Sarcopenia is an Independent Prognostic Factor in Patients With Pancreatic Cancer – a Meta-analysis

Maximilian Thormann, MD, Mattes Hinnerichs, MD, Felix Barajas Ordonez, MD, Sylvia Saalfeld, MD, Aristoteles Perrakis, MD, Roland Croner, MD, Jazan Omari, MD, Maciej Pech, MD, Marina Zamsheva, MSc, Hans-Jonas Meyer, MD, Andreas Wienke, PhD, Alexey Surov, MD

Rationale and Objectives: Sarcopenia is defined as skeletal muscle loss and can be assessed by cross-sectional imaging. Our aim was to establish the effect of sarcopenia on relevant outcomes in patients with pancreatic ductal adenocarcinoma (PDAC) in curative and palliative settings based on a large patient sample.

Materials and Methods: MEDLINE library, EMBASE and SCOPUS databases were screened for the associations between sarcopenia and mortality in patients with PDAC up to March 2022. The primary endpoint of the systematic review was the hazard ratio of Sarcopenia on survival. 22 studies were included into the present analysis.

Results: The included 22 studies comprised 3958 patients. The prevalence of sarcopenia was 38.7%. Sarcopenia was associated with a higher prevalence in the palliative setting (OR 53.23, CI 39.00-67.45, $p<0.001$) compared to the curative setting (OR 36.73, CI 27.81-45.65, $p<0.001$).
Sarcopenia was associated with worse OS in the univariable (HR 1.79, CI 1.41-2.28, $p<0.001$) and multivariable analysis (HR 1.62, CI 1.27-2.07, $p<0.001$) in the curative setting. For the palliative setting the pooled hazards ratio showed that sarcopenia was associated with overall survival (HR 1.56, CI 1.21-2.02, $p<0.001$) as well as in multivariable analysis (HR 1.77, CI 1.39-2.26, $p<0.001$). Sarcopenia was not associated with a higher rate of post-operative complications in univariable analysis (OR 1.10, CI 0.70-1.72, $p = 0.69$).

Conclusion: Sarcopenia occurs in 38.7% of patients with pancreatic cancer, significantly more in the palliative setting. Sarcopenia is associated with overall survival in both settings. The assessment of sarcopenia is therefore relevant for personalized oncology. Sarcopenia is not associated with postoperative complications.

Key Words: meta analysis; systematic review; skeletal muscle; pancreatic cancer.

Abbreviations: DFS disease free survival, **DLT** dose limiting toxicity, **LBM** lean body mass ,LSMM, low skeletal muscle mass, **NOS** newcastle-Ottawa scale, **NSCLC** non-small cell lung cancer, **OS** overall survival, **ROC** receiver operating characteristics, **PDAC** pancreatic ductal adenocarcinoma, **PMI** psoas muscle index, PRISMA, preferred reporting items for systematic reviews and meta-analyses statement, **SCLC** small cell lung cancer, **SMI** skeletal muscle index

INTRODUCTION

Sarcopenia is a common secondary condition in cancer patients (1,2). It is defined as the loss of skeletal muscle mass and function and can be secondary to inadequate nutrition, systemic inflammation, and physical inactivity (3,4). In oncologic patients, sarcopenia has been associated with adverse clinical outcomes, such as colorectal cancer, esophageal cancer, prostate cancer, and lymphoma (5–9). In oncologic patients undergoing surgery for gastrointestinal tumors, sarcopenia was associated with increased risk of post-operative complications Clavien-Dindo $\geq$ 3 after resection (10–12).

Pancreatic ductal adenocarcinoma (PDAC) is among the leading causes of cancer deaths worldwide in both men and

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From the Clinic for Radiology and Nuclear Medicine, University Hospital Magdeburg, Leipziger Str. 44,Magdeburg, Germany, 39120 (M.T., M.H., F.B.O., J.O., M.P., A.S.); Research Campus STIMULATE, Otto-von-Guericke University Magdeburg, Magdeburg, Germany (S.S.); Department of General - Visceral, Vascular and Transplant Surgery, University Hospital Magdeburg, Magdeburg, Germany (A.P., R.C.); Institute of Medical Epidemiology, Biometry, and Informatics, Martin Luther University, Germany (M.Z., A.W.); Department for Radiology, University Clinic Leipzig, Leipzig, Germany (H.-J.M.); Department of Simulation and Graphics, University of Magdeburg, Magdeburg, Germany (S.S.). Received August 9, 2022; revised October 8, 2022; accepted October 26, 2022. Address correspondence to: e-mail: maximilian.thormann@med.ovgu.de

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women with a low 5-years survival rate (13). Complete surgical resection is the only available curative treatment. Because symptoms usually present late in the disease, only a minor fraction of patients is eligible for surgery (14). Even following resection, recurrence rates are up to 80 %, despite adjuvant chemotherapy being the standard of care following surgery (15,16). Despite improved outcomes in recent years, resection is still associated with high post-operative mortality and morbidity (14,17,18). Most patients, however, present with advanced disease, precluding resection. Patients with borderline resectable cancer may become eligible for resection after neo-adjuvant therapy. Neo-adjuvant regimens lead to comparable survival rates with primarily resectable tumors and adjuvant therapy (16).

The prevalence of sarcopenia in patients with pancreatic cancer has been described as ranging from 30 to 65 % (19). Several studies have examined the influence of sarcopenia on different clinical outcomes in pancreatic cancer patients. However, some of these studies included mixed patient cohorts with cancer types other than PDAC (20). Previous analyses focused on surgical patient cohorts with promising preliminary results in first pooled analyses. However, no systematic review provided data regarding the influence of sarcopenia in advanced, palliative patients (21,22).

This systematic review and meta-analysis aims to determine the influence of sarcopenia on different outcomes in the palliative and curative setting in patients with pancreatic cancer based on a large sample.

MATERIAL & METHODS

For the present analysis we performed a literature search within MEDLINE library, Cochrane, Web of Science, and SCOPUS data bases using the (PRISMA) (Fig 1) up to March 2022 (23,24).

The following search criteria were used: "pancreatic cancer OR pancreas cancer OR carcinoma AND sarcopenia OR low skeletal muscle mass OR body composition OR skeletal muscle index AND postoperative complications OR postoperative complication OR survival".

Inclusion criteria for the articles were:

- original investigations with humans;
- patients with confirmed PDAC treated by surgical resection with or without neoadjuvant therapy
- patients with confirmed PDAC treated in the palliative setting
- estimation of presurgical LSMM/sarcopenia on cross-sectional imaging;
- reported data about influence of low skeletal muscle mass (LSMM)/sarcopenia on occurrence of postoperative complications (Odds ratios and 95% CIs).

