European Review for Medical and Pharmacological Sciences 2021; 25: 3670-3678

The role of sarcopenia in the pancreatic adenocarcinoma

B. PESSIA[1], A. GIULIANI[2], L. ROMANO[2], F. BRUNO[3], F. CARLEI[2], V. VICENTINI[1], M. SCHIETROMA[2]

[1]Department of Hepato-Bilio-Pancreatic Surgery, San Salvatore Hospital, L'Aquila, Italy
[2]Department of Surgery, San Salvatore Hospital, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy
[3]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

Abstract. – OBJECTIVE: Pancreaticoduodenectomy is still associated with prolonged hospitalization and with a lot of complications. For these reasons, it is fundamental to improve strategies for preoperative risk stratification, and sarcopenia is one of the new identified markers of frailty. The purpose of our study was to retrospectively detect sarcopenia in patients undergoing pancreaticoduodenectomy and evaluate its importance as a preoperative marker.

PATIENTS AND METHODS: We retrospectively identified a total amount of 76 consecutive patients who underwent pancreaticoduodenectomy for pancreatic head adenocarcinoma. Patients' and tumor's characteristics were recorded retrospectively.

RESULTS: It appears that sarcopenia might be a useful preoperative prognostic factor for patients undergoing PD for PA. We found that Recurrence Free Survival may be influenced by presence or absence of preoperative sarcopenia, and we can confirm that in sarcopenic patients the average hospital stay is 20% longer than in non sarcopenic ones.

CONCLUSIONS: Sarcopenia has a central role because it is a very common condition found in pancreatic cancer patients; there is growing evidence showing that it is associated with worse surgical outcomes. We can state that evaluating sarcopenia in cancer patients could improve the postoperative outcomes, overall survival rates and, nevertheless, the recurrence free survival ones.

Key Words:
Pancreaticoduodenectomy, Sarcopenia, Preoperative marker, Pancreatic adenocarcinoma.

Introduction

The great majority of pancreatic adenocarcinomas are located in the head of pancreas, which approximatively represents the 70% of the entire organ. Due to this location the most frequent pancreatic surgery required and carried out for radical purpose is the open pancreaticoduodenectomy (PD)[1]. Despite the most recent innovations in surgical techniques and perioperative management, this procedure is still associated with prolonged hospitalization and is still burdened by a lot of complications, first of all the postoperative pancreatic fistula that often leads to a fatal outcome[2-5].

For these reasons it is fundamental to improve strategies for preoperative risk stratification, not only based on oncological factors but also on nutritional ones: in fact the identification of high-risk patients leads to a more reasonable management of economical sources and, above all, allows to provide, for patients with modifiable risk factors, adequate preoperative rehabilitation in order to improve postoperative outcomes: this is possible, for example, using adequate and personalized "training" programs as shown in the conclusions of this study[2,3,6,7].

In this context, sarcopenia is one of the relatively new identified markers of frailty, especially in elderly people[8-18]. It is a morphometric parameter characterized by quantitative and qualitative loss of skeletal muscle mass and it is known that the muscular compartment is a homeostatic reserve that reflects the general state of health[10,17,19].

Sarcopenia is a common condition in pancreatic cancer patients and, in several studies, it has emerged to be strictly related to augmented morbidity, prolonged hospitalization, worse prognosis and generally to a decreased quality of life in patients undergoing pancreatic resections. Despite the confirmed importance of sarcopenia, literature appears to show contrasting and contradictory results[20-34].

Corresponding Author: Lucia Romano, MD; e-mail: lucia.romano@graduate.univaq.it

Therefore, the purpose of our study was to retrospectively detect sarcopenia in patients undergoing pancreaticoduodenectomy in Hepato-Pancreatic-Biliary Surgery Department of L'Aquila, Italy, and to evaluate the importance of sarcopenia itself as a preoperative marker of overall survival, disease-free survival and prolonged time of hospitalization.

Patients and Methods

We retrospectively identified a total amount of 76 consecutive patients who underwent pancreaticoduodenectomy (PD) for pancreatic head adenocarcinoma with curative intent between June 2013 and May 2019 in a single center, Hepato-biliary-pancreatic Surgery Department of L'Aquila (Italy). The data were recorded in collaboration with the Department of Surgery of the University of L'Aquila (L'Aquila, Italy).

All patients enrolled in the study presented eligible criteria for PD, according to ESMO guidelines[35] and AIOM 2019 guidelines[36] for pancreatic cancers. We enrolled patients with available preoperative staging CT images and we decided to include in the study only patients with resectable disease, excluding borderline resectable.

