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Skeletal Muscle Mass Index Reduction Rate as a Prognostic Indicator for Patients Undergoing Pancreatectomy for Pancreatic Cancer

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Abstract. *Background/Aim: There have been many studies on skeletal muscle depletion before surgery, and skeletal muscle depletion is a known risk factor for poor prognosis. However, reports on the association between changes in skeletal muscle mass and prognosis after surgery for pancreatic cancer are very few. Patients and Methods: The data of 137 patients who underwent pancreatectomy for pancreatic cancer between 2005 and 2022 were reviewed. Muscle areas were measured at the third lumbar vertebral level, and skeletal muscle mass index (SMI) reduction rates were calculated. Patients were divided into two groups using receiver operating characteristic (ROC) curve analysis based on the SMI reduction rate with a cutoff of 14% reduction rate. The clinicopathological factors, overall survival (OS), and recurrence-free survival (RFS) were compared between the two groups. Survival rates were analyzed both univariately and multivariately to clarify the factors associated with poor prognosis after pancreatectomy. Results: A total of 102 patients met the inclusion criteria. SMI reduction rate ≥14% significantly correlated with advanced age and higher incidence of postoperative complications. In the multivariate Cox regression analysis, preoperative prognostic nutritional index (PNI) <40 and SMI reduction rate ≥14% were significantly associated with poor OS. Tumor size ≥3.0 cm, preoperative neutrophile-lymphocyte ratio ≥3.0, and SMI reduction rate ≥14% were significantly associated with poor RFS. Conclusion: The rate of skeletal muscle mass reduction after pancreatic surgery is an independent prognostic factor for survival in patients with pancreatic cancer.*

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Key Words: Skeletal muscle mass, SMI, sarcopenia, pancreatectomy, nutrition.

Pancreatic cancer is the seventh leading cause of cancer-related deaths worldwide, and 80-85% of cases are unresectable at diagnosis (1, 2). Surgical resection is the most effective treatment for pancreatic cancer. However, despite advancements in perioperative therapy and surgical techniques, the postoperative prognosis for pancreatic cancer remains poor. Several indicators, such as nutritional index and skeletal muscle mass index (SMI), have been reported as prognostic markers of pancreatic cancer (3-5). The pathophysiological mechanisms of SMI reduction are complex, with various causes, such as aging and chronic inflammation (6). Several reports have focused on SMI reduction before surgery and stated that it is a risk factor for poor prognosis (4, 5). However, reports on the association between postoperative SMI reduction and prognosis of pancreatic cancer are few. We hypothesized that the postoperative SMI reduction rate may be a new predictor of long-term prognosis, especially after highly invasive surgeries, such as pancreatectomy. This study aimed to assess the postoperative SMI reduction rate for pancreatic cancer using computed tomography (CT) to determine whether this change affects overall (OS) and disease-free survival.

Patients and Methods

Patients and data collection. The data of 137 patients who underwent pancreatectomy for pancreatic cancer at the Department

of Surgery, Hiroshima Red Cross & Atomic Bomb Survivors Hospital, Japan, between July 2005 and March 2022 were reviewed. Patients who did not undergo preoperative CT or died within 90 days after surgery were excluded. Preoperative and postoperative clinical data were obtained from electronic records and available for all patients. This study was approved by the ethics committee of our hospital according to the ethical guidelines of the Japanese government (approval number: 2023-030), and all patients provided consent for the research use of their clinical data.

Evaluation of skeletal muscle mass using CT images. Abdominal CT was used to examine skeletal muscle mass. The CT images used were either 1.25- or 5-mm thick contrast-enhanced or unenhanced multiphase acquisitions. Skeletal muscle borders were manually outlined (manual trace method) using a SYNAPSE VINCENT volume analyzer (Fujifilm, Tokyo, Japan). The masses of the rectus abdominis, abdominal lateral and oblique muscles, psoas, and paraspinal muscles were calculated. We measured the areas of skeletal muscle at the level of the third lumbar vertebral body (L3) on the CT images and normalized them by height in meters squared (m^2) to calculate the lumbar skeletal muscle index (SMI, cm^2/m^2). All included patients underwent abdominal CT within two months before surgery, and the first follow-up CT scan was performed 3-9 months after surgery. The SMI reduction rate was calculated afterwards.

