

Impact of reduced skeletal muscle volume on clinical outcome after esophagectomy for esophageal cancer

A retrospective study

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Abstract

The aim of the study was to clarify the impact of reduced skeletal muscle volume on the morbidity of patients who underwent esophagectomy for esophageal cancer.

Malnutrition and reduced skeletal muscle volume, that is, presarcopenia, are reportedly associated with a high frequency of postoperative complications after esophagectomy. However, it remains unclear whether the reduction of skeletal muscle volume following esophagectomy may affect clinical outcomes including pneumonia occurred beyond the preoperative period.

From February 2009 to June 2015, in 123 patients, we retrospectively evaluated the postoperative changes of the psoas muscle index (PI) on computed tomography and assessed their impact on the incidence of pneumonia after esophagectomy.

There was a significant reduction in the PI 6 months after surgery compared to the preoperative value. The incidence of pneumonia as of 6 months after surgery was 23.6%, which was higher in patients of advanced age ($P = .02$), those with a lower body mass index ($P = .02$), and those with a greater reduction of PI during 6 months after surgery ($P = .03$). It was not associated with preoperative nutritional data, pulmonary function, operative procedure, and preoperative PI. Multivariate analysis demonstrated that age and postoperative PI reduction were independently associated with the incidence of pneumonia 6 months after surgery (hazard ratio [HR] = 2.92, 95% confidence interval [CI] 1.16–7.32, $P = .02$; HR = 3.25, 95% CI 1.15–9.15, $P = .03$, respectively). Patients with pneumonia 6 months after surgery had significantly poorer overall survival than those without pneumonia at that time.

Postoperative reduction of skeletal muscle volume was independently associated with the occurrence of pneumonia beyond the preoperative period, which might indicate the importance of a postoperative nutritional support after perioperative period in esophageal cancer patients.

Abbreviations: BMI = body mass index, CT = computed tomography, OS = overall survival, PI = psoas muscle index, RFS = relapse-free survival.

Keywords: enteral nutrition, esophageal cancer, long-term morbidity from pneumonia, presarcopenia

1. Introduction

Esophagectomy for esophageal cancer is associated with high morbidity and mortality. Although there have been advances in perioperative management including surgical techniques, postoperative care, and treatment strategies, postoperative pulmonary

complications occur in 20% to 40% of all cases.^[1,2] Pneumonia is one of the most serious complications after esophagectomy and is reported to be associated with poor surgical outcomes.^[3–5] The causes of postoperative pneumonia are multifactorial and the prediction of pneumonia remains to be elucidated.^[1,2,6]

Recent advances in adequate multimodal therapies have increased the number of patients cured of esophageal cancer after esophagectomy.^[7] Ghaly et al reported that the most frequent causes of death in patients who were disease free after 5 years were pulmonary diseases such as pneumonia (about 30% of patients),^[8] which were more frequent than the recurrence of esophageal cancer. Thus, long-term morbidity from pneumonia and in-hospital pneumonia after esophagectomy are essential factors of non-cancer-related mortality.

Preoperative dysphagia, due to obstruction by tumor, and esophagectomy could cause malnutrition and weight loss in esophageal cancer patients.^[9,10] Preoperative malnutrition and reduced skeletal muscle volume, that is, presarcopenia, are reportedly associated with a higher frequency of postoperative complications and worse short-term outcomes.^[9] However, it remains unclear whether nutritional alterations following esophagectomy affect long-term pneumonia-related morbidity and long-term outcomes.

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The present study aimed to evaluate the impact of pre- and postoperative reduced skeletal muscle volume on long-term pneumonia-related morbidity in patients who underwent esophagectomy for esophageal cancer.

2. Methods

2.1. Patients

This retrospective study was performed using the database of 123 patients who underwent esophagectomy for esophageal cancer at the National Defense Medical College Hospital from February 2009 to June 2015. The study included patients who underwent radical esophagectomy and received chest and abdominal computed tomography (CT) image preoperatively and 6 months after surgery. For patients who underwent neoadjuvant chemotherapy, we evaluated the data only after neoadjuvant chemotherapy.

Postoperative care, including respiratory and nutritional care, was uniform during this period. Thoracic epidural analgesia was administered to all patients. Intrathoracic or cervical esophagogastric anastomoses using staplers were individually chosen depending on the tumor location. A chest drainage tube was inserted in the upper mediastinum in all patients. At the time of surgery, a Witzel tube jejunostomy was performed at the proximal jejunum and enteral feeding was started on postoperative day 1 in all patients. This was a non-randomized study. All patients provided their written informed consent prior to study initiation. This study protocols were reviewed and approved by the Institutional Review Board at the National Defense Medical College.

