의학석사 학위논문

절제 가능 췌장 선암에서 근감소증과 근지방증이 예후에 미치는 영향

Prognostic value of sarcopenia and myosteatosis in patients with resectable pancreatic ductal adenocarcinoma

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안혜민

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국 문 요 약

연구 목적

췌장 선암은 근 손실을 많이 일으키는 대표적인 질환이다. 본 연구에서는 절제 가능 췌장 선암 환자에서 근감소증(sarcopenia)과 근지방증(myosteatosis)이 예후에 미치는 영향에 대해서 알아보고자 하였다.

연구 방법

2014 년 1 월에서 2017 년 1 월 사이의 절제 가능한 췌장 선암 환자 중 수술(upfront surgery)을 시행한 347 명의 환자를 후향적으로 연구하였다. 수술 전 시행한 컴퓨터 단층 촬영의 제 3 번 요추 위치에서 자동 영상분할 기법(automatic segmentation)을 이용하여 골격근을 분류하였다. 근감소증은 분류된 골격근 영역(skeletal muscle area, SMA)을 키로 나눈 지표(skeletal muscle index, SMI)를 이용하여 평가하였다. 근지방증은 컴퓨터 단층 촬영에서 각 픽셀의 감쇄 정도를 반영하여 만드는 muscle quality map 을 이용하여, 골격근 영역을 정상 감쇄 근육 영역(normal-attenuation muscle area, NAMA)과 낮은 감쇄 근육 영역(low-attenuation muscle area)으로 분류하여 평가하였다. Muscle quality map 을 이용한 근지방증 평가에 적절한 지표가 아직 개발된 바 없기 때문에, 본 연구에서는 근감소증 지표 (SMI)와 가장 상관관계가 적은 근지방증 지표를 Pearson's r 방법을 이용하여 탐색하였다. 근감소증과 근지방증의 진단기준은 Contal 과 O'Quiegley 방법을 이용하여 결정하였다. 이 진단 기준에 따라 환자군을 정상, 근감소형, 근지방형, 혼합형 근육형으로 분류하였다. 각 근육 형에 따른 전제생존기간과 무재발생존기간을 단변량 및 다변량 콕스 회귀분석을 이용하여 평가하였다.

결과

정상 감쇄 근육 영역(NAMA)을 골격근 영역(SMA)으로 나눈 값을 근지방증 지표로 선정하였다. 진단기준에 따라 환자군은 정상, 근감소형, 근지방형, 혼합형 근육형 각각 78 명 (22.5%), 81 명 (23.3%), 100 명 (28.8%), 88 명 (25.4%)으로 분류되었다. 근감소증 혹은 근지방증이 하나라도 있는 경우 정상 근육형과 비교하였을 때 나쁜 전체생존기간을 보였다 (위험비 [95% 신뢰구간]: 근감소형=1.58 [1.05-2.38], 근지방형=1.50 [1.00-2.25],

혼합형=1.66 [1.12–2.46]). 근지방형은 정상 근육형과 비교했을 때 나쁜 무재발생존기간과 연관이 있었다 (위험비 [95% 신뢰구간], 1.49 [1.01–2.20]).

결론

절제 가능 췌장 선암 환자에서 수술 전 근감소증 혹은 근지방증이 있는 경우 수술 후 전제생존기간 및 무재발생존기간의 나쁜 예후와 연관이 있다.

차 례

표 차례

그림 차례

I. 서론 (Introduction)

Sarcopenia, defined as loss of skeletal muscle mass and strength (1), is associated with poor prognosis in patients with various diseases (2, 3). Recently, several studies have reported that muscle quality, associated with muscle fat deposition leading to declining muscle strength (4, 5), is regarded as an independent prognostic factor (6). Myosteatosis, a term referring to the loss of muscle quality, is now considered a distinct disease from sarcopenia (7, 8).

Computed tomography (CT) is a common, noninvasive method of muscle assessment that measures the difference in radiodensity between muscle and other tissues (9, 10). Sarcopenia can be diagnosed through quantitative measurement of muscle mass, which can be segmented on CT imaging. Muscle quality assessment for diagnosis of myosteatosis can also be conducted by measuring radiodensity of a segmented muscle area, given the inverse linear relationship between radiodensity and degree of fat deposition (11).

Pancreatic ductal adenocarcinoma (PDAC) is a dismal disease with a 5-year survival rate of as low as 6% (12). PDAC causes body composition change, and many patients develop muscle loss as the disease progresses (13, 14). Along with other malignancies (6), 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 myosteatosis on overall survival (OS) and recurrence-free survival (RFS) among patients in PDAC undergoing curative-intent surgery (15-20).

Currently, the use of neoadjuvant chemotherapy is increasing in advanced PDAC. The National Comprehensive Cancer Network (NCCN) proposes that non-metastatic PDAC be classified into resectable, borderline resectable, and locally advanced PDAC according to tumor-vascular contact on pre-treatment imaging (21), and upfront surgery remains as standard treatment only in patients with resectable PDAC. In contrast with previous studies that included all patients undergoing surgery, we believe selective inclusion of only those receiving upfront surgery in accordance with the standard

treatment options would allow for more accurate evaluation of the association between preoperative muscle status and prognosis.

Therefore, we aimed to investigate the prognostic effects of sarcopenia and myosteatosis in patients with resectable PDAC who underwent upfront surgery by using quantitative muscle measurement on preoperative CT imaging.

II. 재료 및 방법 (Materials and Methods)

This retrospective observational study was approved by the Institutional Review Board of Asan Medical Center, and the requirement of informed consent was waived given the retrospective nature of the study.

Patients

Patients with PDAC at our tertiary institution between January 2014 and January 2017 were retrospectively and consecutively enrolled as part of the study population in a previous study (22), evaluating the prognosis of PDAC according to CT characteristics of the tumor. Patients meeting the following criteria were included: (a) resectable PDAC according to the NCCN criteria (21) and (b) curative-intent surgery without neoadjuvant treatment. Briefly, resectable PDAC referred to no arterial (celiac axis, superior mesenteric artery, or common hepatic artery) contact nor tumor contact with the superior mesenteric vein or portal vein < 180 degrees without contour irregularity and thrombus (23).

Exclusion criteria were (a) no pancreatic protocol CT before surgery, (b) palliative surgery or macroscopic residual tumor (R2) after surgery, (b) other coexisting malignancies within 5 years before PDAC diagnosis, and (d) insufficient clinical data.

CT Protocol

Multiphasic CT was performed using a 64-channel multidetector CT scanner (Discovery CT 750HD, GE Medical Systems, Milwaukee, Wisconsin; and Somatom Definition AS+ or Definition Edge, Siemens, Erlangen, Germany), and the pancreatic CT protocol was performed according to the NCCN guidelines (21). Unenhanced and biphasic contrast-enhanced imaging, including arterial phase (10 seconds after descending aorta enhancement to 100 HU) and portal venous phase (72 seconds after contrast administration), which were were obtained after intravenous administration of 150 mL of ioversol (Optiray 320; Guerbet, Villepinte, France) at a rate of 3 mL/seconds. Unenhanced axial images were reconstructed at 5 mm thickness and 2.5–3.0 mm for arterial and portal venous phases in the axial

and coronal planes. Other scan parameters included a tube voltage of 100 or 120 kVp, tube current of 200–400 mA with automatic exposure control, a pitch of 0.6 or 1, and a field of view to fit. We reconstructed images using iterative reconstruction algorithms (SAFIRE1 or SAFIRE2, Siemens; or ASIR 20%, GE Healthcare), and routinely generated volume-rendered and maximal intensity projection reconstructed images of arterial and venous structures.

Evaluation of muscle quantity and quality on CT

Muscle quantity and quality were measured in a single slice of an axial CT image on the portal venous phase, following semi-automatic selection of the CT slice at the inferior endplate level of the L3 vertebra (Ha J, In press). All skeletal muscles (psoas, paraspinal, transversus abdominis, rectus abdominis, quadratus lumborum, internal oblique, and external oblique muscles) on the selected image were automatically segmented using a convolutional neural network (AID-U™, iAID Inc., Seoul, Korea), which had a Dice similarity coefficient of 0.96–0.97 (24). By using a predetermined threshold of the Hounsfield unit (HU), density from –29 to 150 HU within the segmented muscle area was defined as the skeletal muscle area (SMA; i.e., representing muscle area) to remove the area of intermuscular fat **(Figure 1)**. SMA was additionally subcategorized by CT density per pixel, which were: (a) normal-attenuation muscle area (NAMA; with threshold from 30 to 150 HU) representing the area of good muscle quality, or (b) low-attenuation muscle area (with a threshold from –29 to 29 HU) representing the area of low muscle quality **(Figure 1)** (7, 24).

Clinicopathologic Data Collection

Demographic and laboratory data relevant to prognosis (i.e., age, sex, height, weight, cancer antigen 19-9) were collected from electronic medical records and measured within 1 month before surgery. Surgical and pathologic data, including type of surgery, cancer staging 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. Confirmation of adjuvant treatment, typically initiated 3–10 weeks after surgery, was also obtained.

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

Determination of patients with sarcopenia and myosteatosis

We used the skeletal muscle index (SMI), defined as SMA divided by height squared (cm^2/m^2), to determine patients with sarcopenia (6). Given the lack of muscle quality assessment index, particularly in muscle quality map of CT, we evaluated the correlation between possible indexes of muscle quality (i.e. NAMA [cm2], NAMA/height2 [cm2/m2], and NAMA/SMA [%]) and SMI using the Pearson correlation coefficient (Pearson's r). We selected an appropriate index to identify patients with myosteatosis, which would be optimal if the index was least dependent on SMI (i.e., the index with the lowest Pearson's r).

Before determination of cutoffs of sarcopenia and myosteatosis, patients were categorized into one of the 6 subgroups which were dichotomized by age (< 65 years vs. ≥ 65 years), sex (male vs. female), and BMI (underweight or normal [BMI < 23 kg/cm^2] vs. overweight or obese [BMI ≥ 23 kg/cm^2]). Cutoffs of sarcopenia and myosteatosis in each subgroup were separately derived using Contal and O'Quigley methods (27) based on log-rank statistics that separate patients according to time to death.

Survival analysis according to muscle type

Sarcopenia and myosteatosis cutoffs subsequently classified patients into the following four muscle type groups: (a) normal muscle type (nMT), patients with neither sarcopenia nor myosteatosis; (b) sarcopenic muscle type (sMT), patients with sarcopenia but no myosteatosis; (c) myosteatotic muscle type (mMT), patients with myosteatosis but no sarcopenia; and (d) combined muscle type (cMT), patients with both sarcopenia and myosteatosis.

