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Preoperative sarcopenia and post-operative accelerated muscle loss negatively impact survival after resection of pancreatic cancer

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Abstract

Background Sarcopenia and post-operative accelerated muscle loss leading to cachexia are commonly observed in patients with pancreatic cancer. This study aimed to assess the influence of body compositions and post-operative muscle change on survival of patients with surgically treated pancreatic cancer.

Methods We analysed data of patients diagnosed with pancreatic adenocarcinoma who underwent surgery from 2008 to 2015. Skeletal muscle areas, muscle attenuation, and visceral and subcutaneous adipose tissue areas were measured from two sets of computed tomography images at L3 vertebral levels. In addition, muscle change was calculated from images obtained before and after cancer resection. We set our own cut-off values of various body compositions based on sex-specific tertiles.

Results A total of 180 patients were analysed. Patients with perioperative sarcopenia (n = 60) showed poorer overall survival than those without perioperative sarcopenia (P = 0.031). Fifty (28.6%) patients with accelerated muscle loss after surgery (>10%/60 days) had poorer survival compared with the others (P = 0.029). Sarcopenia (hazard ratio, 1.79: 95% confidence interval, 1.20–2.65] and post-operative muscle change (%/60 days) (hazard ratio, 0.94: 95% confidence interval, 0.92–0.96) were identified as significant predictors of survival on multivariable analyses.

Conclusions Preoperative sarcopenia identified on CT scan was associated with poor overall survival in patients with pancreatic cancer following surgery. Accelerated muscle loss after surgery also negatively impacted survival in pancreatic cancer patients.

Keywords Sarcopenia; Muscle loss; Pancreatic cancer; Pancreatectomy; Survival

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Introduction

Pancreatic cancer is the 7th leading cause of cancer-related death across both genders worldwide.[1] Pancreatic cancer is an aggressive malignancy with a dismal 5-year survival of about 5%.[2] Surgical resection remains the only curative option for treatment of localized pancreatic cancer.[3,4] Although operative techniques and perioperative care have improved over the past several decades, prognosis following surgery for pancreatic cancer remains poor.[5–7] Previous studies on prognosis following pancreatic cancer resection have focused mainly on tumour-specific factors such as nodal metastasis, margin involvement, and histologic grade;[8–10] however, the prognosis may be related not only to tumour-specific factors but also individual patient factors such as medical comorbidities, performance status, and body compositions.

In recent years, there has been increasing interest in the influence various body compositions on outcomes of oncology

patients. Emerging reports suggest that sarcopenia is associated with poor prognosis in many cancers.[11–13] There have been a few studies showing that preoperative sarcopenia is associated with decreased survival in patients with pancreatic cancer following surgery.[14–16] Some recent reports also suggested that visceral obesity and increased fat content in muscle tissue impact negative clinical outcome in pancreatic cancer.[17,18]

Many patients with pancreatic cancer are not only malnourished prior to surgical resection but also have significant weight loss post-operatively.[19] A previous study reported a post-operative weight loss of approximately 10% in patients who underwent pancreatectomy.[20] However, post-operative muscle changes and their effects on survival in pancreatic cancer patients have not been well studied. Initiation of adjuvant chemotherapy is usually recommended between 3 to 10 weeks after surgery.[6,7] Thus, we hypothesized that accelerated muscle loss during this period would impact long-term survival after pancreatic cancer surgery.

The aim of this study was to assess the impact of body compositions and post-operative muscle change on long-term survival after pancreatic cancer resection.

Materials and methods

Patients and data collection

Patients who underwent curative surgery for pancreatic cancer between 2008 and 2015 at Seoul St. Mary's Hospital, Seoul, Korea, were retrospectively analysed. Patients diagnosed with pancreatic adenocarcinoma after either pancreaticoduodenectomy or distal pancreatectomy were included in this study. Exclusion criteria for the study were (i) pancreatic neuroendocrine tumour, (ii) patients undergoing palliative surgery, and (iii) cases without initial CT scans.

Clinical data were collected including demographics, pre-operative body mass index (BMI), type of operation, adjuvant chemotherapy, presence of diabetes, haemoglobin, albumin, and carbohydrate antigen 19-9 (CA19-9) level. Pathologic data included tumour stage, tumour size, tumour grade, resection margin, lymphatic invasion, vascular invasion, and perineural invasion. Post-operative complications were classified according to the Clavien–Dindo classification with major complications being defined as grade ≥ 3.[21] Data on recurrence and mortality were also collected. The primary outcome of the study was overall survival after surgical resection of pancreatic cancer. The institutional review board approved this study (KC16RISI0963).