2.2. Follow-up

All the patients were observed at our hospital or the outpatient clinic at 3- to 4-month intervals during the first 2 years of the study and every 6 or 12 months thereafter for 3 years. After 5 years, annual follow-up was conducted through telephone conversations with the patient, patient's family, or their practitioner.

2.3. Assessment of skeletal muscle mass and postoperative pneumonia

A cross-sectional CT image of the third lumbar vertebra (L3) in the inferior direction was selected for estimating muscle mass as described previously.^[11] The psoas muscle index (PI) (cm^2/m^2) indicated L3 muscle cross-sectional areas computed from each image normalized for height. Presarcopenia was defined as less than sex-specific cut-off values (4.24 and $2.50 \text{ cm}^2/\text{m}^2$ for men and women, respectively), as previously described.

Postoperative pneumonia was the diagnosis when active infiltration was evident from the CT scan unless the patient did not have any clinical symptom. The CT images were independently and retrospectively evaluated by a radiologist who was blinded to complaints, physical examination findings, and laboratory evaluation.

2.4. Data collection

The patients were retrospectively evaluated for preoperative status, surgical procedures, and postoperative events, including age, gender, body mass index (BMI), total protein and albumin levels, total lymphocyte count, prognostic nutritional index, preoperative therapy, area of lymph node dissection, location of anastomosis, operative time, thoracic surgery time, pathologic stage, and postoperative outcomes based on data from the medical and nursing charts.

2.5. Statistical analysis

Normally distributed continuous data are presented as mean and standard error. Categorical variables are presented as numbers and percentages. Clinical variables were compared using Pearson Chi-squared test or Fisher exact test (categorical data) and Mann–Whitney *U* test, as appropriate. Overall survival (OS) and relapse-free survival (RFS) rates were estimated using the Kaplan–Meier method, and the difference between OS and RFS rates between the subgroups was compared with the log-rank test. For the test of potential risk factors associated with outcomes, univariate analyses of clinically relevant parameters were performed. Variables with a *P*-value of $<.10$ were included in the subsequent multivariate (logistic regression or Cox proportional hazards regression) analysis.

All tests were 2-sided and a *P*-value of $<.05$ was considered statistically significant. The statistical analyses were performed using JMP statistics version 11.0 (SAS Institute Japan Ltd., Tokyo, Japan).

3. Results

Postoperative pneumonia was present in 29/123 (23.6%), 29/123 (23.6%), and 30/100 (30.0%) of patients in-hospital, 6 months, and 12 months after esophagectomy, respectively. There was a significant reduction of PI 6 months after surgery compared to the preoperative value (Fig. 1). Presarcopenia was present in 23.6%, 30.9%, and 28.6% of patients preoperatively, and at 6 and 12 months after esophagectomy, respectively. The demographic data of patients with and without preoperative presarcopenia are shown in Table 1. Patients with preoperative presarcopenia were significantly older and had lower BMI and PI compared to those without preoperative presarcopenia. There was no difference in serum total protein, albumin levels, and total lymphocyte counts between the 2 groups. In addition, there were no differences in the operative procedures and tumor stage. Although there was no difference in the recurrence rate of esophageal cancer within 12 months after surgery, the mortality rate within 12 months after surgery in patients with preoperative presarcopenia tended to be higher than in those without preoperative presarcopenia (24.1% vs 11.7%).

Postoperative pneumonia 6 months after esophagectomy was observed in 23.6% (29/123) of patients (Table 2). There were no

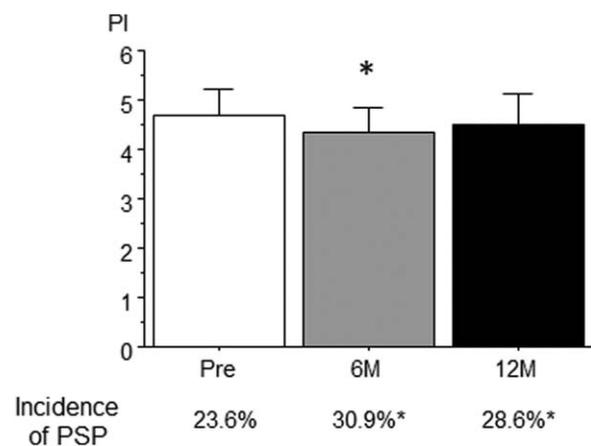


Figure 1. Psoas muscle index and incidence of presarcopenia. Pre: preoperatively; 6M: 6 months after esophagectomy; 12M: 12 months after esophagectomy; PSP: presarcopenia. **P* $<.05$ vs preoperative value.

