



Prognostic Value of Sarcopenia and Myosteatorsis in Patients with Resectable Pancreatic Ductal Adenocarcinoma

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Objective: The clinical relevance of myosteatorsis has not been well evaluated in patients with pancreatic ductal adenocarcinoma (PDAC), although sarcopenia has been extensively researched. Therefore, we evaluated the prognostic value of muscle quality, including myosteatorsis, in patients with resectable PDAC treated surgically.

Materials and Methods: We retrospectively evaluated 347 patients with resectable PDAC who underwent curative surgery (mean age \pm standard deviation, 63.6 \pm 9.6 years; 202 male). Automatic muscle segmentation was performed on preoperative computed tomography (CT) images using an artificial intelligence program. A single axial image of the portal phase at the inferior endplate level of the L3 vertebra was used for analysis in each patient. Sarcopenia was evaluated using the skeletal muscle index, calculated as the skeletal muscle area (SMA) divided by the height squared. The mean SMA attenuation was used to evaluate myosteatorsis. Diagnostic cutoff values for sarcopenia and myosteatorsis were devised using the Contal and O'Quigley methods, and patients were classified according to normal (nMT), sarcopenic (sMT), myosteatortic (mMT), or combined (cMT) muscle quality types. Multivariable Cox regression analyses were conducted to assess the effects of muscle type on the overall survival (OS) and recurrence-free survival (RFS) after surgery.

Results: Eighty-four (24.2%), 73 (21.0%), 75 (21.6%), and 115 (33.1%) patients were classified as having nMT, sMT, mMT, and cMT, respectively. Compared to nMT, mMT and cMT were significantly associated with poorer OS, with hazard ratios (HRs) of 1.49 (95% confidence interval, 1.00–2.22) and 1.68 (1.16–2.43), respectively, while sMT was not (HR of 1.40 [0.94–2.10]). Only mMT was significantly associated with poorer RFS, with an HR of 1.59 (1.07–2.35), while sMT and cMT were not.

Conclusion: Myosteatorsis was associated with poor OS and RFS in patients with resectable PDAC who underwent curative surgery.

Keywords: *Computed tomography; Muscle quality; Myosteatorsis; Pancreatic ductal adenocarcinoma; Sarcopenia*

INTRODUCTION

Sarcopenia, defined as a loss of skeletal muscle mass and strength [1], is a well-known prognostic factor associated with poor prognosis in patients with various diseases [2,3]. Myosteatorsis and fat deposition in the muscle are

considered biomarkers of poor muscle quality [4]. Although several studies have reported the influence of myosteatorsis on muscle strength and physical activity [5,6], as well as poor survival, further evidence is needed to assess the prognostic implications of myosteatorsis in various diseases [7,8].

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Computed tomography (CT) is a common, noninvasive method of muscle assessment that measures differences in radiodensity between muscle and other tissues [9]. Sarcopenia can be diagnosed through the quantitative measurement of muscle mass, which can be segmented on CT. Muscle quality assessment for the diagnosis of myosteatorsis can also be conducted by measuring the radiodensity of a segmented muscle area, given the inverse linear relationship between radiodensity and the degree of fat deposition [10].

Pancreatic ductal adenocarcinoma (PDAC) is a dismal disease with a 5-year survival rate as low as 6% [11]. It causes body composition changes and many patients develop muscle loss with disease progression [12,13]. Along with other malignancies [4], loss of muscle quality and quantity is associated with poor survival in patients with PDAC. Previous studies have reported the effects of preoperative sarcopenia and myosteatorsis on overall survival (OS) and recurrence-free survival (RFS) in patients with PDAC undergoing curative-intent surgery [14-19].

Currently, the use of neoadjuvant chemotherapy in patients with advanced PDAC is increasing. The National Comprehensive Cancer Network (NCCN) proposes that non-metastatic PDAC be classified as resectable, borderline resectable, or locally advanced according to tumor-vascular contact on pretreatment imaging [20]. Curative surgery without neoadjuvant treatment remains the standard treatment only in patients with resectable PDAC. In contrast to previous studies that included all patients undergoing surgery, we believe that the selective inclusion of only those patients receiving curative surgery according to the standard treatment options would allow for a more accurate evaluation of the association between preoperative muscle status and prognosis.

Therefore, we investigated the prognostic value of muscle quality, including myosteatorsis, in patients with resectable PDAC who underwent curative surgery, using quantitative muscle measurements on preoperative CT.

MATERIALS AND METHODS

This retrospective observational study was approved by the Institutional Review Board of Asan Medical Center, which waived the requirement for informed consent owing to the retrospective study design (IRB No. 2020-1924).

