Predictors of changes in skeletal muscle mass after esophagectomy in elderly patients with esophageal cancer

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Research Article

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Abstract

Purpose : Although a change in skeletal muscle mass index (SMI) 4 months after esophagectomy impacts prognosis, predictors of a change in SMI have not been revealed. The purpose of this exploratory retrospective study was to clarify the predictors of a change in SMI after curative esophagectomy in elderly patients with esophageal cancer.

Methods : Fifty-four patients who underwent esophagectomy and perioperative rehabilitation from 2015 to 2018 were enrolled. Preoperative and postoperative SMI (cm 2 /m 2) were calculated using computed tomography images. The ratio change in SMI was calculated as follows: (postoperative SMI − preoperative SMI) ÷ preoperative SMI × 100%. Potential predictors of a change in SMI ratio were analyzed by multiple regression.

Results : The mean ratio change in SMI 4 months after esophagectomy was −7.1% ± 9.4%. The ratio change in quadriceps muscle strength in the first month after surgery ([postoperative strength − preoperative strength] ÷ preoperative strength × 100%) (standardized β = .273, p = .038) and neoadjuvant chemotherapy (NAC) (standardized β = .398, p = .006) were predictors of the ratio change in SMI independent of age, sex, pathological stage, and preoperative SMI.

Conclusion : Quadriceps muscle weakness in the first month after esophagectomy and NAC were predictors of the ratio change in SMI after esophagectomy. Continuous postoperative comprehensive rehabilitation and supportive care may inhibit loss of skeletal muscle mass.

Introduction

The 5-year survival rates of patients with clinical stage II and III esophageal cancer (Union for International Cancer Control tumor–node–metastasis [UICC-TNM] classification, 6th edition) after esophagectomy are approximately 65% and 40% [1], respectively. This type of cancer has a poor prognosis compared with other cancers. The number of elderly patients with esophageal cancer (aged over 70 years) is increasing, and these patients have a poor prognosis after esophagectomy [2-5].

Skeletal muscle mass at pretreatment is an important factor for prognosis in elderly patients with solid tumors, including esophageal cancer [6, 7]. In patients with esophageal cancer, a change in skeletal muscle mass index (SMI) within 6 months after esophagectomy is an important factor for overall survival, independent of pretreatment SMI [4, 8, 9]. A change in skeletal muscle mass is generally associated with four factors: aging, disease, physical function, and nutrition [10-14]. In fact, previous studies reveal that patients with advanced pathological tumor stage and abundant preoperative SMI have a marked loss of skeletal muscle mass 4 months after esophagectomy [4, 9]. However, no studies have investigated the impact of reversible factors, such as physical function and nutrition, on the change in skeletal muscle mass in elderly patients with esophageal cancer after esophagectomy. If reversible factors, such as physical function and nutrition, are predictors of postoperative changes in skeletal

muscle mass in elderly patients with esophageal cancer, appropriate rehabilitation, including exercise and nutrition, may prevent critical loss of skeletal muscle mass and improve prognosis after esophagectomy.

This study aimed to clarify predictors of a change in skeletal muscle mass after curative esophagectomy in elderly patients with esophageal cancer, including indicators of physical function and nutrition.

Methods

1. ***Design and participants***

This study was a retrospective cohort study. Subjects were over 70 years of age and had undergone curative esophagectomy for esophageal cancer at the National Cancer Center East Hospital between September 2015 and December 2018. The inclusion criteria were as follows: 1) completion of physical function and nutritional assessments; 2) computed tomography (CT) within 2 months prior to and 4 ± 2 months after esophagectomy. The exclusion criteria were as follows: 1) readmission, death, or recurrence by the day of postoperative CT; 2) distant metastasis at esophagectomy; 3) untreated or undertreated duplicate cancer; 4) missing data. Informed consent was obtained through an opt-out consent process due to the retrospective nature of the study. This study was approved by the research ethics committee of the National Cancer Center (2019-075) in accordance with the Declaration of Helsinki.

2. ***Perioperative rehabilitation***

Perioperative rehabilitation was performed on all subjects. Preoperative rehabilitation is a home-based intervention, consisting of respiratory training with incentive spirometry; resistance training, such as squats and heel-lift exercises; and aerobic exercise with walking. Postoperative rehabilitation was performed from the first postoperative day at an intensive care unit up until discharge for 20–40 minutes per day, including early mobilization, respiratory training, resistance training, and aerobic exercise depending on the individual's condition.