The primary outcome was OS, defined as the time between surgery and death, and the secondary outcome was RFS, defined as the time between surgery and recurrence or death (28). Patients without death or recurrence were censored at the last follow-up. Kaplan–Meier survival curves for OS and RFS were plotted according to the presence of sarcopenia and myosteatosis and muscle type and compared using the log-rank test. Univariable and multivariable Cox proportional hazard regression analyses was performed, including muscle types and clinicopathologic characteristics (i.e., serum CA 19-9, AJCC cancer staging, tumor differentiation, resection margin status, and adjuvant treatment) which were deemed to be potentially associated with the patients' survival. The association between muscle type and clinicopathologic characteristics was analyzed with Pearson's χ^2 tests.

P-values of less than 0.05 were considered statistically significant. SAS software (version 9.4; SAS Institute, Cary, NC, USA), SPSS (version 21.0, Chicago, IL, USA), and R (version 3.6.0.; R Foundation for Statistical Computing, Vienna, Austria) were used to perform the statistical analyses.

III. 결과 (Results)

Patient Characteristics

Among 456 patients with resectable PDAC, 410 patients underwent successful upfront surgery **(Figure 2)**. Sixty-three patients were excluded due to no pancreatic protocol CT prior to surgery (n = 38), palliative surgery or macroscopic residual tumor (n = 5), coexisting malignancy within 5 years (n = 18), and no sufficient clinical data (n = 2). Finally, 347 patients (mean age ± standard deviation [SD], 63.6 ± 9.6 years; 202 men) were included. All patient characteristics are summarized in **Table 1.** The median interval between CT and surgery was 8 days (range, 1–35 days). 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. Tumor differentiation 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 margin was R0 in 259 (74.6%) patients and R1 in 88 (25.4%) patients. Adjuvant treatment was performed in 226 (65.1%) patients.

Muscle measurement and determination of sarcopenia and myosteatosis

Mean SMA and SMI were 124.0 ± 27.2 cm^2 and 48.9 ± 7.6 cm^2/m^2, respectively, and mean NAMA were 95.3 ± 27.4 cm^2. NAMA/SMA had the weakest correlation with SMI (Pearson's r = 0.32) compared with NAMA (Pearson's r = 0.82) and NAMA/$height^2$ (Pearson's r = 0.87) **(Supplementary Figure 1)**; therefore, it was determined as the optimal index of myosteatosis. Cutoffs of sarcopenia and myosteatosis in each subgroup are summarized in **Table 2**. Based on the cutoffs, 188 (54.2%) patients were diagnosed with sarcopenia and 169 (48.7%) with myosteatosis. Regarding the muscle type, 78 (22.5%), 81 (23.3%), 100 (28.8%), and 88 (25.4%) patients were classified as nMT, sMT, mMT, and cMT, respectively.

Survival analysis

A total of 247 (71.2%) patients died during follow-up, and the median OS was 31.8 months (range, 1.4–84.8 months). Kaplan–Meier curves showed worse OS in patients with sarcopenia than in those without (median, 28.7 vs. 38.1 months; P < 0.01; **Figure 3A**), and worse OS in patients with myosteatosis than those without (median, 27.7 vs. 36.6 months; P = 0.02, **Figure 3B**). Kaplan–Meier curves also indicated a significant difference between the muscle types (P < 0.01, **Figure 3C**).

Tumor recurrence occurred in 238 (68.6%) patients, and the median RFS was 12.3 months (range, 0.1–82.9 months). Kaplan–Meier curves showed no statistical significance according to the presence of sarcopenia (median, 13.8 vs. 11.5 months; P = 0.11, **Figure 4A**) and myosteatosis (median, 16.3 vs. 11.4 months; P = 0.06, **Figure 4B**). Although Kaplan–Meier curves were not significantly different according to muscle types (P = 0.054, **Figure 4C**), nMT tended to have better OS compared with the other muscle types (median RFS: 20.1 months in nMT vs. 10.5 months in sMT, 12.3 months in mMT, and 11.4 months in cMT).

Table 3 summarizes the results of the univariate and multivariate cox proportional analyses of OS and RFS according to muscle types and clinicopathologic characteristics. In the univariable analysis, sMT (hazard ratio [HR], 1.68; 95% confidence interval [CI], 1.13–2.50]; P = 0.01), mMT (HR, 1.63; 95% CI, 1.09–2.43; P = 0.02), and cMT (HR, 1.96; 95% CI, 1.34–2.86; P < 0.001) showed significantly worse OS compared with nMT. In the multivariable analysis, sMT (HR, 1.58; 95% CI, 1.05–2.38; P = 0.03) and cMT (HR, 1.66; 95% CI, 1.12–2.46; P = 0.01) showed significantly worse OS compared with nMT after adjustment for clinicopathologic characteristics. mMT had a marginally worse OS (HR, 1.50; 95% CI, 1.00–2.25; P = 0.05) than nMT in the multivariable analysis. Regarding the RFS, sMT (HR, 1.54; 95% CI, 1.04–2.28; P = 0.03), mMT (HR, 1.59; 95% CI, 1.08–2.33; P = 0.02), and cMT (HR, 1.58; 95% CI, 1.09–2.28; P < 0.001) showed significantly worse outcomes compared with nMT in the univariable analysis. In the multivariable analysis, mMT had a significantly worse RFS compared with nMT (HR, 1.49; 95% CI, 1.01–2.20; P = 0.047). However, sMT (HR, 1.46; 95% CI, 0.98–2.19; P = 0.06) and cMT (HR, 1.32; 95% CI, 0.89–1.93; P = 0.16) did

not have significantly worse RFS compared with nMT in the multivariable analysis. Representative cases are presented in **Supplementary Figure 2** and **3**.

Supplementary Table 2 summarizes the association between muscle types and clinicopathologic characteristics, indicating a significant association between adjuvant treatment and muscle type (P = 0.03). Other clinicopathologic characteristics, including AJCC tumor staging (P = 0.88), tumor differentiation (P = 0.63), and resection margin (P = 0.19) were not significantly associated with muscle type.

IV. 고찰 (Discussion)

Our study revealed that the presence of sarcopenia or myosteatosis before upfront surgery is prognostic for poor overall survival in patients with resectable PDAC, even after adjustment for clinicopathologic factors (HR compared with nMT, sMT = 1.58 [95% CI, 1.05–2.38]; mMT = 1.50 [95% CI, 1.00–2.25]; and cMT = 1.66 [95% CI, 1.12–2.46]). An association in RFS between preoperative sarcopenia and myosteatosis occurred in the univariable analysis; however, only the mMT showed a significantly higher tumor recurrence than nMT in the multivariable analysis (HR, 1.49 [95% CI, 1.01–2.20]).

Our results are supported by previous studies that have reported a significant association between preoperative sarcopenia and myosteatosis and prognosis in patients with abdominal malignancies who underwent curative resection (29-31). Poor prognosis in sarcopenic or myosteatotic conditions is explained by the association with nutritional and immunologic disturbance (32-34). Depletion of skeletal muscle in sarcopenia reduces the proportion of anti-inflammatory cytokines and adipokines, leading to a compromised immune system (35). Insulin resistance caused by diabetogenic alteration of muscle metabolism in myosteatosis may also contribute to poor survival (36). According to our results, in addition, patients with loss of muscle quantity and quality were less likely to conduct adjuvant treatment, likely because of poor postoperative health status, which may have significantly contributed to poor survival (37).

There are several reports suggesting the effect of preoperative sarcopenia or myosteatosis on the survival of patients with PDAC (15-20); however, they were not consistent across studies. For example, some studies showed that sarcopenia and myosteatosis were associated with poor survival (15, 18, 20), whereas others noted that sarcopenia only was a prognostic factor for poor survival (16, 17). The variation in study results may be attributed to the differences in study populations; for example, some might have included patients requiring neoadjuvant chemotherapy. Our study has shown the effect of preoperative sarcopenia and myosteatosis in selective patients with resectable

PDAC (according to NCCN guidelines) requiring upfront surgery and therefore has clinical utility. According to our result, preoperative diagnosis of either sarcopenia or myosteatosis may be promising for risk stratification after surgery and the requirement of nutritional support or physical therapy (15, 38).

Moreover, the variation in the methods of muscle measurement and cutoffs for sarcopenia and myosteatosis may have contributed to the difference in our results compared with those from previous studies. For example, we adopted the muscle quality map to diagnose myosteatosis, in which the segmented area of muscle was categorized according to the radiodensity of each pixel on CT images. To the best of our knowledge, we are the first to determine the cutoff for myosteatosis in patients with malignancy. Compared with conventional methods of muscle quality assessment such as mean radiodensity of the muscle area, the muscle quality map enables visualization of muscle component distribution according to the degree of fat infiltration and facilitates precise evaluation (7). However, no standardization for the diagnosis of myosteatosis has yet been achieved. We propose NAMA/SMA as the index for muscle quality assessment because it depends less on muscle quantity (Pearson's $r = 0.32$), given that myosteatosis is distinct from sarcopenia and is well-correlated with the mean radiodensity of the muscle area (39). In addition, NAMA/SMA may be less susceptible to segmentation error and CT noise than mean radiodensity.

There are several limitations to our study. First, we devised the cutoffs for the diagnosis of sarcopenia and myosteatosis using a relatively small number of patients from a single institution. Therefore, validation and generalization of these cutoffs require further investigation across various somatotypes and ethnicities. Second, we measured muscle quantity and quality at a single timepoint on preoperative CT. The effect of longitudinal interval change of muscle after surgery may also be an important prognostic factor for survival; however, it was not available in the current study because postoperative imaging was obtained at various timepoints and CT protocols across the patients. Lastly, retrospective enrollment of the study population might have led to selection bias.

V. 결론 (Conclusion)

In conclusion, preoperative sarcopenia or myosteatosis in patients with resectable PDAC is associated with poor OS and RFS after upfront surgery. The preoperative assessment of muscle quantity and quality may be valuable for treatment planning and optimizing nutritional support and physical therapy.

VI. 참고문헌 (References)

1. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-31.

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

3. Beaudart C, Zaaria M, Pasleau F, Reginster JY, Bruyère O. Health Outcomes of Sarcopenia: A Systematic Review and Meta-Analysis. PLoS One. 2017;12(1):e0169548.

4. Marcus RL, Addison O, Kidde JP, Dibble LE, Lastayo PC. Skeletal muscle fat infiltration: impact of age, inactivity, and exercise. J Nutr Health Aging. 2010;14(5):362-6.

5. Delmonico MJ, Harris TB, Visser M, Park SW, Conroy MB, Velasquez-Mieyer P, et al. Longitudinal study of muscle strength, quality, and adipose tissue infiltration. Am J Clin Nutr. 2009;90(6):1579-85.

6. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31(12):1539-47.

7. Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, et al. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. Acta Physiol (Oxf). 2014;210(3):489-97.

8. Ahn H, Kim DW, Ko Y, Ha J, Shin YB, Lee J, et al. Updated systematic review and meta-analysis on diagnostic issues and the prognostic impact of myosteatosis: A new paradigm beyond sarcopenia. Ageing Res Rev. 2021;70:101398.

9. Beaudart C, McCloskey E, Bruyère O, Cesari M, Rolland Y, Rizzoli R, et al. Sarcopenia in daily practice: assessment and management. BMC Geriatr. 2016;16(1):170.

