International Journal of Surgery 39 (2017) 45-51



Contents lists available at ScienceDirect

# International Journal of Surgery

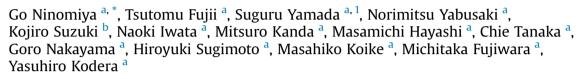
journal homepage: www.journal-surgery.net

Original research

# Clinical impact of sarcopenia on prognosis in pancreatic ductal adenocarcinoma: A retrospective cohort study



CrossMark



<sup>a</sup> Department of Gastroenterological Surgery (Surgery II), Nagoya University Graduate School of Medicine, Japan
<sup>b</sup> Department of Radiology, Nagoya University Graduate School of Medicine, Japan

# HIGHLIGHTS

• Skeletal muscle index was measured in pancreatic ductal adenocarcinoma patients by using preoperative computed tomography.

• Low-skeletal muscle index was an independent prognostic factor for overall survival in patients with Body mass index  $\geq$  22.

• Body mass index and visceral fat area was not associated with prognosis.

• Computed tomography is a simple and useful tool for predicting prognosis.

#### ARTICLE INFO

Article history: Received 8 November 2016 Received in revised form 9 January 2017 Accepted 14 January 2017 Available online 18 January 2017

Keywords: Sarcopenia Pancreatic ductal adenocarcinoma Pancreatic cancer

# ABSTRACT

*Objectives:* To investigate the impact of the body composition such as skeletal muscle, visceral fat and body mass index (BMI) on patients with resected pancreatic ductal adenocarcinoma (PDAC).

*Methods:* A total of 265 patients who underwent curative surgery for PDAC were examined in this study. The total skeletal muscle and fat tissue areas were evaluated in a single image obtained at the third lumber vertebra during a preoperative computed tomography (CT) scan. The patients were assigned to either the sarcopenia or non-sarcopenia group based on their skeletal muscle index (SMI) and classified into high visceral fat area (H-VFA) or low VFA (L-VFA) groups. The association of clinicopathological features and prognosis with the body composition were statistically analyzed.

*Results*: There were 170 patients (64.2%) with sarcopenia. The median survival time (MST) was 23.7 months for sarcopenia patients and 25.8 months for patients without sarcopenia. The MST was 24.4 months for H-VFA patients and 25.8 months for L-VFA patients. However, sarcopenia patients with BMI  $\geq$ 22 exhibited significantly poorer survival than patients without sarcopenia (MST: 19.2 vs. 35.4 months, P = 0.025). There was a significant difference between patients with and without sarcopenia who did not receive chemotherapy (5-year survival rate: 0% vs. 68.3%, P = 0.003). The multivariate analysis revealed that tumor size, positive dissected peripancreatic tissue margin, and sarcopenia were independent prognostic factors.

Conclusions: Sarcopenia is an independent prognostic factor in PDAC patients with a BMI ≥22. Therefore, evaluating skeletal muscle mass may be a simple and useful approach for predicting patient prognosis. © 2017 IJS Publishing Group Ltd. Published by Elsevier Ltd. All rights reserved.

#### 1. Introduction

<sup>1</sup> Contributed equally to this research.

Pancreatic ductal adenocarcinoma (PDAC) continues to have the worst prognosis of all the gastrointestinal malignancies despite the recent development of several preoperative and postoperative treatments [1]. A complete surgical resection offers the only

http://dx.doi.org/10.1016/j.ijsu.2017.01.075 1743-9191/© 2017 IJS Publishing Group Ltd. Published by Elsevier Ltd. All rights reserved.

<sup>\*</sup> Corresponding author. Department of Gastroenterological Surgery (Surgery II), Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi, 466-8550, Japan.

E-mail address: gonino@med.nagoya-u.ac.jp (G. Ninomiya).

possibility of cure. However, less than 20% of patients have localized and potentially curable tumors at the time of diagnosis, and considerable advances in diagnostic techniques are required [2,3]. As a result, only moderate improvements in patient outcomes have been achieved.

Previous studies have identified prognostic factors, including both pancreatic cancer-specific clinicopathological factors and individual patient characteristics. Factors such as weight loss, muscle wasting, and cachexia are hallmarks of PDAC that may be associated with the depletion of both skeletal muscle and adipose tissue [4–6]. Sarcopenia is defined as the degenerative loss of skeletal muscle mass that is quantifiable using cross-sectional imaging computed tomography (CT) measurements of psoas area and muscle density [7]. Visceral adipose tissue loss is also associated with poor survival in pancreatic cancer patients [8]. Cumulatively, these findings suggest that the characterization of changes in the composition of various body compartments may provide important prognostic information for patients with PDAC.

Previous studies have demonstrated that up to 50% of patients with advanced cancer have frank sarcopenia [9,10]. Although only a few studies have examined the association between the presence of sarcopenia and outcomes following surgery, these studies have demonstrated that sarcopenia is associated with poor survival in patients undergoing surgery for melanoma, colorectal liver metastasis, liver transplantation, and pancreatic cancer [11–15]. Therefore, it is important to identify useful prognostic factors and individual patient characteristics to determine the best therapeutic approach in each case. However, the impact of sarcopenia on overall survival in PDAC remains unclear.