3. ***Assessment***

Patient characteristics

We obtained patient characteristics from medical records, and the variables assessed were as follows: age, sex, neoadjuvant chemotherapy (NAC), preoperative C-reactive protein (≥0.5 mg/dL vs. <0.5 mg/dL) [15], neutrophil–lymphocyte ratio (≥3.5 vs. <3.5) [16], pathological UICC-TNM classification 7th edition [17] (pT 3/1–2, pN positive/negative, and pStage III/I–II [4]), presence of postoperative complications, including pneumonia and anastomotic leak (≥I according to Japan Clinical Oncology Group

postoperative complications criteria in line with the Clavien-Dindo classification [18]), and length of hospital stay (≥median vs. <median).

Physical function and nutrition

Preoperative and postoperative physical function, including isometric quadriceps muscle strength (QS) (IsoForce GT-330, OG GIKEN, Japan) [19], usual gait speed of 4 meters [20], preoperative and postoperative nutrition (prognostic nutrition index [PNI] [21]), and body mass index (BMI), were collected from medical records. For isometric QS, the side with a greater muscle strength was analyzed. Physical function and nutrition were measured within 3 months before esophagectomy and at the first visit after discharge (within the first month after discharge). In the variables of physical function and nutrition, the change ratio (%) after esophagectomy was calculated as follows: (postoperative value − preoperative value) ÷ preoperative value × 100%.

Ratio change in SMI

We used SMI [24], which was calculated from CT images at the level of L3, as an indicator of skeletal muscle mass. CT was performed twice within 3 months prior to and 4 ± 2 months after esophagectomy. Regarding preoperative CT images, CT images after NAC were used if the patient was treated with NAC. The cross-sectional area of the Hounsfield unit (−29 to 150) at the level of L3 on axial CT images was measured in the skeletal muscle area using SliceOmatic (Imagelabo, Canada) [22]. SMI was calculated as follows: cross-sectional skeletal muscle area ÷ (height^2) [4, 5, 8, 9, 22]. The ratio change of SMI was calculated as follows: [(post-SMI − pre-SMI) ÷ pre-SMI] × 100% [4, 8, 9].

4. *Statistics*

Descriptive statistics are presented as number of people and mean ± standard deviation. The difference in SMI before, compared with after, esophagectomy was analyzed with a paired t-test. With a univariate analysis, associations between the ratio change in SMI and physical function, nutrition, and patient characteristics were analyzed with simple linear regression. Multiple regression was performed using the forced entry method. The dependent variable was the ratio change in SMI. Explanatory variables were potential predictors of a ratio change in SMI with significance in a univariate analysis. Confounding variables were age, sex, preoperative SMI [9], and pStage [4]. A stratified analysis for SMI was performed using these predictors. Patients were divided into two groups with a median value as a cut-off point if the predictor was a continuous variable. Differences in preoperative and postoperative SMI between the two

groups were compared with one-way analysis of variance adjusted using the Bonferroni method. Then, the association of predictors with other factors was analyzed using logistic regression. Statistical significance was considered as a two-tailed p value of <0.05. All analyses were performed with SPSS version 26 (IBM Corp., Japan) for Windows. Linear regression was drawn using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 54 patients were analyzed (Figure 1). The mean age was 75.3 ± 3.6 years, and the number of males was 42 (78%). There was a significant difference between preoperative SMI (40.3 ± 7.7 cm^2/m^2) and postoperative SMI (37.3 ± 7.4 cm^2/m^2) ($p < 0.001$). The mean ratio change in SMI was −7.1% ± 9.4% (Table 1). Regarding the timing of assessments, the mean number of months of preoperative and postoperative CT scans were 1.3 ± 0.6 months before and 4.1 ± 0.6 months after esophagectomy. The mean days of preoperative and postoperative physical function and BMI were 4.9 ± 7.5 days before and 36.4 ± 12.8 days after esophagectomy. The mean days of preoperative and postoperative PNI were 3.6 ± 2.8 days before and 33.9 ± 9.3 days after esophagectomy.