10. Tosato M, Marzetti E, Cesari M, Savera G, Miller RR, Bernabei R, et al. Measurement of muscle mass in sarcopenia: from imaging to biochemical markers. Aging Clin Exp Res.

2017;29(1):19-27.

11. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. J Appl Physiol (1985). 2000;89(1):104-10.

12. Khorana AA, Mangu PB, Berlin J, Engebretson A, Hong TS, Maitra A, et al. Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016;34(21):2541-56.

13. Wigmore SJ, Plester CE, Richardson RA, Fearon KC. Changes in nutritional status associated with unresectable pancreatic cancer. Br J Cancer. 1997;75(1):106-9.

14. Fearon KC, Voss AC, Hustead DS. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am J Clin Nutr. 2006;83(6):1345-50.

15. Okumura S, Kaido T, Hamaguchi Y, Fujimoto Y, Masui T, Mizumoto M, et al. Impact of preoperative quality as well as quantity of skeletal muscle on survival after resection of pancreatic cancer. Surgery. 2015;157(6):1088-98.

16. Peng YC, Wu CH, Tien YW, Lu TP, Wang YH, Chen BB. Preoperative sarcopenia is associated with poor overall survival in pancreatic cancer patients following pancreaticoduodenectomy. Eur Radiol. 2021;31(4):2472-81.

17. Choi MH, Yoon SB, Lee K, Song M, Lee IS, Lee MA, et al. Preoperative sarcopenia and post-operative accelerated muscle loss negatively impact survival after resection of pancreatic cancer. J Cachexia Sarcopenia Muscle. 2018;9(2):326-34.

18. Okumura S, Kaido T, Hamaguchi Y, Kobayashi A, Shirai H, Yao S, et al. Visceral Adiposity and Sarcopenic Visceral Obesity are Associated with Poor Prognosis After Resection of Pancreatic Cancer. Ann Surg Oncol. 2017;24(12):3732-40.

19. Peng P, Hyder O, Firoozmand A, Kneuertz P, Schulick RD, Huang D, et al. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. J Gastrointest Surg. 2012;16(8):1478-86.

20. Sugimoto M, Farnell MB, Nagorney DM, Kendrick ML, Truty MJ, Smoot RL, et al. Decreased Skeletal Muscle Volume Is a Predictive Factor for Poorer Survival in Patients Undergoing Surgical Resection for Pancreatic Ductal Adenocarcinoma. J Gastrointest Surg. 2018;22(5):831-9.

21. National Comprehensive Cancer network. Pancreatic Adenocarcinoma, Version 2. 2021, NCCN Clinical Practice Guidelines in Oncology [Available from: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf.

22. Kim DW, Lee SS, Kim SO, Kim JH, Kim HJ, Byun JH, et al. Estimating Recurrence after Upfront Surgery in Patients with Resectable Pancreatic Ductal Adenocarcinoma by Using Pancreatic CT: Development and Validation of a Risk Score. Radiology. 2020;296(3):541-51.

23. Al-Hawary MM, Francis IR, Chari ST, Fishman EK, Hough DM, Lu DS, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology. 2014;270(1):248-60.

24. Amini B, Boyle SP, Boutin RD, Lenchik L. Approaches to Assessment of Muscle Mass and Myosteatosis on Computed Tomography: A Systematic Review. J Gerontol A Biol Sci Med Sci. 2019;74(10):1671-8.

25. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93-9.

26. Campbell F, Foulis A, Verbeke C. Dataset for the histopathological reporting of carcinomas of the pancreas, ampulla of Vater and common bile duct. The Royal College of Pathologists. 2010.

27. Contal C, O'Quigley J. An application of changepoint methods in studying the effect of age on survival in breast cancer. Computational Statistics & Data Analysis. 1999;30(3):253-70.

28. Bonnetain F, Bonsing B, Conroy T, Dousseau A, Glimelius B, Haustermans K, et al. Guidelines for time-to-event end-point definitions in trials for pancreatic cancer. Results of the DATECAN initiative (Definition for the Assessment of Time-to-event End-points in CANcer trials). Eur J Cancer. 2014;50(17):2983-93.

29. Aro R, Mäkäräinen-Uhlbäck E, Ämmälä N, Rautio T, Ohtonen P, Saarnio J, et al. The impact

of sarcopenia and myosteatosis on postoperative outcomes and 5-year survival in curatively operated colorectal cancer patients - A retrospective register study. Eur J Surg Oncol. 2020;46(9):1656-62.

30. Dolan RD, Almasaudi AS, Dieu LB, Horgan PG, McSorley ST, McMillan DC. The relationship between computed tomography-derived body composition, systemic inflammatory response, and survival in patients undergoing surgery for colorectal cancer. J Cachexia Sarcopenia Muscle. 2019;10(1):111-22.

31. Zhuang CL, Shen X, Huang YY, Zhang FM, Chen XY, Ma LL, et al. Myosteatosis predicts prognosis after radical gastrectomy for gastric cancer: A propensity score-matched analysis from a large-scale cohort. Surgery. 2019;166(3):297-304.

32. Kim KW, Lee K, Lee JB, Park T, Khang S, Jeong H, et al. Preoperative nutritional risk index and postoperative one-year skeletal muscle loss can predict the prognosis of patients with gastric adenocarcinoma: a registry-based study. BMC Cancer. 2021;21(1):157.

33. Abe T, Nakata K, Kibe S, Mori Y, Miyasaka Y, Ohuchida K, et al. Prognostic Value of Preoperative Nutritional and Immunological Factors in Patients with Pancreatic Ductal Adenocarcinoma. Ann Surg Oncol. 2018;25(13):3996-4003.

34. Öztürk ZA, Kul S, Türkbeyler İ H, Sayıner ZA, Abiyev A. Is increased neutrophil lymphocyte ratio remarking the inflammation in sarcopenia? Exp Gerontol. 2018;110:223-9.

35. Lutz CT, Quinn LS. Sarcopenia, obesity, and natural killer cell immune senescence in aging: altered cytokine levels as a common mechanism. Aging (Albany NY). 2012;4(8):535-46.

36. Miljkovic I, Cauley JA, Wang PY, Holton KF, Lee CG, Sheu Y, et al. Abdominal myosteatosis is independently associated with hyperinsulinemia and insulin resistance among older men without diabetes. Obesity (Silver Spring). 2013;21(10):2118-25.

37. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N Engl J Med. 2018;379(25):2395-406.

38. Mayo NE, Feldman L, Scott S, Zavorsky G, Kim DJ, Charlebois P, et al. Impact of preoperative change in physical function on postoperative recovery: argument supporting

prehabilitation for colorectal surgery. Surgery. 2011;150(3):505-14.

39. Kim HK, Kim KW, Kim EH, Lee MJ, Bae SJ, Ko Y, et al. Age-related changes in muscle quality and development of diagnostic cutoff points for myosteatosis in lumbar skeletal muscles measured by CT scan. Clin Nutr. 2021;40(6):4022-8.

표 (Tables)

Table 1. Patient characteristics

Characteristics	Values
Age (years)	63.6 ± 9.6
Male:female	202:145
Height (m)	162.0 ± 8.6
Body mass index (kg/m^2)	23.2 ± 2.9
Cancer antigen 19-9 (U/mL)†	81 (22.2–322.6)
Tumor location	
Head	216 (62.2)
Body	65 (18.7)
Tail	66 (19.0)
AJCC tumor staging	
IA	36 (10.4)
IB	88 (25.4)
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 mean ± standard deviation for continuous variables and number (percentage) for categorical variables.

† Median with an interquartile range in parenthesis.

Abbreviations: AJCC, the American Joint Committee on Cancer.

Table 2. Cutoff values for sarcopenia (SMI) and myosteatosis (NAMA/SMA) significantly associated with low survival

Body mass index	Age (year)	SMI (cm^2/m^2)		NAMA/SMA (%)	
		Men	Women	Men	Women
Underweight or normal (< 23 kg/m^2)	< 65	45.25	37.39	88.68	83.82
	≥ 65	48.86	38.85	65.17	73.08
Overweight or obese (≥ 23 kg/m^2)	< 65	54.89	44.90	80.61	84.71
	≥ 65	49.66	49.84	77.53	67.23

Abbreviations: NAMA, normal attenuation muscle area; SMA, skeletal muscle area; SMI, skeletal muscle index.

Table 3. Univariable and multivariable Cox proportional hazard analyses of muscle type and clinicopathologic characteristics

Parameter	Overall survival				Recurrence-free survival			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Muscle type		.004		.06		.04		.17
Normal muscle type	1 [reference]		1 [reference]		1 [reference]		1 [reference]	
Sarcopenic muscle type	1.68 (1.13–2.50)	.01	1.58 (1.05–2.38)	.03	1.54 (1.04–2.28)	.03	1.46 (0.98–2.19)	.06
Myosteatotic muscle type	1.63 (1.09–2.43)	.02	1.50 (1.00–2.25)	.05	1.59 (1.08–2.33)	.02	1.49 (1.01–2.20)	.047
Combined muscle type	1.96 (1.34–2.86)	<.001	1.66 (1.12–2.46)	.01	1.58 (1.09–2.28)	.02	1.32 (0.89–1.93)	.16
Cancer antigen 19-9	1.00 (1.00–1.00)	<.001	1.00 (1.00–1.00)	.09	1.00 (1.00–1.00)	.06	1.00 (1.00–1.00)	.12
AJCC tumor staging		<.001		<.001		<.001		<.001
IA or IB	1 [reference]		1 [reference]		1 [reference]		1 [reference]	
IIA or IIB	1.98 (1.47–2.66)	<.001	1.99 (1.47–2.71)	<.001	2.19 (1.61–2.97)	<.001	2.02 (1.47–2.77)	<.001
III	2.72 (1.88–3.93)	<.001	2.87 (1.94–4.24)	<.001	2.87 (1.97–4.19)	<.001	2.84 (1.92–4.19)	<.001
Tumor differentiation		<.001		<.001		<.001		<.001
Well-differentiated	1 [reference]		1 [reference]		1 [reference]		1 [reference]	
Moderate-differentiated	2.11 (1.32–3.39)	.002	2.05 (1.27–3.31)	.003	2.65 (1.59–4.42)	<.001	2.45 (1.45–4.15)	<.001
Poorly/undifferentiated	3.55 (2.01–6.28)	<.001	4.28 (2.39–7.67)	<.001	3.95 (2.12–7.34)	<.001	5.12 (2.69–9.75)	<.001
Resection margin (R1)	1.61 (1.22–2.12)	<.001	1.27 (0.95–1.69)	.1	1.62 (1.22–2.15)	<.001	1.32 (0.99–1.78)	.06
Adjuvant treatment	0.59 (0.46–0.76)	<.001	0.52 (0.40–0.67)	<.001	0.68 (0.52–0.90)	.006	0.59 (0.44–0.79)	<.001

Abbreviations: HR, hazard ratio; CI, confidence interval.