Statistical analyses. Comparisons of the categorical variables were performed using the χ^2 or Fisher's exact tests. The independent-samples *t*-test or Mann–Whitney *U*-test was used to analyze continuous variables. Receiver operating characteristic (ROC) curve analysis of postoperative skeletal muscle loss was performed. The area under the ROC curve (AUC) was established to determine the optimal cut-off values for analyzing OS. Univariate and multivariate survival analyses were performed using Cox proportional hazard models. Cumulative OS and recurrence-free survival (RFS) rates were calculated using the Kaplan–Meier method, and differences between curves were evaluated using the log-rank test. OS was calculated as the time from the date of surgery to the date of last follow-up or death. RFS was defined as the time interval from the date of surgery to the date of disease recurrence. To identify postoperative prognostic factors, variables found to be significant in the univariate analyses were included in the overall multivariate Cox proportional model. All statistical tests were two-sided, and significance was set at $p<0.05$. Statistical analyses were performed using EZR software package 4.1.2 (Saitama Medical Center, Jichi Medical University, Japan).

Results

Patient characteristics. Among the 137 consecutive patients who underwent curative pancreatic surgery between July 2005 and March 2022, 102 patients (54.9% men, mean age 69.1 years) met the inclusion criteria. The ROC curve showed that an SMI reduction rate cutoff of 14% predicts two-year mortality with a specificity of 48% and sensitivity of 92%; moreover, the AUC was 0.71 (Figure 1). A total of 76 patients exhibited an SMI reduction rate <14%, while 26 had SMI reduction rate ≥14%. Meanwhile, 61 patients (59.8%) were defined as having preoperative sarcopenia. The patient characteristics are shown in Table I. Among the 102 patients who underwent

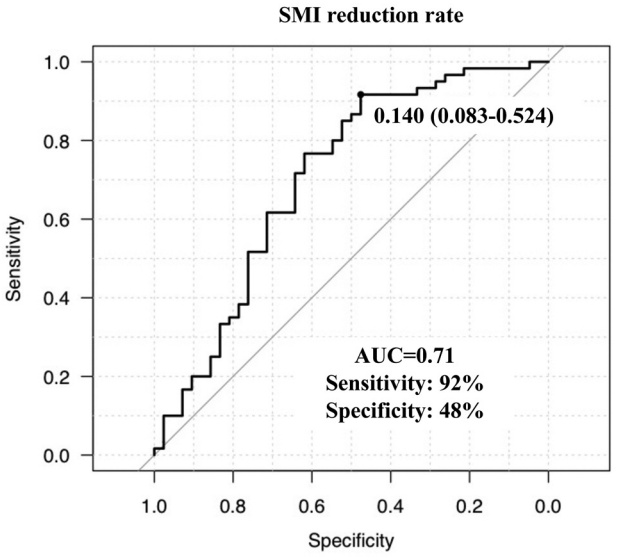

Figure 1. *Receiver operating characteristic (ROC) curve analysis of postoperative skeletal muscle index reduction rate and determination of the optimal cut-off value. The area under the curve (AUC) of the skeletal muscle mass index (SMI) reduction rate was 0.71 (sensitivity, 92%; specificity, 48%). ROC curve analysis detected the cut-off value of SMI reduction rate as 14%.*

pancreatectomy at our institution, pancreatoduodenectomy (PD), distal pancreatectomy (DP), and total pancreatectomy (TP) were performed in 61 (59.8%), 39 (38.2%), and two patients (2.0%), respectively. The median amount of blood loss was 693 g (range=10-4,662 g). The median operative time was 396 min (range=160-695 min). Among the 102 patients, 71 (69.6%) were treated with complete resection (R0). Pathologically, poorly differentiated adenocarcinomas were observed in 33 patients (32.3%). Lymph node metastases were detected in 58 patients (56.9%). Neoadjuvant and adjuvant therapies were administered to 11 patients (10.8%) and 86 patients (84.3%), respectively. The medians of the preoperative inflammatory markers, including albumin, platelet count, and C-reactive protein were as follows: 4.00 g/dl (range=2.6-4.8 g/dl) g/dl, 213,900 μl (range=42,000-442,000 μl), and 0.43 mg/dl (range=0.05-9.27 mg/dl), respectively. SMI reduction rate ≥14% significantly correlated with advanced age (72 *vs*. 68 years; $p=0.043$) and higher incidence of postoperative complications (Clavien–Dindo Classification Grade III-V 34.6% *vs*. 10.5%; $p=0.015$).

