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Research Article

The Postoperative Recovery Course of Skeletal Muscle Mass in Older Esophageal Cancer Patients

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Purpose. Skeletal muscle mass (SMM) is an important biomarker for health in older cancer patients. However, there is limited information on the recovery course of SMM after esophagectomy in older patients. This study aimed to investigate the recovery course of SMM after esophagectomy and the predictors in older cancer patients. *Methods*. We conducted a single-center, retrospective cohort study. Esophageal cancer patients who underwent esophagectomy were included. The skeletal muscle mass index (SMI) was calculated using computed tomography images. The loss of SMI at 4 and 12 months after surgery was calculated as [(preoperative − postoperative SMI) ÷ preoperative SMI] × 100%. Nonrecovery was defined as an SMI loss of ≥2% at 12 months after surgery, considering physiological loss with aging. One-way analysis of variance and multivariate logistic regression analysis was used for statistical analysis. *Results*. A total of 105 older (≥70 years) and 156 nonolder (<70 years) patients were analyzed. Older patients had a significantly larger loss of SMI 4 months (mean: 5.7% vs. 3.1%; $p = 0.021$) and 12 months (mean: 1.0% vs. −1.4%; $p = 0.040$) after surgery than nonolder patients. In older patients, the number of patients with nonrecovery of SMI at 12 months after surgery was 55 (52%). In older patients, significant predictors for the nonrecovery of SMI were preoperative sarcopenia (adjusted OR: 0.297; $p = 0.012$), neoadjuvant chemotherapy (adjusted OR: 0.248; $p = 0.015$), and loss of SMI 4 months after surgery (per 1%; adjusted OR: 1.076; $p = 0.018$). *Conclusions*. It is suggested that older esophageal cancer patients have a larger unmet need for long-term postoperative loss of SMM than nonolder patients. Continuous outpatient rehabilitation, including exercise and nutritional therapy after discharge, which targets improvement in SMM at 4 months, may improve SMI at 12 months after surgery in older esophageal cancer patients.

1. Introduction

The number of older patients aged ≥70 years with esophageal cancer continues to grow globally, and this patient population is reported to have a poor prognosis [1–3]. Esophagectomy is one of the most invasive surgeries and is reported to negatively affect body composition, physical function, the activity of daily living (ADL), and instrumental ADL (IADL) in esophageal cancer patients [4–6]. In particular, postoperative physical sequelae may largely affect healthy life expectancy and prognosis in vulnerable older esophageal cancer patients. In recent research on older cancer patients, health-related outcomes, such as physical function, ADL, and quality of life (QOL), were considered especially important as cancer treatment outcomes, although primary outcomes were overall survival and recurrence or

progression-free survival [7, 8]. Hence, it is important to investigate the long-term physical sequelae of esophagectomy to develop supportive care aimed at optimizing the health of older esophageal cancer patients.

Skeletal muscle mass (SMM) is a critical biomarker for health parameters in older adults with cancer, such as physical function, ADL, IADL, QOL, and prognosis [9–11]. Previous studies showed that the median early postoperative loss of SMM 4 months after esophagectomy was 5%, which affected overall survival in esophageal cancer patients ≥70 years old [12]. However, there is limited information on the postoperative long-term recovery course of SMM. Although comprehensive rehabilitation, including exercise and nutritional therapy, can improve SMM in older adults [13], postoperative supportive care targeting SMM is not established for older esophageal cancer patients. Therefore, we believe that detecting the recovery course and predictors for nonrecovery of SMM in older patients will help promote the development of a novel postoperative supportive care strategy.

This present study aimed to investigate the recovery course of SMM and predictors for nonrecovery of SMM at 12 months after esophagectomy in older esophageal cancer patients (≥70 years).

2. Methods

2.1. Design and Participants. This research was designed as a single-center, retrospective cohort study. Subjects were esophageal cancer patients aged ≥70 years and <70 years who had undergone curative esophagectomy at the National Cancer Center East Hospital in Japan between September 2015 and January 2020. In this study, older patients were defined as ≥70 years old, based on previous studies regarding older patients with esophageal cancer [1, 2, 12]. The exclusion criteria were as follows: R1-R2 esophagectomy, death or relapse within 12 months after surgery, and missing data. Esophagectomy was performed as a minimally invasive surgery or open surgery. For the treatment of clinical stage IB, II, III, and IV esophageal cancer without distant organ metastasis (Union for International Cancer Control tumor-node-metastasis (UICC-TNM) classification, 7th edition), neoadjuvant chemotherapy (NAC) with cisplatin and fluorouracil or docetaxel, cisplatin, and fluorouracil was administered by oncologists according to individual tolerance of patients. This study was approved by the Research Ethics Committee of the National Cancer Center (2019-075) in accordance with the Declaration of Helsinki. An opt-out consent process was followed because of the retrospective nature of the study.