Supplementary Table 1. AJCC 8th staging system for pancreatic adenocarcinoma

Primary tumor (T)		**Regional lymph nodes (N)**		**Distant metastasis (M)**	
Maximal tumor diameter					
T1	≤2 cm	**N0**	0	**M0**	No distant metastasis
T2	>2cm, ≤4 cm	**N1**	1–3	**M1**	Distant metastasis
T3	>4 cm	**N2**	≥4		
T4	Involves the celiac axis or SMA				

Stage			
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1–T3	N1	M0
III	Any T	N2	M0
	T4	Any N	M0
IV	Any T	Any N	M1

Abbreviations: AJCC, the American Joint Committee on Cancer; SMA, superior mesenteric artery

Supplementary Table 2. Association between Muscle Types and Clinicopathologic Characteristics

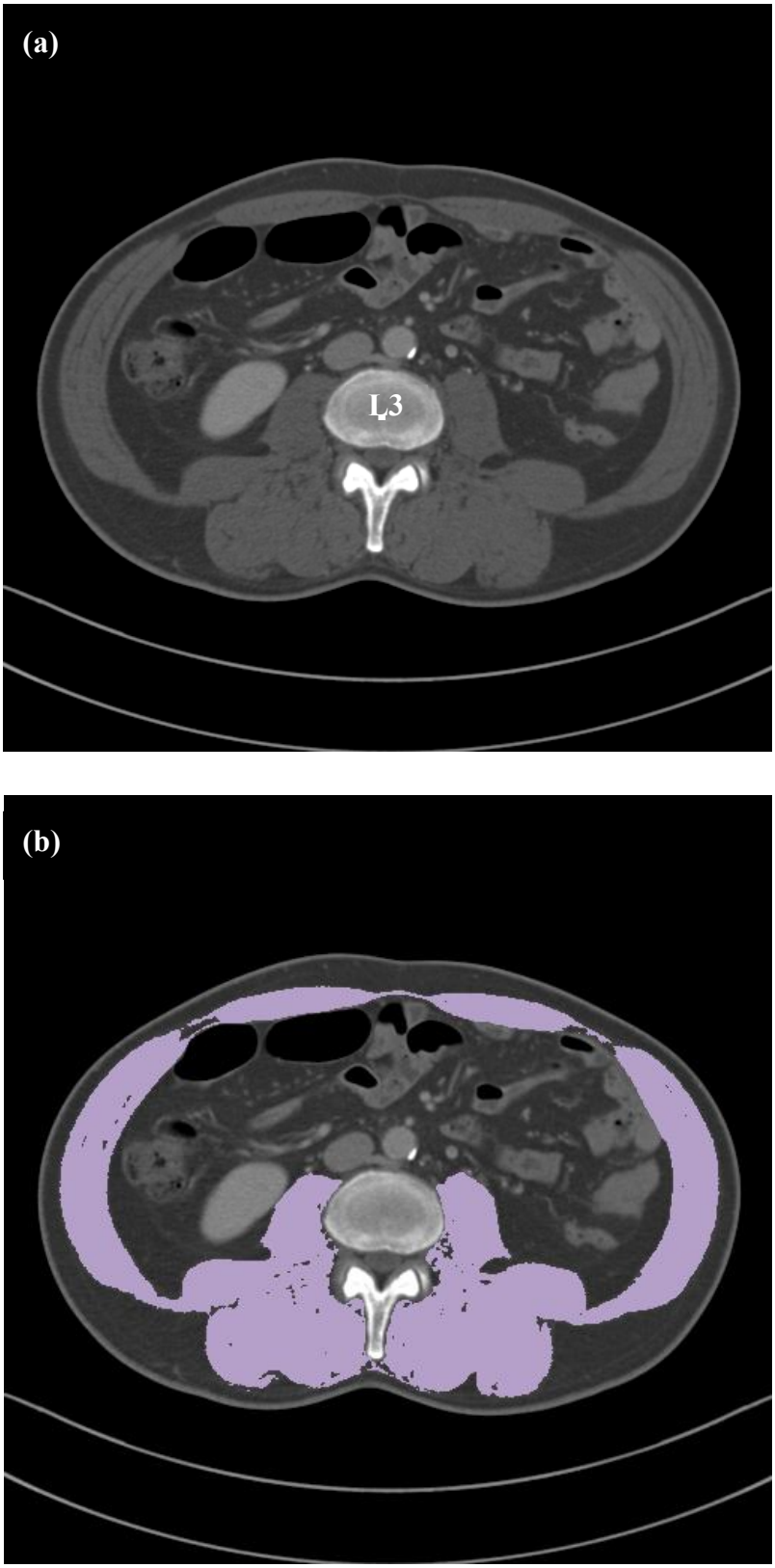
Characteristics	Muscle types				P
	Normal muscle type (n = 73)	Sarcopenic muscle type (n = 84)	Myosteatotic muscle type (n = 86)	Combined muscle type (n = 104)	
AJCC tumor staging					0.88
IA or IB	29 (39.7)	30 (35.7)	27 (31.4)	38 (36.5)	
IIA or IIB	30 (41.1)	42 (50.0)	44 (51.2)	48 (46.2)	
III	14 (19.2)	12 (14.3)	15 (17.4)	18 (17.3)	
Tumor differentiation					0.63
Well-differentiated	11 (15.1)	9 (10.7)	7 (8.1)	13 (12.5)	
Moderately differentiated	53 (72.6)	65 (77.4)	73 (84.9)	78 (75.0)	
Poorly/undifferentiated	9 (12.3)	10 (11.9)	6 (7.0)	13 (12.5)	
Resection margin (R1)	15 (20.6)	27 (32.1)	17 (19.8)	29 (27.9)	0.19
Adjuvant treatment	58 (79.5)	49 (58.3)	55 (64.0)	64 (61.5)	0.03

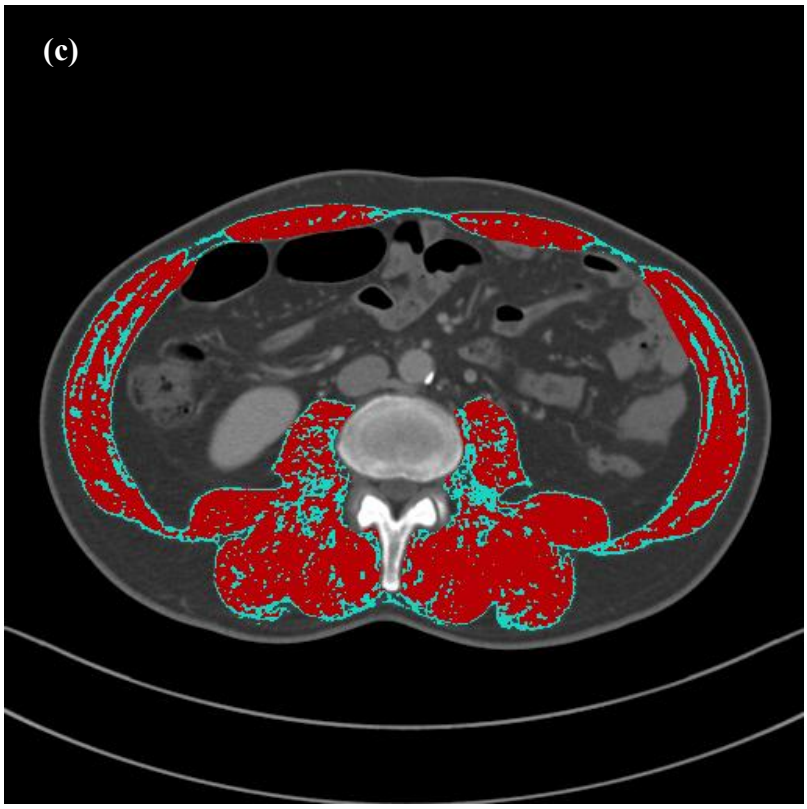
Data are number with percentage in parenthesis.

Abbreviations: AJCC, the American Joint Committee on Cancer.

그림 (Figures)

Figure 1. Evaluation of muscle quantity and quality on CT





(a) Selection of CT slice at L3 level

(b) Automatic segmentation of the muscle area

(c) Generation of muscle quality map using thresholds of radiodensity per pixel (Area in red, normal-attenuation muscle area [NAMA; threshold, from 30 to 150 Hounsfield units]; and area in cyan, low-attenuation muscle area [LAMA; threshold, from -29 to 29 Hounsfield units])