Exclusion criteria were:

- review articles, case reports and letters;
- Non-English language;
- Experimental studies;
- Cancer types other than PDAC included
- Missing of statistical data regarding influence of LSMM/sarcopenia on OS or occurrence of postoperative complications (Odds ratios and 95% CIs).

Articles were divided into four sections for subanalyses:

- Overall survival in the palliative and curative setting
- Disease free survival (DFS)
- Overall post-operative complications
- Post-operative complications grade Clavien-Dindo ≥ 3

The study was approved by the local ethics committee.

Study Outcomes

The primary outcome measures were OS in the palliative and curative setting and overall post-operative complications (Clavien Dindo I-V) and major post-operative complications ($\geq$ Grade III). Clavien-Dindo III and above implies the need for direct surgical or interventional procedures or marks severe organ dysfunction. Secondary outcome measures were disease free survival (DFS) and prevalence of sarcopenia in the palliative and curative setting.

Definition of Sarcopenia

Included studies used cross-sectional CT images at the level of the third lumbar vertebra (L3) to determine sarcopenia. Accepted evaluation of sarcopenia were the skeletal muscle index (SMI) and the psoas muscle index (PMI).

Data Extraction

Three researchers (MT, MH and AS) performed the data extraction. At first, the abstracts were checked. Duplicate articles, review articles, experimental studies, case reports, and non-English publications were excluded. Furthermore, the full texts of the remaining articles were analyzed (Fig 1). The following data were acquired for the analysis: authors, year of publication, type of tumors, type of therapy, number of patients, prevalence of LSMM/sarcopenia, and statistical data about influence of sarcopenia on outcomes (odds ratios and 95% CIs).

Quality Assessment

The quality of the included studies was assessed by the Newcastle-Ottawa Scale (NOS) http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm) (25). Study quality assessment was conducted by two authors (HJM, AS), and mainly included the selection of cases, comparability of the cohort, and outcome assessment of exposure to risks. A score of

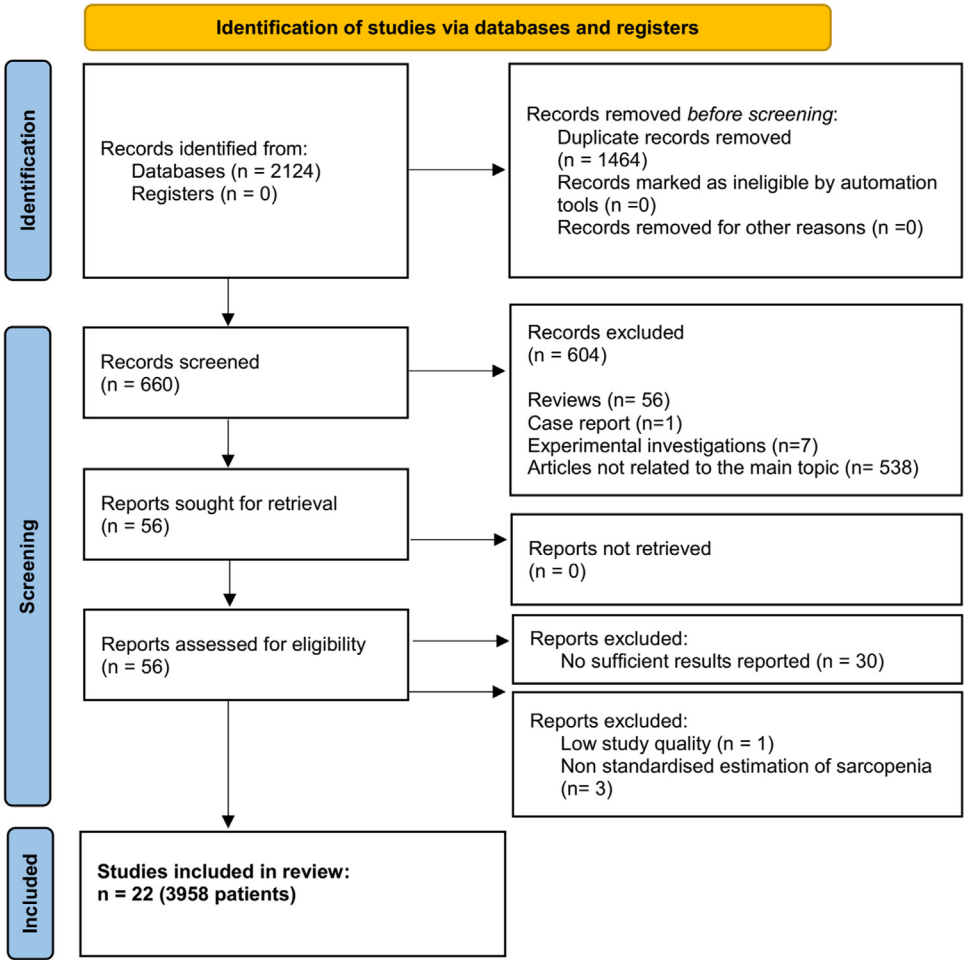

Figure 1. Prisma flow chart of data acquisition. (Color version of figure is available online.)

zero−nine was assigned to each study, and a study with score ≥six was considered to be of high quality.

Meta-analysis

A funnel plot was employed to analyze a possible publication bias and asymmetry was quantified by using the Egger test (26). P value of less than 0.05 indicated publication bias.

The RevMan 5.3 (version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014) was used (27,28). Heterogeneity was calculated by means of the index I^2. DerSimonian and Laird random-effects models with inverse-variance weights were performed (29).

RESULTS

Altogether 26 studies were selected for analysis. Of these, three studies were excluded due to the use of muscle density or muscle volume measurements to define sarcopenia. One further study was excluded due to low quality in the NOS assessment. The included 22 studies comprised 3958 patients. All studies were retrospective in nature (Table 1). The overall risk of publication bias was low identified by the funnel plot. Correspondingly, Egger's test revealed a low publication bias for both treatment groups ($p = 0.43$ and $p = 0.08$) (Supplementary Fig 6). The overall risk of bias can be considered as low, indicated by the high NOS values throughout the studies (Table 2).

Altogether, there were 2268 men (57.3 %) and 1690 women (42.7 %) included in the studies.

Most studies (20/22) applied the SMI to measure sarcopenia. One study converted the SMI into appendicular skeletal muscle mass (ASM) (30). The PMI was used in 2 studies. (Table 1). 15 studies used predefined cut-off values for sarcopenia assessment. Receiver operating characteristics (ROC) were used by two studies and optimum stratification by one study. Three studies used quartiles to obtain cut-off values.