Computed tomography-based image analysis

Initial and follow-up CT images were retrospectively retrieved from a picture arching and communication system for analysis. A radiologist (MH.C), blinded to patient information, measured the total abdominal muscle area (TAMA) from two consecutive axial CT slices at the level of the L3 vertebral body. The TAMA included the psoas, paraspinal, and abdominal wall muscles and excluded intra-abdominal visceral muscles. Measurements were performed in a semi-automated fashion with manual outlining of the skeletal muscle border. The density window setting was between −29 and +150 Hounsfield unit (HU) values, and the results from the two images were then averaged.[22,23] The cross-sectional TAMA value was normalized for height as is conventional for BMI, and the value was labelled skeletal mass index. The radiation attenuation for skeletal muscle was assessed by calculating the average HU value of the muscle area within the range between −29 and +150 HU. Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) areas were also measured automatically using Aquarius Workstation software (TeraRecon Inc., San Mateo, CA, USA). The windows for VAT and SAT were −150 to −50 and −190 to −30 HUs, respectively. The area of VAT and SAT were also corrected for stature to calculate VAT and SAT indexes.

Because body composition varies among ethnicities and comorbidities, we set our own cut-off values for our cohort based on sex-specific tertiles. Cut-off values were set at the lowest tertile for skeletal muscle index and radiation attenuation, and at the highest tertile for VAT and SAT index.

Post-operative skeletal muscle change was assessed based on the difference between the initial and follow-up CT scan, which was performed prior to the first adjuvant chemotherapy session. For patients who did not receive adjuvant chemotherapy, muscle change was analysed by the CT performed around 2 months after surgery. The percent change in TAMA between the first and follow-up scans were then calculated as the percent change per 60 days to provide a standardized unit to allow comparisons between patients.

% change of TAMA/60 days

= [(TAMA at follow-up CT − TAMA at initial CT) × 60 days × 100]

/ [TAMA at initial CT × time interval (days) between CT scans].

Patients with a muscle loss or gain more than 10% per 60 days were classified as 'muscle losers' or 'muscle gainers', respectively. Those who had a muscle change within 10% per 60 days were classified as group of 'No significant muscle change'.

Statistical analysis

Continuous data are presented as the mean ± SD, and categorical data are presented as the quantity and proportion. Descriptive statistics were used to analyse the baseline characteristics of the study population. Characteristics and variables between the sarcopenia and non-sarcopenia groups were compared using a two-sample independent *t*-test for numerical variables and a Pearson $\chi 2$ test for nominal

variables. Overall survival after surgical resection of pancreatic cancer was determined using the Kaplan–Meier method, and the differences among groups were compared by the log-rank test. Survival analysis was performed separately in patients who underwent pancreaticoduodenectomy and distal pancreatectomy. The impact of preoperative sarcopenia and muscle change on overall survival was examined using Cox proportional hazard models. First, multivariable Cox regression analysis was performed with all potential variables that were selected based on a clinical point of view. Then, variables not significantly contributing to the fit of the model were removed from the model using a backward selection method. Statistical analysis was performed using the SPSS 24.0 software (SPSS Inc., Chicago, IL, USA) and R software (version 2.6.2, R foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as $P < 0.05$.

Results

Study population.

A total of 223 patients underwent surgery for pancreatic cancer during the study period. Of these, 23 patients had pancreatic neuroendocrine tumours, 7 patients underwent surgery for the purpose of palliative therapy, and 13 patients had no initial CT scan performed at our hospital. After excluding these 43 patients, the remaining 180 patients were analysed. We could not analyse the post-operative muscle changes in five patients who died or were lost to follow-up within 60 days without follow-up CT scans. There were no missing values for all variables in remaining 175 patients.

Baseline characteristics of study patients (n = 180) are shown in Table 1. The mean age was 64.4 ± 9.3 years and there were 98 (54.4%) males and 82 (45.6%) females. The majority of tumours were stage II (87.8%), with a mean tumour size of 3.7 ± 1.8 cm. Surgical procedures consisted of pancreaticoduodenectomy (72.2%) and distal pancreatectomy (27.8%), and surgical margins were negative (R0) in 116 (64.4%) patients. Lymphatic, vascular and perineural invasion were observed in 103 (57.2%), 64 (35.6%), and 152 (84.4%) patients, respectively. Adjuvant chemotherapy was administered to 151 (86.3%) patients. Means and sex-specific cut-off values for all body composition parameters measured by CT scan are shown in Table 2.