Predictors of a change in SMI

Multiple regression analysis showed that the ratio change in QS in the first month after esophagectomy (standardized $\beta = 0.274$, $p = 0.038$) and NAC (standardized $\beta = 0.387$, $p = 0.008$) was a predictor of the ratio change in SMI, independent of sex, age, preoperative SMI, and pStage (Figure 2, Table 2). The coefficient of determination (R^2) of the model was 0.26. With a stratified analysis, patients with a marked decline in QS tended to have a lower SMI 4 months after esophagectomy, compared with patients with less of a decline. We defined the median value (−9.9%) as the cut-off point (36.3 ± 8.0 cm^2/m^2 vs. 38.4 ± 6.8 cm^2/m^2, Figure 3). There was a significant difference between patients treated with NAC versus those treated without NAC in preoperative SMI (Figure 3). In addition, patients treated with NAC tended to have a lower SMI 4 months after esophagectomy, compared with patients treated without NAC (36.4 ± 7.7 cm^2/m^2 vs. 38.4 ± 7.1 cm^2/m^2, Figure 3b).

Association of predictors with other factors

The massive decline in QS in the first month after surgery (ratio change, ≤−9.9%) was significantly associated with a postoperative change in usual gait speed (odds ratio, 0.955, $p = 0.032$) and a longer length of hospital stay (≥18.5 days) (odds ratio, 4.000, $p = 0.016$) (Table 3). NAC was significantly

associated with preoperative BMI (odds ratio, 0.818, p = 0.047) and preoperative SMI (odds ratio, 0.907, p = 0.017) (Table 3).

Discussion

The present study investigated predictors of a change in skeletal muscle mass after curative esophagectomy in 54 elderly patients with esophageal cancer aged over 70 years. The mean ratio change in SMI 4 months after esophagectomy was −7.1% ± 9.4%. From the multiple regression analysis, a change in QS in the first month after esophagectomy and NAC were predictors for a change in SMI 4 months after esophagectomy.

A decline in isometric QS in the first month after esophagectomy was a significant predictor for loss of SMI 4 months after esophagectomy (Table 2, Figure 2). Previous large cohort studies report that a change in muscle strength precedes a change in skeletal muscle mass in community-dwelling older adults [13, 14]. Our results in elderly patients with esophageal cancer support these previous studies. Regarding recovery of QS after esophagectomy, QS significantly improved from the first month to 3 months after surgery in patients with esophageal cancer [24]. Therefore, due to diversity in QS recovery after esophagectomy, changes in QS in the first month after esophagectomy may be predictive of a decrease in SMI 4 months after surgery.

Moreover, a decline in QS in the first month after esophagectomy was associated with a decline in usual gait speed and a long length of hospital stay in our study (Table 3). Previous studies have shown that QS and gait speed are associated with physical activity [25, 26]. Hence, the change in QS in the first month after esophagectomy may be impacted by physical activity [27-29] before and after discharge. In addition, because physical function is impacted by postoperative complications [24] and physical symptoms [30], a decline in QS may be associated with a long length of hospital stay. Therefore, continuous rehabilitation combined with perioperative supportive care for improving physical activity, preventing complications, and inhibiting symptoms may improve prognosis by preventing loss of skeletal muscle mass in elderly patients with esophageal cancer.

In our study, NAC was a significant predictor for less marked loss of SMI 4 months after esophagectomy. Patients treated with NAC were significantly associated with a lower preoperative SMI and BMI (Table 3) and had a significantly lower preoperative SMI compared with patients who did not receive NAC (Figure 3). NAC reduced skeletal muscle mass by approximately 3% because of side effects, such as fatigue, loss of appetite, and decreased exercise tolerance accompanied by thrombocytopenia [31-35]. It has also been revealed that patients with a low preoperative SMI have less marked loss of SMI after esophagectomy [9]. Therefore, less marked loss of SMI after esophagectomy in patients treated with NAC may be attributed to a decrease in SMI during NAC.

Meanwhile, nutritional factors were not predictors for a change in SMI after surgery. In addition, unlike previous studies, progression of tumors was not a significant predictor of a change in SMI after esophagectomy in the present study. This may be because SMI in vulnerable elderly patients may be

influenced by factors such as physical function and cognitive and social function compared with younger patients [36, 37]. Regarding nutritional factors, we were not able to evaluate actual dietary intake and appetite. Stronger predictive indicators of a change in SMI may have been included in our analysis. Second, the statistical power was low because of the small sample size in the present study. Therefore, the impact of tumor progression and nutrition on changes in SMI in elderly patients after esophagectomy may be poor in the present study.