Patients' and tumor's characteristics were recorded retrospectively, extracting all data from our institutional database. Pathologic diagnosis of all patients enrolled was pancreatic head ductal adenocarcinoma. Data collected included Overall Survival and Recurrences free Survival rates, sex, age at the time of surgery, personal medical history, physical examination as well as routine laboratory testing. In addition, we obtained details on the surgical procedure, on the postoperative course, on length of hospital stay and on the final pathological report. Comorbidities were assessed using the Charlson Age Comorbidity Index (CACI)[37], perioperative complications were reported according to the classification system defined by Dindo et al[38] and fistulas were graded according to the latest consensus definitions[39].

The study protocol was approved by the Ethical Committee of the University of L'Aquila and all patients gave their written informed consent to participate in the study.

Skeletal Muscle Measurement

Patient skeletal muscle mass was retrospectively assessed using measurements of muscle area on the existing diagnostic or staging CT scans. The cross-sectional skeletal muscle area was manually traced and automatically calculated on a single transversal section of the abdomen at the level of the transverse process of the third lumbar vertebra (L3). Muscle attenuation was not taken into account. The calculated area was then normalized for body length, presenting a skeletal muscle index (cm^2/m^2) (SMI), because L3 skeletal muscle area has previously been shown to correlate with the whole-body muscle mass[40].

Cut-offs for sarcopenia were based on the computed tomography-based sarcopenia assessment for cancer patients conducted by Prado et al[18,40] (i.e., L3 skeletal muscle index $\leq$38.5 cm^2/m^2 for women and $\leq$52.4 cm^2/m^2 for men).

CT Hounsfield unit thresholds were -29 to +150 for lean muscle and -190 to -30 HU and -150 to -50 HU for subcutaneous and intramuscular fat and visceral obese tissue, respectively[41].

Results

Seventy-six patients were initially enrolled. Upfront pancreaticoduodenectomy for resectable pancreatic head adenocarcinoma was always considered as the first-line treatment. Patients were stratified with characteristics shown in the Table

Table I. Patient's characteristics.

Characteristics of patients sarcopenic (S) *vs.* non sarcopenic (NS)	Group	
	S (n° = 32)	NS (n° = 36)
BMI (kg/cm^2)	19.6	21.4
Weight (kg)	61.5	65
Albumin levels (mg/dL)	2.8	3,1
Mean age (years)	63	62
Major complications %		
Sec. Clavien-Dindo > 3	20%	14%
Length of stay (days)	21	17

Table II. Muscle Mass Radiological assessment.

Radiological assessment	(S)	vs.	(NS)
SMD (Hu)	6.17		6.68
SMI (cm^2/mm^2)	30.3		50.07

SMD: skeletal muscle radiodensity; SMI: skeletal muscle index.

I. We later decided to exclude 8 patients due to different diagnosis, border-line resectable disease, non resectable or locally advanced disease and tumor located in another pancreatic segment.

Using the Martin et al[42] definition, sarcopenia was defined as SMI less than 52.4 cm^2/m^2 for men and SMI less than 38.5 cm^2/m^2 for women. According to this definition, we identified two different groups: 32 sarcopenic patients and 36 non sarcopenic patients as shown in Table II. The patients' characteristics where otherwise homogeneous (Table I). Several parameters such as weight, BMI, albumin levels, age at the time of surgery were considered, as long as postoperative complications, lengh of the hospitalization and the radiological muscle mass assessment (Table II). The parameters evaluated in both groups were normally distributed, thus the two samples were considered for further analysis. The median follow-up was 24 months (1-48 months).

The primary endpoint was to evaluate median overall survival and as secondary endpoints we evaluated disease-free survival and length of hospital stay.

Data collected between the two groups of patients were considered as continuous variables and were compared with a two-way ANOVA test. For the Overall Survival (OS) a Kaplan-Meier curve was constructed, using survival of all patients as the dependent variables and SMI as the independent one. The Kaplan-Meyer survival analysis indicates that preoperative sarcopenia results in worse overall survival (Figure 1).

The OS rate was significantly different between the two groups based on the Log-rank test (p-value = 0,0057) thus a p-value<0.05 was considered statistically significant. Observing the overall survival data between the two groups it appears that sarcopenia might be a useful preoperative prognostic factor for patients undergoing PD for PA.