2.2. Perioperative Rehabilitation and Nutritional Therapy. All subjects underwent rehabilitation. Preoperative rehabilitation comprised home-based intervention, such as respiratory, resistance, and aerobic exercise. Postoperative rehabilitation, including early mobilization and respiratory, resistance, and aerobic exercise, was initiated on the first postoperative day and continued until discharge. Enteral feeding was administered through a feeding tube placed in the jejunum in all patients. Seven days after surgery, all patients underwent a contrast study to identify any anastomotic leakage. If there was no leakage, oral fluid intake was started immediately. In principle, the caloric and protein targets of enteral feeding and oral intakes were individually determined with the total energy expenditure calculated from the Harris–Benedict equation and estimated intake of protein (>1.5 g/kg [14]). When oral intake was sufficient to provide the daily caloric requirement, the enteral nutrition tube was removed.

2.3. Data Collection. We obtained data from medical records, including age, sex, preoperative Charlson comorbidity index (CCI) [15], histological types, clinical and pathological stage by UICC-TNM classification 7th edition, NAC information, preoperative C-reactive protein (CRP) [16], preoperative neutrophil-lymphocyte ratio (NLR) [17], preoperative prognostic nutritional index (PNI) [18], postoperative complications within 30 days after surgery including pneumonia, anastomotic leakage, and recurrent nerve palsy as per the Japan Clinical Oncology Group postoperative complications criteria in line with the Clavien–Dindo (CD) classification [19], length of stay (LOS), and postoperative duration of enteral feeding. In older patients, preoperative and postoperative grip strength [20] and usual gait speed [21] were measured before surgery and at postoperative discharge. The postoperative changes in the grip strength and usual gait speed were calculated as [(postoperative − preoperative) ÷ preoperative value] × 100%.

2.4. Skeletal Muscle Mass. The skeletal muscle mass index (SMI) [22] was calculated with the cross-sectional area of the Hounsfield unit (−29 to 150) at the level of L3 on axial computed tomography (CT) images using sliceOmatic (TomoVision, Magog, QC, Canada) before NAC, before surgery, and 4 months and 12 months after surgery. SMI was calculated as a cross-sectional skeletal muscle area (cm^2) ÷ height (m^2). The loss of SMI at 4 and 12 months after surgery was calculated as [(preoperative − postoperative SMI) ÷ preoperative SMI] × 100%. In patients treated with NAC, preoperative CT imaging after NAC was used to evaluate preoperative SMI. In older patients, patients with nonrecovery of SMI at 12 months after surgery were defined as having ≥2% loss of SMI at 12 months after surgery to exclude physiological loss of SMI with aging [23–25]. In older patients, preoperative sarcopenia was defined as <median of SMI before surgery by sex [26]. The loss of SMI during NAC was calculated using the formula [(before NAC − after-NAC) ÷ (before NAC) SMI] × 100%.

2.5. Statistics. Descriptive statistics are presented as the number of patients (%), mean (standard deviation (SD)), and median (1st–3rd quartile). In characteristics, the differences between older and nonolder patients were analyzed with the one-way analysis of variance, χ^2 test, and Mann—Whitney *U* test. In older patients, preoperative SMI

