — < 1%

Crossref

26 repub.eur.nl

Internet

11 words — < 1%

27 Hidetaka Wakabayashi, Masato Matsushima, Rimiko Uwano, Naoko Watanabe, Hideyuki Oritsu, Yoshitaka Shimizu. "Skeletal muscle mass is associated with severe dysphagia in cancer patients", Journal of Cachexia, Sarcopenia and Muscle, 2015

10 words — < 1%

Crossref

28 Shinya Uemura, Takuji Iwashita, Hironao Ichikawa, Yuhei Iwasa, Naoki Mita, Makoto Shiraki, Masahito Shimizu. "The impact of sarcopenia and decrease in skeletal muscle mass in patients with advanced pancreatic cancer during FOLFIRINOX therapy", British Journal of Nutrition, 2020

10 words — < 1%

Crossref

29 Young Hak Roh, Young Do Koh, Jung Ho Noh, Hyun Sik Gong, Goo Hyun Baek. "Evaluation of sarcopenia in patients with distal radius fractures", Archives of Osteoporosis, 2016

10 words — < 1%

Crossref

30 edepositireland.ie

Internet

10 words — < 1%

31 hal.archives-ouvertes.fr

Internet

10 words — < 1%



---

32

office.wjgnet.com

Internet

10 words — < 1%

---

33

pubmed.ncbi.nlm.nih.gov

Internet

10 words — < 1%

---

34

pure.uva.nl

Internet

10 words — < 1%

---

---

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 10 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 10 WORDS