There are several limitations to the present study. First, causal relationships between outcomes and predictors were not guaranteed due to the retrospective observational nature of the study. Second, it is necessary to verify external validity due to the small sample size and the fact that the study was conducted at a single institution. Third, potential predictors that had a strong impact may not have been included in the analysis. We were not able to assess the amount of physical activity, dietary intake, and cognitive and social function owing to the retrospective nature of the study. Furthermore, the coefficient of determination (R^2) for the multiple regression analysis was 0.26, which indicated that the fit of the model was poor. In light of these limitations, we have to interpret the results carefully.

Conclusion

In the present study, we clarified predictors of a change in SMI in 54 elderly patients aged over 70 years with esophageal cancer after esophagectomy. Multiple regression showed that the independent predictors of a change in SMI 4 months after esophagectomy were a ratio change in isometric QS in the first month after esophagectomy and NAC. Supportive care and continuous comprehensive rehabilitation after esophagectomy might prevent loss of skeletal muscle mass after esophagectomy in elderly patients with esophageal cancer.

Declarations

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[Conflicts of interest]

The authors declare no potential conflicts of interest with regard to the research, authorship, or publication of this article.

[Ethics 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 to participate]

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

[Consent for publication (include appropriate statements)]

Not applicable.

[Availability of data and materials]

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

[Authors' Contributions]

All authors contributed to the study conception and design. The first draft of the manuscript was written by TH and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Conceptualization: TH, NT, Takeo F, TT. Data collection and analysis: TH, NT, JU, YK, NK, HF, Takeo F. Writing-Reviewing and editing: TH, NT, Takuya F, Takeo F, AY, TT. Supervision: Takeo F, TT.

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Tables

Table 1 Patient characteristics	n = 54
Age (years)	75.3 ± 3.6
Sex (male/female)	42 (78)/12 (22)
Neoadjuvant chemotherapy (with/without)	29 (54)/25 (46)
Upper/middle/lower	2 (4)/48 (89)/4 (7)
Squamous cell carcinoma/adenocarcinoma	2 (4)/52 (96)
Preoperative CRP (<0.5 mg/dL vs. ≥0.5 mg/dL)	45 (83)/9 (17)
Preoperative NLR (<3.5/≥3.5)	43 (80)/11 (20)
Pathological stage (I–II/III)	40 (74)/14 (26)
Pathological T (1–2/3–4)	33 (61)/21 (39)
Pathological N (0/1–3)	32 (59)/22 (41)
Pathological M (0/1)	54 (100)/0 (0)
Complications (Clavien-Dindo classification ≥Grade I)	
Pneumonia	9 (17)
Anastomotic leak	9 (17)
Length of hospital stay (<18.5 days vs. ≥18.5 days)	27 (50)/27 (50)
Preoperative physical function and nutrition	
Quadriceps muscle strength (N)	399 ± 124
Usual gait speed (m/sec)	1.17 ± 0.21
PNI (score)	47.9 ± 4.1
BMI (kg/m^2)	21.1 ± 3.0
Change in physical function and nutrition in the first month after surgery	
Quadriceps muscle strength (%)	−10.8 ± 15.7
Usual gait speed (%)	−4.0 ± 16.2
PNI (%)	−6.9 ± 10.3
BMI (%)	−8.0 ± 3.7
SMI	
Preoperative SMI (cm^2/m^2)	40.3 ± 7.7
Change in ratio of SMI after surgery (%)	−7.1 ± 9.4

Descriptive statistics are presented as number of people (%) and mean ± standard deviation. CRP: C-reactive protein; NLR: neutrophil–lymphocyte ratio; pathological TNM stage (UICC 7th edition); PNI: Onodera's prognostic nutritional index; BMI: body mass index; SMI: skeletal muscle mass index

Table 2 Univariate and multivariate analysis for the ratio change in SMI after surgery