was compared with SMI 4 months and 12 months after surgery using the paired *t*-test. In older patients, associations between the nonrecovery of SMI at 12 months after surgery and potential predictors were analyzed by a logistic regression model. The variables were defined binary variables as follows: high CCI (≥2) [15], high CRP (≥0.5 mg/dL) [16], high NLR (≥3.5) [17], low PNI (<40) [18], low grip strength (<26 kg for males; <18 kg for females) [19], slow usual gait speed (<1.0 m/s) [20], presence of complication (CD grade ≥2), long LOS (days > median), and long-term enteral feeding (days > median). A multiple logistic regression model using the forced entry method was applied to detect predictors of SMI nonrecovery at 12 months after surgery. Explanatory variables were potential factors with a p value of <0.05 in the univariate logistic regression models. Age, sex, and preoperative sarcopenia were then selected as potential confounding variables. In older patients, the cutoff point of significant parametric continuous variables was analyzed by receiver-operating characteristic analysis for nonrecovery of SMI. Statistical significance was considered a two-tailed p value of <0.05. All analyses were performed with R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Differences in SMI Recovery between Older and Nonolder Patients. Forty patients among 145 older patients (R1-2 esophagectomy: 13; relapse and death within 1 year postoperatively: 17; missing data: 10) and 77 patients among 233 nonolder patients (R1-2 esophagectomy: 15; relapse and death within 1 year postoperatively: 54; missing data: 8) were excluded, resulting in 105 older patients and 156 nonolder patients for analysis. Older patients had a significantly larger loss of SMI 4 months (mean: 5.7% vs. 3.1%; $p = 0.021$) and 12 months (mean: 1.0% vs. −1.4%; $p = 0.040$) after surgery than nonolder patients (Table 1 and Figure 1). In older patients, there was a significant difference in SMI before surgery and 4 months after surgery ($p < 0.001$), but there was only a marginal significant difference in SMI before surgery and 12 months after surgery ($p = 0.071$). In 53 older patients who received NAC, the mean loss of SMI during NAC was 5.8% (SD, 8.0). In older patients, the median values of preoperative SMI in males and females were 42.5 and 33.5 cm^2/m^2, respectively, used as the cutoff point for sarcopenia.

3.2. Predictors of SMI Nonrecovery in Older Patients. In older patients, the number of patients with nonrecovery of SMI 12 months after surgery was 55 (52%). In older patients, the significant predictors of SMI nonrecovery were preoperative sarcopenia (adjusted odds ratio: 0.297; 95% confidence interval: 0.111 to 0.742; $p = 0.012$), NAC (adjusted odds ratio: 0.248; 95% confidence interval: 0.076 to 0.735; $p = 0.015$), and loss of SMI 4 months after surgery (per 1%; adjusted odds ratio: 1.076; 95% confidence interval: 1.017 to 1.149; $p = 0.018$) (Table 2). In older patients, the subgroup analysis for the loss of SMI 4 months after surgery (per 1%) showed that SMI loss 4 months after surgery was likely to be associated with nonrecovery in all subgroups (odds ratio range: 1.023 to 1.237) (Figure 2).

3.3. Association of Loss of SMI 4 Months after Surgery with Nonrecovery of SMI in Older Patients. In older patients, receiver-operating characteristic analysis showed that the cutoff point of the loss of SMI 4 months after surgery was defined as 5.415% for nonrecovery of SMI. The area under the curve, sensitivity, and specificity were 0.701, 0.714, and 0.607, respectively. In older patients, the major loss of SMI (loss ≥5.415%) 4 months after surgery was significantly associated with nonrecovery of SMI, independent of age, sex, sarcopenia, NAC, and PNI (adjusted odds ratio: 3.606; 95% confidence interval: 1.324 to 10.448; $p = 0.014$). Among older patients, in all subgroups of preoperative sarcopenia and NAC, patients with the major loss of SMI 4 months after surgery were shown to have a greater loss of SMI 4 months and 12 months after surgery than those with the minor loss of SMI 4 months after surgery (Figure 3).

4. Discussion

The present study is the first to investigate the SMI recovery course in older patients after esophagectomy and the differences in postoperative recovery course between older and nonolder patients. Previous studies reported that SMM at 12 months after surgery was significantly lower than the preoperative mass in digestive cancer patients [27, 28]. However, there were critical limitations in clarifying the postoperative recovery course of SMI in older esophageal cancer patients because of the small sample size ($n = 24$ to 45), younger subjects (mean age 63 to 67 years), and inclusion of gastric cancer [27, 28]. In addition, there was no information regarding the differences in the SMI postoperative recovery course between older and nonolder patients in these previous studies [27, 28]. The present study newly found that the SMI of older patients was significantly lower at before, 4 months after, and 12 months after surgery than that of nonolder patients. Additionally, older patients had a significantly larger loss of SMI 4 months and 12 months after surgery than nonolder patients. Thus, this study clarified that older patients aged ≥70 years with esophageal cancer have an especially larger unmet need for long-term postoperative loss of SMM than nonolder patients with esophageal cancer.