Table 1**Clinicopathologic data in patients with and without preoperative presarcopenia.**

Number	With PSP 29	Without PSP 94	P
Age, y	72.7 ± 1.5	69.2 ± 0.8	.04
Sex, male/female	29/0	75/19	.01
Preoperative variables			
Body mass index	18.8 ± 0.6	21.8 ± 0.3	<.01
Psoas muscle index, cm ² /m ²	3.7 ± 0.2	5.2 ± 0.1	<.01
Total protein, g/dL	6.6 ± 0.1	6.5 ± 0.1	.77
Albumin, g/dL	3.8 ± 0.1	3.9 ± 0.1	.13
Total lymphocyte count, /μL	1676 ± 110	1575 ± 61	.86
Prognostic nutritional index	46.1 ± 1.0	46.8 ± 0.6	.34
Preoperative respiratory function			
Predicted VC, %	103 ± 4	108 ± 2	.52
FEV1.0%	74 ± 2	76 ± 1	.37
Preoperative therapy, no/yes	17/12	43/51	.23
Thoracic surgery, VATS/open	22/7	61/33	.27
Lymph node dissection, 2 FL/3 FL	19/10	61/33	.95
Anastomosis, cervical/intrathoracic	19/10	62/32	.97
Operation time, min	467 ± 18	453 ± 10	.66
Thoracic surgery time, min	142 ± 11	141 ± 6	.51
pStage, 0–II/III–IV	16/13	59/35	.46
Recurrence within 12 months	27.6%	30.8%	.74
Mortality within 12 months	24.1%	11.7%	.11
Postoperative pneumonia			
In-hospital (n = 123)	17.2%	26.6%	.29
6M after surgery (n = 123)	34.5%	20.2%	.11
12M after surgery (n = 98)	28.6%	30.4%	>.99

FEV = forced expiratory volume, FL = field, M = month, PSP = presarcopenia, VATS = video-assisted thoracoscopic surgery, VC = vital capacity.

differences in nutritional parameters such as serum total protein, albumin levels, and total lymphocyte counts between the 2 groups. In addition, no differences in preoperative pulmonary functions and operative procedures were noted between the 2 groups. Patients with postoperative pneumonia 6 months after surgery were significantly older and had lower BMI and significant reduction of PI until 6 months after surgery, compared to those without pneumonia 6 months after surgery.

We examined clinical parameters that could affect the incidence of pneumonia 6 months after esophagectomy using univariate and multivariate analyses. In the univariate analysis, age, preoperative BMI, and PI reduction until 6 months after surgery were significantly associated with the incidence of pneumonia 6 months after surgery. Multivariate analysis demonstrated that age and PI reduction until 6 months after surgery were independently associated with the incidence of pneumonia 6 months after surgery (Table 3).

To investigate the clinical impact of postoperative PI reduction and long-term morbidity from pneumonia on long-term mortality, we compared RFS and OS rates between patients with and without significant reduction of PI until 6 months after surgery and patients with and without pneumonia at 6 months after surgery (Table 4). Patients with reduction of PI until 6 months after surgery tended to have poorer OS than those without such reduction, albeit which did not reach statistical significance (Fig. 2). Patients with pneumonia at 6 months after surgery had significantly poorer OS than those without pneumonia at this time; however, there was no difference in RFS (Fig. 3). There were no differences in both RFS and OS between patients with and without pneumonia 12 months after esophagectomy (data not shown).

Table 2**Clinicopathologic data in patients with and without pneumonia 6 months after esophagectomy.**

Number	With pneumonia 29	Without pneumonia 94	P
Age, y	73.7 ± 6.9	68.9 ± 8.3	.01
Sex, male/female	27/2	77/17	.15
Body mass index	19.8 ± 2.5	21.5 ± 3.5	.04
Total protein, g/dL	6.7 ± 0.1	6.5 ± 0.1	.22
Albumin, g/dL	3.8 ± 0.4	3.9 ± 0.5	.51
Total lymphocyte count, /μL	1561 ± 552	1611 ± 609	.79
Prognostic nutritional index	46.1 ± 6.0	46.8 ± 5.4	.40
Preoperative respiratory function			
Predicted VC (%)	104 ± 19	108 ± 19	.50
FEV1.0%	75 ± 13	76 ± 12	.87
Preoperative therapy, no/yes	14/15	46/48	.95
Thoracic surgery, VATS/open	21/8	62/32	.52
Lymph node dissection, 2FL/3FL	19/10	61/33	.95
Anastomosis, cervical/intrathoracic	20/9	61/33	.69
Operation time, min, mean ± SD	442 ± 78	461 ± 104	.48
Thoracic surgery time, min, mean ± SD	142 ± 49	141 ± 53	.71
Preoperative PSP, yes/no	10/19	19/75	.11
Change of PI between preoperative and 6M after surgery	89.7 ± 12.9%	97.4 ± 15.4%	.02

FEV = forced expiratory volume, FL = field, PI = psoas muscle volume index, PSP = presarcopenia, SD = standard deviation, VATS = video-assisted thoracoscopic surgery, VC = vital capacity.