Variables	Univariate analysis		Multivariate analysis		
	B (95% CI)	p	B (95% CI)	β	p
Preoperative physical function and nutrition					
Quadriceps muscle strength (N), per 1N	−0.020 (−0.040 to 0.000)	0.054			
Usual gait speed (m/sec), per 0.1 m/sec	2.496 (−9.772 to 14.765)	0.685			
PNI (score), per 1 score	−0.021 (−0.666 to 0.624)	0.948			
BMI (kg/m^2), per 1 kg/m^2	−0.107 (−0.968 to 0.754)	0.804			
Postoperative change ratio in physical function and nutrition (first month after surgery)					
Quadriceps muscle strength (%), per 1%	0.167 (0.007 to 0.327)	**0.041***	0.169 (0.010 to 0.318)	0.274	**0.038***
Usual gait speed (%), per 1%	−0.079 (−0.239 to 0.081)	0.325			
PNI (%), per 1%	0.131 (−0.119 to 0.382)	0.298			
BMI (%), per 1%	0.514 (−0.170 to 1.198)	0.138			
Patient characteristics					
Neoadjuvant chemotherapy (vs. without)	7.352 (2.580 to 12.125)	**0.003***	7.222 (2.013 to 12.430)	0.387	**0.008***
Age (years), per 1 year	−0.126 (−0.851 to 0.599)	0.729	0.263 (−0.426 to 0.953)	0.101	0.446
Male (vs. female)	−4.536 (−10.634 to 1.562)	0.142	−4.647 (−11.473 to 2.179)	−0.208	0.177
Preoperative SMI (cm^2/m^2), per 1 cm^2/m^2	−0.200 (−0.535 to 0.135)	0.237	0.076 (−0.312 to 0.465)	0.099	0.694
pStage III (vs. I–II)	−1.071 (−6.671 to 4.830)	0.717	−0.969 (−6.391 to 4.453)	−0.046	0.721
pT stage 3–4 (vs. 0–2)	2.401 (−2.868	0.365			

	to 7.669)	
pN stage 1–3 (vs. 0)	−1.642 (−6.891 to 3.607)	0.533
Preoperative CRP ≥0.5 mg/dL (vs. <0.5 mg/dL)	6.126 (−0.608 to 12.861)	0.074
Preoperative NLR ≥3.5 (vs. <3.5)	4.592 (−1.708 to 10.892)	0.150
Pneumonia grade ≥1 (vs. 0)	2.263 (−4.655 to 9.181)	0.514
Anastomotic leak grade ≥1 (vs. 0)	−3.142 (−10.033 to 3.750)	0.365
Hospital stay ≥18.5 days (vs. <18.5 days)	−0.669 (−5.845 to 4.506)	0.796

Multiple regression was used for the multivariate analysis of ratio change in SMI in 54 patients who underwent esophagectomy. Multiple regression was performed with potential predictors detected by a univariate analysis and confounding factors. The above categorical variables were analyzed as dummy variables (1 vs. 0). The multiple regression model was adjusted for age, sex, preoperative SMI, and pStage. B: partial regression coefficient; CI: confidence interval; β: standardized partial regression coefficient; p: p value; PNI: Onodera's prognostic nutritional index; BMI: body mass index; SMI: skeletal muscle mass index; pStage: pathological stage (UICC 7th edition); pT and pN: pathological TNM stage (UICC 7th edition); CRP: C-reactive protein; NLR: neutrophil–lymphocyte ratio; grade: JCOG postoperative complication criteria according to the Clavien-Dindo classification; *: $p < 0.05$

Table 3 Logistic regression analysis of predictors

Variables	Massive decline in QS in the first month after surgery (−9.9% and lower)		Treatment with NAC	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Preoperative physical function and nutrition				
Quadriceps muscle strength (N), per 1N	1.001 (0.997 to 1.006)	0.608	0.998 (0.994 to 1.003)	0.400
Usual gait speed (m/sec), per 0.1 m/sec	1.988 (0.156 to 2.386)	0.597	3.882 (0.289 to 52.063)	0.306
PNI (score), per 1 score	1.071 (0.934 to 1.228)	0.327	0.980 (0.858 to 1.121)	0.772
BMI (kg/m^2), per 1 kg/m^2	0.997 (0.835 to 1.191)	0.975	0.818 (0.671 to 0.998)	**0.047***
Postoperative change in physical function and nutrition (the first month after surgery)				
Quadriceps muscle strength (%), per 1%	-	**-**	1.012 (0.977 to 1.049)	0.492
Usual gait speed (%), per 1%	0.955 (0.916 to 0.996)	**0.032***	0.982 (0.949 to 1.017)	0.316
PNI (%), per 1%	0.963 (0.911 to 1.017)	0.178	1.005 (0.954 to 1.059)	0.854
BMI (%), per 1%	0.891 (0.766 to 10.037)	0.135	1.032 (0.893 to 1.192)	0.674
Patient characteristics				
Neoadjuvant chemotherapy (vs. without)	0.638 (0.218 to 1.874)	0.414	-	-
Age (years), per 1 year	1.031 (0.887 to 1.197)	0.695	0.867 (0.737 to 1.019)	0.084
Male (vs. female)	1.000 (0.277 to 3.608)	1.000	0.500 (0.130 to 1.917)	0.312
Preoperative SMI (cm^2/m^2), per 1 cm^2/m^2	0.985 (0.918 to 1.056)	0.668	0.907 (0.837 to 0.983)	**0.017***
pStage III (vs. I–II)	0.455 (0.129 to 1.600)	0.219	1.206 (0.354 to 4.115)	0.764
pT stage 3–4 (vs. 0–2)	0.856 (0.286 to 2.558)	0.780	3.393 (1.051 to 10.951)	0.041