Frequency

Sarcopenia was identified in 1531 patients (38.7 %). The fraction of sarcopenic patients ranged from 9.7 % to 87.8 % in the palliative setting. In the curative setting, the prevalence ranged from 17.2 % to 58.7 %. Sarcopenia was associated

TABLE 1. Characteristics of Included Studies with Sex-Specific Cut-off Values

	Year	Country	Sample Size	Study Design	LSMM Assessment	Treatment	Sex-specific Cut-off Values	Definition of Cut-off Values
Tan et al. (53)	2009	Canada	111	Retrospective	SMI	Palliative	Males: 59.1 cm2 /m2; females 48.4 cm2 /m2	Prado et al. 2008 (54)
Basile et al. (55)	2019	Italy	94	Rétrospective	SMI	Palliative	Males: 43 cm2 /m2 (BMI <25); 53 cm2 /m2 (BMI >25) ; Females: 41 cm2 /m2	Martin et al. 2013 (56)
Choi et al. (57)	2015	South Korea	484	Retrospective	SMI	Palliative	Males: 42.2 cm2 /m2; Females: 33.9 cm2 /m2	receiver operating characteristic
Kim et al. (58)	2021	South Korea	251	Retrospective	SMI	Palliative	Males: 43 cm2 /m2 (BMI <25); 53 cm2 /m2 (BMI >25) ; Females: 41 cm2 /m2	Martin et al. 2013 (56)
Kays et al. (59)	2018	USA	53	Retrospective	SMI	Palliative	Males: 52.4 cm^2 /m^2; females 38.5 cm^2 /m^2	Prado et al. 2008 (54)
Dalal et al. (60)	2012	USA	41	Retrospective	SMI	Palliative	Males: 52.4 cm^2 /m^2; females 38.5 cm^2 /m^2	Prado et al. 2008 (54)
Park et al. (30)	2016	South Korea	88	Retrospective	ASM	Palliative	Males: 7.50 kg/m2; Females 5.38 kg/m2 (class I); Males: 6.58 kg/m2; Females 4.59 kg/m2 (class II)	Kim et al. 2012 (61)
Nakano et al. (62)	2020	Japan	55	Retrospective	SMI	Palliative	Males: 42.2 cm^2 /m^2; females 33.9 cm^2 /m^2	Choi et al. 2015 (57)
Sakamoto et al. (63)	2020	Japan	74	Retrospective	PMI	Palliative	Males: 6.36 cm2/m2; Females 3.92 cm2/m2	Groot et al. 2019 (64)
Kurita et al. (65)	2019	Japan	82	Retrospective	SMI	Palliative	Males: 45.3 cm2/m2, Females 37.1 cm2/m2	optimum stratification
Cho et al. (66)	2020	South Korea	299	Retrospective	SMI	Palliative	Males: 36.2 cm2/m2; Females : 29.6 cm2/m2	Fujiwara et al. 2015 (67)
Uemura et al. (68)	2021	Japan	69	Retrospective	SMI	Palliative	Males. 42 cm2/m2; Females 38 cm2/m2	Chen et al. 2014 (69)
Takeda et al. (70)	2021	Japan	80	Retrospective	SMI	Palliative	Males: 43 cm2 /m2 (BMI <25); 53 cm2 /m2 (BMI >25) ; Females: 41 cm2 /m2	Martin et al. 2013 (56)
Sato et al. (71)	2021	Japan	112	Retrospective	SMI	Palliative	Males. 42 cm2/m2; Females 38 cm2/m2	Nishikawa et al. 2016 (72)
Okumura et al. (73)	2017	Japan	301	Retrospective	SMI	DFS/compl.	Males: 47.1 cm2/m2; Females : 36.6 cm2/m2	receiver operating characteristic

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TABLE 1. (Continued)

	Year	Country	Sample Size	Study Design	LSMM Assessment	Treatment	Sex-specific Cut-off Values	Definition of Cut-off Values
Peng et al. (74)	2012	USA	557	Retrospective	PMI	Curative	Males. 492 mm2/m2 ; Females : 362 mm2/m2	lowest quartile
Choi et al. (75)	2018	South Korea	180	Retrospective	SMI	Curative	Males: 45.3 cm2/m2; Females : 39.3 cm2/m2	lowest tertile
Gruber et al. (76)	2019	Austria	133	Retrospective	SMI	Curative	Males: 59.1 cm2 /m2; females 48.4 cm2 /m2	Prado et al. 2008 (54)
Ryu et al. (77)	2020	South Korea	548	Retrospective	SMI	Curative	Males: 50.18 cm2/m2; Females 38.63 cm2/m2	Moon et al. 2016 (78)
Peng et al. (79)	2020	Taiwan	116	Retrospective	SMI	Curative	Males: 42.2 cm^2 /m^2; females 33.9 cm^2 /m^2	Choi et al. 2015 (57)
Jin et al. (80)	2021	China	119	Retrospective	SMI	Curative	Males: 41 cm2/m2; Females 38.5cm2/m2	undefined
Rom et al. (81)	2021	Israel	111	Retrospective	SMI	Curative	Males : 44.35 cm2/m2; Females 34.82 cm2/m2	lowest quartile

LSMM, low skeletal muscle mass.

with a higher frequency in the palliative setting (OR 53.23, CI 39.00-66.45) compared to the curative setting (OR 33.73, CI 27.81-45.65) (Fig 2).

OS in the Palliative Setting

The influence of sarcopenia on OS in the palliative setting was reported in 14 studies (1893 patients). The pooled odds ratio showed that sarcopenia was associated with overall survival (HR 1.56, CI 1.21-2.02) (Fig 3a). In studies reporting multivariable analyses, sarcopenia was associated with worse overall survival in the palliative setting (HR 1.77, CI 1.39-2.26) (Fig 3b). Heterogeneity between studies was moderate (I^2 = 61 % for the univariable and 54% for the multivariable analysis, respectively). All patients received first and/or second line chemotherapies. There were no patients on best supportive care. Due to heterogenous treatment regimens, a subgroup analysis stratified by different chemotherapies could not be performed.

OS in the Curative Setting

In all studies sarcopenia assessment was performed at initial diagnosis before the surgery.

The influence of sarcopenia on OS in the curative setting was reported in 8 studies (2065 patients). Sarcopenia was associated with worse OS in the univariable (HR 1.79, CI 1.41-2.28) and multivariable analysis (HR 1.62, CI 1.27-2.07) (Figs3c + d). Heterogeneity between studies was moderate with 69 % and 66 %, respectively. Due to only a small portion of patients receiving neo-adjuvant therapies, no subgroup-analysis could be performed.

DFS

Four studies (647 patients) analyzed the association between sarcopenia and DFS. Sarcopenia was associated with worse OS in the univariable (OR 1.70, CI 1.29-2.24) and multivariable analysis (OR 1.86, CI 1.34-2.60). Heterogeneity between studies was moderate, with 39 % and 36 %, respectively (Fig 4).