Subsequently we also found that Recurrence Free Survival may be influenced by presence or absence of preoperative sarcopenia: statistical comparison of the two groups was evaluated with

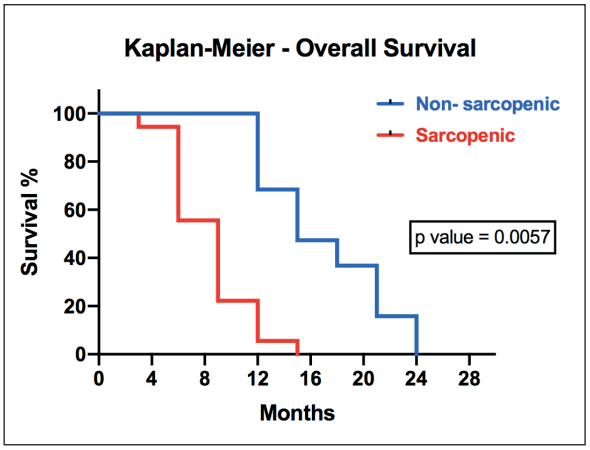

Figure 1. Kaplan-Meyer survival analysis.

the two-way ANOVA multiple comparison test, obtaining a p-value as 0.0011 (Figure 2). Thus, the analysis supports the significancy of longer Disease Free Survival in non-sarcopenic patients.

Finally, we also evaluated the medium length of hospital stay, concluding that in sarcopenic and non-sarcopenic patients the average time of hospitalization was respectively of 21 days and 17 days (Figure 3). Therefore, as shown in literature's findings, we can confirm that in sarcopenic patients the average hospital stay is 20% longer than in non sarcopenic ones.

Summing up, our study can state that, after PD, preoperative sarcopenia results in worse overall survival (Figure 1), worse recurrences free survival (Figure 2), and augmented medium hospital stay (Figure 3).

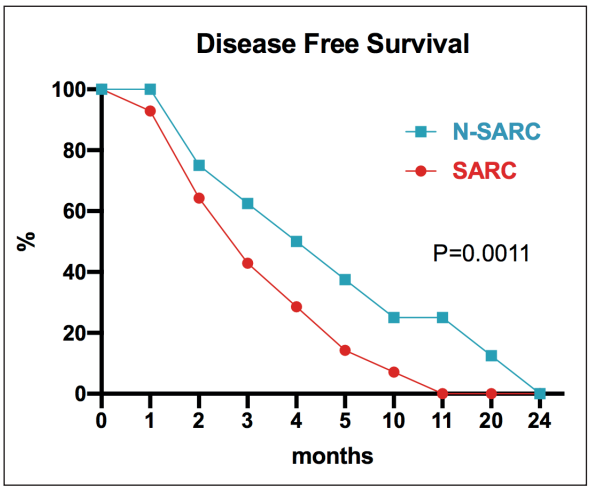

Figure 2. Desease free survival.

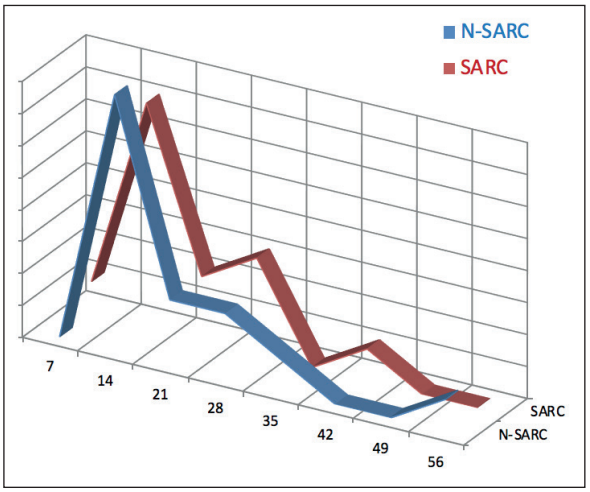

Figure 3. Lenght of hospitalization.

Discussion

Pancreatic adenocarcinoma is one of the most life-threatening tumors with a life expectancy of ~5% at 5 years, expectancy that has seen no improvement over the past 20 years, with incidence and mortality rate remaining unchanged in the past decade[30,43,44]. This happens because of two important factors: first because the great majority of patients progresses to metastatic or locally advanced disease without manifesting symptoms; secondly because only a small percentage, about 15-20%, is resectable and can be surgically treated with a radical aim, obtaining a 5 years survival-rate of about the 20% of patients[1,19,35,45], despite the enormous developments achieved by radiological techniques, by adjuvant or neoadjuvant therapies or radiotherapy that has managed to reach high standards of efficacy and tolerability[1,19,46]. Except for tumors located in the pancreas body or in the pancreas tail (30%), pancreaticoduodenectomy (PD), also known as whipple procedure, is by far the most frequent surgery to undertake.

Recently, literature has proved how the systematic clinical evaluation of factors related to the nutritional status can act as an important predictive corollary in the preoperative risk assessment of patient undergoing major surgery for cancer[4,19,23,26,47].

In fact, patients with cancer frequently experience nutritional status disorders, and the risk of muscle depletion comes from two different types of wasting disorders that can be related but are not synonyms: cachexia and sarcopenia. Cachexia is defined as a cytokine-mediated degradation of muscle and sometimes adipose depots, while Sarcopenia is defined as the age-related decreasing in muscle mass, associated with changes in muscle synthesis signaling pathways.