Effects of postoperative SMI reduction on OS. The Kaplan–Meier OS curves for patients with high and low SMI reduction are shown in Figure 2, which revealed that OS (log-rank $p<0.001$) was significantly shorter in the SMI reduction rate ≥14% group than in the SMI reduction rate <14% group. The median OS rates in the SMI reduction rate ≥14% and

Table I. *Characteristics of patients with pancreatic cancer who underwent pancreatectomy.*

	SMI reduction rate <14% (n=76)	SMI reduction rate ≥14% (n=26)	*p*-Value
Age (years)	68 (45-86)	72 (57-87)	0.043
Sex, male/female	41/35	15/11	0.821
BMI (kg/m^2)	21.8 (14.9-30.3)	21.4 (15.2-25.7)	0.461
Preoperative sarcopenia +	48 (63.1%)	13 (50.0%)	0.255
Tumor size (cm)	2.9 (0.3-8.0)	2.9 (1.1-6.0)	0.927
Operative procedure PD/DP/TP	41/33/2	20/6/0	0.136
Blood loss (ml)	734 (10-2,380)	571 (60-4,662)	0.298
Operation time (min)	382.1 (160-695)	435.7 (215-681)	0.058
R0 resection	57 (76.0%)	14 (53.8%)	0.051
Histology: Poor differentiation	21 (27.6%)	12 (46.2%)	0.094
N0/N+	37/39	7/19	0.068
Neoadjuvant chemotherapy +	8 (10.5%)	3 (11.5%)	1.000
Adjuvant chemotherapy +	65 (85.5%)	21 (80.8%)	0.546
POPF(–) or BL / Grade B or C	60/16	20/6	0.790
Complication 0-GII / >GIII	57/19	13/13	0.026
TNM stage I-II/III	65/11	19/7	0.231
Alb (g/dl)	4.0 (2.6-4.8)	3.9 (2.6-4.6)	0.133
T-bil (mg/dl)	0.9 (0.2-5.3)	1.1 (0.2-7.8)	0.557
T-chol (mg/dl)	187.5 (117-289)	186.2 (124-239)	0.891
Plt (×10^4/μl)	21.2 (6.2-44.2)	22.0 (4.2-35.2)	0.589
CRP (mg/dl)	0.4 (0.05-5.84)	0.6 (0.05-9.27)	0.305
CA19-9 (U/ml)	253.5 (0.8-5,027.2)	395.6 (0.8-3,581.8)	0.366
CEA (ng/ml)	10.5 (1.1-511)	9.0 (1.4-79.6)	0.897
PNI	48.9 (35.8-61.6)	47.2 (33.9-56.5)	0.185
CAR	0.10 (0.01-1.82)	0.19 (0.01-3.09)	0.253
LCR	18522.4 (99.4-75,950)	16545.9 (129.8-42,120)	0.555
LMR	5.8 (1.7-24.5)	4.6 (1.2-12.3)	0.155
NLR	2.3 (0.5-6.1)	2.3 (0.6-7.2)	0.862
PLR	145.3 (24.7-583.0)	139.8 (44.4-246.6)	0.760
TLC	1720.7 (615-4,889.4)	1690.8 (754-2,951.2)	0.863

BMI: Body mass index; PD: pancreatoduodenectomy; DP: distal pancreatectomy; TP: total pancreatectomy; POPF: postoperative pancreatic fistula; PNI: prognostic nutritional index; CAR: CRP-albumin ratio; LCR: lymphocyte-CRP ratio; LMR: lymphocyte-monocyte ratio; NLR: neutrophile-lymphocyte ratio; PLR: platelet-lymphocyte ratio; TLC: total lymphocyte count.