Figure 2. Flow diagram of study patients

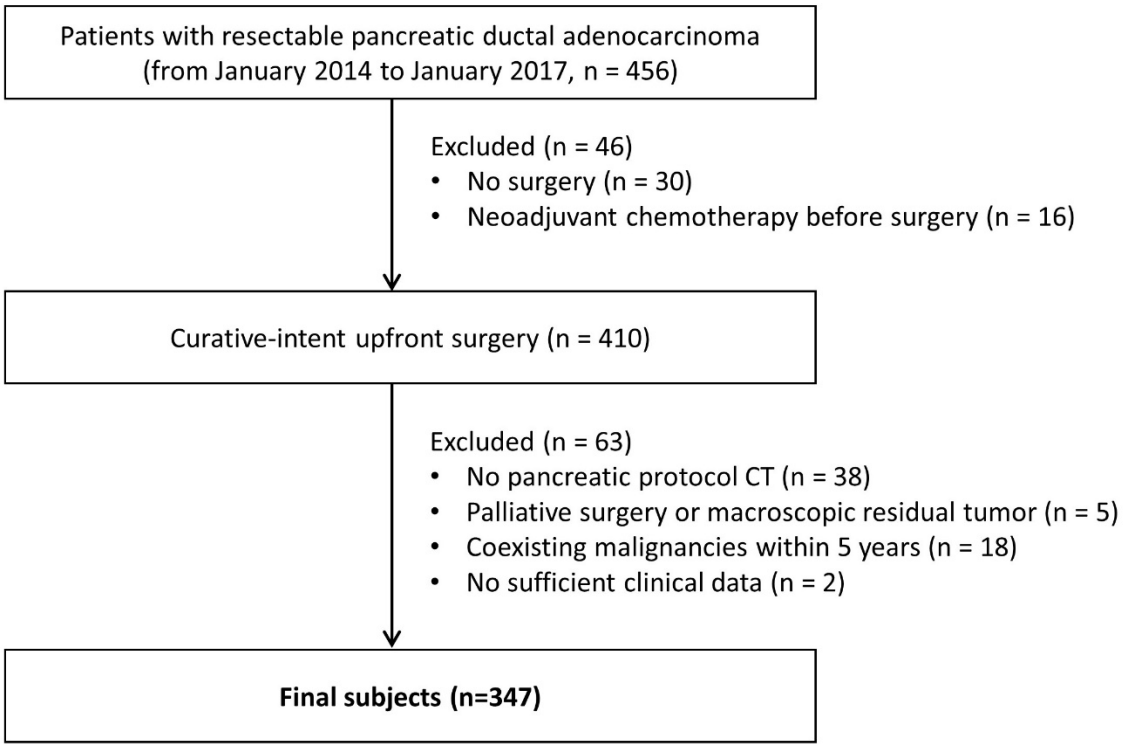
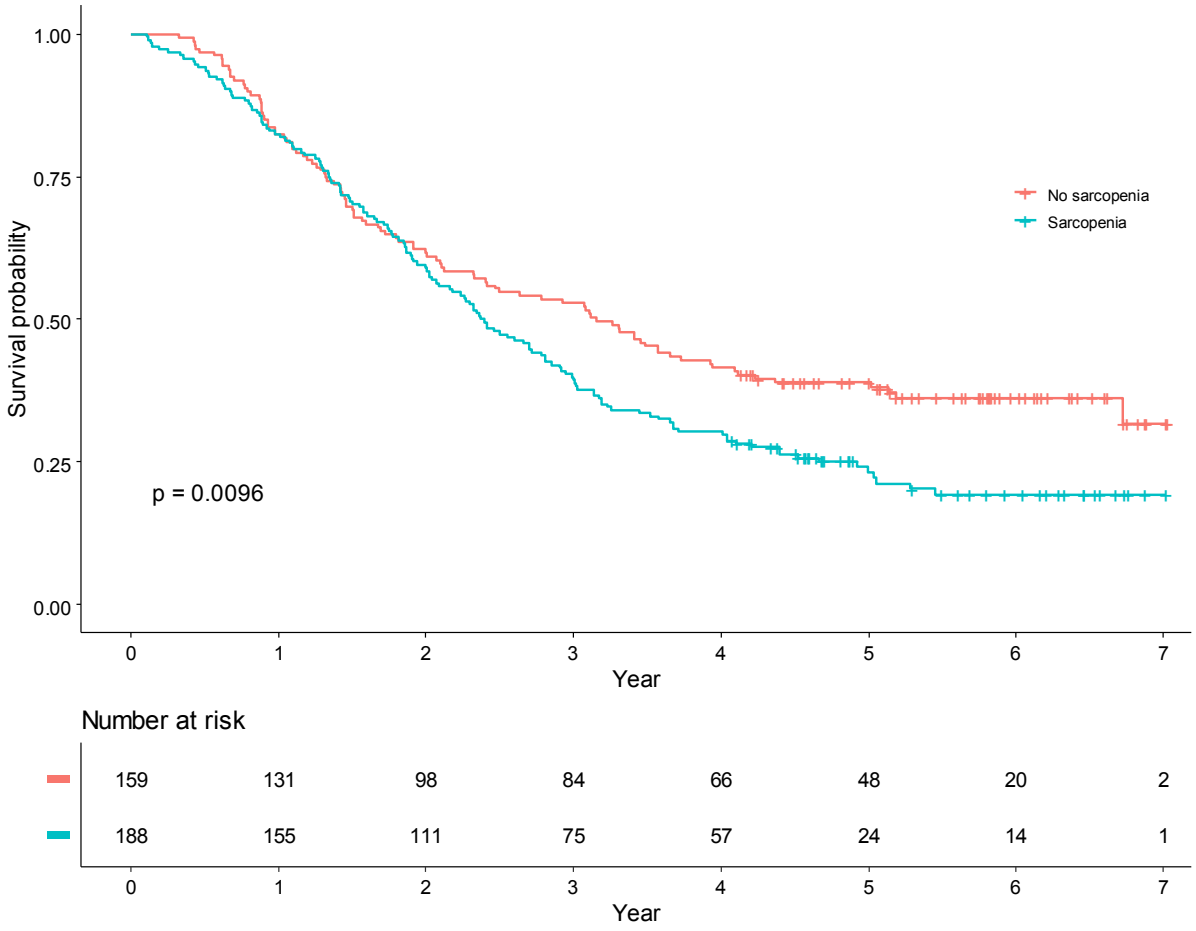
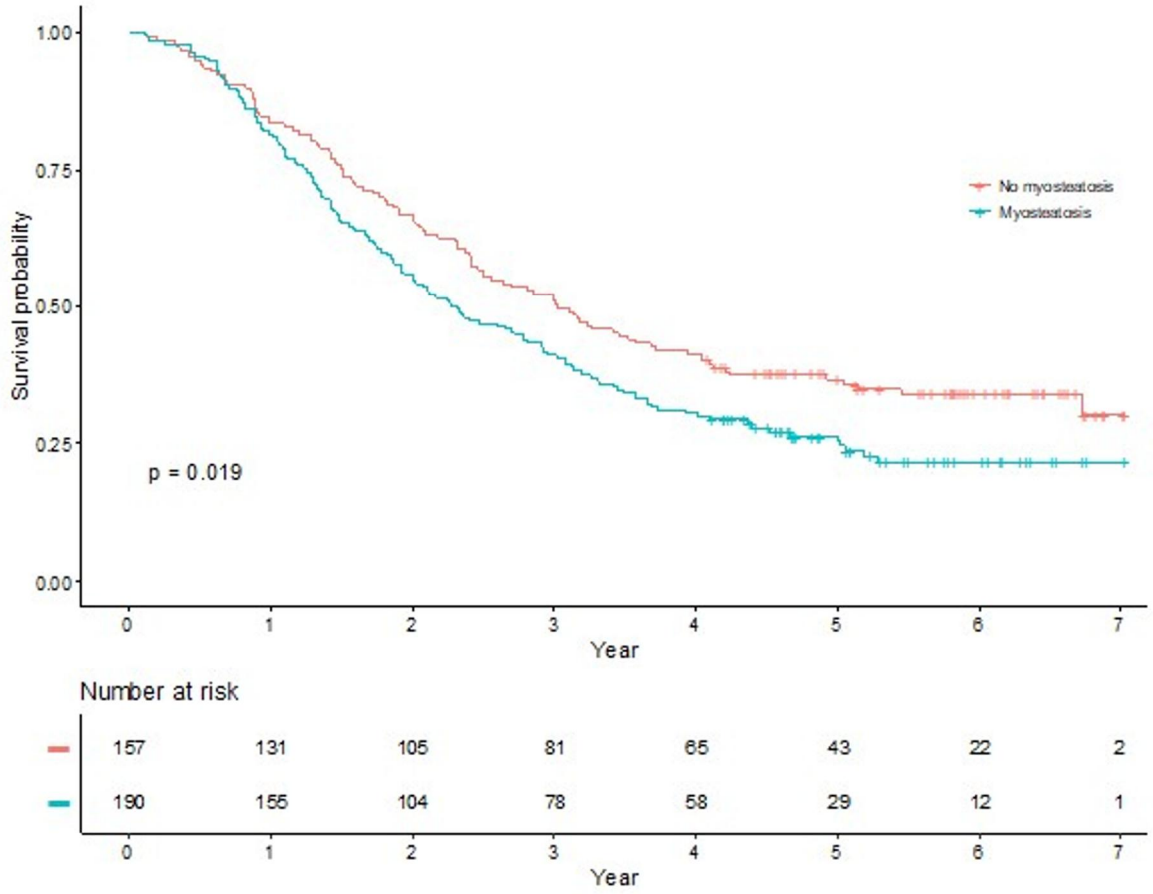


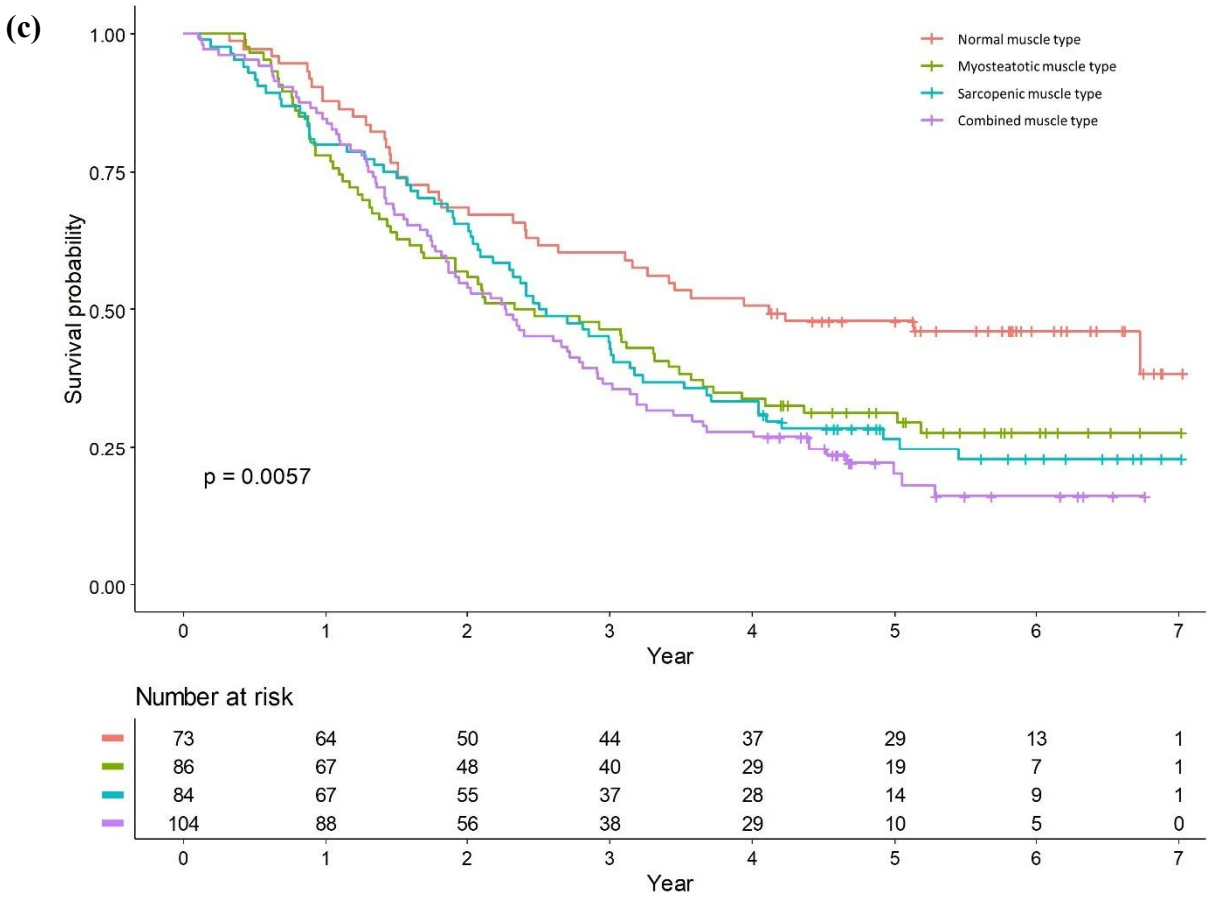
Figure 3. Kaplan–Meier curves of overall survival according to the presence of sarcopenia (a) and myosteatosis (b), and according to muscle types (c)

(a)



(b)