Post-operative Complications

Three studies assessed the association between sarcopenia and overall post-operative complications (Clavien Dindo I-V) (848 patients). Sarcopenia was not associated with a higher rate of post-operative complications in univariable analysis (OR 1.10, CI 0.70-1.71). There were not enough data available for multivariable analysis (Fig 5).

Post-operatice Complications Clavien-Dindo >3

The influence of sarcopenia on post-operative complications Clavien-Dindo >three was assessed in eight studies (2065 patients). No association with sarcopenia was found (OR

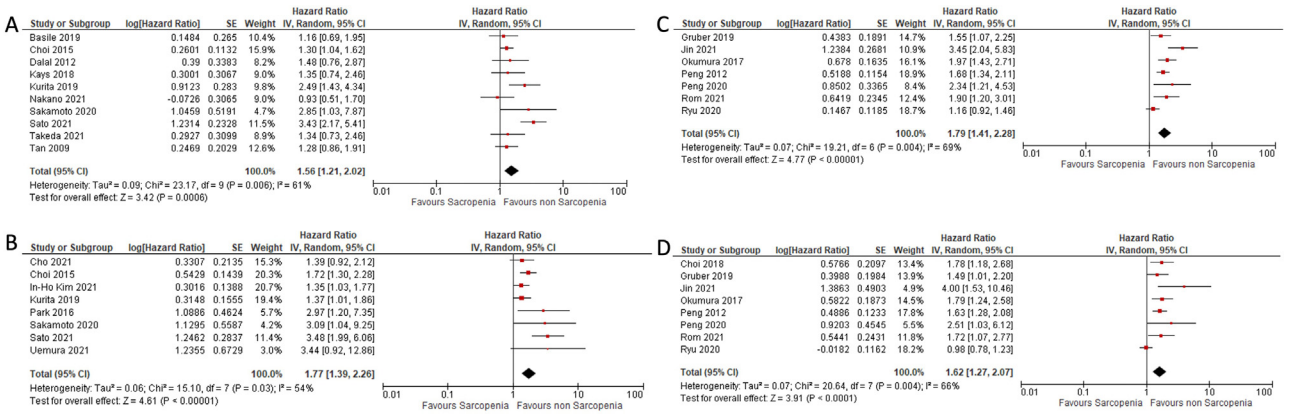

Figure 2. Prevalence of sarcopenia in the palliative (a) and the curative setting (b). Overall prevalence in the entire cohort was 38.7 %.

1.06, 95 % CI 0.77-1.47). Heterogeneity between studies was low (I^2 = 26 %). There were not enough data available for multivariable analysis (Fig 5).

DISCUSSION

Increasing evidence suggests that sarcopenia is an essential marker in oncologic patients, with influence on therapeutic response and clinical outcomes (3). This is the first study reporting on the association between sarcopenia and outcome in both the palliative and curative treatment setting for PDAC. We found a significant yet moderate influence of sarcopenia on OS in both groups. Heterogeneity between studies was moderate to high. Likewise, sarcopenia was associated with lower DFS. We did not identify an association between sarcopenia and overall or major post-operative complications. The prevalence of sarcopenia was significantly higher in the palliative than in the curative setting.

The association between sarcopenia and outcomes in patients with PDAC has been assessed in earlier meta-analyses, with different emphases. Mintziras et al. examined the influence of sarcopenia on mortality and post-operative complications in PDAC patients. They found an association between sarcopenia and OS, but no meta-analysis on post-operative complications was performed (20). However, the analysis included malignancies other than PDAC, for example cholangiocarcinoma and ampullary carcinoma. While 41.7 % of included patients received palliative treatment only, no separate sub-group analysis between curative and palliative settings were performed. As show in our analysis, the prevalence between both groups differs significantly, with 54.3 and 37.0 % in the palliative and curative group, respectively.

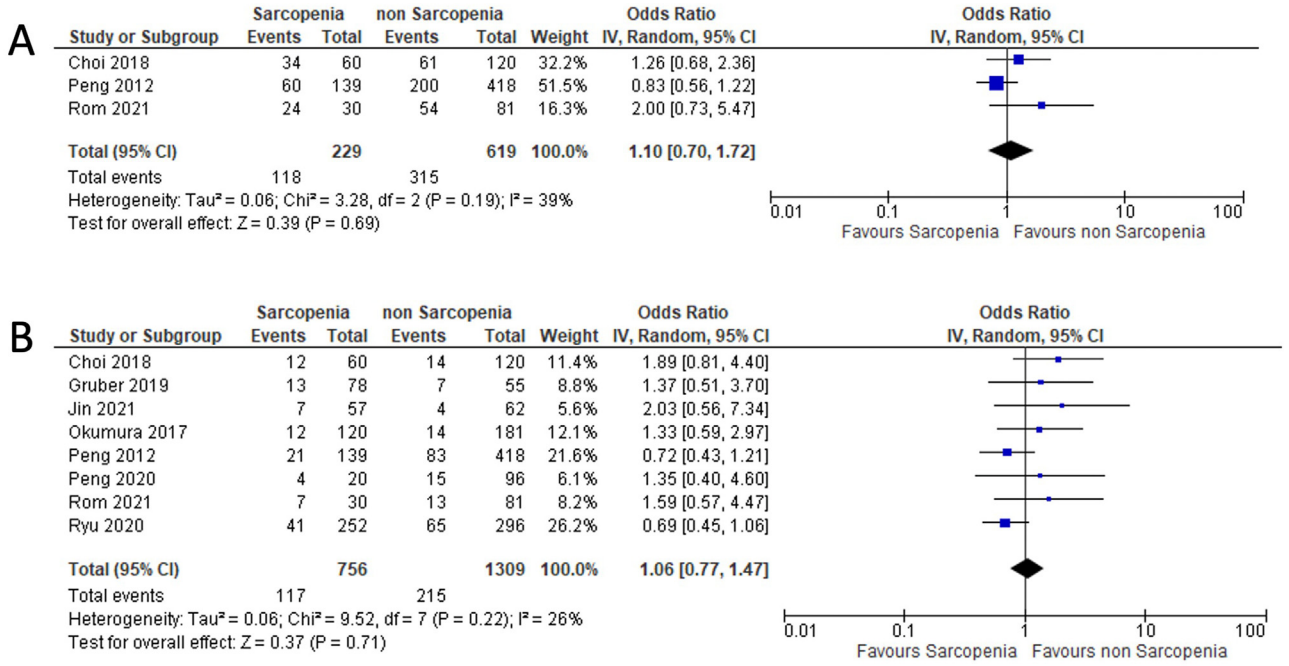

Figure 3. Forest plots comparing overall survival (OS) in sarcopenic vs. non-sarcopenic patients in univariate and multivariate analysis for the palliative (c+b) and curative (c+d) treatment group.