The aim of this study was to identify the impact of the body composition such as skeletal muscle, visceral fat, and BMI in patients undergoing resection for PDAC and to investigate the relationship between various body composition characteristics, clinical factors, and outcomes of patients with PDAC.

#### 2. Materials and methods

# 2.1. Patients

Two hundred and sixty-five patients who underwent surgery with curative intent for PDAC between May 2005 and November 2014 in the Department of Gastroenterological Surgery, Nagoya University Hospital were recruited. All patients were confirmed to have a histological diagnosis of PDAC. A total of 187 patients underwent pancreaticoduodenectomy, and 60 patients underwent distal pancreatectomy. 18 patients underwent total pancreatectomy. Pancreatectomy and systematic lymphadenectomy were performed with curative intent in all patients. We excluded patients for the following reasons: received neoadjuvant chemoradiation therapy (n = 41), and underwent middle pancreatectomy due to different preoperative diagnosis (n = 1). Conversely, we included patients as follows: diagnosed as having distant metastasis during surgery (n = 22), and surgical death (n = 2).

All patients were evaluated for the expression of CA19-9 and examined by CT every 6 months after discharge. 164 patients had recurrence, and the breakdowns are as follows: liver recurrence (n = 2), local recurrence (n = 42), peritoneal recurrence (n = 34), lymph node recurrence (n = 22), lung recurrence (n = 8), remnant pancreas recurrence (n = 4), and bone recurrence (n = 2).

The median follow-up duration was 16.3 months (range, 0.4–107.7 months). A total of 174 patients were treated with adjuvant chemotherapy (gemcitabine and/or S-1, oral 5-fluorouracil prodrug tegafur with oteracil, and gimeracil). Gemcitabine was administered at a dose of 1000 mg/m<sup>2</sup> weekly for 3 weeks, followed by 1 week of withdrawal. Oral S-1 was

administered at a dose of 80 mg/m<sup>2</sup> from days 1–14, followed by a 1-week withdrawal period. All chemotherapy treatments were initiated within 2 months of surgery in eligible patients, and the treatment continued for a minimum of 6 months. Written informed consent for inclusion in the study, as required by the Institutional Review Board of Nagoya University, was obtained from all patients.

#### 2.2. Image analysis

All patients underwent preoperative abdominal CT within 30 days of surgery. The total skeletal muscle and fat tissue area  $(cm^2)$ were evaluated in a single image at the 3rd lumber vertebra (L3) using Hounsfield unit thresholds of -29 to +150 for skeletal muscle and -200 to -50 for visceral and subcutaneous fat tissues. The preoperative CT images were used for all assessments. All CT images were analyzed using SYNAPSE VINCENT software version 4.0 (Fuji Film, Tokyo, Japan). The cross-sectional skeletal muscle area  $(cm^2)$  was normalized by the square of the height  $(m^2)$  to obtain the L3 skeletal muscle index (SMI,  $cm^2/m^2$ ). The cut-off values for skeletal muscle were defined as 43.75 cm<sup>2</sup>/m<sup>2</sup> for men and  $38.5 \text{ cm}^2/\text{m}^2$  for women [16]. The cut-off values for visceral fat area (VFA) were defined as 103 cm<sup>2</sup> for men and 69.0 cm<sup>2</sup> for women. These values are associated with metabolic abnormalities in Japan [17]. These cut-off values were used to assign patients to the sarcopenia or non-sarcopenia groups and the high VFA (H-VFA) or low VFA (L-VFA) groups.

# 2.3. Statistical analysis

All differences in the numerical data between groups were evaluated using Fisher's exact test or the  $\chi^2$  test. The patient overall survival rates were calculated using the Kaplan-Meier method. The difference in survival curves was analyzed using the log-rank test. The independent prognostic factors were analyzed with a Cox proportional hazards regression model. All data are expressed as the means  $\pm$  SD. The presence of a statistically significant difference was denoted by P < 0.05. The data were analyzed using JMP version 10 software (JMP, SAS Institute, Cary, NC).

## 3. Results

# 3.1. Patient demographics

The clinical and pathological characteristics of the 265 patients included in this study are shown in Table 1. The average patient age in this study population was 65.4 years. There were 164 (62%) male patients and 101 (38%) female patients. The tumor was located at the head of the pancreas in 198 patients. The tumor was larger than 2 cm in diameter in the majority of patients (74.7%). The pathological analysis indicated that 62.6% of patients had lymph node metastasis. Additionally, portal vein invasion was observed in 40.0% of the patients. There were 145 patients (54.7%) with postoperative complications  $\geq$  Clavien-Dindo II. There were no deaths within 90 days of resection.

The average SMI was 40.2 cm<sup>2</sup>/m<sup>2</sup> after normalizing by patient height. The SMI was significantly higher in males than females (43.6 vs. 34.6 cm<sup>2</sup>/m<sup>2</sup>, P < 0.001). The SMI and VFA values in the high BMI ( $\geq$ 22) group were significantly higher than those in the low BMI (<22) group regardless of gender. The average VFA and Subcutaneous fat area (SFA) were significantly different between male and female patients (105.3 vs. 71.9 cm<sup>2</sup>, P < 0.001, 69.0 vs. 93.6 cm<sup>2</sup>, P < 0.001; Table 1).