pN stage 1–3 (vs. 0)	0.538 (0.179 to 1.618)	0.270	1.444 (0.482 to 4.325)	0.511
Preoperative CRP ≥0.5 mg/dL (vs. <0.5 mg/dL)	1.307 (0.310 to 5.509)	0.715	3.659 (0.684 to 19.567)	0.129
Preoperative NLR ≥3.5 (vs. <3.5)	1.257 (0.333 to 4.748)	0.736	0.660 (0.174 to 2.496)	0.540
Pneumonia grade ≥1 (vs. 0)	2.286 (0.508 to 10.291)	0.282	1.094 (0.259 to 4.613)	0.903
Anastomotic leak grade ≥1 (vs. 0)	4.375 (0.817 to 23.424)	0.085	1.094 (0.259 to 4.613)	0.903
Hospital stay ≥18.5 days (vs. <18.5 days)	4.000 (1.290 to 12.402)	**0.016***	2.125 (0.715 to 6.135)	0.175

Logistic regression models were used for univariate analysis of predictors. A decline in QS in the first month after surgery (−9.9% or more) and treatment with neoadjuvant chemotherapy (NAC). The above categorical variables were analyzed as dummy variables (1 vs. 0). CI: confidence interval; β: standardized partial regression coefficient; p: p value; PNI: Onodera's prognostic nutritional index; BMI: body mass index; SMI: skeletal muscle mass index; pStage: pathological stage (UICC 7th edition); pT and pN: pathological TNM stage (UICC 7th edition); CRP: C-reactive protein; NLR: neutrophil–lymphocyte ratio; grade: JCOG postoperative complication criteria according to the Clavien-Dindo classification; *: p value < 0.05