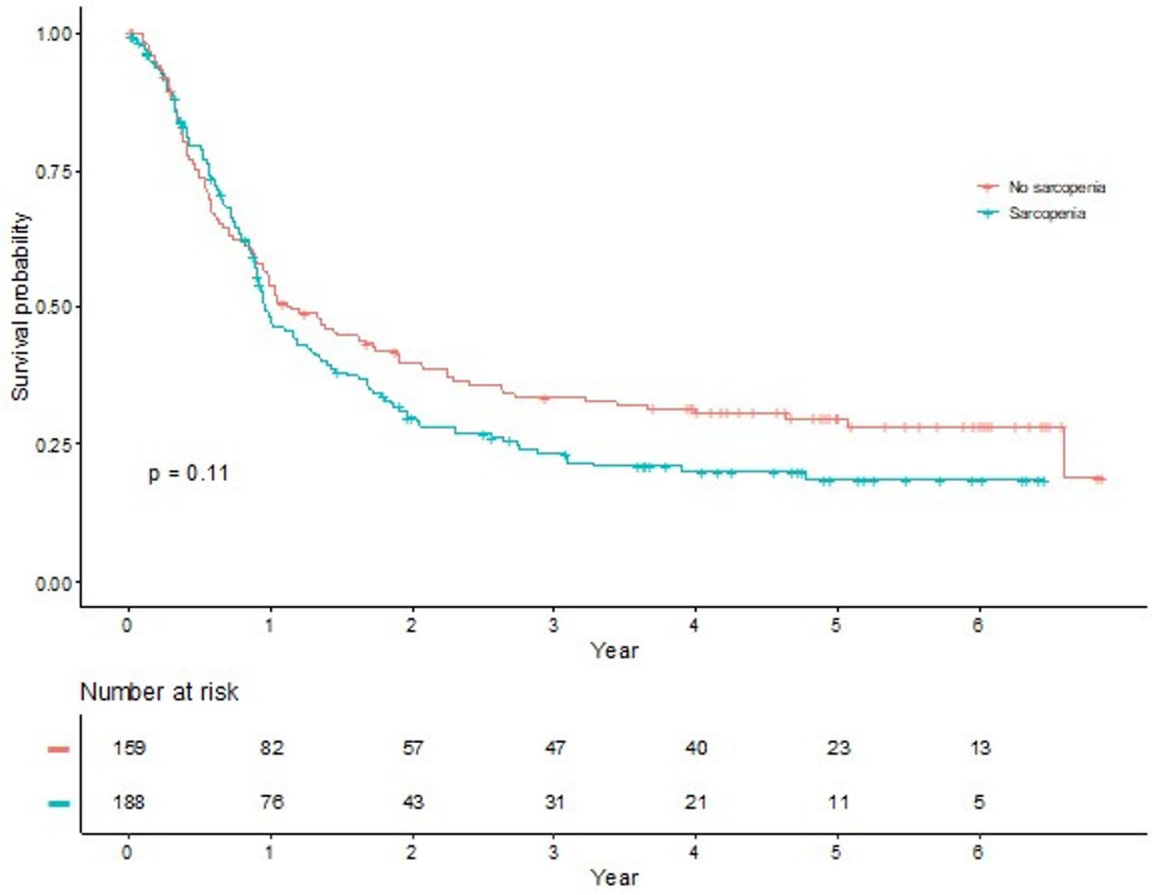

1.00
0.75
0.50
0.25
0.00
Survival probability
No myostastasis
Myostastasis
p = 0.019
0
1
2
3
4
5
6
7
Year
Number at risk
157
131
105
81
65
43
22
2
190
155
104
78
58
29
12
1
0
1
2
3
4
5
6
7
Year

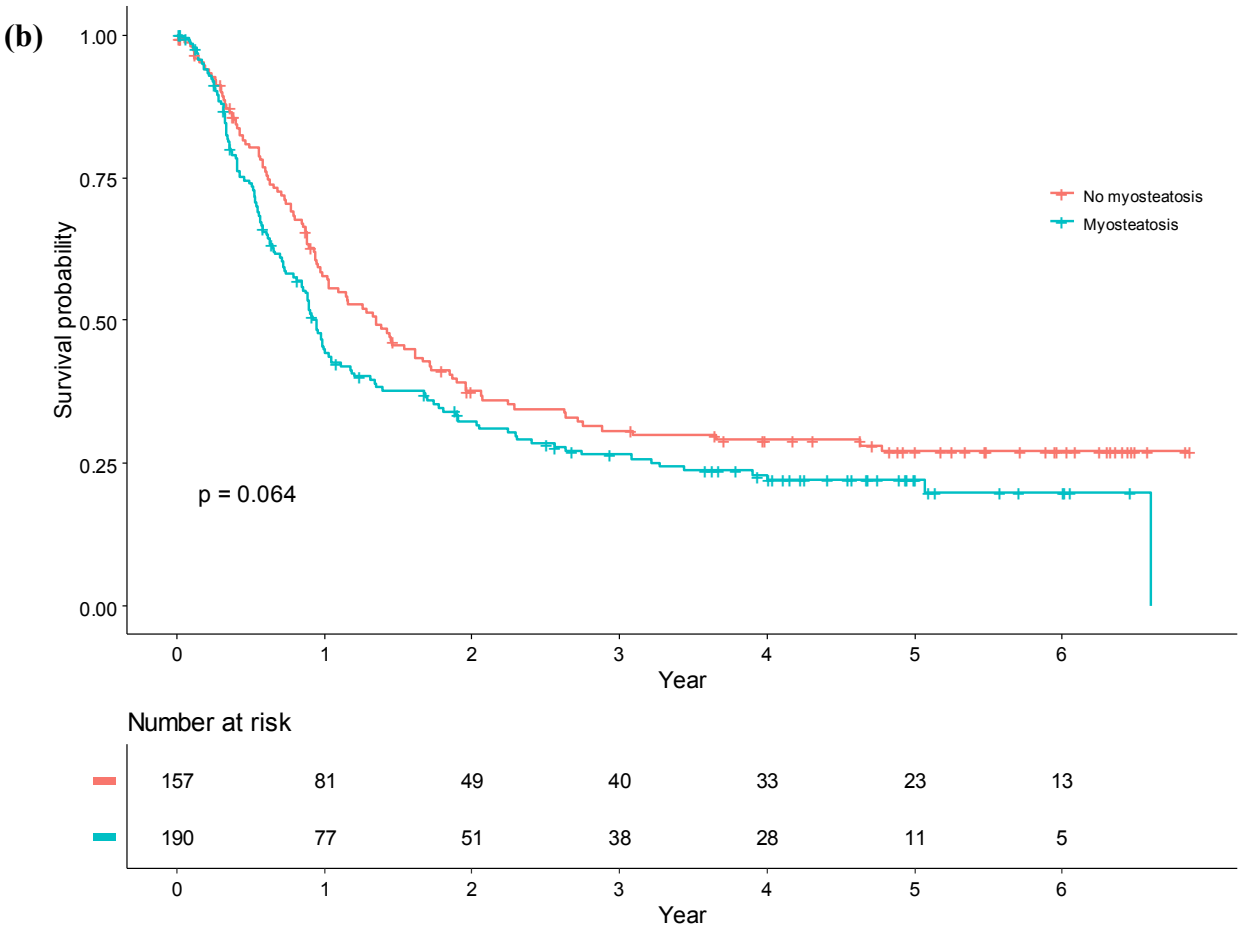


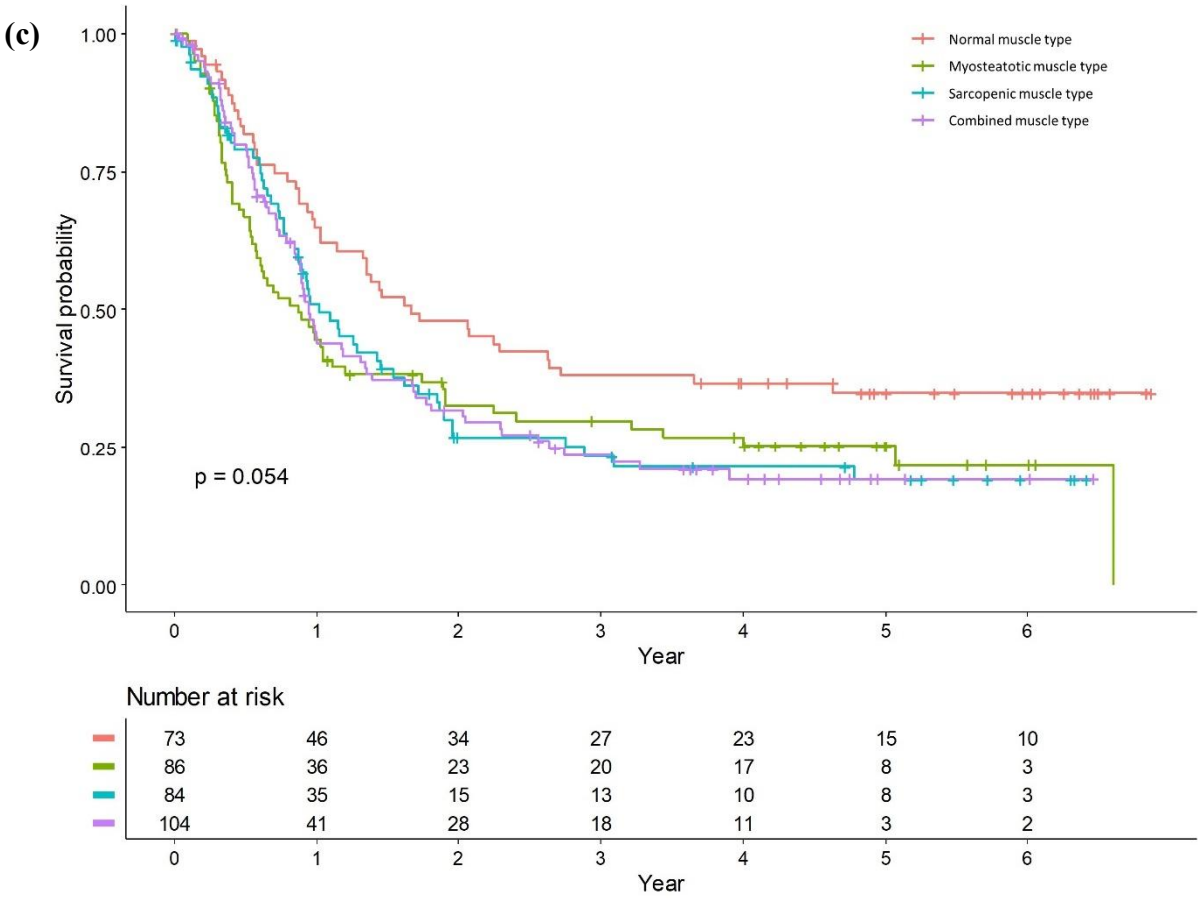
Kaplan–Meier curves indicate worse OS in patients with sarcopenia compared with those without sarcopenia (median, 28.7 vs. 38.1 months; P < 0.01; **Figure 3A**), and worse OS in patients with myosteatosis than those without myosteatosis (median, 27.7 vs. 36.6 months; P = 0.02, **Figure 3B**). Kaplan–Meier curves were significantly different according to muscle types (P < 0.01, **Figure 3C**).