Table 1
Patient demographics.

	Male (n = 164)	Female ( $n = 101$ )	<i>P</i> -value	
Age (mean $\pm$ SD, range), (years)	65 ± 10.5	66 ± 9.3	0.279	
BMI (mean $\pm$ SD), (kg/m <sup>2</sup> )	21.7 ± 2.8	$21.5 \pm 3.6$	0.261	
Tumor location (head/body and tail)	122 (74.7%)/42 (25.3%)	76 (75.3%)/25 (24.7%)	0.673	
TNM stage (I//IIA/IIB/III/IV)	6/47/99/1/11	1/25/63/1/11	0.476	
Tumor size $\geq 2$ cm	116 (72.5%)	85 (84.2%)	0.029 <sup>a</sup>	
Lymph node metastasis	92 (56.1%)	74 (73.3%)	0.005 <sup>a</sup>	
Portal vein invasion	57 (35.0%)	49 (48.5%)	0.029 <sup>a</sup>	
$CA19-9 \ge 100 (U/ml)$	91 (55.5%)	64 (63.4%)	0.206	
Chemotherapy	109 (66.6%)	65 (64.3%)	0.672	
Postoperative complication (>Clavien Dindo II)	97 (59.2%)	48 (47.5%)	0.065	
Skeletal muscle area (mean $\pm$ SD), (cm <sup>2</sup> )	$119.7 \pm 20.6$	80.0 ± 13.3	< 0.001 <sup>a</sup>	
SMI (mean $\pm$ SD), (cm <sup>2</sup> /m <sup>2</sup> )	$43.6 \pm 6.9$	$34.6 \pm 5.5$	< 0.001 <sup>a</sup>	
VFA (mean $\pm$ SD), (cm <sup>2</sup> )	$105.7 \pm 68.3$	71.9 ± 51.5	<0.001 <sup>a</sup>	
SFA (mean $\pm$ SD), (cm <sup>2</sup> )	67.6 ± 36.70	94.8 ± 52.9	<0.001 <sup>a</sup>	
Total body FM (mean $\pm$ SD), (kg)	$7.8 \pm 4.1$	7.5 ± 4.1	0.591	
FM index (mean $\pm$ SD), (kg/m <sup>2</sup> )	$2.8 \pm 1 \ 0.5$	3.2 ± 1.7	0.043 <sup>a</sup>	
BSA (mean $\pm$ SD), (m <sup>2</sup> )	$1.65 \pm 0.1$	$1.44 \pm 0.1$	< 0.001 <sup>a</sup>	

BMI Body mass index, TNM tumor node metastasis, SMI Skeletal muscle index, VFA visceral fat area, SFA Subcutaneous fat area, FM Fat mass, BSA Body surface area. <sup>a</sup> Statistically significant.

# 3.2. Comparison of clinical factors based on SMI or VFA or BMI

There were 170 (64.2%) cases with sarcopenia based on the SMI among the 265 patients with resected PDAC. A comparison of clinical factors in the sarcopenia and non-sarcopenia groups showed that the BMI (20.6 vs. 23.4 kg/m<sup>2</sup>, P < 0.001), SMI (36.0 vs. 47.6 cm<sup>2</sup>/m<sup>2</sup>, P < 0.001), VFA (82.7 vs. 111.1 cm<sup>2</sup>, P < 0.001), and fat mass (FM) index (2.8 vs. 3.3 kg/m<sup>2</sup>, P = 0.006) of patients with sarcopenia were significantly lower than those of the patients without sarcopenia (Table 2).

The BMI of the L-VFA group was significantly lower than that of the H-VFA group (19.9 vs. 23.6 kg/m<sup>2</sup>, P < 0.001). Additionally, the surgical time was significantly shorter (402 vs. 443 min, P = 0.006) and the blood loss was lower (929 vs. 1247 ml, P = 0.006) in the L-VFA group than in H-VFA group. The number of dissected lymph nodes was lower in the H-VFA group (29.6 vs. 24.3, P = 0.006). The postoperative complication rate was higher in the H-VFA group than in the L-VFA group (65.8 vs. 45.7%, P < 0.001; Table 3).

The SMI, VFA values, and FM index of high BMI ( $\geq$ 22) group were significantly higher than those in the low BMI (<22) group (43.6 vs. 37.6, 133.9 vs. 62.8, 4.1 vs. 2.1, P < 0.001). The postoperative complication rate was higher in the high BMI ( $\geq$ 22) group than that in the low BMI (<22) group (50.5 vs. 28.1%, P < 0.001; Table 4).

# 3.3. Overall survival in the patients with resected PDAC according to sarcopenia presence

The overall survival curves for the patients with or without sarcopenia and VFA are shown in Fig. 1. The median survival time (MST) of the patients with sarcopenia was 23.7 months. The MST of patients without sarcopenia was 25.8 months (P = 0.185). The MST was 24.4 months in the H-VFA group and 25.8 months in the L-VFA group (P = 0.757). As a result, there were no significant differences in the SMI and VFA when all the enrolled patients were analyzed.