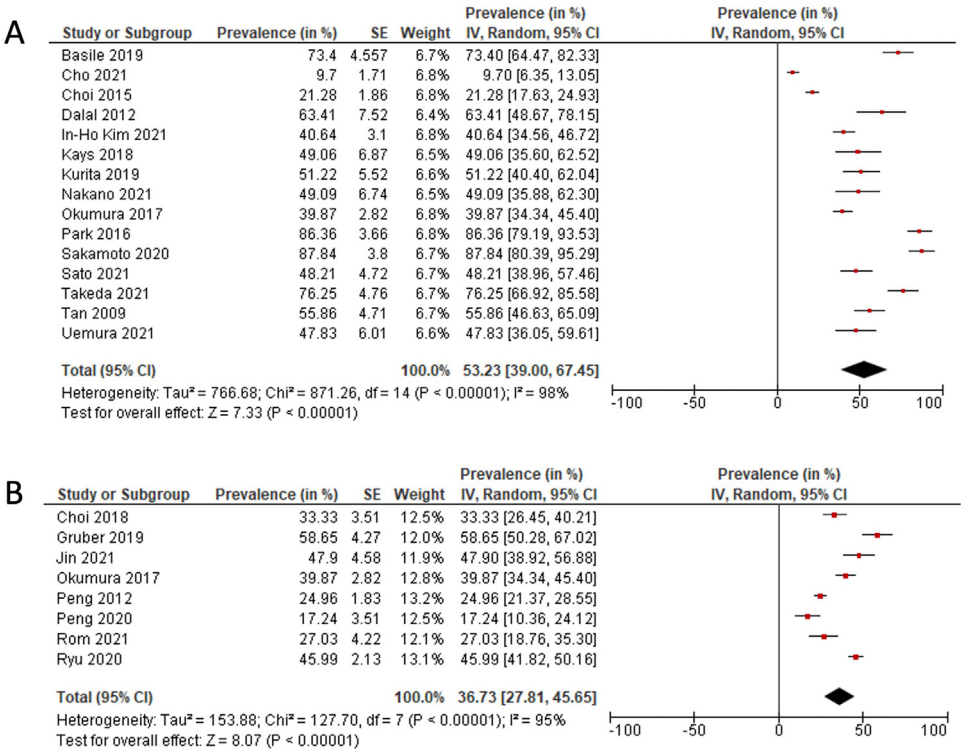

Figure 4. Forest plots comparing disease free survival (DFS) in sarcopenic vs. non-sarcopenic patients in univariate (a) and multivariate (b) analysis.

The meta-analysis by Ratnayake et al. analyzed 13 studies with 3608 patients regarding an association between sarcopenia and post-operative complications in patients receiving pancreatic resection. Only 55.3 % of patients had PDAC. No influence of sarcopenia on post-operative outcomes was detected (22). In the meta-analysis by Bundred et al. sarcopenia was associated with OS and peri-operative mortality. No association was found for overall post-operative complications (21). Of the 42 included studies only 34 assessed sarcopenia by means of computed tomography. Only ten studies analyzed the influence of pre-operative sarcopenia on overall survival. No sub-group analysis for patients receiving palliative or curative treatment was performed. Pierobon et al. reported an influence of sarcopenia on OS after surgery for pancreatic cancer, but no association with post-operative complications (31).

In accordance with the above-mentioned meta-analyses, our study did not find an association between sarcopenia and post-operative complications. It is known that sarcopenia has an important effect on homeostasis, with low muscle mass potentially resulting in low tolerability of certain cancer therapies and worse post-operative wound healing (32,33). In the analysis by Bundred et al., sarcopenic patients exhibited higher post-operative mortality (21). Furthermore it can be

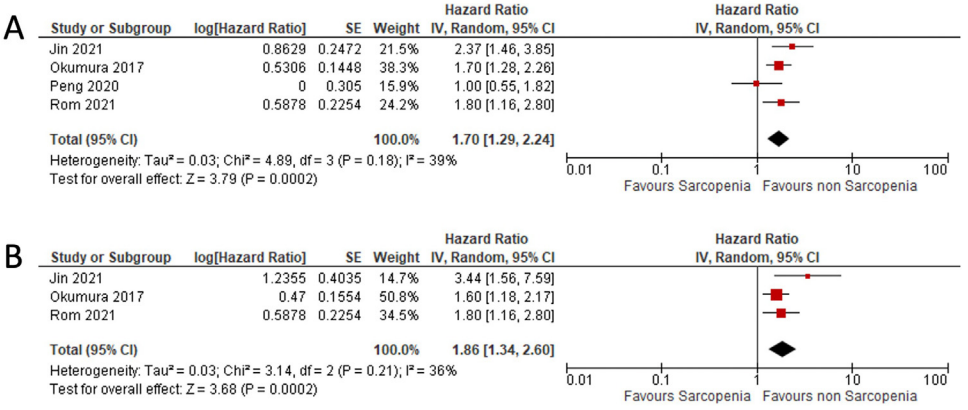

Figure 5. Forest plots comparing overall postoperative complications (a) and postoperative complications Clavien Dindo ≥ 3 (b) in sarcopenic vs. non-sarcopenic patients in univariate analysis. There were not enough data available for multivariate analysis.

assumed that certain cancer therapies, such as neo-adjuvant therapies negatively affect body composition (34). Apparently, the effect of sarcopenia on post-operative complications is heterogeneous and varies across cancer types. The adverse effect of sarcopenia on post-operative outcomes has been described for other gastrointestinal malignancies, such as gastric (35) and colorectal cancer (10,36) hepatobiliary cancers (37). No association was found in a study including patients with esophageal cancer (38). In another study, sarcopenia was associated with higher pulmonary complications after esophagectomy (39). A possible explanation may be found in the role of visceral fat. Keith et al. showed that in patients undergoing pancreaticoduodenectomy, BMI and perirenal fat thickness were associated with post-operative pancreatic fistulas (40). In patients undergoing gastrectomy, those with higher visceral fat area had higher postoperative complications (41,42). The underlying mechanisms are uncertain for now.

