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RESPONSIBLE EDITORS FOR THIS ISSUE

Sarcopenia in pancreatic cancer: Effect on patient outcomes

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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

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

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related deaths in both men and women worldwide[1]. Although overall cancer mortality continues to decrease in both sexes, the mortality rate of pancreatic cancer is still increasing[2]. Further, despite advances in cancer treatment, the 5-year survival rate remains poor at approximately 8%. Less than 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.*, folinic acid, fluorouracil, irinotecan hydrochloride, and oxaliplatin (FOLFIRINOX), and gemcitabine plus nab-paclitaxel][3,4].

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 mass. 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 tomo-graphy (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[5]. 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[6].

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 and 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[7]. 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^2/m^2). In pancreatic cancer, the lumbar skeletal muscle index (cm^2/m^2), 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 lumbar skeletal muscle index suggested by Prado *et al*[8] (52.4 cm^2/m^2 for males and 38.5 cm^2/m^2 for females) have been widely used in early Western studies[9-11]. 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*[12] reported a new sex- and body mass index-specific threshold value of sarcopenia applicable to both obese and non-obese cancer patients as follows: < 43 cm^2/m^2 for males with body mass index < 25 kg/m^2 or < 53 cm^2/m^2 for males with body mass index > 25 kg/m^2 and < 41 cm^2/m^2 for females. This definition of sarcopenia has also been widely used in studies on pancreatic cancer[13-17]. 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[18,19]. Therefore, many Eastern studies on pancreatic cancer have applied the following criteria based on a consensus report of the Asian Working Group for Sarcopenia[20]: 42 cm^2/m^2 for males and 38 cm^2/m^2 for females[21-23]. 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[18,24,25].

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 [26], 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[27]. Finally, patients with pancreatic cancer can exhibit endocrine insufficiency, usually resulting in pancreatogenic diabetes.

SURGICAL TREATMENT

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. 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[7,9,10,18,19,24,25,28-30]. In 2012, Peng *et al*[24] evaluated 557 patients with pancreatic cancer who underwent curative resection at 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*[7] 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 [31]. Bundred *et al*[31] analyzed 43 studies assessing body composition in patients with pancreatic cancer before surgery, of which 30 studies assessed body composition using CT. Among these, 10 studies reported the impact of preoperative sarcopenia on postoperative outcomes. Sarcopenia was associated with perioperative mortality (odds ratio: 2.40; 95% confidence interval: 1.19-4.85) and overall survival (hazard ratio: 1.95; 95% confidence interval, 1.54-2.05) but not with overall complications (odds ratio: 0.96; 95% confidence interval, 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[9,10,28,30]. 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.

Table 1 Studies analyzing the effect of sarcopenia on surgical outcomes of pancreatic cancer