The "European Working Group on Sarcopenia in Older People" (EWGSOP) has recently described Sarcopenia as a progressive and generalized loss of skeletal muscle mass and strength, recommending that the definition, and, therefore, the diagnosis, should always include low muscle strength and functionality, even if these two parameters are difficult to evaluate in clinical practice[19].

Sarcopenia is a universal phenomenon with a complex, multi-factorial etiology. Many of the potential causes vary by the age of the individual. The major factors considered to be involved include genetic heritability[48,49], nutritional status (protein intake, energy intake, and vitamin D status)[50-52], physical activity[53-55], hormonal changes (declines in serum testosterone and growth hormone), insulin resistance[56-58], atheroscelorosis[59-61] and changes in circulating pro-inflammatory cytokines[62].

Over the age span from 20 to 80 years of age, there is approximately a 30% reduction in muscle mass and a decline in cross-sectional area of about 20%[63]. This is due to a decline in both muscle fiber size and number. There is no consensus on whether there is a selective loss of specific muscle fiber types. Early cross-sectional studies demonstrated a shift in muscle fiber composition with a higher type I/type II fiber ratio with advancing age[64]. Larsson et al[65] suggested a preferential loss of type II fibers with advancing age, potentially starting in early adulthood. Type II fibers demonstrate selective atrophy (with a preservation of Type I fiber area) with age[66]. This is due to a reduction in high intensity activities that recruit these fibers, while type I fibers are used for most activities of daily living and during submaximal exercise (e.g. walking)[67].

Muscle protein metabolism depends on muscle protein breakdown (MPB) and muscle protein synthesis (MPS)[68]. In elderly the balance between these parameters is altered, with the loss of skeletal muscle mass[68].

In the last years, has gained more interest the role of inlammation in the regulation of muscle protein metabolism.

Aging is in fact associated with a chronic state of inflammation, with the presence in the plasma of pro-inflammatory markers (TNFα, IL-6 and

CRP). This state is often referred to increased numbers of cells that are in the state of cellular senescence: it seems to be an association between senescence and the production of pro-inflammatory cytokines, maybe linked to the irreparable DNA damage[69,70].

Moreover, age-related reduction in motor nerve cells responsible for sending signals from the brain to the muscles to initiate movement also occurs. Satellite cells are small mononuclear cells that abut muscle fibers and are normally activated upon injury or exercise. In response to these signals, satellite cells differentiate and fuse into the muscle fiber, helping to maintain muscle function. One current hypothesis is that sarcopenia is caused, in part, by a failure in satellite cell activation[71,72] (Figure 4).

Sarcopenia has been historically considered as prevalent in elderly people, but it is important to consider that this condition can also be connected, as we just stated, to deregulation in muscle signaling activity, and it often happens in chronic disease, systemic inflammation, physical inactivity and, usually, in cancer (secondary sarcopenia)[17,30].

Sarcopenic patients seems more likely to have poorer surgical outcomes and poor prognosis in many cancers, not only pancreatic ones[22,30,73]. Moreover, sarcopenia is also involved in a vicious circle made of mutual negative interactions between sarcopenia itself and chemotherapy. Indeed, there is a wide agreement showing that sarcopenic patients show a decreased response to chemotherapy because they are often forced to reduce chemotherapy dosage (or to delay the cycles of administration) due to increased toxicity. Conversely, some evidences reveal that chemotherapy can also act as a cause of sarcopenia, causing a 24-fold more rapid muscle loss compared with loss occurring in normal aging process.

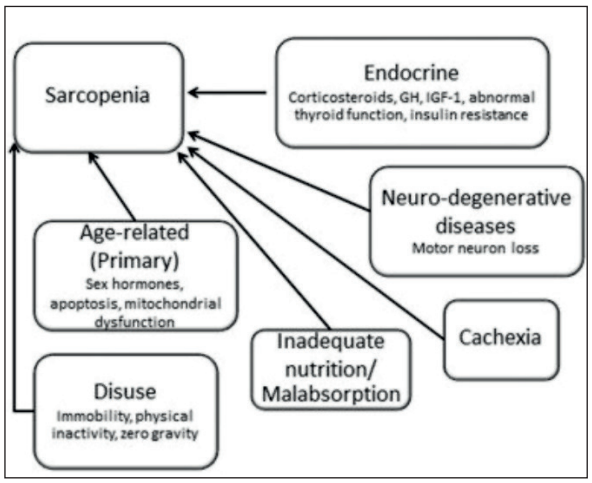

Figure 4. Pathogenesis of sarcopenia[72].