Comparison of characteristics of patients with and without preoperative sarcopenia

Table 1 summarizes comparisons of baseline characteristics between patients with and without preoperative sarcopenia.

Table 1 Patient and tumour characteristics

Parameters	Total (n = 180)	Sarcopenia (n = 60)	No sarcopenia (n = 120)	P
Patient Characteristics				
Age, years	64.4±9.3	65.4±9.7	63.9 ± 9.1	0.282
Sex, male (%)	98 (54.4%)	33 (55.0%)	65 (54.2%)	0.916
Preoperative body mass index (kg/m^2)	22.9 ± 3.3	20.9 ± 2.2	23.9 ± 3.3	<0.001
Adjuvant chemotherapy (%)	152 (84.4%)	50 (83.3%)	102 (85.0%)	0.771
Diabetic on diagnosis (%)	53 (29.4%)	15 (25.0%)	38 (31.7%)	0.355
Haemoglobin (g/dL)	11.9±1.5	11.6 ± 1.5	12.1 ± 1.4	0.031
Albumin (g/dL)	3.2±0.8	3.2 ± 1.1	3.2 ± 0.7	0.723
CA 19-9, median (IQR), (U/mL)	93 (23–344)	103 (34–354)	89 (21–342)	0.417
Tumour Characteristics				
Tumour size, cm	3.7 ± 1.8	3.8 ± 2.1	3.6 ± 1.6	0.381
Stage of tumour				0.702
Stage I (%)	14 (7.8%)	4 (6.7%)	10 (8.3%)	
Stage IIa (%)	56 (31.1%)	17 (28.3%)	39 (32.5%)	
Stage IIb (%)	102 (56.7%)	35 (58.3%)	67 (55.8%)	
Stage III (%)	8 (4.4%)	4 (6.7%)	4 (3.3%)	
Grade of tumour				0.894
Well differentiated (%)	22 (12.2%)	9 (15.0%)	15 (12.5%)	
Moderately differentiated (%)	134 (74.4%)	44 (73.3%)	90 (75.0%)	
Poorly differentiated (%)	24 (13.3%)	7 (11.7%)	15 (12.5%)	
Type of operation				0.638
Pancreaticoduodenectomy (%)	130 (72.2%)	42 (70.0%)	88 (73.3%)	
Distal pancreatectomy (%)	50 (28.8%)	18 (30.0%)	32 (26.7%)	
Resection margin				0.441
R0 resection (%)	116 (64.6%)	41 (68.3%)	75 (62.5%)	
R1 resection (%)	64 (35.4%)	19 (31.7%)	45 (37.5%)	
Lymphatic invasion (%)	103 (57.2%)	34 (56.7%)	69 (57.5%)	0.915
Vascular invasion (%)	64 (35.6%)	23 (38.3%)	41 (34.2%)	0.582
Perineural invasion (%)	152 (84.4%)	48 (80.0%)	104 (86.7%)	0.245

IQR, interquartile ranges.

Table 2 Means and sex-specific cut-off values for all body composition measurements at the level of third vertebra body

	Male (n = 98)		Female (n = 82)		Total (n = 180)
	Mean (SD)	Cut-off	Mean (SD)	Cut-off	Mean (SD)
Skeletal muscle index (cm^2/m^2)	49.4 (7.7)	45.3	40.9 (6.2)	39.3	45.5 (8.2)
Radiation attenuation (HU)	43.9 (7.4)	40.8	37.3 (7.3)	33.9	40.9 (8.0)
Visceral adipose tissue index (cm^2/m^2)	38.9 (24.0)	48.2	36.6 (20.7)	43.4	37.8 (22.5)
Subcutaneous adipose tissue index (cm^2/m^2)	28.9 (15.2)	33.3	57.3 (22.7)	66.0	41.8 (23.6)

Sex-specific cut-off values set at the lowest tertile for skeletal muscle index and radiation attenuation, and at the highest tertile for visceral and subcutaneous adipose tissue index. HU, Hounsfield units; SD, standard deviation.