The difference in loss of SMI 4 months and 12 months after surgery between older and nonolder patients may have been caused by preoperative frailty and NAC. First, frailty is a state of increased vulnerability to poor resolution of homeostasis after a stressor event, which increases the risk of adverse outcomes, including falls, delirium, and disability [29, 30]. In comparison with their counterparts without frailty, adults with frailty more slowly recover to baseline health status when health status decreases with stressor events [30]. SMM and comorbidity are known to be related to frailty [29–32]. In the present study, older patients had significantly lower preoperative SMI and had a higher rate of

Table 1: Characteristics of nonolder (<70 years) and older (≥70 years) patients.

Variables	Nonolder ($n = 156$)	Older ($n = 105$)	p value
Age			
Mean ± SD (years)	61.5 ± 6.8	75.5 ± 4.1	<0.001[a**]
Sex			
Male	125 (80)	84 (80)	1.000[b]
Charlson comorbidity index			
≥2	12 (8)	22 (21)	0.003[b**]
Histological type			
Squamous cell carcinoma	138 (88)	94 (90)	0.947[b]
Main tumor location			0.055[b]
Cervical	4 (3)	4 (4)	
Thoracic	126 (81)	93 (88)	
Abdominal	28 (16)	8 (8)	
Clinical stage			
III-IV	70 (45)	53 (50)	0.445[b]
Clinical T stage			
T3-4	77 (49)	55 (52)	0.724[b]
Clinical N stage			
Positive	90 (58)	63 (60)	0.808[b]
Pathological stage			
III-IV	32 (21)	27 (26)	0.404[b]
Pathological T stage			
T3-T4	35 (22)	35 (33)	0.071[b]
Pathological N stage			
Positive	52 (33)	38 (36)	0.731[b]
Adjuvant therapy			
Neoadjuvant chemotherapy	98 (63)	52 (50)	0.045[b*]
Preoperative CRP			
≥0.5 mg/dL	16 (10)	21 (20)	0.042[b*]
Preoperative NLR			
≥3.5	22 (14)	25 (24)	0.066[b]
Preoperative PNI			
<40	40 (26)	25 (24)	0.850[b]
Preoperative grip force			
<26 kg (male), <18 kg (female)	NA	18 (17)	NA
Preoperative gait speed			
<1.0 m/s	NA	25 (24)	NA
Postoperative complication			
≥CD grade 2	63 (40)	49 (47)	0.380[b]
Postoperative pneumonia			
Presence	12 (8)	18 (17)	0.032[b*]
Postoperative anastomosis leakage			
Presence	27 (17)	13 (12)	0.364[b]
Postoperative recurrent nerve palsy			
Presence	36 (23)	31 (30)	0.305[b]
Length of hospital stay			
Median (Q1–Q3) (days)	16 (14–22)	18 (15–25)	0.004[c**]
Postoperative change in grip force			
Mean ± SD (%)	NA	−6.9 ± 9.8	NA
Postoperative change in gait speed			
Mean ± SD (%)	NA	−4.5 ± 20.8	NA
Preoperative SMI			
Mean ± SD (cm^2/m^2)	44.0 ± 7.2	42.3 ± 6.7	0.001[a**]
SMI 4 months after surgery			
Mean ± SD (cm^2/m^2)	42.5 ± 6.8	40.5 ± 6.2	<0.001[a**]
SMI 12 months after surgery			
Mean ± SD (%)	44.4 ± 6.6	41.1 ± 6.5	<0.001[a**]
Postoperative loss of SMI 4 months after surgery			
Mean ± SD (%)	3.1 ± 7.8	5.7 ± 10.0	0.021[a*]
Postoperative loss of SMI 12 months after surgery			
Mean ± SD (%)	−1.4 ± 8.1	1.0 ± 10.5	0.040[a*]

CD, Clavien–Dindo classification; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; PNI, prognostic nutritional index; SMI, skeletal muscle mass index. [a]One-way analysis of variance. [b]χ^2 test. [c]Mann–Whitney U test. * $p < 0.05$; ** $p < 0.01$.