SMI reduction rate <14% groups were 1.60 years [95% confidence interval (CI)=0.96-2.24] and 3.94 years (95%CI=3.28-4.61), respectively. Univariate and multivariate analyses were used to identify factors influencing OS following pancreatectomy (Table II). Univariate analysis revealed the following factors as significantly associated with poor OS: blood loss ≥500 ml [hazard ratio (HR)=1.58, 95%CI=1.00-2.54; p=0.048), lymph node metastases-positive (HR=1.72, 95%CI=1.08-2.74; p=0.024), tumor size ≥3.0 cm (HR=1.90, 95%CI=1.21-2.99; p=0.006), preoperative albumin <3.5 (HR=2.16, 95%CI=1.16-4.03; p=0.016), preoperative prognostic nutritional index (PNI) <40 (HR=4.91, 95%CI=2.24-10.78; p<0.001), and SMI reduction rate ≥14% (HR=3.23, 95%CI=1.95-5.34; p<0.001). Multivariate analysis identified the following factors as independently correlated with poor OS: preoperative PNI <40 (HR=3.93, 95%CI=1.11-13.93; p=0.034) and SMI reduction rate ≥14% (HR=2.68, 95%CI=1.57-4.59; p<0.001).

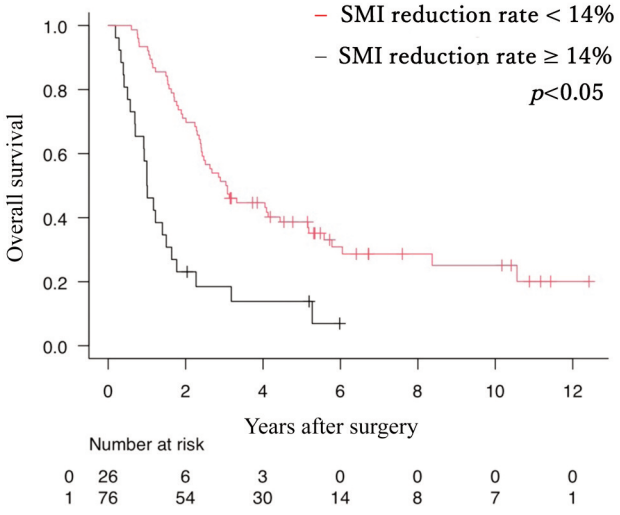

Figure 2. *Overall survival of patients with high and low skeletal muscle mass index reduction rate after pancreatectomy for pancreatic cancer.*

Effects of postoperative loss of SMI on RFS. The Kaplan–Meier RFS curves for patients with high and low SMI reduction are shown in Figure 3, which reveals that RFS (log- rank $p<0.001$) were significantly shorter in the SMI reduction rate ≥14% group than in the SMI reduction rate <14% group. The median RFS rates in the SMI reduction rate ≥14% and SMI reduction rate <14% groups were 0.95 (95%CI=0.41-1.48) and 2.50 years (95%CI=1.99-3.02), respectively. Univariate and multivariate analyses were used to identify factors influencing RFS following pancreatectomy (Table III). Univariate analysis revealed the following factors as significantly associated with poor RFS: blood loss ≥500 ml (HR=1.65, 95%CI=1.05-2.58; $p=0.029$), lymph node metastases-positive (HR=1.69, 95%CI=1.08-2.63; $p=0.021$), tumor size ≥3.0 cm (HR=2.12, 95%CI=1.37-3.27; $p<0.001$), preoperative albumin <3.5 (HR=1.95, 95%CI=1.04-3.63; $p=0.036$), preoperative neutrophile-lymphocyte ratio (NLR) ≥3.0 (HR=1.86, 95%CI=1.09-3.16; $p<0.022$), preoperative PNI <40 (HR=3.23, 95%CI=1.44-7.23; $p<0.004$), and SMI reduction rate ≥14% (HR=2.61, 95%CI=1.58-4.31; $p<0.001$). Multivariate analysis identified the following factors as independently correlated with poor RFS: tumor size ≥3.0 cm (HR=1.68, 95%CI=1.02-2.75; $p=0.040$), preoperative NLR ≥3.0 (HR=1.97, 95%CI=1.13-3.44; $p=0.017$), and SMI reduction rate ≥14% (HR=2.82, 95%CI=1.64-4.85; $p<0.001$).