Table 3 Operative variables and complications following pancreatic cancer surgery

Parameters	Total (n = 180)	Sarcopenia (n = 60)	No sarcopenia (n = 180)	P
Operation time, minute	323 ± 101	315 ± 101	328 ± 101	0.421
Perioperative blood transfusion (%)	120 (66.7%)	41 (68.3%)	79 (65%)	0.429
Length of hospital stay after surgery, days	16.7 ± 9.9	15.6 ± 7.9	17.2 ± 10.8	0.303
Length of ICU care, days	2.3 ± 2.1	2.4 ± 3.1	2.3 ± 1.3	0.574
Any complication (%)	95 (52.8%)	34 (56.7%)	61 (50.8%)	0.460
Major grade III-IV complication (%)	20 (11.1%)	5 (8.3%)	15 (12.5%)	0.402

ICU, intensive care unit; NA, not available.

Preoperative BMI was lower in the sarcopenia group compared with the non-sarcopenia group (20.9 ± 2.2 vs. 23.9 ± 3.3, $P < 0.001$). Age, percentage of patients receiving adjuvant chemotherapy, presence of diabetes, haemoglobin and albumin levels, and tumour characteristics (including size, stage, grade, and margin status) were not significantly different between the two groups.

Post-operative complications

The overall and major post-operative complication rates were 52.8% and 11.1% in entire patients. There were no significant differences of the overall and major post-operative complication rates between sarcopenic (56.7% and 8.3%) and non-sarcopenic patients (50.8% and 12.5%) (Table 3). Operation time, perioperative transfusion rate, and length of hospital or intensive care unit care after surgery were not significantly different between the two groups. Lower muscle attenuation and higher VAT and SAT index also were not associated with any post-operative complications.

Impact of preoperative body compositions on survival after resection of pancreatic cancer

The life table of all patients is shown in Table 4. The median overall survival after surgery for the entire cohort was 18.0 months. Overall 1-, 3-, and 5-year survival was 67.3%, 23.9%, and 16.0%, respectively. Patients with perioperative sarcopenia showed poorer overall survival than those without perioperative sarcopenia (P = 0.031 by the log-rank test, *Figure* 1A). Median survival after pancreatic cancer surgery for sarcopenic and non-sarcopenic patients was 13.9 and 21.9 months, respectively. When only patients with pancreaticoduodenctomy were analysed, patients with sarcopenia showed poorer overall survival than those without sarcopenia (*Figure* 1B, P = 0.014). Meanwhile, in patients with distal pancreatectomy, there were no difference in survival rates between the two groups (*Figure* 1C, P = 0.721). Recurrence-free survival was not significantly different between patients with and without sarcopenia.

Table 4 Life table for pancreatic cancer patients following surgery

Interval	No. alive at start of interval	No. of deaths during interval	No. censored
0–30 days	180	0	0
30–90 days	180	4	2
90 days–1 year	174	53	16
1–2 years	105	46	19
2–3 years	42	10	8
3–4 years	24	7	7
4–5 years	10	0	0

Lower muscle attenuation (*Figure* 1D, P = 0.817), higher VAT index (*Figure* 1E, P = 0.810), and higher SAT index (*Figure* 1F, P = 0.237) were not related to poorer overall survival. Also, recurrence-free survivals were not associated with muscle attenuation, VAT index, and SAT index.

Muscle changes after resection of pancreatic cancer

Five of the 180 enrolled patients died or were lost to follow-up within 60 days without follow-up CT scan. Among the 175 patients with a follow-up CT scan, the median duration

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Figure 1 (A) Overall survival curves after operation according to skeletal mass index; (B) overall survival curves after operation according to skeletal mass index in patients undergoing pancreaticoduodenectomy; (C) overall survival curves after operation according to skeletal mass index in patients undergoing distal pancreatectomy; (D) overall survival curves after operation according to skeletal muscle attenuation; (E) overall survival curves after operation according to visceral adipose tissue index; and (F) overall survival curves after operation according to subcutaneous adipose tissue index. VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