To date there has been no meta-analysis regarding an association between sarcopenia and DFS for PDAC. A meta-analysis by Shachar et al. on the influence of sarcopenia on solid tumors included 38 studies, 6 of which dealt with pancreaticobiliary cancer (2). A significant effect of sarcopenia as measured by SMI on OS and DFS was found. However, only one study with pancreatic cancer was included in the DFS analysis. Our results are in line with results published for other gastrointestinal malignancies. Deng et al. found that sarcopenic patients with esophageal cancer after esophagectomy had a lower DFS (6). In their meta-analysis including primary hepatic malignancies, Zhang et al. found that sarcopenic patients had a significant reduction in DFS at 5 years, while no difference was found for DFS at 1 and 3 years (43). A similar effect was reported for gastrointestinal oncology patients not including patients with PDAC, showing worse DFS in sarcopenic patients (44). In patients with early stage surgically treated NSCLC, sarcopenia was associated with lower 5-year DFS, while no influence was found in the overall cohort (45). In contrast, Yang et al. did not find an influence of sarcopenia on DFS in a meta-analysis including both patients with NSCLC and SCLC (46). In head and neck cancer, sarcopenic patients showed shorter DFS (47).

To our knowledge this is the first meta-analysis assessing the prevalence of sarcopenia in PDAC patients in the palliative and curative treatment setting. We found that the rate of sarcopenic patients was higher in the palliative than in the curative setting. Whether there is a causal relationship affecting treatment decisions can only be speculated on. However, it may be assumed that sarcopenic patients are less able to tolerate chemotherapies than non-sarcopenic patients. It is known that tumor-associated inflammation attributes to the genesis of sarcopenia in cancer patients (48). Proinflammatory cytokines such as tumor necrosis factor-alpha, interleukin 1, and interleukin six lead to alterations in metabolic and endocrine pathways and have catabolic effects, leading to muscle loss (49–52). For example, Interleukin 6 is produced by the tumor or surrounding cells, activates acute-phase protein reaction in the liver. This raises the need for certain amino acids, which, if consumed in insufficient quantities, may be supplied through the breakdown of skeletal muscle (50). Low skeletal muscle mass may itself contribute to local inflammation, further driving systemic inflammation. This could increase tumor aggressiveness and impair treatment response, leading to reduced survival (49–51). A recent-meta analysis reported that sarcopenia was associated with dose limiting toxicity (DLT) in oncologic patients (53). Sarcopenia may alter the distribution of drugs and lead to increased plasma concentrations, as has been shown for colorectal and hepatocellular cancer (54,55). Skeletal muscle is part of lean body mass (LBM). It has been shown that that the dose of anti cancer drugs per kg LBM was associated with higher toxicity in colorectal cancer patients receiving 5-FU and breast cancer patients (54,56). Furthermore, palliative patients usually present with more advanced tumor stage and worse physical condition, affecting body composition. Given the high prevalence of sarcopenia in both treatment groups and the adverse association on outcome, our study underlines the need for peri-therapeutic interventions to reduce this influence. Preventive treatments can include exercise, dietary supplementation and pharmaceutical approaches (57,58).

Our meta-analysis has several limitations. It included only studies in English language, potentially leading to selection bias. All studies included were retrospective in nature. Only certain measurements of sarcopenia, including the SMI and PMI, were accepted for inclusion. We opted for a standardized method for skeletal muscle measurement. However, this leaves out other possible assessments of body composition that may have an influence on outcome, including visceral fat and bioelectric impedance. Cut-off values varied across studies, leading to heterogeneity in the definition of sarcopenia and limits the interpretation of results. A number of studies had to be excluded as they reported results in mixed cohorts with cancer types other than PDAC. Due to the heterogeneity of studies, a subgroup analysis accounting for the influen−ce of confounders, such as ECOG or tumor stage, was not possible.

CONCLUSION

Our meta-analysis shows that sarcopenia is associated with worse OS in patients with PDAC in both the palliative and the curative treatment setting. The prevalence of sarcopenia is higher in the palliative than in the curative group. Patients with sarcopenia also show lower rates of DFS. We did not find an association between sarcopenia and post-operative outcomes. The assessment of sarcopenia is relevant for personalized oncology and can be helpful for risk-stratification in oncologic patients.

FUNDING

No funding was received.

SUPPLEMENTARY DATA

Figure 6 (supplemental). Funnel plot for overall survival (OS) for the palliative treatment group (A, $p = 0.43$) and the curative treatment group (B, $p = 0.08$)

Table 2 (supplemental). The quality of the included studies by NOS (Newcastle-Ottawa Scale) scale. In the column "Comparability of cases and controls on the basis of the design or analysis" a maximum of two stars. (★) can be allotted to each paper.