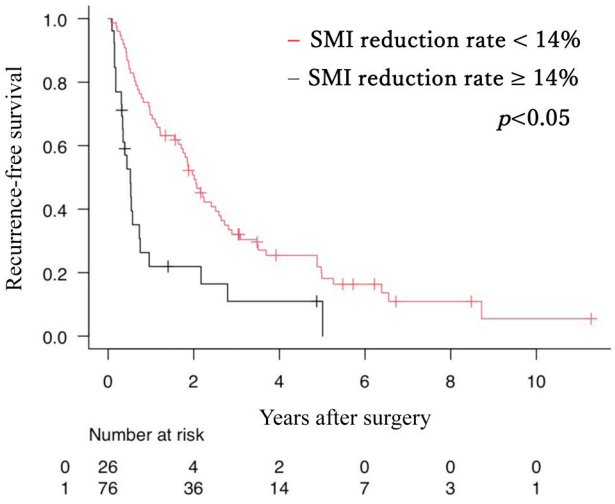

Figure 3. *Recurrence-free survival of patients with high and low skeletal muscle mass index reduction rate after pancreatectomy for pancreatic cancer.*

Discussion

Regardless of cancer type, SMI reduction in the postoperative period occurs easily because of physical inactivity, malnutrition, and hypercatabolism (6). The correlation between skeletal muscle mass and prognosis has been recognized in various cancers (7). This study suggests that postoperative SMI reduction negatively affects the prognosis of patients undergoing pancreatectomy for pancreatic cancer.

Despite advancements in surgical techniques, pancreatic cancer surgery remains associated with a high risk of complications and poor nutrition, which are associated with increased morbidity and mortality (8). In addition, as pancreatic surgery often alters the gastrointestinal anatomy, muscle loss after surgery for pancreatic cancer is thought to be greater than that in other types of cancers (9). Thus, prevention and management of complications, malnutrition, and hypercatabolism are crucial for postoperative pancreatic cancer treatment. Most previous studies have focused on the preoperative loss of skeletal muscle mass (10). However, whether the loss of postoperative skeletal muscle mass affects the prognosis of pancreatic cancer is unclear.

SMI is a widely used parameter to evaluate muscle mass and calculated by dividing the cross-sectional area of all skeletal muscles at the L3 vertebral level, which is obtained by axial CT scan, by the square of the height (m^2) (11). It is significantly correlated with the whole-body skeletal muscle tissue (12). Thus, the assessment of skeletal muscle mass using CT scans at the L3 vertebral level is increasingly used and has become a research hotspot in the examination of its correlation with the prognosis of various diseases (10). In this study, SMI changes were calculated using CT scans before surgery and approximately 3-9 months after surgery in patients with pancreatic cancer. Our data revealed a SMI reduction rate ≥14% after surgery was associated with poor clinical outcomes.

In our study, the SMI reduction rate significantly correlated with advanced age and a higher incidence of postoperative complications. Age-related loss of skeletal muscle mass is caused by decrease in motor nerve activity, impairment in neuromuscular junctions, and reduction in hormone production (13). Low preoperative SMI was also correlated with postoperative complications in patients with pancreatic cancer (14, 15). Previous studies have suggested that SMI reduction is associated with increases in the concentration of circulating inflammatory cytokines and with high complication rates (16, 17).