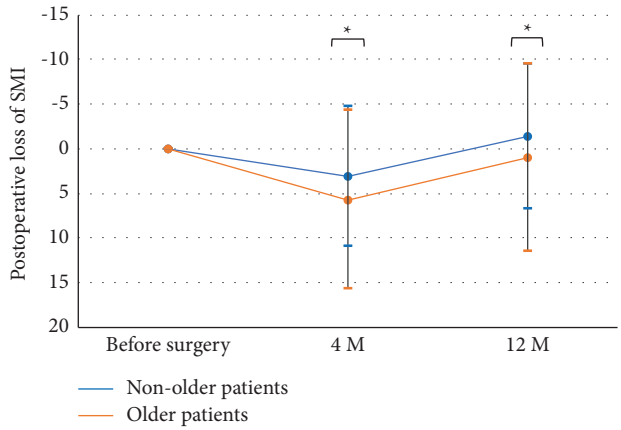

Figure 1: Postoperative recovery course of the skeletal muscle mass index (SMI) in nonolder and older patients. Circles and error bars indicate the means and standard errors, respectively, of loss of SMI (%). Blue and orange lines indicate nonolder and older patients. 4M and 12M indicate 4 months and 12 months, respectively, after surgery. $^{*}p < 0.05$ (one-way analysis of variance).

Table 2: Predictors of nonrecovery of SMI 12 months after surgery in older patients.

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age ≥75 years	0.989 (0.457–2.146)	0.979	0.385 (0.126–1.071)	0.077
Male	0.953 (0.234–2.519)	0.922	0.745 (0.227–2.368)	0.620
Preoperative sarcopenia	0.319 (0.141–0.700)	0.005**	0.297 (0.111–0.742)	0.012*
CCI ≥2	1.886 (0.733–5.038)	0.193		
Squamous cell carcinoma	1.056 (0.298–3.891)	0.932		
Clinical stage III-IV	0.767 (0.354–1.652)	0.498		
Clinical T3-4	0.568 (0.259–1.227)	0.152		
Clinical N positive	0.682 (0.309–1.492)	0.339		
Pathological stage III-IV	1.323 (0.549–3.210)	0.531		
Pathological T3-4	0.667 (0.289–1.508)	0.334		
Pathological N positive	1.496 (0.656–3.263)	0.357		
Neoadjuvant chemotherapy	0.269 (0.117–0.596)	0.001**	0.248 (0.076–0.735)	0.015*
Preoperative high CRP	0.645 (0.234–1.693)	0.381		
Preoperative high NLR	0.701 (0.274–1.730)	0.445		
Preoperative low PNI	0.352 (0.125–0.903)	0.036*	0.341 (0.105–1.027)	0.061
Preoperative low grip force	0.376 (0.113–1.090)	0.085		
Preoperative slow gait speed	1.324 (0.536–3.291)	0.541		
Postoperative complication	1.622 (0.751–3.544)	0.220		
Postoperative pneumonia	0.512 (0.165–1.443)	0.218		
Postoperative anastomosis leakage	2.925 (0.884–11.131)	0.092		
Postoperative recurrent nerve palsy	1.103 (0.474–2.563)	0.819		
Long length of hospital stay (17 days)	0.735 (0.322–1.652)	0.459		
Long-term enteral feeding (9 days)	1.522 (0.706–3.315)	0.286		
Postoperative major decline in grip force (per 1%)	1.023 (0.984–1.069)	0.265		
Postoperative major decline in gait speed (per 1%)	0.987 (0.965–1.006)	0.194		
Loss of SMI 4 months after surgery (per 1%)	1.095 (1.042–1.161)	<0.001**	1.076 (1.017–1.149)	0.018*

CI, confidence interval; CCI, Charlson comorbidity index; CRP, C-reactive protein; NAC, neoadjuvant chemotherapy; NLR, neutrophil-lymphocyte ratio; PNI, prognostic nutritional index; SMI, skeletal muscle mass index. $^{*}p < 0.05$; $^{**}p < 0.01$.

high CCI than nonolder patients, which suggested that older patients had more progression of frailty than nonolder counterparts. In fact, older patients not only had significantly higher rates of postoperative pneumonia and longer LOS but also had a larger loss of SMI 4 months after surgery than nonolder patients. Second, it is reported that patients treated with NAC have lower loss of SMM 4 months after esophagectomy [12]. In the present study, older patients had a significantly lower rate of NAC than nonolder patients. The difference in the rate of NAC between older and nonolder patients may have influenced the recovery of SMI at 4 months and 12 months after surgery. Thus, the differences in preoperative frailty, such as low SMM and comorbidity, and the rate of treatment with NAC may have caused the difference in the SMI postoperative recovery course between older and nonolder patients with esophageal cancer.