REFERENCES

1. Chan MY, Chok KSH. Sarcopenia in pancreatic cancer – effects on surgical outcomes and chemotherapy. World J Gastrointest Oncol 2019; 11:527.
2. Shachar SS, Williams GR, Muss HB, et al. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. Eur J Cancer 2016; 57:58–67.
3. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019; 48:16–31.
4. Chumlea WC, Cesari M, Evans WJ, et al. International working group on Sarcopenia. J Nutr Heal aging 2011 156 2011; 15:450–455.
5. Sun G, Li Y, Peng Y, et al. Can sarcopenia be a predictor of prognosis for patients with non-metastatic colorectal cancer? A systematic review and meta-analysis. Int J Colorectal Dis 2018; 33:1419–1427.
6. Deng H-Y, Zha P, Peng L, et al. Preoperative sarcopenia is a predictor of poor prognosis of esophageal cancer after esophagectomy: a comprehensive systematic review and meta-analysis. Dis Esophagus 2019; 32. doi:10.1093/dote/doy115.
7. Karmali R, Alrifai T, Fughhi IAM, et al. Impact of cachexia on outcomes in aggressive lymphomas. Ann Hematol 2017; 96:951–956.
8. Camus V, Lanic H, Kraut J, et al. Prognostic impact of fat tissue loss and cachexia assessed by computed tomography scan in elderly patients with diffuse large B-cell lymphoma treated with immunochemotherapy. Eur J Haematol 2014; 93:9–18.
9. Meyer HJ, Wienke A, Surov A. CT-defined low-skeletal muscle mass as a prognostic marker for survival in prostate cancer: a systematic review and meta-analysis. Urol Oncol 2022; 40(103):e9–103. .e16.
10. Simonsen C, de Heer P, Bjerre ED, et al. Sarcopenia and postoperative complication risk in gastrointestinal surgical oncology. Ann Surg 2018; 268:58–69.
11. Kamarajah SK, Bundred J, Tan BHL. Body composition assessment and sarcopenia in patients with gastric cancer: a systematic review and meta-analysis. Gastric Cancer 2019; 22:10–22.
12. Nishigori T, Okabe H, Tanaka E, et al. Sarcopenia as a predictor of pulmonary complications after esophagectomy for thoracic esophageal cancer. J Surg Oncol 2016; 113:678–684.
13. Pourshams A, Sepanlou SG, Ikuta KS, et al. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. Lancet Gastroenterol Hepatol 2019; 4:934–947.
14. Strobel O, Neoptolemos J, Jäger D, et al. Optimizing the outcomes of pancreatic cancer surgery. Nat Rev Clin Oncol 2018 161 2018; 16:11–26.
15. Kleeff J, Reiser C, Hinz U, et al. Surgery for recurrent pancreatic ductal adenocarcinoma. Ann Surg 2007; 245:566–572.
16. Gillen S, Schuster T, Büschenfelde CM Z, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med 2010; 7. doi:10.1371/JOURNAL.PMED.1000267.
17. Merkow RP, Bilimoria KY, Tomlinson JS, et al. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. Ann Surg 2014; 260:372–377.
18. Tonini V, Zanni M. Pancreatic cancer in 2021:what you need to know to win. World J Gastroenterol 2021; 27(5851).
19. Ozola Zalite I, Zykus R, Francisco Gonzalez M, et al. Influence of cachexia and sarcopenia on survival in pancreatic ductal adenocarcinoma: a systematic review. Pancreatology 2015; 15:19–24.
20. Mintziras I, Miligkos M, Wächter S, et al. Sarcopenia and sarcopenic obesity are significantly associated with poorer overall survival in patients with pancreatic cancer: systematic review and meta-analysis. Int J Surg 2018; 59:19–26.
21. Bundred J, Kamarajah SK, Roberts KJ. Body composition assessment and sarcopenia in patients with pancreatic cancer: a systematic review and meta-analysis. HPB 2019; 21:1603–1612.
22. Ratnayake CB, Loveday BP, Shrikhande SV, et al. Impact of preoperative sarcopenia on postoperative outcomes following pancreatic resection: a systematic review and meta-analysis. Pancreatology 2018; 18:996–1004.
23. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339:b2535.. –b2535.
24. Kalkum E, Klotz R, Seide S, et al. Systematic reviews in surgery-recommendations from the study center of the German society of surgery. Langenbeck's. Arch Surg 2021; 406:1723–1731.
25. Wells G, Shea B, O'Connell D, et al. The newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2008.Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed April 11,2022.
26. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629–634.
27. Leeflang MMG. Systematic reviews of diagnostic test accuracy. Ann Intern Med 2008; 149:889.
28. Zamora J, Abraira V, Muriel A, et al. Meta-diSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol 2006; 6:31.
29. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7:177–188.
30. Park I, Choi SJ, Kim YS, et al. Prognostic factors for risk stratification of patients with recurrent or metastatic pancreatic adenocarcinoma who were treated with gemcitabine-based chemotherapy. Cancer Res Treat 2016; 48:1264–1273.
31. Pierobon ES, Moletta L, Zampieri S, et al. The prognostic value of low muscle mass in pancreatic cancer patients: a systematic review and meta-analysis. J Clin Med 2021; 10(10):3033.. 3033-2021.
32. Pratesi A. Skeletal muscle: an endocrine organ. Clin CASES Miner BONE Metab 2013; 10:11–14.
33. Surov A, Wienke A. Sarcopenia predicts overall survival in patients with malignant hematological diseases: a meta-analysis. Clin Nutr 2021; 40:1155–1160.
34. Pin F, Couch ME, Bonetto A. Preservation of muscle mass as a strategy to reduce the toxic effects of cancer chemotherapy on body composition. Curr Opin Support Palliat Care 2018; 12:420–426.
35. Yang Z, Zhou X, Ma B, et al. Predictive value of preoperative sarcopenia in patients with gastric cancer: a meta-analysis and systematic review. J Gastrointest Surg 2018; 22:1890–1902.
36. Xie H, Wei L, Liu M, et al. Preoperative computed tomography-assessed sarcopenia as a predictor of complications and long-term prognosis in patients with colorectal cancer: a systematic review and meta-analysis. Langenbeck's. Arch Surg 2021; 406:1775–1788.
37. Cao Q, Xiong Y, Zhong Z, et al. Computed tomography-assessed sarcopenia indexes predict major complications following surgery for hepatopancreatobiliary malignancy: A meta-analysis. Ann Nutr Metab 2019; 74:24–34.
38. Papaconstantinou D, Vretakakou K, Paspala A, et al. The impact of preoperative sarcopenia on postoperative complications following esophagectomy for esophageal neoplasia: a systematic review and meta-analysis. Dis Esophagus 2020; 33. doi:10.1093/dote/doaa002.
39. Ida S, Watanabe M, Yoshida N, et al. Sarcopenia is a predictor of postoperative respiratory complications in patients with esophageal cancer. Ann Surg Oncol 2015; 22:4432–4437.
40. Roberts KJ, Sutcliffe RP, Marudanayagam R, et al. Scoring system to predict pancreatic fistula after pancreaticoduodenectomy: a UK multicenter study. Ann Surg 2015; 261:1191–1197.
41. Okada K, Nishigori T, Obama K, et al. The incidence of postoperative complications after gastrectomy increases in proportion to the amount of preoperative visceral fat. J Oncol 2019; 2019. doi:10.1155/2019/8404383.
42. J Yang S, R Li H, H Zhang W, et al. Visceral fat area (VFA) superior to BMI for predicting postoperative complications after radical gastrectomy: a prospective cohort study. J Gastrointest Surg 2020; 24:1298–1306.
43. Zhang G, Meng S, Li R, et al. Clinical significance of sarcopenia in the treatment of patients with primary hepatic malignancies, a systematic review and meta-analysis. Oncotarget 2017; 8:102474.