Hence, several studies ended up focusing on sarcopenia with the aim to identify a further prognostic risk factor of post-operative outcomes, in order to better select patients fit for surgery. Selecting adequate candidates for pancreas resection is crucial to implement the surgery benefits, since PD is still a high-risk operation, especially in elderly patients.

There is a wide array of assessment tools for sarcopenia and, each of them, differs in applicability in research settings and clinical settings[30]. Since different studies often utilize different appliances for assessment and not even unified cut-off values, is particularly difficult to interpret and compare results across literature. The measurable parameters of sarcopenia are the amount of muscle and its function. Several imaging techniques have been used for estimating muscle mass or lean body mass: computed tomography (CT), magnetic resonance imaging (MRI) and dual energy X-ray absorptiometry (DXA). CT and MRI are the most accurate methods that can distinguish between fat tissue and other soft tissues (firstly muscular), DXA, on the other hands, is an attractive alternative method to distinguish fat, bone mineral and lean tissues[74]. Thus, CT appears to be the best instrument, neither expensive nor time-consuming, for specific detection of sarcopenia because it is an accurate, fully available and well-recognized approach for the quantification of skeletal muscle mass, with a reported precision error of about 1.3% for lean muscle mass[75,76].

As in previous studies, we used cross-sectional CT, at the L3 level, to evaluate skeletal muscle and abdominal adipose tissue. We calculated a skeletal muscle area including Psoas, Paraspinal muscles (Erector Spinae, Multifidus and Quadratus Lumborum) and abdominal wall muscles (Transversus abdominis, external and internal Obliques and Rectus abdominis).

Conclusions

The stratification of surgical risk remains one of the great challenges for the surgeon, especially when evaluating oncological patients.

For this purpose, it appears fundamental to consider, side by side with the traditional prognostic factors related to the oncological disease

and to the patient's comorbidity, the nutritionals factors as well, that seem mandatory to be evaluated, and possibly treated, before surgery as claimed by the results of our study and by the evidences proposed by literature.

Within these factors, sarcopenia has a central role because it is a very common condition found in pancreatic cancer patients and because there are growing evidences showing that sarcopenia is associated with worse surgical outcomes, survival and chemotherapy[30].

Summing up we can state that evaluating and remediating sarcopenia in cancer patients, with a more proactive approach, could improve the postoperative outcomes, overall survival rates and, nevertheless, the recurrence free survival ones.

Acknowledgements

The following study was carried out thanks to the valuable support of the non-profit association L'Aquila Per La Vita Onlus, which for years has been fighting cancer, supporting doctors and patients.

Conflict of Interest

Pessia Beatrice and other co-authors have no conflict of interest.

References

1) Pedrazzoli S, Silvestrini R, Avogaro F, Bassi C, Boggi U, Caletti G. Basi scientifiche per la definizione di line guida in ambito clinico per i Tumori del Pancreas. Istituto Superiore di Sanità ISS. Marzo 2010.
2) Ratnayake CB, Loveday BP, Shrikhande SV, Windsor JA, Pandanaboyana S. Impact of preoperative sarcopenia on postoperative outcomes following pancreatic resection: a systematic review and meta-analysis. Pancreatology 2018; 18: 996-1004.
3) Greenblatt DY, Kelly KJ, Rajamanickam V, Wan Y, Hanson T, Rettammel R, Winslow ER, Cho CS, Weber SM. Preoperative factors predict perioperative morbidity and mortality after pancreaticoduodenectomy. Ann Surg Oncol 2011; 18: 2126-2135.
4) Giuliani A, Lazzarin G, Romano L, Coletti G, Vicentini V, Fatayer MWA, Schietroma M, Valiyeva S, Carlei F. A case report of three synchronous tumors in the same pancreatic specimen. Ann Med Surg (Lond) 2019; 44: 79-82.
5) Le'clerc Nicolas J, Romano L, Giuliani A. Acute pancreatitis: an overview. Minerva Gastroenterol Dietol 2020; 66: 290-291.
6) Uzunoglu FG, Reeh M, Vettorazzi E, Ruschke T, Hannah P, Nentwich MF, Vashist YK, Bogoevski D, König A, Janot M, Gavazzi F, Zerbi A, Todaro V, Malleo G, Uhl W, Montorsi M, Bassi C, Izbicki JR, Bockhorn M. Preoperative Pancreatic Resection (PREPARE) score: a prospective multicenter-based morbidity risk score. Ann Surg 2014; 260: 857-864.
7) Mlján de la Torre A. El músculo, elemento clave para la supervivencia en el enfermo neoplásico. Nutr Hosp 2016; 33: 175.
8) Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S, Baracos VE. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011; 12: 489-495.
9) Hasselager R, Gögenur I. Core muscle size assessed by perioperative abdominal CT scan is related to mortality, postoperative complications, and hospitalization after major abdominal surgery: a systematic review. Langenbecks Arch Surg 2014; 399: 287-295.
10) Carrara G, Pecorelli N, De Cobelli F, Cristel G, Damascelli A, Beretta L, Braga M. Preoperative sarcopenia determinants in pancreatic cancer patients. Clin Nutr 2017; 36: 1649-1653.
11) 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.
12) Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, Boirie Y, Bosaeus I, Cederholm T, Costelli P, Fearon KC, Laviano A, Maggio M, Rossi Fanelli F, Schneider SM, Schols A, Sieber CC. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr 2010; 29: 154-159.
13) Ukuda Y, Asaoka T, Eguchi H, Sasaki K, Iwagami Y, Yamada D, Noda T, Kawamoto K, Gotoh K, Kobayashi S, Ito T, Takeda Y, Tanemura M, Mori M, Doki Y. Clinical impact of preoperative sarcopenia on the postoperative outcomes after pancreas transplantation. World J Surg 2018; 42: 3364-3371.
14) Rosenberg IH. Sarcopenia: origins and clinical relevance. Clin Geriatr Med 2011; 27: 337-339.
15) Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, Garry PJ, Lindeman RD. Epidemiology of sarcopenia among the elderly in New Mexico. J Epidemiol 1998; 147: 755-763.
16) Borges TC, Gomes TLN, Pimentel GD. Sarcopenia as a predictor of nutritional status and comorbidities in hospitalized patients with cancer: a cross-sectional study. Nutrition 2020; 73: 110703.