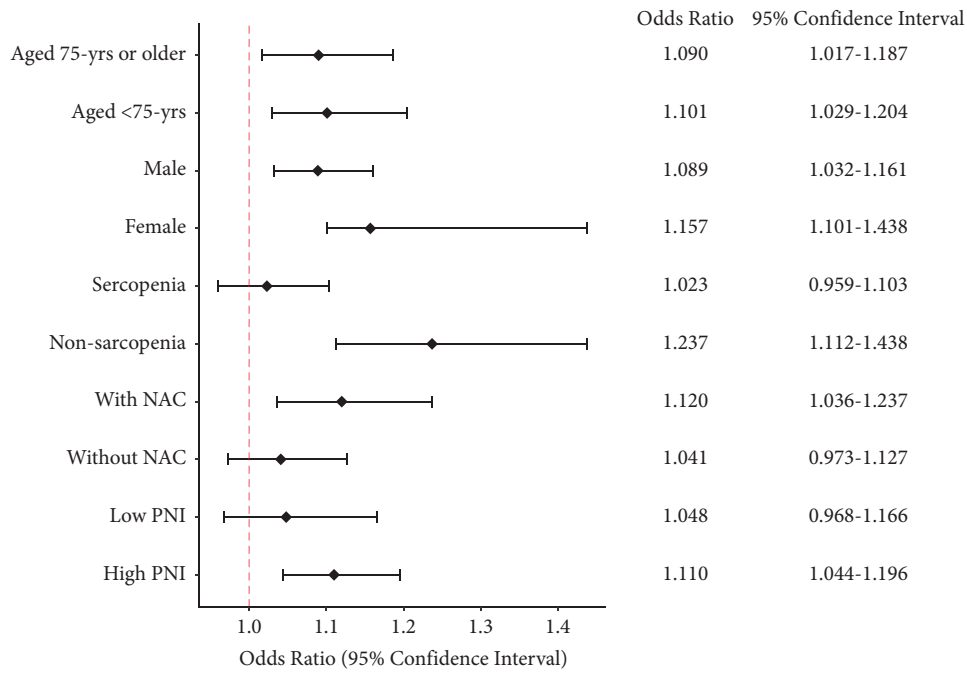

Figure 2: Subgroup analysis of the association of the loss of the skeletal muscle mass index (SMI) 4 months after surgery (per 1%) with nonrecovery of SMI 12 months after surgery in older patients. The diamonds and lines indicate odds ratios and 95% confidence intervals, respectively.

In older patients, the present study also newly found that predictors of nonrecovery of SMI at 12 months after surgery were preoperative sarcopenia and NAC. Previous studies showed that patients with low preoperative SMI had less early postoperative loss of SMI than those with high preoperative SMI [33, 34]. Chemotherapy, including NAC, leads to loss of SMM [35, 36]. In the present study, patients without NAC may have had higher preoperative SMI than those with NAC because the mean loss of SMI during NAC was 5.8%. Hence, in older patients, it is possible that factors associated with low preoperative SMI, such as sarcopenia and NAC, may have caused lower loss of SMI 12 months after surgery. Additionally, this study newly showed that early loss of SMI 4 months after surgery predicted nonrecovery of SMI 12 months after surgery independent of preoperative factors. The loss of SMM is well known to progress to frailty in older patients, resulting in low resilience against stressors [12, 29, 30]. Therefore, in older patients with esophageal cancer, postoperative progression of frailty with SMM 4 months after surgery may impact the recovery status of SMM 12 months after surgery independent of preoperative characteristics. The most recent study reported that the loss of SMI 4 months after surgery was affected by the decline in quadriceps muscle strength in the first month after surgery in older patients with esophageal cancer [37]. Additionally, a previous study reported that esophageal cancer patients with low physical activity after discharge had a higher percentage loss of SMM 6 months after surgery than those with high physical activity [38]. Thus, in postoperative older patients with esophageal cancer after discharge, continuous comprehensive rehabilitation may prevent SMM loss not only at 4 months but also at 12 months after surgery, regardless of preoperative and perioperative factors.