According to the receiver operating characteristic (ROC) curve for BMI and sarcopenia, the optimal cutoff value for BMI was 21.6 (sensitivity, 66.3% and specificity, 70.1%) (data not shown). Therefore, we applied an approximate value of 22, which was considered the standard value [18]. The overall survival was also analyzed after the patients were stratified by BMI and chemotherapy (Fig. 2). When the patients were sub-analyzed by BMI, the sarcopenia patients were found to have a significantly worse prognosis than the non-sarcopenia patients in the group with a BMI  $\geq$ 22 (MST: 19.2 vs. 35.4 months after surgery, P = 0.025). There was also a significant survival difference between the sarcopenia and non-sarcopenia patients who did not receive chemotherapy (5-year survival rate: 0 vs. 68.3%, P = 0.003). Among the elderly patients (age  $\geq$  65 years) with sarcopenia, the MST was 22.1 months. However, the MST in patients without sarcopenia was 38.4 months (P = 0.083, Fig. 3).

Table 2	
Comparison of clinical factors based or	n sarcopenia.

	Sarcopenia (n = 170)	No sarcopenia (n = 95)	P-value
Age (mean $\pm$ SD), (years)	67 ± 9.4	63 ± 10.9	0.006 <sup>a</sup>
Sex (male: female)	90 (52.9%): 80 (47.1%)	74 (77.9%): 21 (22.1%)	<0.001 <sup>a</sup>
BMI (mean $\pm$ SD), (kg/m <sup>2</sup> )	$20.6 \pm 2.7$	$23.4 \pm 3.0$	<0.001 <sup>a</sup>
Tumor location (head/body and tail)	131 (77.1%)/39 (22.9%)	67 (70.5%)/28 (29.5%)	0.241
Tumor size (mean $\pm$ SD), (cm)	2.9 ± 1.18	2.9 ± 1.39	0.887
TNM stage (I//IIA/IIB/III/IV)	3/45/105/2/15	4/27/57/0/7	0.597
SMI (mean $\pm$ SD), (cm <sup>2</sup> /m <sup>2</sup> )	$36.0 \pm 5.1$	$47.6 \pm 5.8$	< 0.001 <sup>a</sup>
VFA (mean $\pm$ SD), (cm <sup>2</sup> )	82.7 ± 62.8	111.1 ± 63.7	<0.001 <sup>a</sup>
FM index (mean $\pm$ SD), (kg/m <sup>2</sup> )	2.8 ± 1.6	3.3 ± 1.6	0.006 <sup>a</sup>
Operation time (mean $\pm$ SD), (min)	418.4 ± 113	427.7 ± 129	0.539
Blood loss (mean $\pm$ SD), (ml)	1023 ± 776	1172 ± 1193	0.218
Number of dissected lymph nodes (mean $\pm$ SD)	28.6 ± 15.8	24.6 ± 14.7	0.019 <sup>a</sup>
Postoperative complication (>Clavien Dindo II)	91 (53.8%)	54 (56.8%)	0.541
90-day mortality	0 (0%)	0 (0%)	N.A.

BMI Body mass index, TNM tumor node metastasis, SMI Skeletal muscle index, VFA visceral fat area, FM Fat mass. <sup>a</sup> Statistically significant.

#### Table 3

Comparison of clinical factors based on visceral fat area.

	Low (n = 142)	High $(n = 123)$	P-value
Age (mean ± SD), years	65 ± 10.4	$66 \pm 9.4$	0.182
Sex (M: F)	85 (59.9%): 57 (40.1%)	79 (64.2%): 44 (35.8%)	0.465
BMI (mean $\pm$ SD), (kg/m <sup>2</sup> )	$19.9 \pm 2.4$	23.6 ± 2.7	< 0.001 <sup>a</sup>
Tumor location (head/body and tail)	111 (78.2%)/31 (21.8%)	87 (70.7%)/36 (29.3%)	0.165
Tumor size (mean $\pm$ SD)	2.9 ± 1.23	$2.8 \pm 1.3$	0.387
TNM stage (IA/IIA/IIB/III/IV)	4/32/89/2/15	3/40/73/0/7	0.185
SMI (mean $\pm$ SD), (cm <sup>2</sup> /m <sup>2</sup> )	$38.7 \pm 7.4$	41.9 ± 7.8	0.007 <sup>a</sup>
VFA (mean $\pm$ SD), (cm <sup>2</sup> )	45.9 ± 25.2	147.3 ± 52.3	< 0.001 <sup>a</sup>
FM index (mean $\pm$ SD), (kg/m <sup>2</sup> )	$1.9 \pm 0.9$	$4.3 \pm 1.2$	< 0.001 <sup>a</sup>
Operation time (mean $\pm$ SD), (min)	$402 \pm 114$	443 ± 121	0.006 <sup>a</sup>
Blood loss (mean $\pm$ SD), (ml)	$929 \pm 792$	$1247 \pm 1078$	0.006 <sup>a</sup>
Number of dissected lymph nodes (mean $\pm$ SD)	$29.6 \pm 14.9$	24.3 ± 15.8	0.006 <sup>a</sup>
Postoperative complication (>Clavien Dindo II)	64 (45.7%)	81 (65.8%)	<0.001 <sup>a</sup>
90-day mortality	0 (0%)	0 (0%)	N.A.