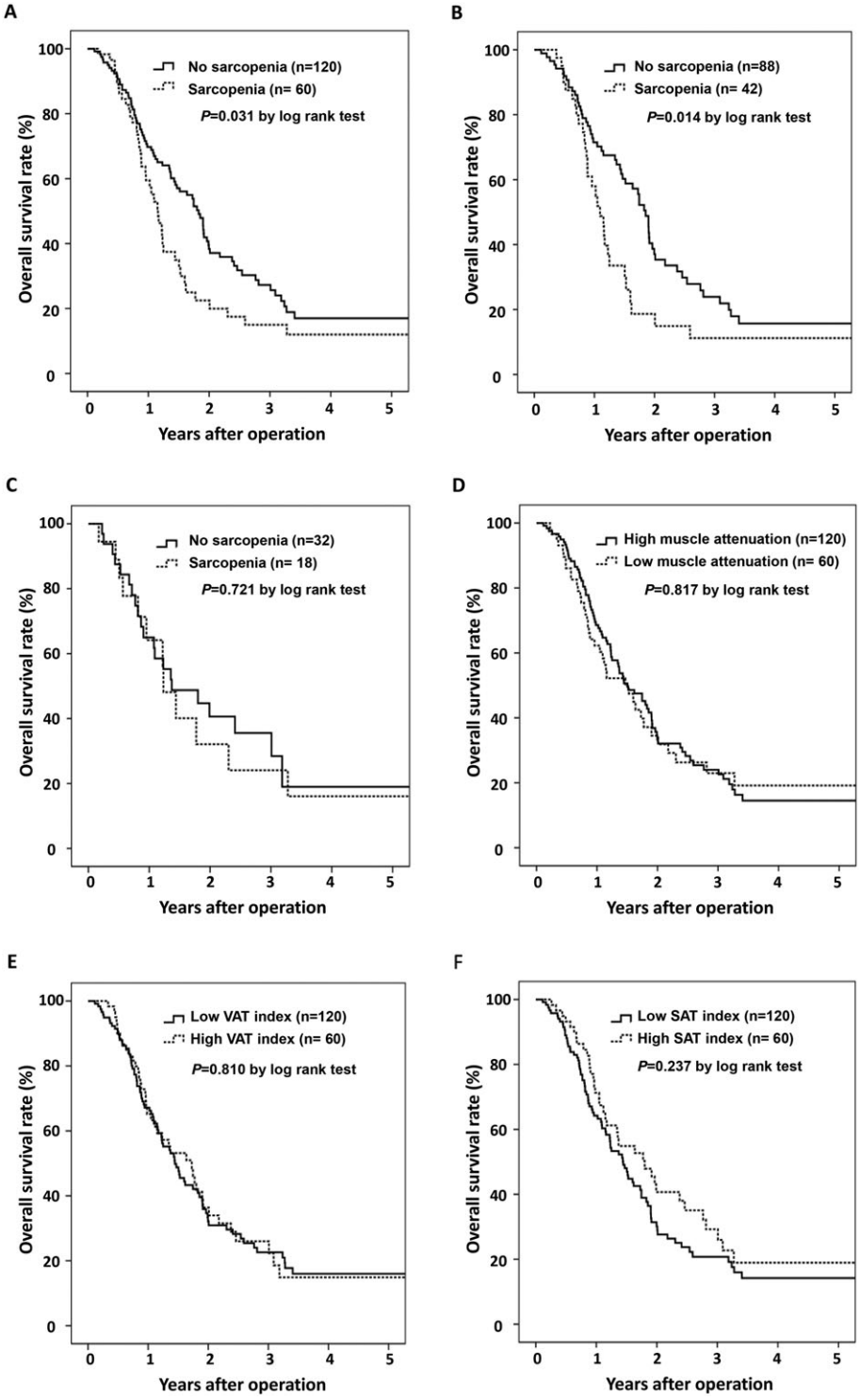

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Table 5 Characteristics of patients according to postoperative muscle change