Patients

Patients with PDAC admitted to our institution between January 2014 and January 2017 were retrospectively and consecutively enrolled as part of the study population in a previous study [21] evaluating the prognosis of PDAC according to the CT characteristics of the tumor. Patients meeting the following criteria were included: 1) resectable PDAC according to the NCCN criteria [20] and 2) curative-intent surgery without neoadjuvant treatment. Briefly, resectable PDAC was defined as PDAC with no arterial (celiac axis, superior mesenteric artery, or common hepatic artery) or tumor contact with the superior mesenteric or portal veins at $< 180^\circ$ without contour irregularity or thrombus [22].

Patients meeting the following criteria were excluded: 1) no pancreatic CT protocol before surgery, 2) palliative surgery or macroscopic residual tumor (R2) after surgery, 3) other coexisting malignancies within 5 years before PDAC diagnosis, and 4) insufficient clinical data.

CT Protocol

Multiphasic CT was performed using multidetector CT scanners (Discovery CT 750HD, GE Medical Systems and Somatom Definition AS+ or Definition Edge, Siemens), and the pancreatic CT protocol was performed according to the NCCN guidelines [20]. Unenhanced and biphasic contrast-enhanced images included the arterial phase (10 seconds after descending aorta enhancement at 100 Hounsfield unit [HU]) and portal venous phase (72 seconds after contrast administration), which were obtained after the intravenous administration of 150 mL of ioversol (Optiray 320; Guerbet) at 3 mL/s. Unenhanced axial images were reconstructed at a 5-mm thickness and 2.5–3.0 mm for the arterial and portal venous phases in the axial and coronal planes, respectively. The other scan parameters included tube voltages of 100 or 120 kVp, tube current of 200–400 mA with automatic exposure control, pitches of 0.6 or 1, and a field of view to fit.

Evaluation of Muscle Quantity and Quality on CT

Muscle quantity and quality were measured in a single slice of an axial CT image of the portal venous phase following the automatic selection of the CT slice at the inferior endplate level of the L3 vertebra (Fig. 1) [23]. All skeletal muscles (psoas, paraspinal, transversus abdominis, rectus abdominis, quadratus lumborum, internal oblique, and external oblique muscles) in the selected image were automatically segmented using a convolutional

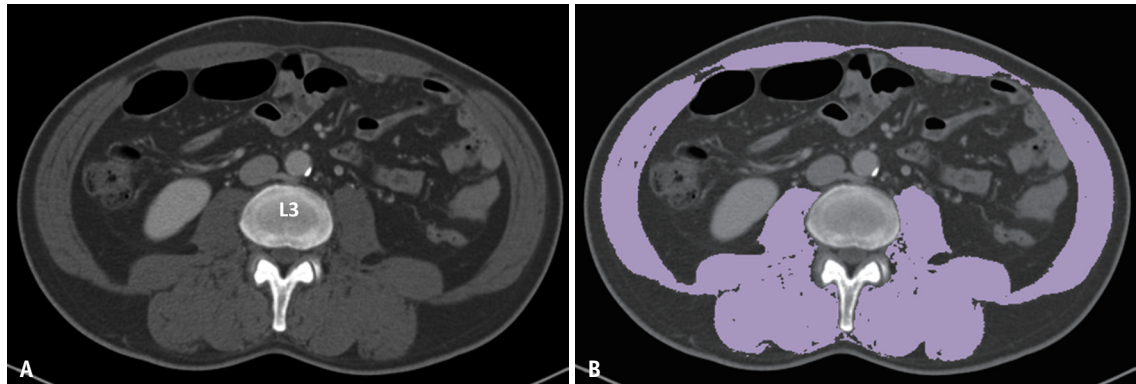


Fig. 1. Evaluation of muscle quantity and quality by CT.

A. Selection of CT slice at the L3 level. **B.** Automatic segmentation of the skeletal muscle area and measurement of the mean attenuation.

neural network (AID-U™, iAID Inc.) with a Dice similarity coefficient of 0.96–0.97 [24].

Clinicopathologic Data Collection

Demographic and laboratory data relevant to patient prognosis (i.e., patient age, sex, height, weight, and cancer antigen 19-9 level) were collected from the electronic medical records and measured within 1 month before surgery. Surgical and pathological data, including the type of surgery, cancer stage according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system (Supplementary Table 1) [25], tumor differentiation, and resection margin status (R0, negative margin vs. R1, microscopically positive margin) [26], were acquired. Adjuvant treatment, typically initiated 3–10 weeks after surgery, was also confirmed.

Data on PDAC recurrence events were collected from radiologic reports of follow-up contrast-enhanced CT scans, routinely acquired every 3 months for the first year and every 3–6 months thereafter. Data on death events were collected from the electronic medical records.

Determination of Patients with Sarcopenia and Myosteatosi s

To identify patients with sarcopenia, we used the skeletal muscle index (SMI), calculated as the skeletal muscle area (SMA) divided by the height squared (cm^2/m^2) [4,27]. To identify patients with myosteatosi s, we used the mean attenuation of the SMA (HU) [4].