Multivariate analyses revealed that low PNI and SMI reduction rate ≥14% were independent factors for OS, while large tumor size, high NLR, and SMI reduction rate ≥14% were independent factors for RFS. Although the strong link between SMI reduction and prognosis remains obscure, we hypothesize that it is associated with multiple factors, including poor caloric intake and physical activity. The PNI is an independent indicator of postoperative outcomes, and cytokine levels are correlated with tumor size and NLR in pancreatic cancer (3, 18, 19). We have reported that the

Table II. *Univariate and multivariate analyses of factors related to overall survival in patients with pancreatic cancer who underwent pancreatectomy (Cox proportional hazards analysis).*

	Univariate			Multivariate		
Variable	Hazard ratio	95%CI	*p*-Value	Hazard ratio	95%CI	*p*-Value
Age ≥71	1.2	0.766-1.89	0.431			
Sex: male	1.17	0.74-1.84	0.506			
BMI ≥22	0.74	0.47-1.17	0.199			
Preoperative sarcopenia	0.68	0.43-1.08	0.104			
Operative procedure: PD or TP	1.44	0.90-2.30	0.132			
Operation time ≥6 h	1.28	0.80-2.04	0.298			
Blood loss ≥500 ml	1.58	1.00-2.54	0.048	1.42	0.87-2.32	0.161
POPF B or C	0.89	0.52-1.54	0.680			
Complication ≥GIII	1.4	0.77-2.56	0.269			
Histology: Poor differentiation	1.43	0.88-2.30	0.142			
Lymph node metastasis	1.72	1.08-2.74	0.024	1.35	0.81-2.26	0.248
Stage ≥III	0.8	0.43-1.48	0.475			
Tumor size ≥3 cm	1.9	1.21-2.99	0.006	1.58	0.97-2.59	0.071
CA19-9 ≥37.0	1.49	0.93-2.36	0.094			
Alb <3.5	2.16	1.16-4.03	0.016	1.09	0.39-3.08	0.872
NLR ≥3	1.33	0.74-2.38	0.335			
Not R0 resection	1.37	0.85-2.21	0.204			
PNI ≤40	4.91	2.24-10.78	<0.001	3.93	1.11-13.93	0.034
SMI reduction rate ≥14%	3.23	1.95-5.34	<0.001	2.68	1.57-4.59	<0.001

BMI: Body mass index; PD: pancreatoduodenectomy; DP: distal pancreatectomy; TP: total pancreatectomy; POPF: postoperative pancreatic fistula; PNI: prognostic nutritional index; CAR: CRP-albumin ratio; LCR: lymphocyte-CRP ratio; LMR: lymphocyte-monocyte ratio; NLR: neutrophile-lymphocyte ratio; PLR: platelet-lymphocyte ratio; TLC: total lymphocyte count.

Table III. *Univariate and multivariate analyses of factors related to recurrence-free survival in patients with pancreatic cancer who underwent pancreatectomy (Cox proportional hazards analysis).*

	Univariate			Multivariate		
Variable	Hazard ratio	95%CI	*p*-Value	Hazard ratio	95%CI	*p*-Value
Age ≥71	0.87	0.57-1.34	0.522			
Sex: male	0.96	0.62-1.49	0.873			
BMI ≥22	0.77	0..50-1.19	0.242			
Preoperative sarcopenia	0.81	0.52-1.25	0.331			
Operative procedure: PD or TP	1.16	0.75-1.81	0.511			
Operation time ≥6 h	1.09	0.70-1.70	0.701			
Blood loss ≥500 ml	1.65	1.05-2.58	0.029	1.51	0.92-2.46	0.103
POPF B or C	0.93	0.55-1.56	0.770			
Complication ≥GIII	0.99	0.54-1.85	0.998			
Histology: Poor differentiation	1.29	0.82-2.06	0.268			
Lymph node metastasis	1.69	1.08-2.63	0.021	1.35	0.82-2.23	0.242
Stage ≥III	0.91	0.52-1.59	0.739			
Tumor size ≥3 cm	2.12	1.37-3.27	<0.001	1.68	1.02-2.75	0.040
CA19-9 ≥37.0	1.47	0.95-2.29	0.085			
Alb <3.5	1.95	1.04-3.63	0.036	1.51	0.59-3.85	0.383
NLR ≥3	1.86	1.09-3.16	0.022	1.97	1.13-3.44	0.017
Not R0 resection	1.41	0.89-2.25	0.144			
PNI ≤40	3.23	1.44-7.23	0.004	1.92	0.58-6.39	0.287
SMI reduction rate ≥14%	2.61	1.58-4.31	<0.001	2.82	1.64-4.85	<0.001