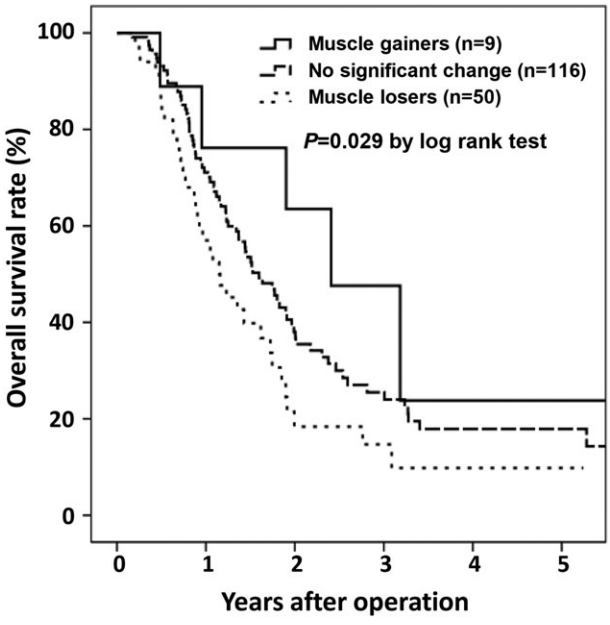
Parameters	Muscle-losers (n = 50)	No significant muscle change (n = 116)	Muscle-gainers (n = 9)	P
Age, years	62.8 ± 10.7	65.3 ± 8.1	62.0 ± 9.1	0.157
Sex, male (%)	30 (60.0%)	52 (44.8%)	5 (55.6%)	0.118
Preoperative sarcopenia (%)	11 (22.0%)	44 (37.9%)	4 (44.4%)	0.108
Diabetic on diagnosis (%)	14 (28.0%)	38 (32.8%)	1 (11.1%)	0.363
CA 19-9, median (IQR), (U/mL)	120 (40–515)	84 (24–328)	28 (7–56)	0.033
Stage of tumour				0.552
Stage I (%)	2 (4.0%)	11 (9.5%)	1 (7.5%)	
Stage IIa (%)	19 (38.0%)	33 (28.4%)	3 (33.3%)	
Stage IIb (%)	25 (50.0%)	68 (58.6%)	5 (55.6%)	
Stage III (%)	4 (8.0%)	4 (3.4%)	0 (0%)	
Type of operation				0.216
Pancreaticoduodenectomy (%)	40 (80.0%)	81 (69.8%)	5 (55.6%)	
Distal pancreatectomy (%)	10 (20.0%)	35 (30.2%)	4 (44.4%)	
Resection margin				0.771
R0 resection (%)	33 (66.0%)	73 (62.9%)	7 (77.8%)	
R1 resection (%)	17 (34.0%)	43 (37.1%)	2 (22.2%)	
Operation time, minute	339 ± 91	322 ± 106	271 ± 93	0.193
Length of hospital stay after surgery, days	19.7 ± 14.0	15.6 ± 7.5	12.2 ± 4.4	0.019
Length of ICU care, days	3.0 ± 3.6	2.0 ± 0.8	1.7 ± 0.7	0.013
Any complication (%)	30 (60.0%)	58 (50.0%)	4 (44.4%)	0.438
Major grade III-IV complication (%)	9 (18.0%)	9 (7.8%)	1 (11.1%)	0.151

IQR, interquartile ranges.

between the initial and follow-up CT was 62 [interquartile range (IQR), 48–77] days.

Fifty patients (28.6%) had decreased muscle mass and 9 (5.1%) patients had increased muscle mass after surgery. The remaining 116 (66.3%) did not show a significant post-operative muscle change. Characteristics of patients according to post-operative muscle change are shown in Table 5. Median CA19-9 level was higher in muscle-losers [120, interquartile ranges (IQR) 40–515 U/mL] than patients without significant muscle change (84, IQR 24–328) and muscle-gainers (28, IQR 7–56). Length of hospital stay and ICU care after surgery were also longer in muscle-losers (19.7 ± 14.0 and 3.0 ± 3.6 days) compared with patients without significant muscle change (15.6 ± 7.5 and 2.0 ± 0.8) and muscle-gainers (12.2 ± 4.4 and 1.7 ± 0.7).

Figure 2 Overall survival rate after operation according to post-operative muscle change.



There was a significant difference in overall survival according to the post-operative muscle change (P = 0.029 by the log-rank test, *Figure* 2). Median survival for muscle-losers, patient without significant muscle change, and muscle-gainers were 13.9, 19.1, and 28.8 months, respectively.

Cox regression analyses

The total number of deaths for all 180 patients was 122. Known sample rule suggests that the maximal number of predictors within Cox regression model in our study should be 12. Age, sex, preoperative sarcopenia, post-operative muscle change (%/60 days), tumour size, nodal status, histologic differentiation, type of surgery, resection status, post-operative complication, and hospitalization period were selected as possible predictors. Cox proportional hazards models for overall survival after resection of pancreatic cancer are summarized in Table 6. Multivariable Cox analysis including all predictors showed that preoperative sarcopenia [hazard ratio (HR), 1.68; 95% confidence intervals (CI), 1.18–2.68] and post-operative muscle change (%/60 days) (HR, 0.94; 95% CI, 0.92–0.97) significantly associated with overall survival after pancreatic cancer surgery. On multivariable analysis using a