Before determining the cutoff values for sarcopenia and myosteatosi s, the patients were categorized into one of eight subgroups dichotomized by age (< 65 vs. \geq 65 years), sex (male vs. female), and body mass index (BMI) (underweight or normal [$\text{BMI} < 23 \text{ kg}/\text{m}^2$] vs. overweight or obese [BMI

$\geq 23 \text{ kg}/\text{m}^2$]). The optimal cutoff values for sarcopenia and myosteatosi s in each subgroup were separately derived using the outcome-based Contal and O'Quigley method [28], which is used to obtain survival-related cutoffs by calculating the maximum value of log-rank statistics. In our study, the cutoff values were determined based on the time to death.

Survival Analysis according to Muscle Type

The cutoff values for sarcopenia and myosteatosi s were used to classify the patients into the following four muscle types: 1) normal muscle type (nMT), patients with neither sarcopenia nor myosteatosi s, 2) sarcopenic muscle type (sMT), patients with sarcopenia but no myosteatosi s, 3) myosteatosi c muscle type (mMT), patients with myosteatosi s but no sarcopenia, and 4) combined muscle type (cMT), patients with both sarcopenia and myosteatosi s.

The primary outcome was OS, defined as the survival time between surgery and death. The secondary outcome was RFS, defined as the survival time between surgery and recurrence or death [29]. Patients without death or recurrence were excluded at the last follow-up visit. Kaplan–Meier survival curves for OS and RFS were plotted according to muscle type and the presence of sarcopenia and myosteatosi s and compared using log-rank tests. The univariable and multivariable Cox proportional hazard regression analyses included muscle types and clinicopathologic characteristics (i.e., serum cancer antigen 19-9 level, AJCC cancer stage, tumor differentiation, resection margin status, and adjuvant treatment), which are considered to be potentially associated with patient survival.

The associations between muscle type and clinicopathologic characteristics were analyzed using

Pearson's χ^2 tests. The intervals between the surgery date and the first date of adjuvant treatment were analyzed according to muscle type using one-way analysis of variance.

Statistical significance was set at $p < 0.05$. SAS (version 9.4; SAS Institute), SPSS (version 21.0; IBM Corp.), and R (version 3.6.0; R Foundation for Statistical Computing) were used to perform statistical analyses.

RESULTS

Patient Characteristics

Among the 456 patients with resectable PDAC, 410 underwent successful curative surgery (Fig. 2). Sixty-three patients were excluded because of the absence of a pancreatic CT protocol before surgery ($n = 38$), palliative surgery or macroscopic residual tumor ($n = 5$), coexisting malignancy within 5 years ($n = 18$), and insufficient clinical data ($n = 2$). Finally, 347 patients (mean age \pm standard deviation, 63.6 ± 9.6 years; 202 male) were included. The patient characteristics are summarized in

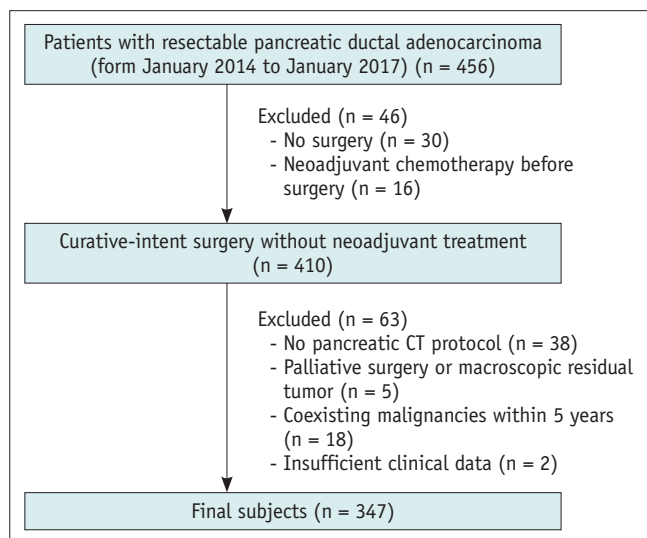


Fig. 2. Flow diagram of the study patients.

Table 1. The median interval between CT and surgery was 8 days (range: 1–35 days). The AJCC tumor stage was IA or IB in 124 (35.7%) patients, IIA or IIB in 164 (47.3%) patients, and III in 59 (17.0%) patients. The tumor was well differentiated in 40 (11.5%) patients, moderately differentiated in 269 (77.5%) patients, and poorly differentiated or undifferentiated in 38 (11.0%) patients. The resection margins were R0 in 259 (74.6%) patients and R1 in 88 (25.4%) patients. Adjuvant treatment was administered to 226 patients (65.1%).