44. Su H, Ruan J, Chen T, et al. CT-assessed sarcopenia is a predictive factor for both long-term and short-term outcomes in gastrointestinal oncology patients: a systematic review and meta-analysis. Cancer Imaging 2019; 19:1–15.
45. Deng H-Y, Hou L, Zha P, et al. Sarcopenia is an independent unfavorable prognostic factor of non-small cell lung cancer after surgical resection: a comprehensive systematic review and meta-analysis. Eur J Surg Oncol 2019; 45:728–735.
46. Yang M, Shen Y, Tan L, et al. Prognostic value of sarcopenia in lung cancer: a systematic review and meta-analysis. Chest 2019; 156:101–111.
47. Surov A, Wienke A. Low skeletal muscle mass predicts relevant clinical outcomes in head and neck squamous cell carcinoma. A meta analysis. Ther Adv Med Oncol 2021; 13:175883592110088.
48. Williams GR, Dunne RF, Giri S, et al. Sarcopenia in the older adult with cancer. J Clin Oncol 2021; 39:2068.
49. Feliciano EMC, Kroenke CH, Meyerhardt JA, et al. Association of systemic inflammation and sarcopenia with survival in nonmetastatic colorectal cancer: results from the C SCANS study. JAMA Oncol 2017; 3:e172319. –e172319.
50. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J 2010; 9:1–16.
51. Durham WJ, Dillon EL, Sheffield-Moore M. Inflammatory burden and amino acid metabolism in cancer cachexia. Curr Opin Clin Nutr Metab Care 2009; 12:72.
52. Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: molecular mechanisms and promising therapies. Nat Rev Drug Discov 2015; 14:58–74.
53. Surov A, Pech M, Gessner D, et al. Low skeletal muscle mass is a predictor of treatment related toxicity in oncologic patients. A meta-analysis. Clin Nutr 2021; 40:5298–5310.
54. Williams GR, Deal AM, Shachar SS, et al. The impact of skeletal muscle on the pharmacokinetics and toxicity of 5-fluorouracil in colorectal cancer. Cancer Chemother Pharmacol 2018; 81:413–417.
55. Mir O, Coriat R, Blanchet B, et al. Sarcopenia predicts early dose-limiting toxicities and pharmacokinetics of sorafenib in patients with hepatocellular carcinoma. PLoS One 2012; 7:e37563.
56. Prado CMM, Baracos VE, McCargar LJ, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res 2009; 15:2920–2926.
57. Maddocks M, Murton AJ, Wilcock A. Improving muscle mass and function in cachexia: non-drug approaches. Curr Opin Support Palliat Care 2011; 5:361–364.
58. Uchitomi R, Oyabu M, Kamei Y. Vitamin D and sarcopenia: potential of vitamin D supplementation in sarcopenia prevention and treatment. Nutrients 2020; 12:1–12.
59. Kays JK, Shahda S, Stanley M, et al. Three cachexia phenotypes and the impact of fat-only loss on survival in FOLFIRINOX therapy for pancreatic cancer. Journal of Cachexia, Sarcopenia and Muscle 2018; 9:673–684.
60. Dalal S, Hui D, Bidaut L, et al. Relationships Among Body Mass Index, Longitudinal Body Composition Alterations, and Survival in Patients With Locally Advanced Pancreatic Cancer Receiving Chemoradiation: A Pilot Study. Journal of Pain and Symptom Management 2012; 44:181–191.
61. Kim YS, Lee Y, Chung YS, et al. Prevalence of sarcopenia and sarcopenic obesity in the Korean population based on the Fourth Korean National Health and Nutritional Examination Surveys. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 2012; 67:1107–1113.
62. Nakano O, Kawai H, Kobayashi T, et al. Rapid decline in visceral adipose tissue over 1 month is associated with poor prognosis in patients with unresectable pancreatic cancer. Cancer Medicine 2021; 10:4291–4301.
63. Sakamoto T, Yagyu T, Uchinaka E, et al. Sarcopenia as a prognostic factor in patients with recurrent pancreatic cancer: a retrospective study. World Journal of Surgical Oncology 2020; 18:221.
64. Groot VP, Gemenetzis G, Blair AB, et al. Defining and Predicting Early Recurrence in 957 Patients With Resected Pancreatic Ductal Adenocarcinoma. Annals of Surgery 2019; 269:1154–1162.
65. 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 Jan; 19(1):127–135.
66. Cho WK, Il Yu J, Park HC, et al. Impact of sarcopenia on survival of pancreatic cancer patients treated with concurrent chemoradiotherapy. Tumori Journal 2020. 030089162093779.
67. Fujiwara N, Nakagawa H, Kudo Y, et al. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. Journal of Hepatology 2015; 63:131–140.
68. Uemura S, Iwashita T, Ichikawa H, et al. The impact of sarcopenia and decrease in skeletal muscle mass in patients with advanced pancreatic cancer during FOLFIRINOX therapy. The British Journal of Nutrition 2021; 125:1140–1147.
69. Chen LK, Liu LK, Woo J, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. Journal of the American Medical Directors Association 2014; 15:95–101.
70. Takeda T, Sasaki T, Suzumori C, et al. The impact of cachexia and sarcopenia in elderly pancreatic cancer patients receiving palliative chemotherapy. International Journal of Clinical Oncology 2021; 26:1293–1303.
71. Sato H, Goto T, Hayashi A, et al. Prognostic significance of skeletal muscle decrease in unresectable pancreatic cancer: Survival analysis using the Weibull exponential distribution model. Pancreatology?: Official Journal of the International Association of Pancreatology (IAP) ... [et Al.] 2021; 21:892–902.
72. Nishikawa H, Shiraki M, Hiramatsu A, et al. Japan Society of Hepatology guidelines for sarcopenia in liver disease (1st edition): Recommendation from the working group for creation of sarcopenia assessment criteria. Hepatology Research?: The Official Journal of the Japan Society of Hepatology 2016; 46:951–963.
73. Okumura S, Kaido T, Hamaguchi Y, et al. Visceral Adiposity and Sarcopenic Visceral Obesity are Associated with Poor Prognosis After Resection of Pancreatic Cancer. Annals of Surgical Oncology 2017; 24:3732–3740.
74. Peng P, Hyder O, Firoozmand A, et al. Impact of Sarcopenia on Outcomes Following Resection of Pancreatic Adenocarcinoma. Journal of Gastrointestinal Surgery 2012; 16:1478–1486.
75. Choi MH, Yoon SB, Lee K, et al. Preoperative sarcopenia and post-operative accelerated muscle loss negatively impact survival after resection of pancreatic cancer. Journal of Cachexia, Sarcopenia and Muscle 2018; 9:326–334.
76. Gruber ES, Jomrich G, Tamandl D, et al. Sarcopenia and sarcopenic obesity are independent adverse prognostic factors in resectable pancreatic ductal adenocarcinoma. PLOS ONE 2019; 14:e0215915.
77. Ryu Y, Shin SH, Kim J-H, et al. The effects of sarcopenia and sarcopenic obesity after pancreaticoduodenectomy in patients with pancreatic head cancer. HPB 2020; 22:1782–1792.
78. Moon JH, Kim KM, Kim JH, et al. Predictive Values of the New Sarcopenia Index by the Foundation for the National Institutes of Health Sarcopenia Project for Mortality among Older Korean Adults. PloS One 2016; 11:e0166344.
79. Peng Y-C, Wu C-H, Tien Y-W, et al. Preoperative sarcopenia is associated with poor overall survival in pancreatic cancer patients following pancreaticoduodenectomy. European Radiology 2021; 31:2472–2481.
80. 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(1):100–109.
81. Rom H, Tamir S, Van Vugt JLA, et al. Sarcopenia as a Predictor of Survival in Patients with Pancreatic Adenocarcinoma After Pancreatectomy. Annals of Surgical Oncology 2022; 29:1553–1563.

SUPPLEMENTARY MATERIALS

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