17) Nishida Y, Kato Y, Kudo M, Aizawa H, Okubo S, Takahashi D, Nakayama Y, Kitaguchi K, Gotohda N, Takahashi S, Konishi M. Preoperative sarcopenia strongly influences the risk of postoperative pancreatic fistula formation after pancreaticoduodenectomy. J Gastrointest Surg 2016; 20: 1586-1594.

18) 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.

19) Okumura S, Kaido T, Hamaguchi Y, Fujimoto Y, Masui T, Mizumoto M, Hammad A, Mori A, Takaori K, Uemoto S. Impact of preoperative quality as well as quantity of skeletal muscle on survival after resection of pancreatic cancer. Surgery 2015; 157: 1088-1098.

20) Shimizu A, Tani M, Kawai M, Hirono S, Miyazawa M, Uchiyama K, Yamaue H. Influence of visceral obesity for postoperative pulmonary complications after pancreaticoduodenectomy. J Gastrointest Surg 2011; 15: 1401-1410.

21) Gianotti L, Sandini M. Reply to: Re: Nutritional support and therapy in pancreatic surgery: a position paper of the International Study Group on Pancreatic Surgery (ISGPS). Surgery 2019; 165: 1249.

22) Ozola Zalite I, Zykus R, Francisco Gonzalez M, Saygili F, Pukitis A, Gaujoux S, Charnley RM, Lyadov V. Influence of cachexia and sarcopenia on survival in pancreatic ductal adenocarcinoma: a systematic review. Pancreatology 2015; 15: 19-24.

23) Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: a meta-analysis and systematic review. Eur J Cancer 2016; 57: 58-67.

24) Joglekar S, Nau PN, Mezhir JJ. The impact of sarcopenia on survival and complications in surgical oncology: A review of the current literature. J Surg Oncol 2015; 112: 503-509.

25) Levolger S, van Vugt JL, de Bruin RW, IJzermans JN. Systematic review of sarcopenia in patients operated on for gastrointestinal and hepatopancreatobiliary malignancies. Br J Surg 2015; 102: 1448-1458.

26) Onesti JK, Wright GP, Kenning SE, Tierney MT, Davis AT, Doherty MG, Chung MH. Sarcopenia and survival in patients undergoing pancreatic resection. Pancreatology 2016; 16: 284-289.

27) 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.

28) Kumar A, Moynagh MR, Multinu F, Cliby WA, McGree ME, Weaver AL, Young PM, Bakkum-Gamez JN, Langstraat CL, Dowdy SC, Jatoi A, Mariani A. Muscle composition measured by CT scan is a measurable predictor of overall survival in advanced ovarian cancer. Gynecol Oncol 2016; 142: 311-316.

29) 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.

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

31) Wagner D, Büttner S, Kim Y, Gani F, Xu L, Margonis GA, Amini N, Kamel IR, Pawlik TM. Clinical and morphometric parameters of frailty for prediction of mortality following hepatopancreaticobiliary surgery in the elderly. Br J Surg 2016; 103: e83-e92.

32) Sur MD, Namm JP, Hemmerich JA, Buschmann MM, Roggin KK, Dale W. Radiographic sarcopenia and self-reported exhaustion independently predict NSQIP serious complications after pancreaticoduodenectomy in older adults. Ann Surg Oncol 2015; 22: 3897-3904.