Table 1. Patient Characteristics

Characteristics	Values
Age, year	63.6 \pm 9.6
Male:female	202:145
Height, m	162.0 \pm 8.6
Body mass index, kg/m ²	23.2 \pm 2.9
Cancer antigen 19-9 level, U/mL*	81 (22.2–322.6)
Tumor location	
Head	216 (62.3)
Body	65 (18.7)
Tail	66 (19.0)
AJCC tumor stage	
IA	36 (10.4)
IB	88 (25.3)
IIA	17 (4.9)
IIB	147 (42.4)
III	59 (17.0)
Tumor differentiation	
Well-differentiated	40 (11.5)
Moderately differentiated	269 (77.5)
Poorly differentiated or undifferentiated	38 (11.0)
Resection margin	
R0	259 (74.6)
R1	88 (25.4)
Adjuvant treatment	226 (65.1)

Unless otherwise specified, data are presented as mean \pm standard deviation for continuous variables and numbers (percentages) for categorical variables. *Median with an interquartile range in parenthesis. AJCC = American Joint Committee on Cancer

Table 2. Cutoff Values for Sarcopenia (SMI) and Myosteatorsis (Mean Attenuation of SMA) according to Using the Contal and O'Quigley Methods

Body Mass Index	Age (Year)	SMI (cm ² /m ²)		Mean Attenuation of SMA (HU)	
		Male	Female	Male	Female
Underweight or normal (< 23 kg/m ²)	< 65	45.25	37.39	51.71	49.05
	\geq 65	48.86	38.85	44.73	48.82
Overweight or obese (\geq 23 kg/m ²)	< 65	54.89	44.90	49.72	40.33
	\geq 65	49.66	49.84	49.36	43.89

HU = Hounsfield unit, SMA = skeletal muscle area, SMI = skeletal muscle index

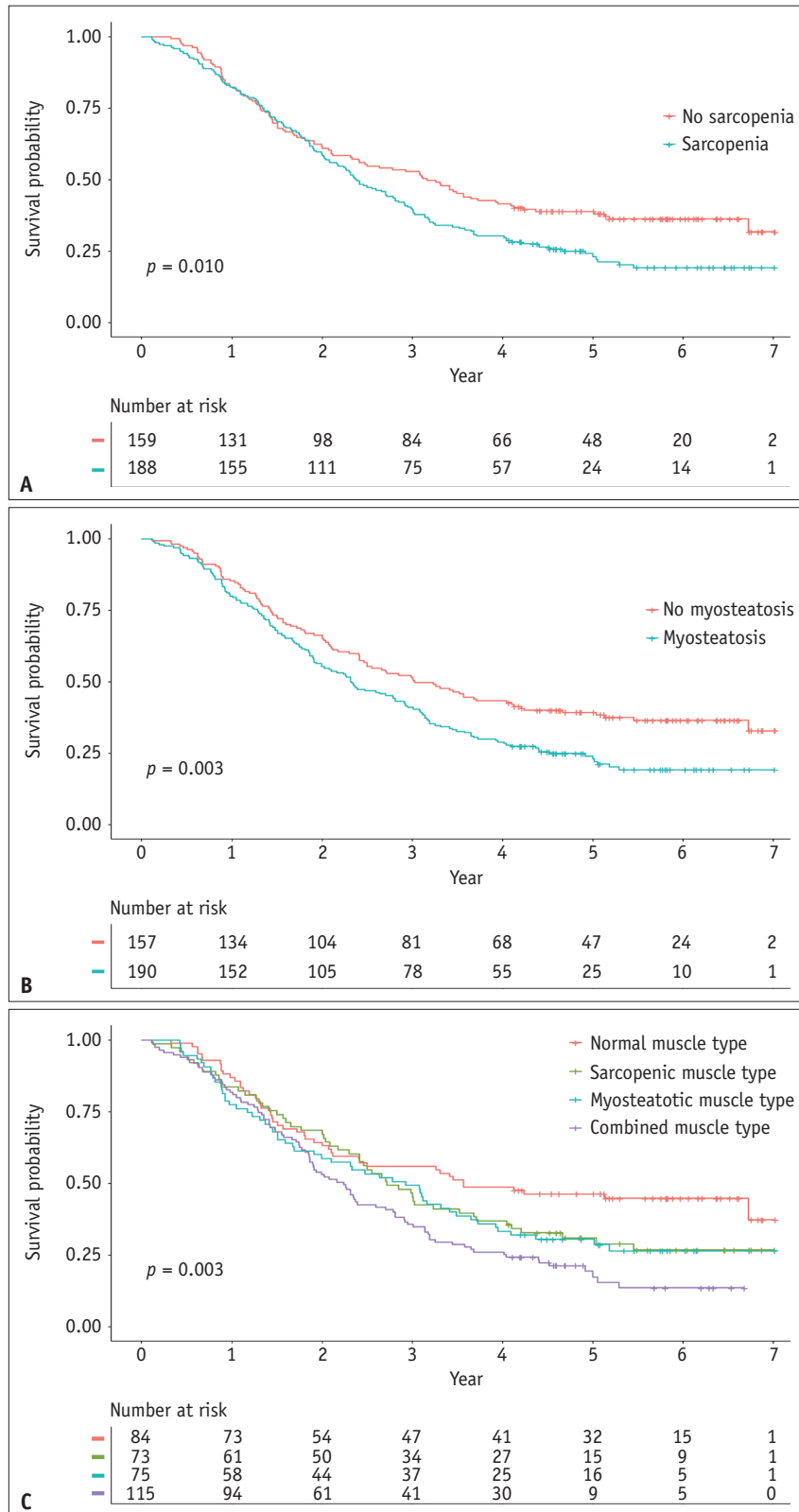


Fig. 3. Kaplan–Meier curves of the OS according to the presence of sarcopenia (A) and myosteatosi s (B) and according to the muscle types (C).