Figure 4. Kaplan–Meier curves of recurrence-free survival according to the presence of sarcopenia (a) and myosteatosis (b), and according to muscle types (c)

(a)



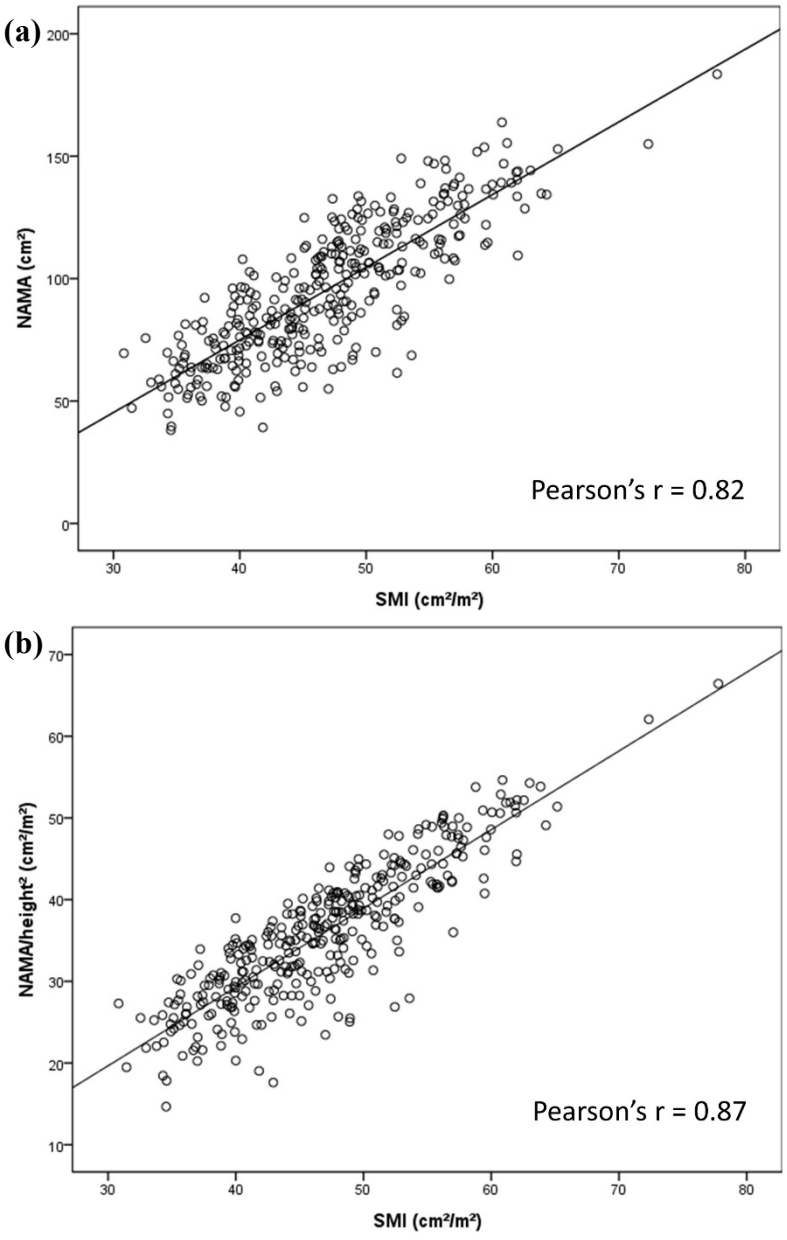

(b)
1.00
0.75
0.50
0.25
0.00
Survival probability
No myosteatosis
Myosteatosis
p = 0.064
0
1
2
3
4
5
6
Year
Number at risk
157
81
49
40
33
23
13
190
77
51
38
28
11
5
0
1
2
3
4
5
6
Year



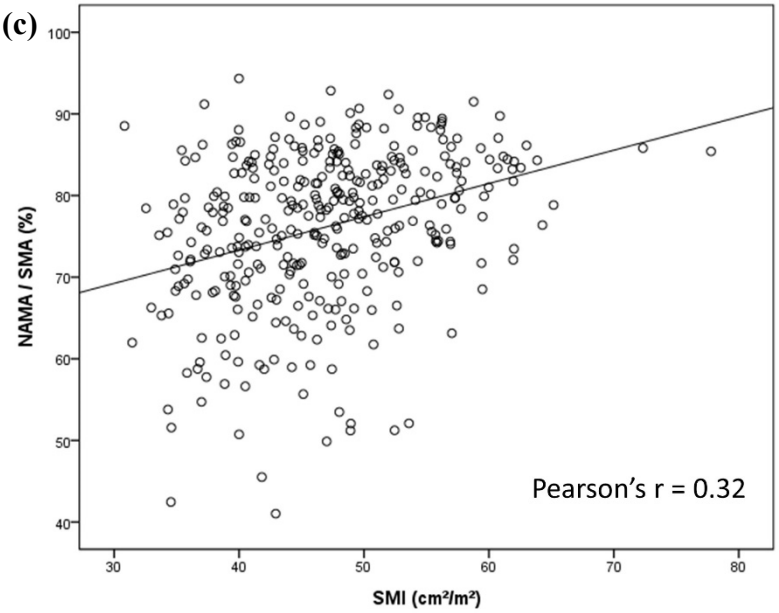
Kaplan–Meier curves did not show statistical significance according to the presence of sarcopenia (median, 13.8 vs. 11.5 months; P = 0.11, **Figure 4A**) and myosteatosis (median, 16.3 vs. 11.4 months; P = 0.06, **Figure 4B**). Although Kaplan–Meier curves were not significantly different according to muscle types (P = 0.054, **Figure 4C**), nMT had better OS compared with the remaining muscle types (median RFS: 20.1 in nMT vs. 10.5 in sMT, 12.3 in mMT, and 11.4 in cMT).

cMT = combined muscle type; mMT = myosteatotic muscle type; nMT = normal muscle type; sMT = sarcopenic muscle type

Supplementary Figure 1. Correlation between skeletal muscle index (SMI) and possible indexes of myosteatosis (normal-attenuation muscle area [NAMA] (a), NAMA/height^2 (b), NAMA/skeletal muscle area [SMA] (c))

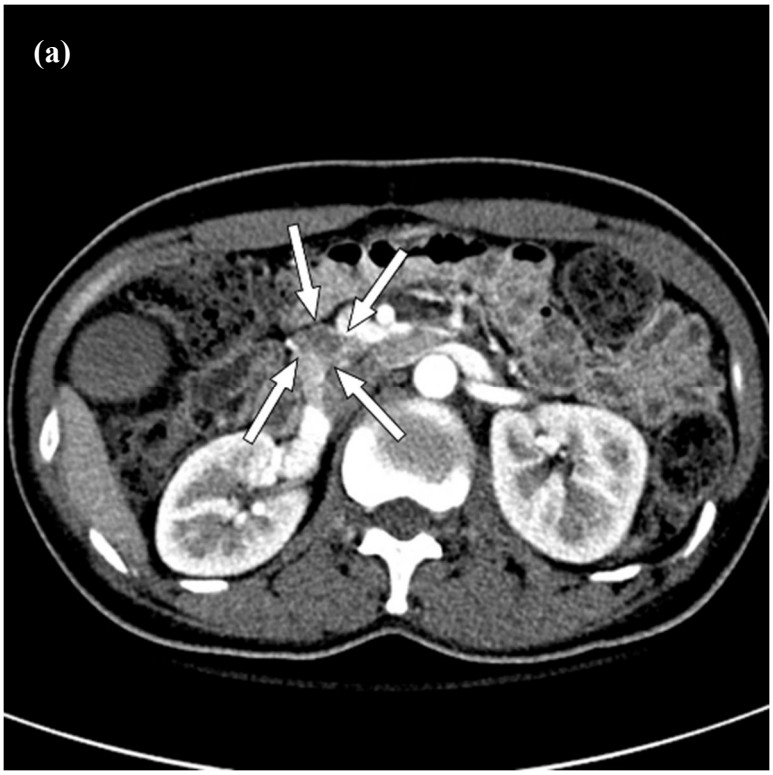


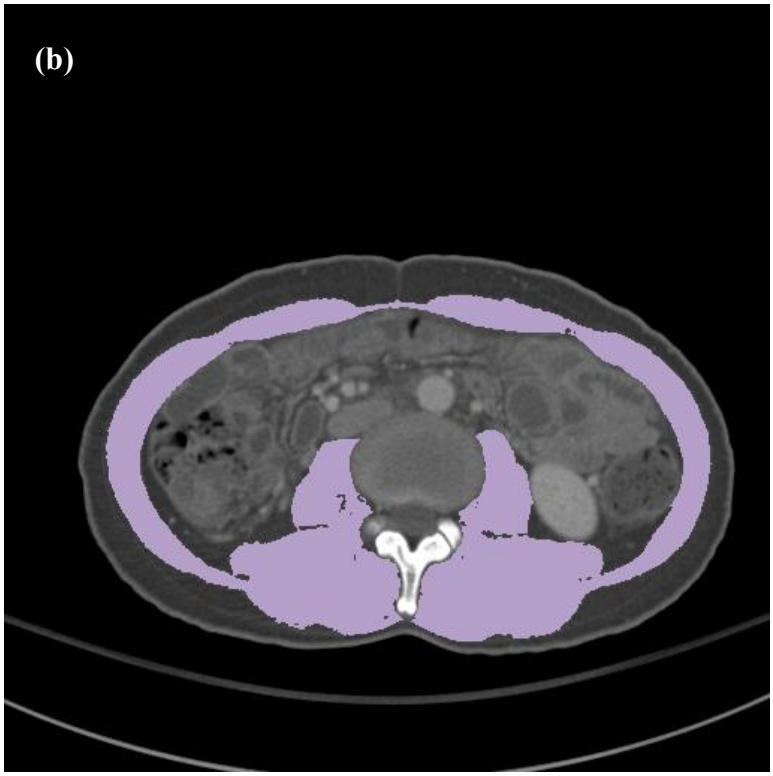
(c)

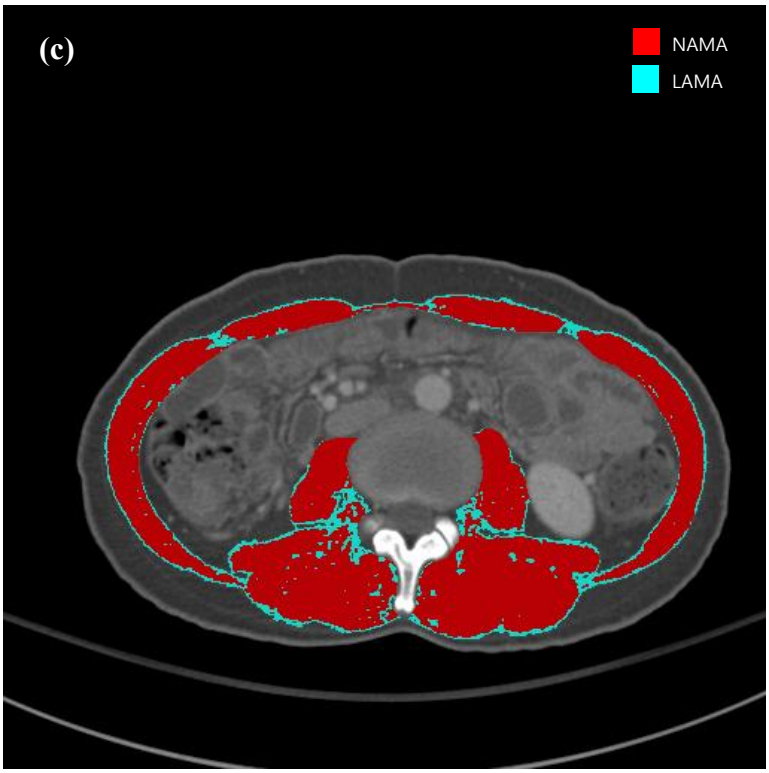


As there was no widely used myosteatosis index, particularly in the muscle quality map, we evaluated the correlation of possible myosteatosis index, less dependent on SMI. NAMA/SMA had the lowest correlation with SMI (Pearson's r = 0.32) compared with NAMA (Pearson's r = 0.82) and NAMA/height2 (Pearson's r = 0.87), and was determined as the optimal myosteatosis index.