BMI Body mass index, TNM tumor node metastasis, SMI Skeletal muscle index, VFA visceral fat area, FM Fat mass.

<sup>a</sup> Statistically significant.

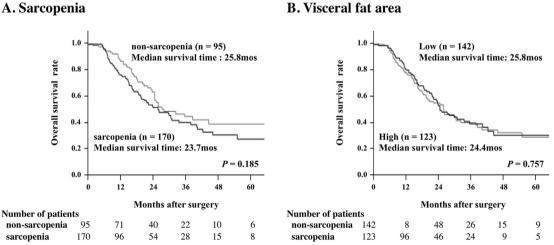
# Table 4

Comparison of clinical factors based on Body mass index.

	BMI (≥22, n = 112)	BMI (<22, n = 153)	P-value
Age (mean $\pm$ SD), (years)	65 ± 10.8	66 ± 9.5	0.395
Sex (male: female)	71 (63.4%): 41 (36.6%)	93(60.8%): 60 (39.2%)	< 0.666
BMI (mean $\pm$ SD), (kg/m <sup>2</sup> )	$24.4 \pm 2.3$	$19.6 \pm 1.8$	< 0.001 <sup>a</sup>
Tumor location (head/body and tail)	77 (68.8%)/35 (31.2%)	121 (79.1%)/32 (20.9%)	0.056
Tumor size (mean $\pm$ SD), (cm)	$2.8 \pm 1.21$	3.0 ± 1.28	0.103
TNM stage (I//IIA/IIB/III/IV)	4/32/72/0/4	3/40/90/2/18	0.099
SMI (mean $\pm$ SD), (cm <sup>2</sup> /m <sup>2</sup> )	$43.6 \pm 8.0$	$37.6 \pm 6.5$	< 0.001 <sup>a</sup>
VFA (mean $\pm$ SD), (cm <sup>2</sup> )	133.9 ± 63.1	$62.8 \pm 46.6$	<0.001 <sup>a</sup>
FM index (mean $\pm$ SD), (kg/m <sup>2</sup> )	$4,1 \pm 1.5$	$2.1 \pm 1.1$	< 0.001 <sup>a</sup>
Operation time (mean $\pm$ SD), (min)	437.1 ± 123	$410.5 \pm 114$	0.073
Blood loss (mean $\pm$ SD), (ml)	1153 ± 1037	$1020 \pm 875$	0.273
Number of dissected lymph nodes (mean $\pm$ SD)	25.1 ± 16.1	$28.6 \pm 14.9$	0.073
Postoperative complication (>Clavien Dindo II)	56 (50.5%)	43 (28.1%)	< 0.001 <sup>a</sup>
90-day mortality	0 (0%)	0 (0%)	N.A.

BMI Body mass index, TNM tumor node metastasis, SMI Skeletal muscle index, VFA visceral fat area, FM Fat mass.

<sup>a</sup> Statistically significant.



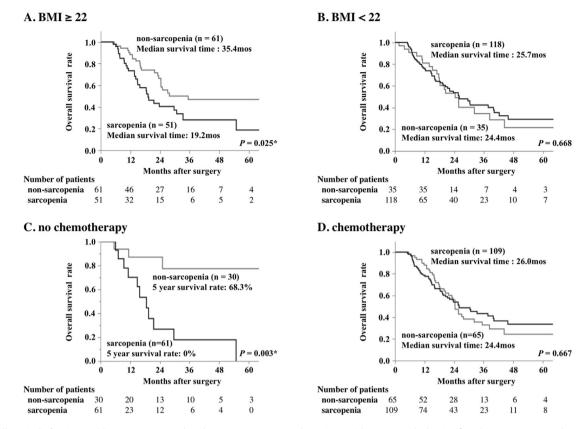
# **B.** Visceral fat area

Fig. 1. Overall survival of patients with pancreatic cancer based on sarcopenia (A) and visceral fat area (B). The MSTs were not significantly different.

# 3.4. Univariate and multivariate analyses of overall survival in patients with BMI $\geq$ 22

The univariate analysis indicated the following significant prognostic factors for overall survival in patients with a BMI >22, tumor size, lymph node metastasis, positive pathological dissected

peripancreatic tissue margin, positive pathological plexus, high serum CA19-9 levels (≥100 U/ml), and sarcopenia. The multivariate analysis showed that the significant prognostic factors for overall survival were tumor size, positive pathological dissected peripancreatic tissue margin (pDPM), and sarcopenia (Table 5).



**Fig. 2.** Overall survival of patients with pancreatic cancer based on sarcopenia status. The patients with sarcopenia had a significantly worse prognosis than patients without sarcopenia among the patients with BMI  $\geq$  22 (A, B). With regard to chemotherapy, there was a significant survival difference between the sarcopenia and non-sarcopenia groups among the patients who did not receive chemotherapy (C, D).