33) Peng P, Hyder O, Firoozmand A, Kneuertz P, Schulick RD, Huang D, Makary M, Hirose K, Edil B, Choti MA, Herman J, Cameron JL, Wolfgang CL, Pawlik TM. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. J Gastrointest Surg 2012; 16: 1478-1486.

34) Di Sebastiano KM, Yang L, Zbuk K, Wong RK, Chow T, Koff D, Moran GR, Mourtzakis M. Accelerated muscle and adipose tissue loss may predict survival in pancreatic cancer patients: the relationship with diabetes and anaemia. Br J Nutr 2013; 109: 302-312.

35) Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, Seufferlein T, Haustermans K, Van Laethem JL, Conroy T, Arnold D; ESMO Guidelines Committee. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26: v56-v68.

36) Giuliani A, Romano L, Coletti G, Walid A Fatayer M, Calvisi G, Maffione F, Muolo C, Vicentini V, Schietroma M, Carlei F. Lymphangiomatosis of the ileum with perforation: a case report and review of the literature. Ann Med Surg (Lond) 2019; 41: 6-10.

37) Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994; 47: 1245-1251.

38) Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240: 205-213.

39) Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, Allen P, Andersson R, Asbun HJ, Besselink MG, Conlon K, Del Chiaro M, Falconi M, Fernandez-Cruz L, Fernandez-Del Castil-

lo C, Fingerhut A, Friess H, Gouma DJ, Hackert T, Izbicki J, Lillemoe KD, Neoptolemos JP, Olah A, Schulick R, Shrikhande SV, Takada T, Takaori K, Traverso W, Vollmer CR, Wolfgang CL, Yeo CJ, Salvia R, Buchler M; International Study Group on Pancreatic Surgery (ISGPS). The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery 2017; 161: 584-591.

40) Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 2008; 33: 997-1006.

41) Vehmas T, Kairemo KJ, Taavitsainen MJ. Measuring visceral adipose tissue content from contrast enhanced computed tomography. Int J Obes Relat Metab Disord 1996; 20: 570-573.

42) 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.

43) Schietroma M, Pessia B, Carlei F, Amicucci G. Intestinal permeability changes, systemic endotoxemia, inflammatory serum markers and sepsis after Whipple's operation for carcinoma of the pancreas head. Pancreatology 2017; 17: 839-846.

44) Wolfgang CL, Herman JM, Laheru DA, Klein AP, Erdek MA, Fishman EK, Hruban RH. Recent progress in pancreatic cancer. CA Cancer J Clin 2013; 63: 318-348.

45) Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11-30.

46) Dijk F, Veenstra VL, Soer EC, Dings MPG, Zhao L, Halfwerk JB, Hooijer GK, Damhofer H, Marzano M, Steins A, Waasdorp C, Busch OR, Besselink MG, Tol JA, Welling L, van Rijssen LB, Klompmaker S, Wilmink HW, van Laarhoven HW, Medema JP, Vermeulen L, van Hooff SR, Koster J, Verheij J, van de Vijver MJ, Wang X, Bijlsma MF. Unsupervised class discovery in pancreatic ductal adenocarcinoma reveals cell-intrinsic mesenchymal features and high concordance between existing classification systems. Sci Rep 2020; 10: 337.

47) Schietroma M, Pessia B, Carlei F, Amicucci G. Septic complications after pancreatoduodenectomy for pancreatic adenocarcinoma: are increased gut permeability and inflammatory serum markers responsible? Pancreas 2016; 45: e47-e48.

48) Carey KA, Farnfield MM, Tarquinio SD, Cameron-Smith D. Impaired expression of Notch signaling genes in aged human skeletal muscle. J Gerontol A Biol Sci Med Sci 2007; 62: 9-17.

49) Schrager MA, Roth SM, Ferrell RE, Metter EJ, Russek-Cohen E, Lynch NA, Lindle RS, Hurley BF. Insulin-like growth factor-2 genotype, fat-free mass, and muscle performance across the adult life span. J Appl Physiol 2004; 97: 2176-2183.

50) Volpi E, Sheffield-Moore M, Rasmussen BB, Wolfe RR. Basal muscle amino acid kinetics and protein synthesis in healthy young and older men. JAMA 2001; 286: 1206-1212.

51) Katsanos CS, Kobayashi H, Sheffield-Moore M, Aarsland A, Wolfe RR. Aging is associated with diminished accretion of muscle proteins after the ingestion of a small bolus of essential amino acids. Am J Clin Nutr 2005; 82: 1065-1073.

52) Campbell WW, Trappe TA, Wolfe RR, Evans WJ. The recommended dietary allowance for protein may not be adequate for older people to maintain skeletal muscle. J Gerontol A Biol Sci Med Sci 2001; 56: M373-380.