A–C. The Kaplan–Meier curves indicate a worse OS in patients with sarcopenia compared to the OS in patients without sarcopenia (median, 28.7 vs. 38.1 months; $p = 0.010$; **A**) and in patients with myosteatosi s compared to the OS in patients without myosteatosi s (median, 28.0 vs. 36.5 months; $p = 0.003$; **B**). The Kaplan–Meier curves differed significantly according to muscle type ($p = 0.003$; **C**). OS = overall survival

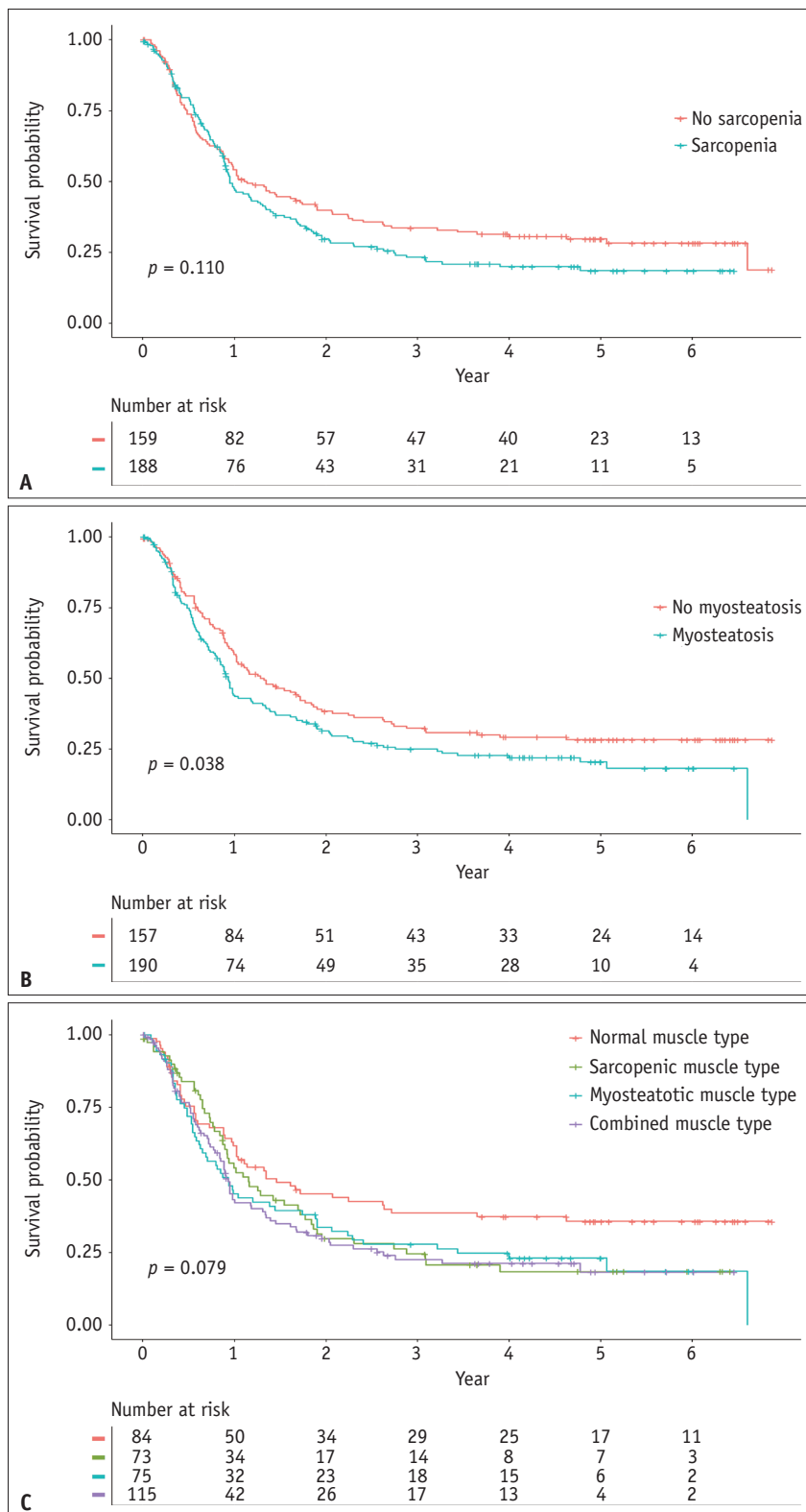


Fig. 4. Kaplan–Meier curves of the RFS according to the presence of sarcopenia (A) and myosteatorsis (B) and muscle types (C). A–C. RFS and sarcopenia showed no significant association (median, 11.5 vs. 13.8 months; $p = 0.110$; A). In contrast, the Kaplan–Meier curves showed a worse RFS in patients with myosteatorsis compared to that in patients without myosteatorsis (median, 11.3 vs. 16.0 months; $p = 0.038$; B). Although the Kaplan–Meier curves did not differ significantly according to muscle type ($p = 0.079$; C), normal muscle type was associated with a better RFS compared to that in the other muscle types (median RFS: 17.6 months for normal muscle type vs. 14.0 months for sarcopenic muscle type, 11.3 months for myosteatortic muscle type, and 11.3 months for combined muscle type). RFS = recurrence-free survival

Muscle Measurement and Determination of Sarcopenia and Myosteatosi s

The mean SMA and SMI were 124.0 ± 27.2 cm² and 48.9 ± 7.6 cm²/m², respectively. The mean value of the mean attenuation of SMA was 46.3 ± 8.1 HU.

The cutoff values for sarcopenia and myosteatosi s in each subgroup are summarized in Table 2. Based on the cutoff values, 188 (54.2%) patients were diagnosed with sarcopenia and 190 (54.8%) with myosteatosi s. Regarding muscle types, 84 (24.2%), 73 (21.0%), 75 (21.6%), and 115 (33.1%) patients were classified as nMT, sMT, mMT, and cMT, respectively.

Univariable Survival Analysis

A total of 247 (71.2%) patients died during follow-up, with a median OS of 31.8 months (range, 1.4–84.8 months). The Kaplan–Meier curves showed a worse OS in patients with sarcopenia compared to that in patients without sarcopenia (median, 28.7 vs. 38.1 months; *p* = 0.010) (Fig. 3A) and in patients with myosteatosi s compared to patients without myosteatosi s (median, 28.0 vs. 36.5 months; *p* = 0.003) (Fig. 3B). The Kaplan–Meier curves also revealed a significant difference between muscle types (*p* = 0.003) (Fig. 3C).