Table 6 Cox proportional hazards models for overall survival after resection of pancreatic adenocarcinoma

	Multivariable analysis including all possible predictors		Multivariable analysis using a backward selection method	
Factor	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.01 (0.99–1.03)	0.602	—	—
Male	1.33 (0.91–2.00)	0.139	—	—
Preoperative sarcopenia	1.78 (1.18–2.68)	0.006	1.79 (1.20–2.65)	0.004
Post-operative muscle change (%/60 days)	0.94 (0.92–0.97)	<0.001	0.94 (0.92–0.96)	<0.001
Adjuvant chemotherapy	0.35 (0.20–0.61)	<0.001	0.36 (0.22–0.62)	<0.001
Tumour size (cm)	1.09 (0.96–1.23)	0.172	—	—
Lymph node metastasis	2.10 (1.39–3.18)	<0.001	2.02 (1.36–2.99)	<0.001
Poorly differentiated	2.38 (1.38–4.14)	0.002	2.46 (1.45–4.12)	0.001
Pancreaticoduodenectomy	1.00 (0.65–1.53)	0.999	—	—
R1 resection	1.34 (0.90–2.01)	0.150	1.44 (0.98–2.14)	0.067
Major grade III–IV complication	1.44 (0.75–2.76)	0.275	—	—
Hospitalization period (days)	0.99 (0.97–1.01)	0.993	—	—

HR, hazard ratio; CI, confidence interval.

backward selection method, preoperative sarcopenia (HR, 1.79; 95% CI, 1.20–2.65), post-operative muscle change (HR, 0.94; 95% CI, 0.92–0.96), adjuvant chemotherapy (HR, 0.36; 95% CI, 0.22–0.62), nodal metastasis (HR, 2.02; 95% CI, 1.36–2.99), and poor histological differentiation (HR, 2.46; 95% CI, 1.45–4.12) remained as significant risk factors for poorer overall survival after pancreatic cancer surgery.

Discussion

In this study, preoperative sarcopenia was associated with poor overall survival in patients with pancreatic cancer following surgery. Additionally, accelerated muscle loss after surgery negatively impacted survival in pancreatic cancer patients.

In our present study, CT scans were used to quantify skeletal muscle mass. All patients with pancreatic cancer routinely undergo CT scanning for staging prior to surgery and chemotherapy; therefore, no additional radiation exposure or extra cost was incurred in our evaluation of sarcopenia. CT has a high degree of validity in determining body composition analysis and is the current gold standard method for estimating fat or muscle volumes.[24]

Among many definitions of sarcopenia, the cut-off values for sex-specific skeletal muscle index published by Prado *et al*.[11] have been the most widely used in recent studies.[25,26] However, these cut-offs were derived from Canadian patients with respiratory or gastrointestinal tract cancer. These cut-off values of sarcopenia for male and female are 52.4 and 38.5 cm^2/m^2, respectively. Compared with our own cut-off values based on sex-specific tertiles (45.3 cm^2/m^2 in male and 39.3 cm^2/m^2 in female), the cut-off value from Canadian Cohort is significantly higher in male. If the cut-off value by Prado *et al*. is applied to our patient population, more than two-thirds of males are classified as sarcopenia. On the other hand, in the Dutch cohort of patients with resectable pancreatic head cancer,[16] the cut-off values of sarcopenia (45.1 cm^2/m^2 in male and 36.9 cm^2/m^2 in female) were similar to those of our patients. However, the means of VAT and SAT index in male were significantly higher in the Dutch cohort (68.2 and 49.8 cm^2/m^2) than those in our cohort (48.2 and 33.3 cm^2/m^2). Because various body compositions vary widely in sex, race, and underlying disease, it is important to identify and set appropriate cut-off values for their own patient population.

The adverse effect of sarcopenia on survival was more pronounced in patients who underwent pancreaticoduodenectomy than those who underwent distal pancreatectomy. Patients with pancreaticoduodenectomy who had relatively more complications and longer hospital stay might be more vulnerable to the negative effects of sarcopenia. Meanwhile, visceral obesity had little effect on survival and complications in our study, presumably because VAT index in Korean patients was significantly lower than that of Western patients. In Korean patients with pancreatic cancer, severe accumulation of visceral fat that adversely affects prognosis may be not common.