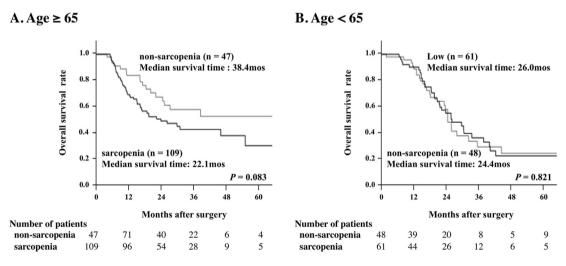


Fig. 3. Overall survival of patients with pancreatic cancer based on sarcopenia stratified by age (A, B).

#### 4. Discussion

Recent advances in surgical procedures, perioperative care, and chemotherapy after resection have improved the outcomes following pancreatic surgery [19–21]. However, the prognosis of PDAC patients remains poor. Previous studies have identified multiple prognostic factors in PDAC. These factors include both tumor-specific clinicopathological factors and individual patient characteristics. Thus, it is critical to identify clinically useful prognostic factors and individual patient characteristics to facilitate

employment of the best therapeutic approach. Our study showed that sarcopenia was an independent predictor following pancreatic surgery and that the sarcopenic patients (BMI  $\geq$  22) had a 2.1- fold increased risk of death at 5 years.

Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength [22,23]. This condition is associated with a risk of adverse outcomes, such as physical disability, poor quality of life, and death [24,25]. However, a widely accepted definition of sarcopenia suitable for use in research and clinical practice is still lacking. Several studies have

#### Table 5

Univariate and multivariate analysis of overall survival in patients with BMI >22.

	Univariate analysis		Multivariate analysis			
	HR	95% CI	P-value	HR	95% CI	P-value
Sex (male)	1.1	0.6-2.0	0.698			
Age	1.0	1.0-1.0	0.991			
Sarcopenia	1.9	1.1-3.3	0.027 <sup>a</sup>	2.1	1.2-3.7	0.013 <sup>a</sup>
VFA ( $\geq 103 \text{ cm}^2$ in men/69 cm <sup>2</sup> in women)	1.5	0.8-3.5	0.262			
Tumor location (head)	0.9	0.5-1.7	0.723			
Tumor size $\geq 2$ cm	2.9	1.4-7.2	0.003 <sup>a</sup>	2.2	1.0-5.7	0.054
Lymph node metastasis	2.4	1.3-4.7	0.006 <sup>a</sup>	1.4	0.7-2.9	0.343
pDPM (+)	2.2	1.3-3.9	0.006 <sup>a</sup>	2.1	1.2-3.9	0.017 <sup>a</sup>
pPL (+)	2.5	1.3-4.6	0.009 <sup>a</sup>	1.4	0.7-2.8	0.376
Portal vein invasion	1.6	0.9-2.9	0.083			
Peritoneal washing cytology (+)	1.9	0.8-3.8	0.127			
$CA19-9 \ge 100 (U/ml)$	2.1	1.2-3.8	0.013 <sup>a</sup>	1.8	1.0-3.5	0.051
Chemotherapy (+)	1.2	0.7-2.3	0.532			
Postoperative complication (>Clavien Dindo II)	1.2	0.7-2.3	0.521			

HR hazard ratio, CI confidence interval, VFA visceral fat area, pDPM pathological dissected peripancreatic tissue margin, pPL pathological plexus, Follow-up duration was 16.3 months (range, 0.4–107.7 months).

<sup>a</sup> Statistically significant.

demonstrated that sarcopenia has a negative impact on cancer outcomes following resection [26–28]. Overweight or obese (BMI  $\geq$  22) patients with sarcopenia exhibited worse survival than patients without sarcopenia. This result is consistent with our finding. Our results did not indicate that L-VFA and BMI were independent predictors of survival in the patients with resected PDAC. A previous study reported that there was a significant association between increased body weight and poor survival in PDAC patients [29,30]. Conversely, another study failed to demonstrate that BMI and VFA were correlated with cancer outcome [31]. The results of our study indicate that the preoperative evaluation of skeletal muscle mass may be more clinically useful than that of BMI or VFA in resected pancreatic cancer patients.

The molecular mechanisms regulating sarcopenia have not been elucidated. Muscle wasting is a known complication associated with insulin resistance found commonly in obesity [32]. Adipose tissue synthesizes and secretes circulating hormones and adipokines that act as systemic inflammatory mediators and signals of nutritional status [33]. Furthermore, various cancer-related mediators stimulate the initial loss of muscle. Thus, being overweight perpetuates and enhances muscle loss or loss of muscle function and can lead to poor survival. Therefore, preoperative nutritional support and maintenance of muscle strength are necessary to prevent muscle wasting and could lead to increased survival. The preoperative nutritional support for muscle strength maintenance includes the use of branched-chain amino acids (BCAAs) and vitamin D [34,35].