Ref.	Country	No. of patients	Imaging modality	Level	Time	Definition and cutoff	Sarcopenia prevalence before surgery	Types of surgery	Perioperative complications	Survival	Additional meaningful findings or comments
Peng *et al*[24], 2012	United States	557	CT	L3	Before surgery	TPAI (mm^2/m^2), lowest quartile: < 564.2 (M), < 414.5 (F)	25%	PD, DP	(-)	(+) OS	Sarcopenia was an independent predictor of survival in multivariable analysis
Amini *et al*[7], 2015	United States	763	CT	L3	Before surgery	TPAI (mm^2/m^2), < 564.2 (M), 414.5 (F); TPVI (cm^3/m^2), < 17.2 (M), < 12.0 (F)	25% by TPAI, 20% by TPVI	PD, DP. TP	(+) Overall Cx. by TPVI	(+) OS by TPVI	TPVI was a better measure for defining sarcopenia rather than TPAI
Pecorelli *et al* [9], 2016	Italy	202	CT	L3	Before surgery	LSMI, < 52.4 cm^2/m^2 (M), < 38.5 cm^2/m^2 (F)[1]	65%	PD	(-)	NE	The combination of visceral obesity and sarcopenia was a predictor of perioperative Cx
Ninomiya *et al* [28], 2017	Japan	265	CT	L3	Before surgery	LSMI, < 43.75 cm^2/m^2 (M), < 38.5 cm^2/m^2 (F)	64%	PD, DP. TP	(-)	(-)	Sarcopenia was an independent prognostic factor only in patients with BMI ≥ 22 kg/m^2
Okumura *et al* [29], 2017	Japan	301	CT	L3	Before surgery	LSMI, clinically relevant cutoff: < 47.1 cm^2/m^2 (M), < 36.6 cm^2/m^2 (F)	40%	PD, DP. TP	(-)	(+) OS and RFS	Low muscle attenuation, as well as low muscle mass, was associated with worse OS and RFS
Choi *et al*[18], 2018	South Korea	180	CT	L3	Before and after 60 d of surgery	LSMI, the lowest tertile; < 45.3 cm^2/m^2 (M), < 39.3 cm^2/m^2 (F)	33%	PD, DP	(-)	(+) OS	Accelerated muscle loss after surgery negatively impacts OS
Sugimoto *et al* [19], 2018	United States	323	CT	L3	Before surgery	LSMI, < 55.4 cm^2/m^2 (M), < 38.9 cm^2/m^2 (F)	62%	PD, DP. TP	NE	(-)	Smaller sex-standardized LSMI as a continuous variable is associated with a shorter OS
Gruber *et al* [10], 2019	Austria	133	CT	L3	Before surgery	LSMI, < 52.4 cm^2/m^2 (M), < 38.5 cm^2/m^2 (F)[1]	59%	PD, DP	(-)	(+) OS	Obese patients (BMI ≥ 25) with sarcopenia have higher incidence of major post-operative Cx
Ryu *et al*[30], 2020	South Korea	548	CT	L3	Before surgery	LSMI, < 50.18 cm^2/m^2 (M), < 38.63 cm^2/m^2 (F)	46%	PD	(-)	(+) OS	Sarcopenic obesity is a predictive factor for post-operative pancreatic fistula after PD
Rom *et al*[25], 2022	Israel	111	CT	L3	Before surgery	LSMI, the lowest quartile: < 44; 35 cm^2/m^2 (M), < 34.82 cm^2/m^2 (F)	25%	PD, DP	(+) Overall Cx.	(+) OS, DSS, and RFS	High intramuscular adipose tissue content correlates with poor OS and DSS

[1]This cutoff value for sarcopenia was defined by Prado *et al*[8] (2008). BMI: Body mass index; CT: Computed tomography; Cx.: Complications; DP: Distal pancreatectomy; DSS: Disease-specific survival; F: Female; L3: Level of the lumbar 3 vertebral body; LSMI: Lumbar skeletal muscle index; M: Male; NE: Not evaluated; OS: Overall survival; PD: Pancreaticoduodenectomy; RFS: Recurrence-free survival; TPAI: Total psoas area index; TPVI: Total psoas volume index; TP: Total pancreatectomy.

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[25,29]. 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[32]. Thus, efforts should be made to evaluate and monitor muscle quantity and quality closely.

Choi *et al*[18] demonstrated that preoperative sarcopenia and post-operative accelerated muscle loss were associated with poor overall survival in pancreatic cancer patients undergoing surgery. Postoperative 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.

NAT

In recent years, 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[33]. 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[34]. 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[13-15,35-37].

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*[37] 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, 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[13,14,35-37]. 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* [13] reported that patients who underwent resection after NAT had skeletal muscle gain, whereas 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

Approximately 80% of pancreatic cancer patients are diagnosed at an advanced stage, including locally advanced or metastatic disease. Combination chemotherapy with FOLFIRINOX or gemcitabine plus nab-paclitaxel is associated with more prolonged overall survival than gemcitabine monotherapy, with acceptable adverse events[3,4]. 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 3)[11,16,17,21-23,38-40]. Kim *et al* [17] investigated the clinical impact of sarcopenia in 330 patients with metastatic pancreatic cancer who were treated with first-line gemcitabine-based chemotherapy. All grade ≥ 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*[23] in 2022 showed that major adverse events, including hematologic toxicity, occurred more frequently in sarcopenia patients. Remarkably, the grade ≥ 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

Table 2 Studies analyzing the effect of sarcopenia on neoadjuvant therapy outcomes of pancreatic cancer