Tumor recurrence occurred in 238 (68.6%) patients, with a median RFS of 12.3 months (range, 0.1–82.9 months). RFS and sarcopenia were not significantly associated (median, 11.5 vs. 13.8 months; *p* = 0.110) (Fig. 4A). In contrast, the Kaplan–Meier curves showed a worse RFS in patients with myosteatosi s compared to that in patients without myosteatosi s (median, 11.3 vs. 16.0 months; *p* = 0.038) (Fig. 4B). Although the Kaplan–Meier curves did not differ significantly according to muscle type (*p* = 0.079) (Fig. 4C), nMT tended to be associated with a better RFS compared to that in the other muscle types (median RFS: 17.6 months for nMT vs. 14.0 months for sMT, 11.3 months for mMT, and 11.3 months for cMT).

Multivariable Survival Analysis

Table 3 summarizes the results of the univariable and multivariable Cox proportional analyses of OS and RFS according to the muscle types and clinicopathologic characteristics (also see the representative cases in Supplementary Figs. 1, 2). In the univariable analysis, mMT (hazard ratio [HR], 1.49; 95% confidence interval [CI], 1.01–2.21; *p* = 0.046) and cMT (HR, 1.92; 95% CI, 1.35–2.74; *p* < 0.001) were associated with a significantly

Table 3. Univariable and Multivariable Cox Proportional Hazard Analyses of the Muscle Type and Clinicopathologic Characteristics

Parameter	Overall Survival			Recurrence-Free Survival		
	Univariable		Multivariable	Univariable		Multivariable
	HR (95% CI)	<i>P</i>	HR (95% CI)	HR (95% CI)	<i>P</i>	HR (95% CI)
Muscle type						
Normal muscle type	1 [reference]		1 [reference]	1 [reference]		1 [reference]
Sarcopenic muscle type	1.41 (0.95–2.09)	0.090	1.40 (0.94–2.10)	1.39 (0.94–2.06)	0.096	1.43 (0.96–2.13)
Myosteototic muscle type	1.49 (1.01–2.21)	0.046	1.49 (1.00–2.22)	1.49 (1.02–2.18)	0.040	1.59 (1.07–2.35)
Combined muscle type	1.92 (1.35–2.74)	< 0.001	1.68 (1.16–2.43)	1.56 (1.09–2.22)	0.014	1.35 (0.93–1.96)
Cancer antigen 19-9 level	1.00 (1.00–1.00)	< 0.001	1.00 (1.00–1.00)	1.00 (1.00–1.00)	0.063	1.00 (1.00–1.00)
AJCC tumor stage						
IA or IB	1 [reference]		1 [reference]	1 [reference]		1 [reference]
IIA or IIB	1.98 (1.47–2.66)	< 0.001	1.99 (1.47–2.71)	2.19 (1.61–2.97)	< 0.001	2.05 (1.50–2.82)
III	2.72 (1.88–3.93)	< 0.001	2.78 (1.88–4.11)	2.87 (1.97–4.19)	< 0.001	2.80 (1.89–4.16)
Tumor differentiation						
Well-differentiated	1 [reference]		1 [reference]	1 [reference]		1 [reference]
Moderately differentiated	2.11 (1.32–3.39)	0.002	2.10 (1.30–3.39)	2.65 (1.59–4.42)	< 0.001	2.53 (1.49–4.28)
Poorly differentiated or undifferentiated	3.55 (2.01–6.28)	< 0.001	4.41 (2.45–7.91)	3.95 (2.12–7.34)	< 0.001	5.28 (2.77–10.08)
Resection margin (R1)	1.61 (1.22–2.12)	< 0.001	1.29 (0.96–1.72)	1.62 (1.22–2.15)	< 0.001	1.36 (1.01–1.82)
Adjuvant treatment	0.59 (0.46–0.76)	< 0.001	0.53 (0.40–0.69)	0.68 (0.52–0.90)	0.006	0.60 (0.45–0.80)