The current study has some limitations. The most frequently used cut-off values of sarcopenia for muscle mass in the Western population are 7.26 kg/m<sup>2</sup> in men and 5.45 kg/m<sup>2</sup> in women. These values were obtained by dual-energy x-ray absorptiometry (DEXA) from the study by Gallagher [36,37]. These values were converted to CT measurements of 52.4  $\text{cm}^2/\text{m}^2$  for men and 38.5  $\text{cm}^2/\text{m}^2$  for women by a regression equation to correlate the area of L3 skeletal muscle [38]. However, these values were not applied because recent Asian studies reported that the cut-off values for sarcopenia from the previous Western studies were inappropriate for Asian patients [26,39,40]. Some studies concerning the cut-off values of sarcopenia in Asia have been reported so far [39–42]. Furthermore, Asian Working group for sarcopenia (AWGS) reported that the cutoff values of muscle mass and muscle strength in Asian populations might differ from those in Caucasians because of ethnicities, body size, lifestyles, and cultural backgrounds [43]. Hence, the study

regarding the sarcopenia should be considered based on respective area of the patients, and further study is required. Additionally, muscle strength and/or physical performance could not be evaluated preoperatively. Therefore, it is necessary to investigate both skeletal muscle mass and perioperative muscle strength.

In conclusion, sarcopenia could be a valuable preoperative prognostic factor for overall survival in resected pancreatic cancer patients with BMI  $\geq$ 22. Because sarcopenia is important for determining the prognosis of patients with PDAC, evaluation of skeletal muscle mass using preoperative CT is a simple and useful tool for predicting prognosis.

#### **Ethical approval**

None.

Funding

None.

## Author contribution

Study design: Tsutomu Fujii, Suguru Yamada, Kojiro Suzuki. Data collections: Go Ninomiya.

Data analysis: Go Ninomiya, Tsutomu Fujii, Suguru Yamada, Norimitsu Yabusaki,Hiroyuki Sugimoto, Mitsuro Kanda, Goro Nakayama, Masahiko Koike, Michitaka Fujiwara, Yasuhiro Kodera. Writing: Go Ninomiya, Tsutomu Fujii, Suguru Yamada.

#### **Conflicts of interest**

The authors have no conflicts of interest to declare.

# Research registration unique identifying number (UIN)

1845.

#### Guarantor

Tsutomu Fujii, Suguru Yamada.

# References

[1] C.J. Wray, S.A. Ahmad, J.B. Matthews, et al., Surgery for pancreatic cancer:

recent controversies and current practice, Gastroenterology 128  $\left(2005\right)$  1626–1641.

- [2] J.L. Cameron, T.S. Riall, J. Coleman, et al., One thousand consecutive pancreatic oduodenectomies, Ann. Surg. 244 (2006) 10–15.
- [3] M. Hidalgo, Pancreatic cancer, N. Engl. J. Med. 362 (2010) 1605-1617.
- [4] P. Peng, O. Hyder, A. Firoozmand, et al., Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma, J. Gastrointest. Surg. 16 (2012) 1478–1486.
- [5] S. Dalal, D. Hui, L. Bidaut, 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, J. Pain Symptom Manage. 44 (2012) 181–191.
- [6] B.H. Tan, L.A. Birdsell, L. Martin, et al., Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer, Clin. Cancer Res. 15 (2009) 6973–6979.
- [7] T.N. Kim, K.M. Choi, Sarcopenia: definition, epidemiology, and pathophysiology, J. Bone Metab. 20 (2013) 1–10.
- [8] K.M. Di Sebastiano, L. Yang, K. Zbuk, et al., Accelerated muscle and adipose tissue loss may predict survival in pancreatic cancer patients: the relationship with diabetes and anaemia, Br. J. Nutr. 109 (2013) 302–312.
- [9] K. Fearon, F. Strasser, S.D. Anker, et al., Definition and classification of cancer cachexia: an international consensus, Lancet Oncol. 12 (2011) 489–495.
- [10] K.C.H. Fearon, Cancer cachexia and fat-muscle physiology, N. Engl. J. Med. 365 (2011) 565-567.
- [11] P.D. Peng, M.G. van Vledder, S. Tsai, et al., Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis, HPB Oxf. 13 (2011) 439–446.
- [12] M.S. Sabel, J. Lee, S. Cai, et al., Sarcopenia as a prognostic factor among patients with stage iii melanoma, Ann. Surg. Oncol. 18 (2011) 3579–3585.
- [13] M.J. Englesbe, S.P. Patel, K. He, et al., Sarcopenia and mortality after liver transplantation, J. Am. Coll. Surg. 211 (2010) 271–278.
- [14] S. Itoh, K. Shirabe, Y. Matsumoto, et al., Effect of body composition on outcomes after hepatic resection for hepatocellular carcinoma, Ann. Surg. Oncol. 21 (2014) 3063–3068.
- [15] K.W. Reisinger, J.L. van Vugt, J.J. Tegels, et al., Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery, Ann. Surg. 261 (2015) 345–352.
- [16] C.M. Prado, V.E. Baracos, L.J. McCargar, 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. 15 (2009) 2920–2926.
- [17] H. Kashihara, J.S. Lee, K. Kawakubo, et al., Criteria of waist circumference according to computed tomography-measured visceral fat area and the clustering of cardiovascular risk factors, Circ. J. 73 (2009) 1881–1886.
- [18] Standard for the Diagnosis of Obesity, Japan Society for the Study of Obesity, 2011.
- [19] T.M. Pawlik, A.L. Gleisner, J.L. Cameron, et al., Prognostic relevance of lymph node ratio following pancreaticoduodenectomy for pancreatic cancer, Surgery 141 (2007) 610–618.
- [20] M.B. Slidell, D.C. Chang, J.L. Cameron, et al., Impact of total lymph node count and lymph node ratio on staging and survival after pancreatectomy for pancreatic adenocarcinoma: a large, population-based analysis, Ann. Surg. Oncol. 15 (2008) 165–174.
- [21] B. Asiyanbola, A. Gleisner, J.M. Herman, et al., Determining pattern of recurrence following pancreaticoduodenectomy and adjuvant 5-flurouracil-based chemoradiation therapy: effect of number of metastatic lymph nodes and lymph node ratio, J. Gastrointest. Surg. 13 (2009) 752–759.
- [22] I.H. Rosenberg, Summary comments: epidemiological and methodological problems in determining nutritional status of older persons, Am. J. Clin. Nutr.