BMI: Body mass index; PD: pancreatoduodenectomy; TP: total pancreatectomy; POPF: postoperative pancreatic fistula; NLR: neutrophile-lymphocyte ratio; PNI: prognostic nutritional index; SMI: skeletal muscle mass index.

postoperative NLR level represents the levels of circulating cytokines and is an independent predictor of survival after pancreatectomy (20). The skeletal muscle contains a large number of leukocytes, which play critical roles in antitumor immunity and are the same as those in total blood (4, 21). These findings indicate that high cytokine levels and loss of antitumor immunity would lead to cancer progression, resulting in a shorter RFS. Therefore, we suspect that the combination of tumor aggressiveness and patient factors, such as nutritional and physical conditions, affect the prognosis of patients with pancreatic cancer. To improve the prognosis after surgery of pancreatic cancer, prophylactic strategies, including nutritional support and physiotherapy, are important to prevent skeletal muscle loss. According to some studies, enteral nutrition is preferred over total parenteral nutrition (TPN) as postoperative nutritional support (22). TPN is associated with a longer period of first bowel movement, weight loss, and increased complications. Although oral feeding is the best way to provide nutrition postoperatively, patients often need to abstain from food because of complications or delayed gastric emptying and require alternative nutrition therapy. Jejunostomy tube (J-tube) placement is a safe method commonly used for early enteral feeding after pancreatic surgery. However, there were no differences in complications or prognosis between patients with and without J-tube feeding after pancreaticoduodenectomy (23). Thus, nutritional support therapy after pancreatic surgery remains a challenging and important issue. Some nutrients have been shown to be associated with muscle mass and complication rates. The early postoperative arginine-rich enteral nutrition could improve nitrogen balance and suppress weight loss in patients after abdominal surgery (24). The arginine-rich nutrition also contributes wound healing and increases hormone secretion with protein synthesis. In animal models, it could suppress bacterial translocation in the intestinal lumen (25). Another report indicates vitamin D is associated with muscle mass, and low vitamin D level is one of the risk factors of postoperative complications (26). The blood testing for such nutritional deficiencies would be important to reduce muscle mass loss and complication after surgery.

Postoperative complications of pancreatic cancer were significantly reduced not only by postoperative rehabilitation, but also by preoperative rehabilitation called prehabilitation (27, 28). Home prehabilitation has proven to reduce muscle mass loss in the early postoperative period (29). In addition, the personalized home-based prehabilitation can reduce the rate of postoperative complications after abdominal surgery (30). Enhanced recovery of patient care pathways (ERAS) is becoming the standard of care for surgery (31). According to the ERAS 2019 recommendations, avoidance of postoperative nasogastric tubes, early diet, early mobilization, and near-zero fluid balance to avoid excessive fluid administration are encouraged to improve patient outcomes (32, 33). A multi-disciplinary team approach for perioperative management, such as nutritional and physical therapy, is becoming increasingly important as the number of patients with sarcopenia increases with population aging. In our case, preoperative sarcopenia was identified in 60% of patients. Despite previously published reports, sarcopenia was not found to be associated with prognosis (34, 35). This might be because more patients were sarcopenic in our study than in previous reports, and there was no statistically significant difference between the SMI reduction rate and preoperative sarcopenia.

Study limitations. This retrospective, small-cohort study was conducted at a single center using only CT image analysis. However, the strength of this study is that we used the objective index of CT to evaluate postoperative SMI changes. In the future, large-scale investigations using different analytical methods should be conducted.

Conclusion

SMI reduction rate after pancreatic surgery is an independent prognostic factor for survival in patients with pancreatic cancer. We believe that nutritional support and physiotherapy focused on preventing skeletal muscle loss require further development.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

JM designed the study and wrote the initial draft of the article. ET and TM contributed to interpretation of the data and critical revision of the article for important intellectual content. All other Authors (NH, RM, YO, AS, ST, RM, TO, TK, SY, KK, KH) contributed to data collection and interpretation and critically reviewed the article.

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