Ref.	Country	No. of patients	Inclusion	Imaging modality	Level	Time	Definition and cutoff	Sarcopenia prevalence before NAT	Resectability	Survival	Additional meaningful findings or comments
Cooper *et al* [35], 2015	United States	89	RPC	CT	L3	Before and after NAT	LSMI, < 55.4 cm^2/m^2 (M), < 38.9 cm^2/m^2 (F)	55%	(-)	(-)	SKM loss during NAT was correlated with DFS
Cloyd *et al* [36], 2018	United States	127	RPC, BRPC, LAPC	CT	L3	Before and after NAT, 3 mo and 12 mo after surgery (PD)	LSMI, < 55.4 cm^2/m^2 (M), < 38.9 cm^2/m^2 (F)	63%	NE	(-)	SKM gain between the postoperative period and 1-yr follow-up was correlated with improved OS
Sandini *et al* [13], 2018	United States and Italy	193	BRPC, LAPC	CT	L3	Before and after NAT	LSMI, < 43 cm^2/m^2 (M) where BMI < 25 kg/m^2, < 53 cm^2/m^2 (M) where BMI > 25 kg/m^2, < 41 cm^2/m^2 (F)[1]	44%	(-)	NE	SKM gain during NAT is correlated with better resectability
Griffin *et al* [14], 2019	Ireland	78	BRPC	CT	L3	Before and after NAT	LSMI, < 43 cm^2/m^2 (M) where BMI < 25 kg/m^2, < 53 cm^2/m^2 (M) where BMI > 25 kg/m^2, < 41 cm^2/m^2 (F)[1]	50%	(-)	(-)	Low muscle attenuation before NAT and SKM loss during NAT was correlated with decreased OS
Takeda *et al* [15], 2021	Japan	62	RPC	CT	L3	Before NAT	LSMI, < 43 cm^2/m^2 (M) where BMI < 25 kg/m^2, < 53 cm^2/m^2 (M) where BMI > 25 kg/m^2, < 41 cm^2/m^2 (F)[1]	40%	(-)	NE	Sarcopenia before NAT did not correlate with antitumor response and toxicity of therapy
Jin *et al*[37], 2022	China	119	RPC	CT	L3	Before and after NAT	LSMI, < 41 cm^2/m^2 (M), < 38.5 cm^2/m^2 (F)	48%	NE	(+) OS, DFS	SKM and fat wasting during NAT was correlated with decreased OS and DFS

[1]This cutoff value for sarcopenia was defined by Martin *et al*[12] reported in 2013. BMI: Body mass index; BRPC: Borderline resectable pancreatic cancer; CT: Computed tomography; DFS: Disease-free survival; F: Female; L3: Level of the lumbar 3 vertebral body; LAPC: Locally advanced pancreatic cancer; LSMI: Lumbar skeletal muscle index; M: Male; NAT: Neoadjuvant therapy; NE: Not evaluated; OS: Overall survival; PD: Pancreaticoduodenectomy; RPC: Resectable pancreatic cancer; SKM: Skeletal muscle.

aggressive preventive interventions to reduce chemotherapy-related toxicity.

A study by Kurita *et al*[38] 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 gemcitabine plus nab-paclitaxel, 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)[23]. Skeletal muscle mass can also be used as a critical prognostic factor in patients receiving second-line FOLFIFIRNOX chemotherapy for advanced pancreatic cancer[39]. 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.

Table 3 Studies analyzing the effect of sarcopenia on palliative chemotherapy outcomes of pancreatic cancer