50 (1989) 1231-1233.

- [23] I.H. Rosenberg, Sarcopenia: origins and clinical relevance, J. Nutr. 127 (1997) 990S-991S.
- [24] M.J. Delmonico, T.B. Harris, J.S. Lee, et al., Alternative definitions of sarcopenia, lower extremity performance, and functional impairment with aging in older men and women, J. Am. Geriatr. Soc. 55 (2007) 769–774.
- [25] B.H. Goodpaster, S.W. Park, T.B. Harris, et al., The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study, J. Gerontol. Biol. Sci. Med. Sci. 61 (2006) 1059–1064.
- [26] M.G. Van Vledder, S. Levolger, N. Ayez, et al., Body composition and outcome in patients undergoing resection of colorectal liver metastases, Br. J. Surg. 99 (2012) 550–557.
- [27] N. Harimoto, K. Shirabe, Y.I. Yamashita, et al., Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma, Br. J. Surg. 100 (2013) 1523–1530.
- [28] S. Levolger, J.L. van Vugt, R.W. de Bruin, et al., Systematic review of sarcopenia in patients operated on for gastrointestinal and hepato pancreatobiliary malignancies, Br. J. Surg. 102 (2015) 1448–1458.
- [29] E.E. Calle, C. Rodriguez, K. Walker-Thurmond, et al., Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults, N. Engl. J. Med. 348 (2003) 1625–1638.
- [30] S.C. Larsson, N. Orsini, A. Wolk, Body mass index and pancreatic cancer risk: a meta-analysis of prospective studies, Int. J. Cancer 120 (2007) 1993–1998.
- [31] J.M. Genkinger, C.M. Kitahara, L. Bernstein, et al., Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies, Ann. Oncol. 26 (2015) 2257–2266.
- [32] X. Wang, Z. Hu, J. Hu, et al., Insulin resistance accelerates muscle protein degradation: activation of the ubiquitin-proteasome pathway by defects in muscle cell signaling, Endocrinology 147 (2006) 4160–4168.
- [33] S.E. Shoelson, L. Herrero, A. Naaz, Obesity, inflammation, and insulin resistance, Gastroenterology 132 (2007) 2169–2180.
- [34] L. Ceglia, Vitamin D and its role in skeletal muscle, Curr. Opin. Clin. Nutr. Metab. Care 12 (2009) 628–633.
- [35] D. Paddon-Jones, M. Sheffield-Moore, X.J. Zhang, Amino acid ingestion improves muscle protein synthesis in the young and elderly, Am. J. Physiol. Endocrinol. Metab. 286 (2004) 321–328.
- [36] R.N. Baumgartner, K.M. Koehler, D. Gallagher, et al., Epidemiology of sarcopenia among the elderly in new Mexico, Am. J. Epidemiol. 147 (1998) 755–763.
- [37] D. Gallagher, M. Visser, R.E. De Meersman, et al., Appendicular skeletal muscle mass: effects of age, gender, and ethnicity, J. Appl. Physiol. 83 (1997) 229–239.
- [38] M. Mourtzakis, C.M. Prado, J.R. Lieffers, et al., 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. 33 (2008) 997–1006.
- [39] X. Wen, M. Wang, C.M. Jiang, et al., Are current definitions of sarcopenia applicable for older Chinese adults? J. Nutr. Health Aging 15 (2011) 847–851.
- [40] E.M. Lau, H.S. Lynn, J.W. Woo, et al., Prevalence of and risk factors for sarcopenia in elderly Chinese men and women, J. Gerontol. Biol. Sci. Med. Sci. 60 (2005) 213–216.
- [41] M.Y. Chien, T.Y. Huang, Y.T. Wu, Prevalence of sarcopenia estimated using a bioelectrical impedance analysis prediction equation in community-dwelling elderly people in Taiwan, J. Am. Geriatr. Soc. 56 (2008) 1710–1715.
- [42] K. Sanada, M. Miyachi, M. Tanimoto, et al., A cross-sectional study of sarcopenia in Japanese men and women: reference values and association with cardiovascular risk factors, Eur. J. Appl. Physiol. 110 (2010) 57–65.
- [43] L.K. Chen, L.K. Liu, J. Woo, et al., Sarcopenia in Asia: consensus report of the Asian working group for sarcopenia; prevalence of and risk factors for sarcopenia, J. Am. Med. Dir. Assoc. 15 (2014) 95–101.