In older adults, SMM is an important factor associated not only with health but also with prognosis [9–11]. In esophageal cancer patients ≥70 years old, previous studies showed that an SMI loss of 5% or more 4 months after surgery affected overall survival independent of preoperative patient characteristics [12]. In particular, postoperative SMM loss in esophageal cancer patients aged ≥70 years had a more substantial impact on overall survival than in patients younger than 70 years [12]. In the present study, 5.6% or more SMI loss 4 months after surgery affected the recovery of SMI at 12 months after surgery in esophageal cancer patients aged ≥70 years (adjusted OR 3.606). Considering the present results and those of previous studies, 5% or more loss of SMI at 4 months after surgery may be an important factor for postoperative long-term healthy life expectancy and survival in older patients after esophagectomy. In a recent meta-analysis, comprehensive rehabilitation consisting of exercise with protein supplementation was reported to improve SMM in older adults [13]. We hypothesize that, in older esophageal cancer patients, continuous outpatient rehabilitation, including exercise and nutritional therapy after discharge, which targets improvement in SMM at 4 months, may not only recover SMI at 12 months after surgery but also improve prognosis.

This study does have several limitations. First, it was conducted as a single-center, retrospective cohort study with a small sample size. Second, the external validity and generalizability of the recovery course of SMI and predictors should be examined. Third, the mechanisms of the early postoperative loss and recovery of SMI 12 months after