Ref.	Country	No. of patients	Inclusion (%)	Imaging modality	Level	Time	Definition and cutoff	Sarcopenia prevalence before CTX	CTX regimen	CTX toxicity	PFS	OS	Additional meaningful findings or comments
Kays *et al* [11], 2018	United States	53	LAPC (49), MPC (51)	CT	L3	Before and during CTX (median 5.6 times)	LSMI, < 52.4 cm^2/m^2 (M), < 38.5 cm^2/m^2 (F)[1]	49%	1st line FOLFIRINOX	NE	NE	(-)	No muscle wasting during CTX improved OS
Basile *et al* [16], 2019	Italy	94	LAPC (50), MPC (50)	CT	L3	Before and after 12 wk of CTX	LSMI, < 43 cm^2/m^2 (M) where BMI < 25 kg/m^2, < 53 cm^2/m^2 (M) where BMI > 25 kg/m^2, < 41 cm^2/m^2 (F)[2]	73%	Various	NE	(-)	(-)	Loss of skeletal muscle mass (≥ 10%) was associated with worse OS and PFS
Kurita *et al* [38], 2019	Japan	82	LAPC (35), MPC (65)	CT	L3	Before CTX	LSMI, clinically relevant cut-off: < 45.3 cm^2/m^2 (M), < 37.1 cm^2/m^2 (F)	51%	1st line FOLFIRINOX	(-)	(+)	(+)	Sarcopenic obesity was associated with hematologic toxicity
Lee *et al* [39], 2019	South Korea	57	LAPC (5), MPC (95)	CT	L3	Before and after 8 wk of CTX	LSMI, median level: unknown	50%	2nd line FOLFIRINOX	NE	(+)	(+)	Baseline LSMI was an independent predictor of survival in multivariable analysis
Kim *et al* [17], 2021	South Korea	251	MPC (100)	CT	L3	Before and after 8 wk of CTX	LSMI, < 43 cm^2/m^2 (M) where BMI < 25 kg/m^2, < 53 cm^2/m^2 (M) where BMI > 25 kg/m^2, < 41 cm^2/m^2 (F)[2]	41%	1st line gemcitabine-based CTX	(+) Overall grade ≥ 3 toxicity	(-)	(-)	Sarcopenia was a prognostic factor for OS but not for PFS in multivariable analysis
Uemura *et al* [21], 2021	Japan	69	LAPC (29), MPC (71)	CT	L3	Before and after 8 wk of CTX	LSMI, < 42 cm^2/m^2 (M), < 38 cm^2/m^2 (F)[3]	48%	1st line FOLFIRINOX	(-)	(-)	(-)	Loss of skeletal muscle mass (≥ 7.9%) is associated with worse OS
Williet *et al* [40], 2021	France	79	MPC (100)	CT	L3	Before CTX	TPAI, clinically relevant cutoff: 5.73 cm^2/m^2 (M), 4.37 cm^2/m^2 (F)	38%	Various	(-)	(+)	(+)	Measuring TPAI was less time-consuming than measuring LSMI
Asama *et al* [22], 2022	Japan	124	LAPC (29), MPC (60), RePC (15)	CT	L3	Before CTX	LSMI, < 42 cm^2/m^2 (M), < 38 cm^2/m^2 (F)[3]	49%	1st line Gem-Nab	(-)	(-)	(-)	In elderly patients (> 70 yr), sarcopenia was associated with worse OS
Emori *et al* [23], 2022	Japan	176	LAPC (14), MPC (86)	CT	L3	Before CTX	LSMI, < 42 cm^2/m^2 (M), < 38 cm^2/m^2 (F)[3]	53%	1st line Gem-Nab	(+) Overall grade ≥ 3 toxicity	(+)	(+)	Propensity score matching analysis was performed

[1]This cutoff value for sarcopenia was defined by Prado *et al*[8] (2008).

[2]This cutoff value for sarcopenia was defined by Martin *et al*[12] (2013).

[3]This cutoff value for sarcopenia was defined by the Asian Working Group for Sarcopenia (Chen *et al*[20]) reported in 2014.

BMI: Body mass index; CT: Computed tomography; CTX: Chemotherapy; F: Female; FOLFIRINOX: Folinic acid, fluorouracil, irinotecan hydrochloride, and oxaliplatin; Gem-Nab: Gemcitabine plus nab-paclitaxel; L3: Level of the lumbar 3 vertebral body; LAPC: Locally advanced pancreatic cancer; LSMI: Lumbar skeletal muscle index; M: Male; MPC: Metastatic pancreatic cancer; NE: Not evaluated; OS: Overall survival; PFS: Progression-free survival; RePC:

Recurrent pancreatic cancer; TPAI: Total psoas area index.

Some studies have reported the negative impact of accelerated muscle loss during palliative chemotherapy on the clinical outcomes of advanced pancreatic cancer[16,21]. Basile *et al*[16] 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*[21], patients with a greater decrease in skeletal muscle index (≥ 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 skeletal muscle index. The races of study participants, clinical stages, and treatment methods could affect skeletal muscle index. 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[41]. In the IMPACT study by Basile *et al*[16], 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[26]. 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.

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[42]. It is recommended to use validated techniques and appropriate diagnostic criteria based on the study populations[43]. 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 reflects 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[44].

CONCLUSION

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. Further prospective studies are necessary to confirm the prognostic role of sarcopenia and the effects of multimodal interventions in patients with pancreatic cancer.

FOOTNOTES

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