53) Kuh D, Bassey EJ, Butterworth S, Hardy R, Wadsworth ME; Musculoskeletal Study Team. Grip strength, postural control, and functional leg power in a representative cohort of British men and women: associations with physical activity, health status, and socioeconomic conditions. J Gerontol A Biol Sci Med Sci 2005; 60: 224-231.

54) Hughes VA, Roubenoff R, Wood M, Frontera WR, Evans WJ, Fiatarone Singh MA. Anthropometric assessment of 10-y changes in body composition in the elderly. Am J Clin Nutr 2004; 80: 475-482.

55) Kortebein P, Symons TB, Ferrando A, Paddon-Jones D, Ronsen O, Protas E, Conger S, Lombeida J, Wolfe R, Evans WJ. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. JAMA 2007; 297: 1772-1774.

56) Guillet C, Boirie Y. Insulin resistance: a contributing factor to age-related muscle mass loss? Diabetes Metab 2005; 31: 5S20-5S6.

57) Park SW, Goodpaster BH, Lee JS, Kuller LH, Boudreau R, de Rekeneire N, Harris TB, Kritchevsky S, Tylavsky FA, Nevitt M, Cho YW, Newman AB; Health, Aging, and Body Composition Study. Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. Diabetes Care 2009; 32: 1993-1997.

58) Park SW, Goodpaster BH, Strotmeyer ES, de Rekeneire N, Harris TB, Schwartz AV, Tylavsky FA, Newman AB. Decreased muscle strength and quality in older adults with type 2 diabetes: the health, aging, and body composition study. Diabetes 2006; 55: 1813-1818.

59) McDermott MM, Liu K, Greenland P, Guralnik JM, Criqui MH, Chan C, Pearce WH, Schneider JR, Ferrucci L, Celic L, Taylor LM, Vonesh E, Martin GJ, Clark E. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. JAMA 2001; 286: 1599-1606.

60) McDermott MM, Guralnik JM, Albay M, Bandinelli S, Miniati B, Ferrucci L.Impairments of muscles and nerves associated with peripheral arterial disease and their relationship with lower extremity functioning: the InCHIANTI Study. J Am Geriatr Soc 2004; 52: 405-410.

61) McDermott MM, Guralnik JM, Ferrucci L, Tian L, Pearce WH, Hoff F, Liu K, Liao Y, Criqui MH. Physical activity, walking exercise, and calf skele-

tal muscle characteristics in patients with peripheral arterial disease. J Vasc Surg 2007; 46: 87-93.

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

63) Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R. Aging of skeletal muscle: a 12–yr longitudinal study. J Appl Physiol 2000; 88: 1321-1326.

64) Larsson L. Morphological and functional characteristics of the aging skeletal muscle in man. Acta Physiol Scand Suppl 1978; 457: 1-36.

65) Larsson L. Histochemical characteristics of human skeletal muscle during aging. Acta Physiol Scand 1983; 117: 469-471.

66) Lexell J, Taylor CC, Sjostrom M. What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15– to 83–year–old men. J Neurol Sci 1988; 84: 275-294.

67) Reeves ND, Narici MV, Maganaris CN. Myotendinous plasticity to ageing and resistance exercise in humans. Exp Physiol 2006; 91: 483-498.

68) Churchward-Venne TA, Breen L, Phillips SM. Alterations in human muscle protein metabolism with aging: protein and exercise as countermeasures to offset sarcopenia. Biofactors 2014; 40: 199-205.

69) Dirks AJ, Hofer T, Marzetti E, Pahor M, Leeuwenburgh C. Mitochondrial DNA mutations, energy metabolism and apoptosis in aging muscle. Ageing Res Rev 2006; 5: 179-195.

70) Tchkonia T, Zhu Y, van Deursen J, Campisi J, Kirkland JL. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. J Clin Invest 2013; 123: 966-972.

71) Booth FW, Chakravarthy MV, Spangenburg EE. Review exercise and gene expression: physiological regulation of the human genome through physical activity. J Physiol 2002; 543: 399-411.

72) Ruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in older People. Age Ageing 2019; 48: 601.

73) Braga M, Capretti G, Pecorelli N, Balzano G, Doglioni C, Ariotti R, Di Carlo V. A prognostic score to predict major complications after pancreaticoduodenectomy. Ann Surg 2011; 254: 702-708.

74) Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res 2009; 15: 6973-6979.

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

76) Voron T, Tselikas L, Pietrasz D, Pigneur F, Laurent A, Compagnon P, Salloum C, Luciani A, Azoulay D. Sarcopenia impacts on short- and long-term results of hepatectomy for hepatocellular carcinoma. Ann Surg 2015; 261: 1173-1183.