Figures

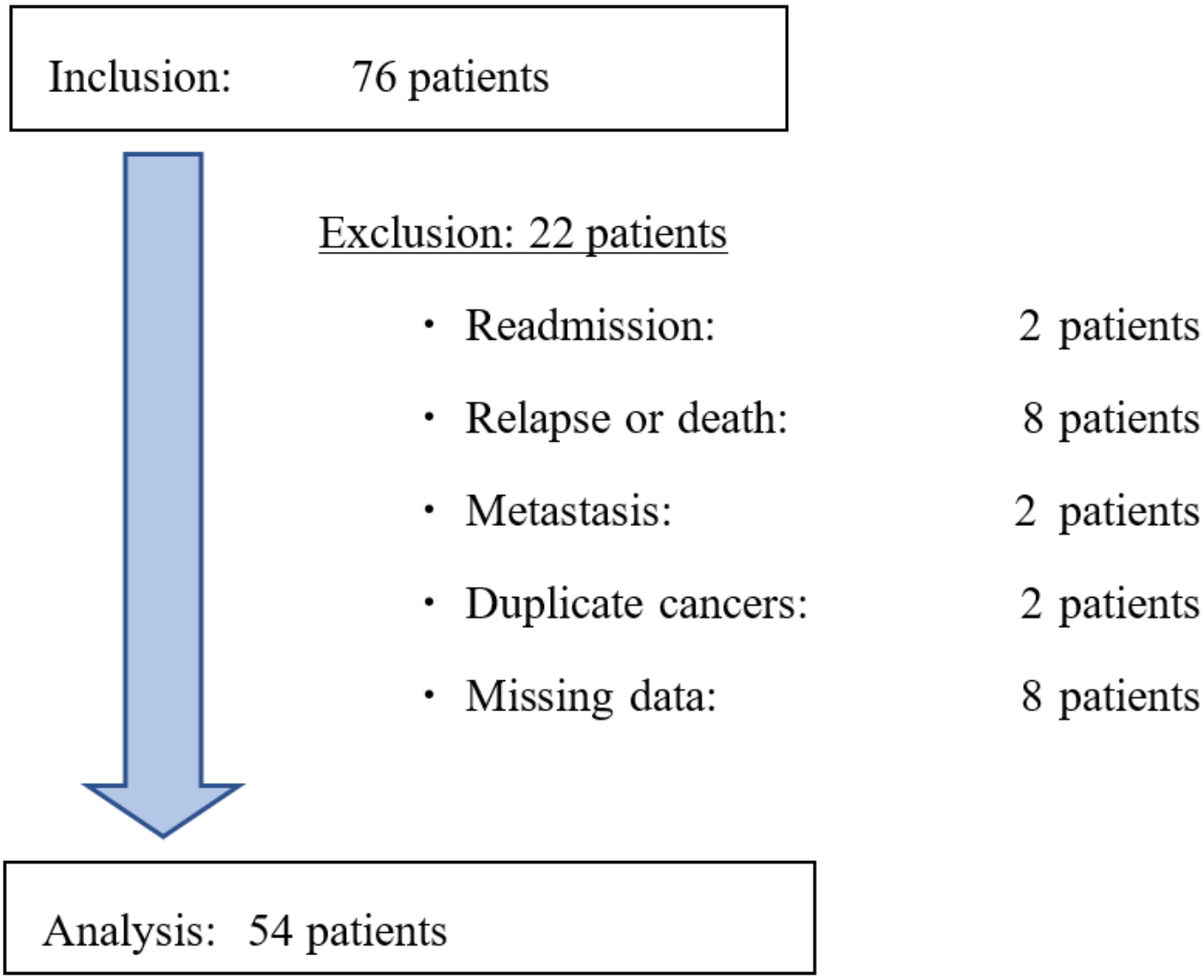

Figure 1

Recruitment flow diagram

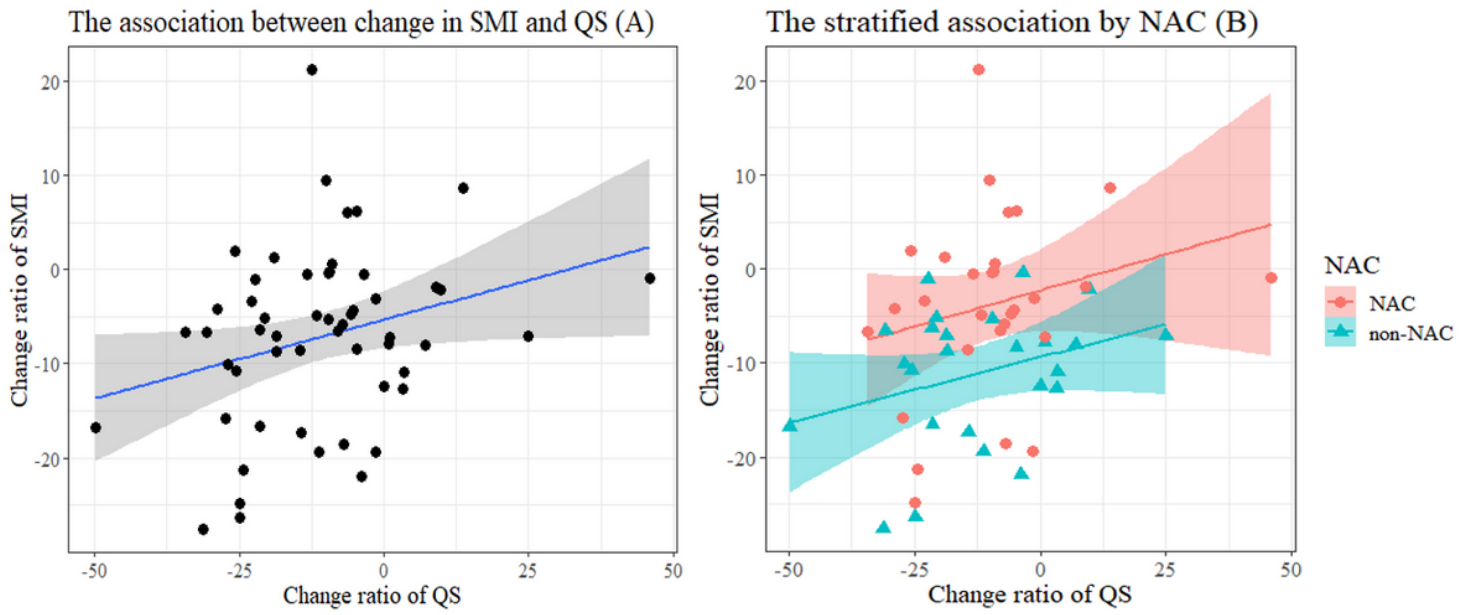

Figure 2

Association between the change in SMI 4 months after esophagectomy and quadriceps muscle strength in the first month after esophagectomy (left: A). Stratified association by NAC (right: B). The lines and area indicate linear regression and 95% confidence intervals, respectively. QS: quadriceps muscle strength; NAC: neoadjuvant chemotherapy; SMI: skeletal muscle mass index