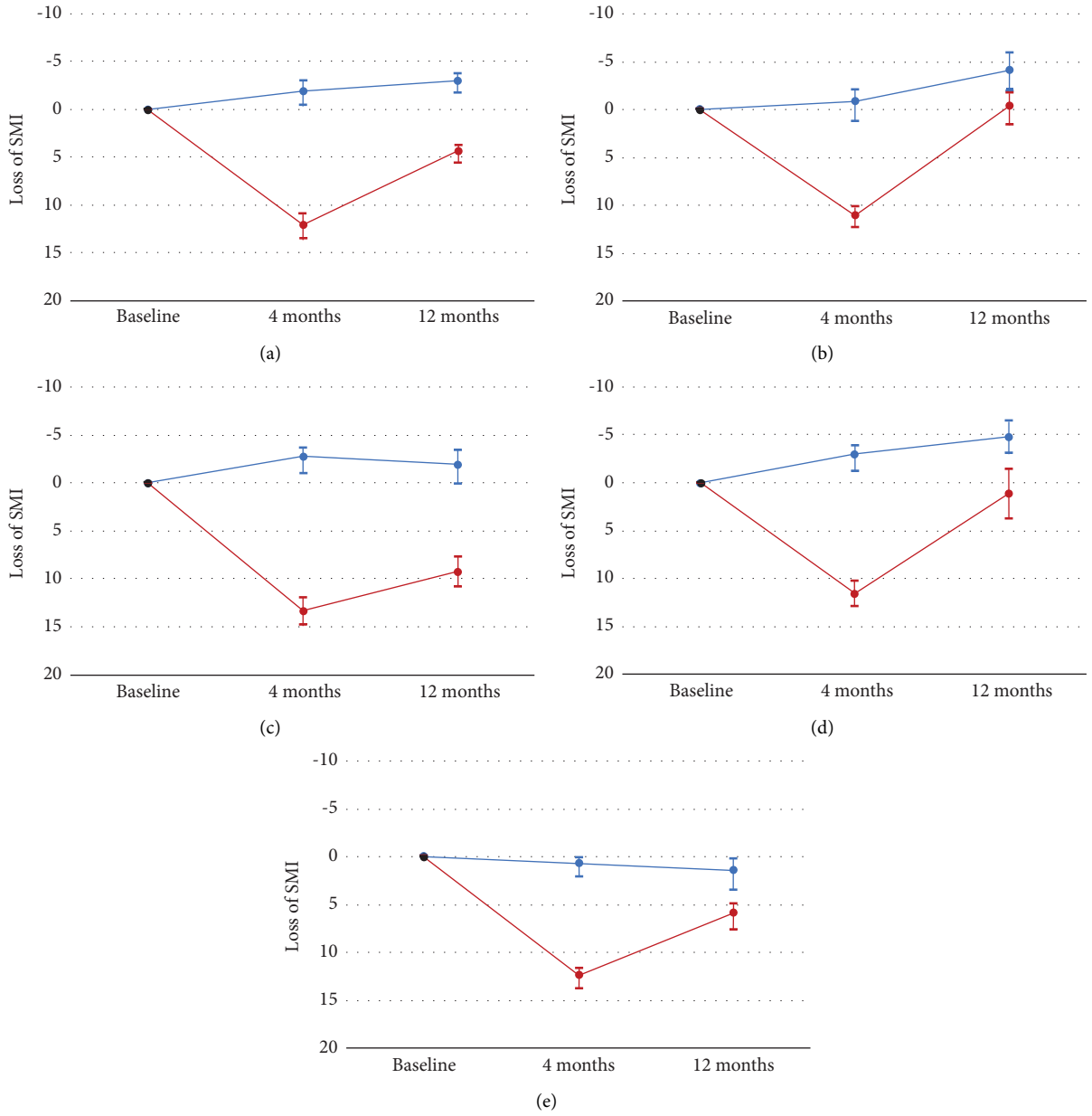

Figure 3: Postoperative recovery course of the skeletal muscle mass index (SMI) in groups with major loss of SMI (≥5.415%) and minor loss of SMI (<5.415%) 4 and 12 months after surgery in older patients. The postoperative recovery courses of SMI in all patients (a) and the subgroups of preoperative sarcopenia (b), nonsarcopenia (c), surgery with NAC (d), and surgery without NAC (e) Circles and error bars indicate the means and standard errors, respectively, of loss of SMI (%). Red and blue lines indicate the groups with major and minor loss, respectively, of SMI 4 months after surgery.

surgery are unclear because of the retrospective nature of the study design. In particular, the status of nutritional support and physical activities represents important information for clarifying the mechanisms, but there is a lack of such information in the present study. Finally, the associations of nonrecovery of SMI 12 months after surgery with the actual clinical circumstances, such as physical function, QOL, health, and prognosis, were unclear. Future studies investigating the mechanism of the loss of SMI and actual clinical impacts on recovery of SMI with large sample sizes enrolled from multiple centers will be required to develop continuous postoperative rehabilitation and supportive care for older patients. Regarding the present study, we should interpret these results while considering that baseline preoperative SMI was defined using post-NAC CT images in patients treated with NAC. Those treated with NAC in older and nonolder groups accounted for 50% and 63% of patients, respectively. Therefore, if baseline preoperative SMI were defined using pre-NAC CT images, the postoperative loss percentage of SMI 12 months after surgery would be larger than that reported in the present study in older and nonolder patients because of the addition of the preoperative loss

percentage of SMM during NAC. In the future, for patients treated with NAC, the postoperative long-term recovery course of SMI requires further investigation, considering the preoperative loss of SMM during NAC.

In conclusion, the loss of SMI in 105 older patients with esophageal cancer at 4 months and 12 months after esophagectomy was significantly larger than that in 156 nonolder patients with esophageal cancer, which suggested that older patients aged ≥70 years have a larger unmet need for long-term postoperative loss of SMM than nonolder patients. In older patients, the loss of SMI 4 months after surgery predicted nonrecovery of SMI at 12 months after surgery independent of preoperative factors, suggesting that continuous outpatient rehabilitation, including exercise and nutritional therapy after discharge, which targets improvement in SMM at 4 months, may improve SMI at 12 months after surgery.

Data Availability

The participants of this study did not agree for their data to be shared publicly. The data of participants are not available.

Ethical Approval

This study was approved by the Research Ethics Committee of the National Cancer Center (2019-075) in accordance with the Declaration of Helsinki.

Consent

Informed consent was obtained through an opt-out consent process.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

All the authors made substantial contributions to the conception and design of the work. The first draft of the manuscript was written by Harada T, and all the authors commented on the manuscript. All the authors have read and approved the final manuscript. Harada T, Tatematsu N, Ueno J, Koishihara Y, Konishi N, and Yanagisawa T collected data and carried out data analysis. Harada T, Tsuji T, Tatematsu N, Ueno J, Koishihara Y, Konishi N, Yanagisawa T, Hijikata N, Ishikawa A, and Fujita T wrote, reviewed, and edited the manuscript.

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