Two recent studies evaluated the association between sarcopenia and long-term survival in pancreatic cancer patients undergoing resection and showed contradictory results.[14,27] One study showed that patients with sarcopenia had increased risk of long-term mortality, whereas the other study found no association between sarcopenia and poor survival. In these previous studies, only the psoas muscle area was measured in assessing the presence or absence of sarcopenia. Psoas muscle is not symmetrical in shape and includes only low proportion of total trunk muscles (<10%). Psoas-only approach showed high measurement error with a large variance and failed to predict the clinical outcome of overall survival in cancer patients.[28,29] We measured the total muscle area at the L3 vertebral level including the paraspinal and abdominal wall muscles, as well as the psoas muscle. Our

method is more validated and widely used for patients with cancer.[26,30,31] Recently, it has been reported that measuring not only trunk muscles but also appendicular muscles by ultrasound helps to predict whole lean body mass.[32,33] It is expected that the method of measuring whole muscles through CT scan will be realized soon.[34]

The other strength of our study is that muscle areas were measured before and after surgery to identify muscle change following surgery. Hospitalization itself is associated with reduced caloric intake, lack of exercise, or prolonged bed rest and can lead to decrease in muscle mass. In a recent study, among general elderly patients without sarcopenia at admission, 14.7% developed sarcopenia during hospitalization.[35] Pancreatic surgery is a complicated procedure that leaves an altered gastrointestinal anatomy. Therefore, muscle loss after surgery for pancreatic cancer was expected to be greater than for general hospitalized patients. In our study, 28.6% of patients showed significant muscle loss of more than 10% over 60 days. Consequently, accelerated muscle loss after surgery led to poor long-term survival.

The mechanism that links sarcopenia with poor survival in pancreatic cancer patients has not been clarified. In our study, preoperative sarcopenia only affected overall survival, not recurrence-free survival, which suggests that sarcopenia does not have a direct impact on tumour biology, but rather influences survival as a patient-related factor. Reduced muscle mass can cause aberrant energy homeostasis, impaired cell growth, and immune dysfunction, leading to decreased survival.[36,37] Another disadvantage of sarcopenia is that chemotherapy may be insufficiently administrated due to toxicity. Most patients with pancreatic cancer receive chemotherapy in the adjuvant or palliative setting. Because the dose of anticancer drugs is generally determined by body weight or body surface area, chemotherapy toxicities can occur more frequently in patients with sarcopenia.[30,38]

The factors associated with post-operative accelerated muscle loss were length of hospital stay and ICU care and preoperative CA19-9 levels. The fact that periods of hospital stay and ICU care were associated with muscle loss after surgery was consistent with a previous study conducted in general hospitalized patients.[35] Physical inactivity and malnutrition during hospital stay may have a negative synergic effect on muscle protein synthesis. Interestingly, preoperative CA19-9 also was associated with muscle loss after surgery. High preoperative CA19-9 may reflect aggressiveness of tumour biology or microscopic residual tumour burden after surgery. The change in skeletal muscle after surgery for pancreatic cancer is thought to be influenced by both patient-related and tumour-related factors.

According to a recent phase II trial, a multimodal intervention including polyunsaturated fatty acid nutritional supplements, exercise, and anti-inflammatory medication was feasible and safe in patient with inoperable pancreatic and lung cancer.[39] In addition, the positive effect of multimodal intervention on weight suggested that cachexia is not an inevitable consequence and can be prevented in cancer patients. Nutritional counselling and oral nutritional supplements or non-steroidal anti-inflammatory also can be interventional options for cachexia.[40,41] The effects of multimodal interventions on cancer cachexia will be demonstrated in an ongoing large phase III trial.

There were some limitations to our study. First, given its retrospective nature, we were unable to identify a causal relationship between sarcopenia and poor survival, and only revealed an association between them. Second, our study included only East Asian (Korean) individuals. Further studies on muscle change after surgery for pancreatic cancer in Western patients would be helpful to elaborate and generalize the findings of our study.

We have demonstrated that preoperative sarcopenia and post-operative accelerated muscle loss are major prognostic factors for overall survival in patients undergoing pancreatic cancer surgery. As with tumour-specific prognostic factors, assessment of these patient-related factors may be important in informing clinical decision-making and helping to risk stratify patients with surgically treated pancreatic cancer.

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Declaration of interest

The authors have no conflicts of interest.

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