Supplementary Figure 2. A 38-year-old woman (body mass index, 20.97) with resectable PDAC.



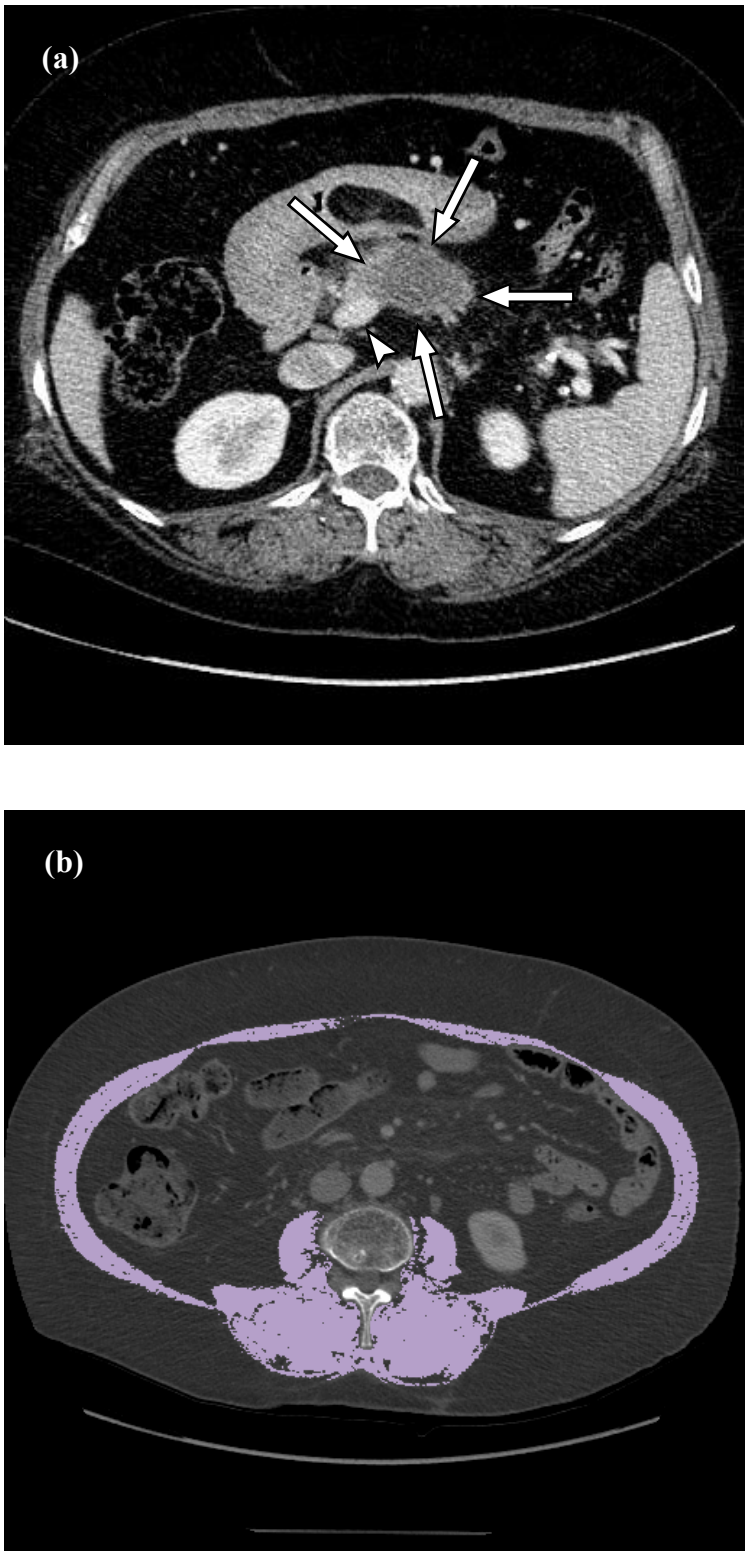


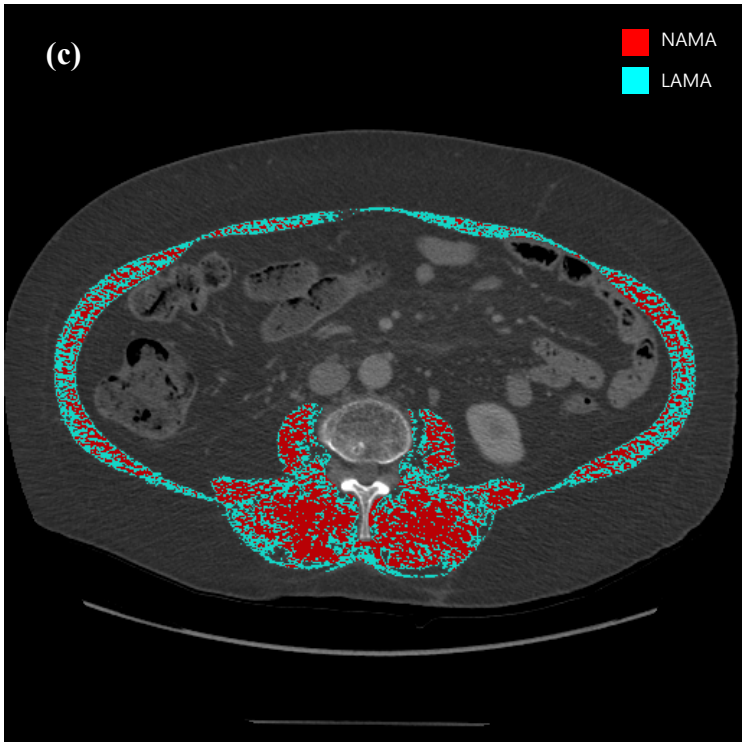


An axial CT image on portal venous phase (a) shows a 1.3 cm-sized low-attenuation mass (arrows) in the pancreas uncinate process. The mass shows less than 180 degrees of contact with the superior mesenteric vein. Automatic muscle segmentation (b) and muscle quality map (c) calculated that SMI and NAMA/SMA were 46.31 cm2/m2 and 86.77%, respectively, indicating normal muscle type (diagnostic cutoff of sarcopenia < 37.39 cm2/m2; diagnostic cutoff of myosteatosis < 83.82 %). After upfront surgery, the patient was alive without tumor recurrence for 82.6 months until last follow-up.

Abbreviations: NAMA = normal-attenuation muscle area; SMA = skeletal muscle area; SMI, skeletal muscle index; PDAC = pancreatic ductal adenocarcinoma.

Supplementary Figure 3. A 64-year-old woman (body mass index, 36.4) with resectable PDAC.





An axial CT image on portal venous phase (a) shows a 4.7 cm-sized low-attenuation mass (arrows) in the pancreatic body. The mass shows less than 180 degrees of contact with the superior mesenteric vein (arrowhead). Automatic muscle segmentation (b) and muscle quality map (c) calculated that the SMI and NAMA/SMA were 48.91 cm^2/m^2 and 51.2%, respectively, indicating myosteatotic muscle type (diagnostic cutoff of sarcopenia < 44.90 cm^2/m^2; diagnostic cutoff of myosteatosis < 84.71%). The patient underwent upfront surgery; however, the tumor recurred 4.5 months later. The patient died at 11.1 months post-op.

Abbreviations: NAMA = normal-attenuation muscle area; SMA = skeletal muscle area; SMI, skeletal muscle index; PDAC = pancreatic ductal adenocarcinoma.

영 문 요 약

Background

Pancreatic ductal adenocarcinoma (PDAC) leads to extensive muscle loss. This study investigated the prognostic effect of sarcopenia and myosteatosis in patients with resectable PDAC.

Methods

We retrospectively included 347 patients with resectable PDAC who underwent upfront surgery between January 2014 and January 2017 (mean age ± standard deviation, 63.6 ± 9.6 years; 202 men). Automatic muscle segmentation was performed on preoperative computed tomography (CT). Sarcopenia was evaluated using segmented skeletal muscle area (SMA) divided by height squared (skeletal muscle index, SMI). To evaluate myosteatosis, we generated a muscle quality map according to CT density per pixel, and categorized SMA into normal-attenuation muscle area (NAMA) and low-attenuation muscle area. The optimal index for myosteatosis that least dependent on SMI was determined using Pearson's r. Diagnostic cutoffs of sarcopenia and myosteatosis were devised using Contal and O'Quigley methods, and patients were classified according to normal (nMT), sarcopenic (sMT), myosteatotic (mMT), or combined (cMT) muscle type. Univariate and multivariate Cox regression analyses were conducted to assess the effect of muscle type on overall survival (OS) and recurrence-free survival (RFS).

Results

NAMA divided by SMA had the weakest correlation with SMI (r = 0.32) and was determined as the myosteatosis index. Based on the cutoffs, 78 (22.5%), 81 (23.3%), 100 (28.8%), and 88 (25.4%) patients were classified as nMT, sMT, mMT, and cMT, respectively. Either having sarcopenia or myosteatosis (hazard ratio [95% confidence interval]: sMT=1.58 [1.05–2.38], mMT=1.50 [1.00–2.25], and cMT=1.66 [1.12–2.46]) showed poor OS compared with nMT. mMT showed poor RFS compared with nMT (hazard ratio [95% confidence interval], 1.49 [1.01–2.20]).

Conclusions

Preoperative sarcopenia or myosteatosis are associated with poor OS and RFS after upfront surgery in patients with resectable PDAC.