AJCC = American Joint Committee on Cancer, CI = confidence interval, HR = hazard ratio

Table 4. Association between the Muscle Types and Clinicopathologic Characteristics

Characteristics	Muscle Type				P
	Normal Muscle Type (n = 84)	Sarcopenic Muscle Type (n = 73)	Myosteatotic Muscle Type (n = 75)	Combined Muscle Type (n = 115)	
AJCC tumor stage					0.971
IA or IB	31 (36.9)	26 (35.6)	25 (33.3)	42 (36.5)	
IIA or IIB	37 (44.0)	37 (50.7)	37 (49.3)	53 (46.1)	
III	16 (19.0)	10 (13.7)	13 (17.3)	20 (17.4)	
Tumor differentiation					0.694
Well-differentiated	10 (11.9)	7 (9.6)	8 (10.7)	15 (13.0)	
Moderately differentiated	63 (75.0)	57 (78.1)	63 (84.0)	86 (74.8)	
Poorly differentiated or undifferentiated	11 (13.1)	9 (12.3)	4 (5.3)	14 (12.2)	
Resection margin (R1)	18 (21.4)	25 (34.2)	14 (18.7)	31 (27.0)	0.131
Adjuvant treatment	66 (78.6)	49 (67.1)	47 (62.7)	64 (55.7)	0.009

Data are presented as numbers (percentages). AJCC = American Joint Committee on Cancer

worse OS compared to nMT. In the multivariable analysis, mMT (HR, 1.49; 95% CI, 1.00–2.22; $p = 0.0496$) and cMT (HR, 1.68; 95% CI, 1.16–2.43; $p = 0.006$) were associated with significantly worse OS compared to nMT after adjusting for clinicopathologic characteristics. AJCC tumor stage ($p < 0.001$), tumor differentiation ($p < 0.001$), and adjuvant treatment ($p < 0.001$) were significantly associated with OS.

Meanwhile, the univariable analysis indicated that mMT (HR, 1.49; 95% CI, 1.02–2.18; $p = 0.040$) and cMT (HR, 1.56; 95% CI, 1.09–2.22; $p = 0.014$) were related to a significantly worse RFS compared to nMT. In the multivariable analysis, mMT was associated with a significantly worse RFS compared to nMT (HR, 1.59; 95% CI, 1.07–2.35; $p = 0.020$). However, sMT (HR, 1.43; 95% CI, 0.96–2.13; $p = 0.076$) and cMT (HR, 1.35; 95% CI, 0.93–1.96; $p = 0.116$) were not related to RFS. In addition, AJCC tumor stage ($p < 0.001$), tumor differentiation ($p < 0.001$), resection margins ($p = 0.043$), and adjuvant treatment ($p < 0.001$) were significantly associated with RFS.

Association between Muscle Types and Clinicopathologic Characteristics

Table 4 summarizes the associations between muscle type and clinicopathological characteristics, demonstrating a significant association between adjuvant treatment and muscle type ($p = 0.009$). Patients undergoing adjuvant treatment with available information ($n = 184$), showed significant differences between the intervals from the date of surgery to the first date of adjuvant treatment (mean interval \pm standard deviations; 38.8 ± 15.5 days for nMT, 45.8 ± 19.5 days for sMT, 49.1 ± 20.1 days for mMT, and 45.5 ± 16.5 days for cMT; $p = 0.04$). The other

clinicopathological characteristics, including AJCC tumor stage ($p = 0.971$), tumor differentiation ($p = 0.694$), and resection margin ($p = 0.131$), were not significantly associated with muscle type.