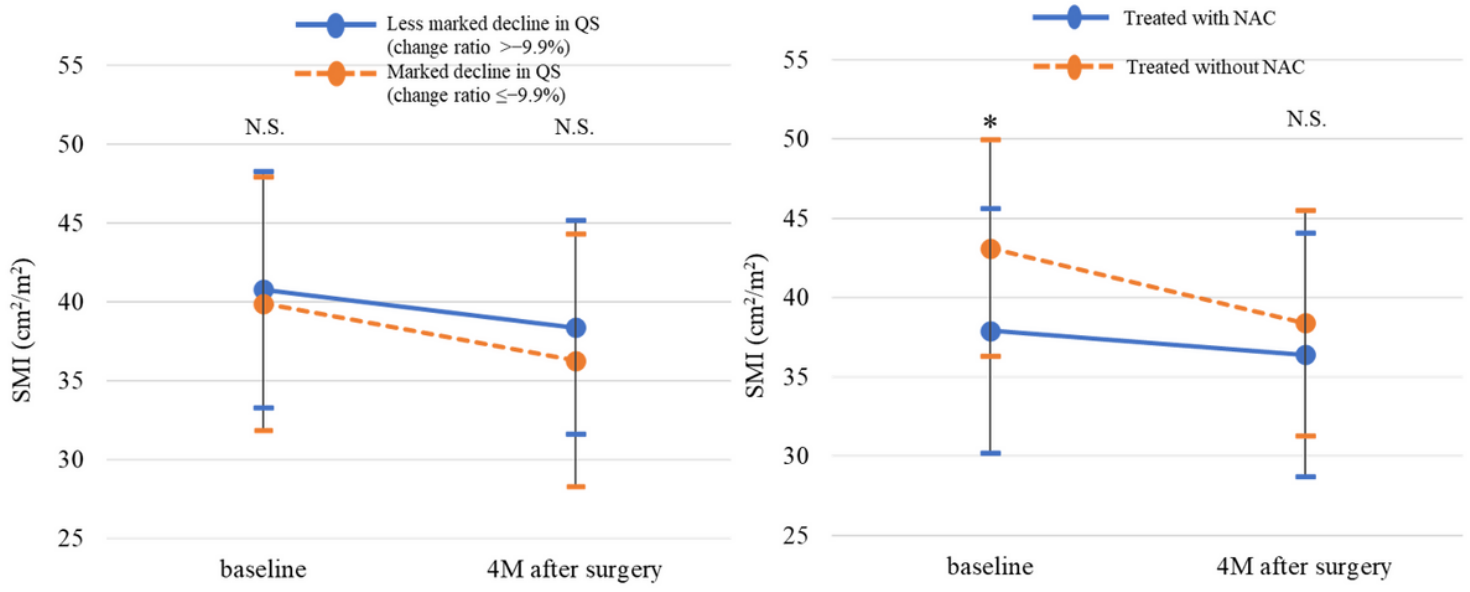

Figure 3

SMI (mean ± standard deviation) at baseline and 4 months after surgery in two stratified groups: marked decline and minimal decline in quadriceps muscle strength (left). Treated with and without NAC (right). *: $p < 0.05$; N.S.: non-significant (analysis of variance adjusted with the Bonferroni method); QS: quadriceps muscle strength; NAC: neoadjuvant chemotherapy; SMI: skeletal muscle mass index