DISCUSSION

The results of our study revealed that muscle types with myosteatosis, regardless of the presence of sarcopenia (i.e., mMT and cMT), were linked to poor OS in patients with resectable PDAC (HR vs. nMT, mMT = 1.49 [95% CI, 1.00–2.22] and cMT = 1.68 [95% CI, 1.16–2.43]). In addition, mMT and cMT were associated with RFS in the univariable analysis; however, only mMT was associated with a significantly higher tumor recurrence rate than nMT in the multivariable analysis (HR, 1.59; 95% CI, 1.07–2.35).

Our results indicated that myosteatosis is a disease entity distinct from sarcopenia and plays an independent prognostic role. This finding is supported by previous studies reporting that myosteatosis, but not sarcopenia, was associated with poor survival in patients with pancreatic or periampullary cancers [30,31]. This result could be attributed to the different mechanisms of sarcopenia and myosteatosis that contribute to nutritional and immunologic disturbances [32]. Unlike sarcopenia, myosteatosis (fat deposition within muscles) leads to the accumulation of lipid intermediates (i.e., diacylglycerol and ceramide) and insulin resistance [8]. It is also associated with increased systemic inflammation and oxidative stress [33,34]. Indeed, myosteatosis is associated with elevated levels of serum inflammatory markers (albumin, white blood cell count, neutrophil-to-lymphocyte ratio, and

C-reactive protein) [30,31]. In addition, Stretch et al. [35] reported that myosteatosi s and sarcopenia were associated with different body compositions, gene expression, and metabolites.

Our results showing a significant association between adjuvant treatment and muscle type suggested that patients with impaired muscle function were less likely to receive adjuvant treatment compared to patients with normal muscle function owing to their poor postoperative health status, which may have significantly contributed to their poor survival [36]. Consistent with our results, a previous study reported an association between myosteatosi s and incomplete adjuvant chemotherapy [37]. Although we could not investigate this further in our retrospective study, a higher risk of postoperative complications and longer hospital stay may also contribute to poor outcomes in patients with sarcopenia and myosteatosi s [8,38].

Several reports have shown the effect of preoperative sarcopenia or myosteatosi s on the survival of patients with PDAC [14-19]; however, their findings were contradictory and contrary to our results. For example, some studies showed that sarcopenia and myosteatosi s were associated with poor survival [14,17,19], while other studies reported that sarcopenia only was a prognostic factor for poor survival [15,16]. The variation in study results may be attributed to differences in study populations. Our study showed the effect of preoperative sarcopenia and myosteatosi s in selected patients with resectable PDAC (according to the NCCN guidelines) requiring curative surgery without neoadjuvant treatment and, therefore, has clinical utility. Moreover, variations in the methods used for muscle measurement and the cutoff values for sarcopenia and myosteatosi s may have contributed to the difference between our results and those of previous studies. Unlike previous studies, in which the cutoffs were arbitrarily determined using the lowest tertile [16,18] or survival outcomes at fixed time points [15,17], our results revealed the prognostic value of sarcopenia and myosteatosi s when determining the optimal cutoffs in consideration of patient survival based on the Contal and O'Quigley methods.

Our results indicated that the preoperative diagnosis of myosteatosi s may be crucial for risk stratification after surgery and for determining management requirements [14,39]. For example, resistance training is the most important element of exercise programs [40,41]. In addition, nutritional support, including vitamin D, β -hydroxy β -methyl butyrate, and omega-3 fatty acids, improves muscle mass

and quality in cancer patients [41,42].

Our study has several limitations. First, the reason for the lack of any significant association between cMT and poor RFS in the multivariable analysis (HR 1.35, 95% CI 0.93–1.96, $p = 0.116$) is unclear. Considering the low prevalence of adjuvant treatment in cMT, the presence of adjuvant treatment may have been a confounder in the statistical analysis, undermining the association between cMT and poor RFS. Second, we calculated the cutoff values for the diagnosis of sarcopenia and myosteatosi s based on a relatively small number of patients from a single institution. Therefore, validation and generalization of these cutoff values require further investigation across various somatotypes and ethnicities. Third, we measured muscle quantity and quality at a single time point on preoperative CT images. The effect of longitudinal interval changes in the muscle after surgery may also be an important prognostic factor for survival; however, data on this were not available in our study because postoperative imaging was conducted at various time points and using various CT protocols. Finally, unlike the pooled results from previous meta-analyses [43,44], margin status was not identified as an independent factor for OS. However, our results are understandable because the prognostic value of margin status was largely affected by the study design, including the definition of R0, the anatomic location of the tumor, the location of the positive margin, and the presence of adjuvant treatment [43,45-47].

In conclusion, preoperative myosteatosi s was associated with poor OS and RFS after curative surgery in patients with resectable PDAC. Preoperative assessment of muscle quality may be valuable for treatment planning and optimization of nutritional support and physical therapy.

Supplement

The Supplement is available with this article at <https://doi.org/10.3348/kjr.2022.0277>.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Seung Soo Lee who is on the editorial board of the *Korean Journal of Radiology* was not involved in the editorial

evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

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