4. Discussion

Invasiveness associated with esophagectomy for esophageal cancer is substantial and frequently involves the abdomen, chest, and neck.^[12] Esophagectomy may be associated with higher morbidity and mortality compared to the other gastrointestinal surgeries.^[13] In addition, pulmonary diseases such as pneumonia are the predominant cause of non-cancer-related death in patients who underwent esophagectomy for esophageal cancer.^[8] Patients who survive the perioperative period may be at risk of not only cancer recurrence but also various diseases associated with malnutrition and pneumonia after esophagectomy. Thus, the prevention of short- and long-term morbidity from pneumonia is essential to improve mortality due to esophageal cancer.

In this study, we demonstrated that a relatively higher rate of patients had asymptomatic pneumonia at 6 (23.6%) and 12 (30.0%) months after esophagectomy than expected. The causes of pneumonia after esophagectomy appeared multifactorial because esophageal cancer patients were relatively older and subclinical aspiration frequently occurred due to dysphagia and dystussia caused by the esophagectomy which was enhanced by the frailty associated with malnutrition and reduced skeletal muscle.^[14,15] The loss of skeletal muscle mass and strength is recognized as a major complication of several diseases, such as cancer, liver failure, chronic heart and renal failures, and aging.^[16] There is increasing evidence that preoperative presarcopenia may be related to in-hospital infectious complications such as pneumonia after esophagectomy.^[9] A reduction of skeletal muscle mass is common in the swallowing muscles. Molfter et al demonstrated that the decreased pharyngeal muscle mass assessed with magnetic resonance image (MRI) consequently results in an increased pharyngeal lumen size, which makes the swallowing motion difficult.^[17] Thus, a reduction of skeletal muscle volume, which was monitored

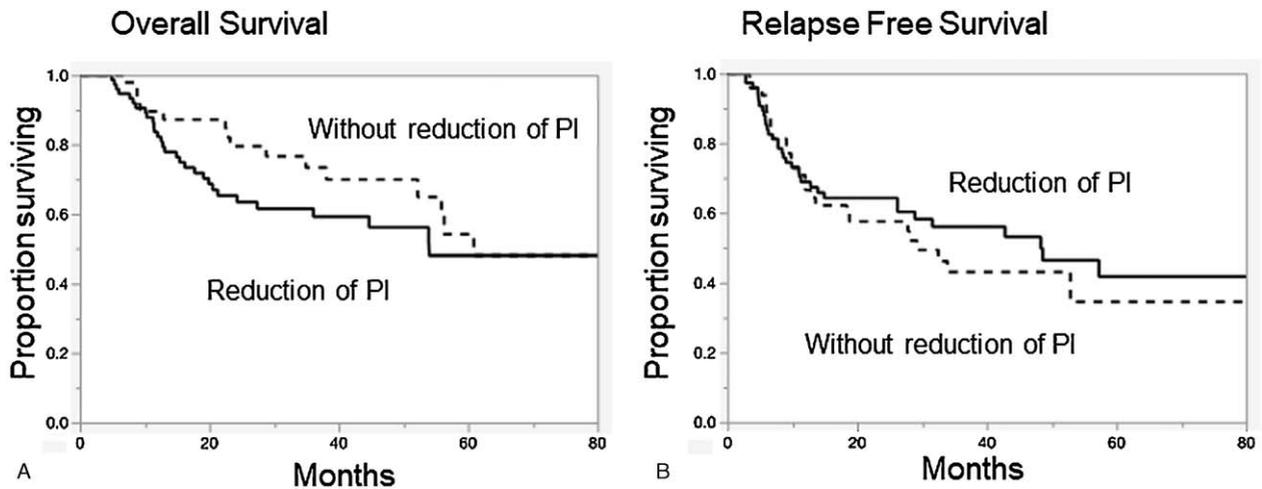


Figure 2. Overall survival and relapse-free survival in patients with and without reduction of psoas muscle index (PI) until 6 months after esophagectomy. (A) Overall survival. (B) Relapse-free survival. Bold lines: patients without reduction of PI until 6 months after surgery. Dotted lines: patients with reduction of PI until 6 months after surgery.

psoas mass volume in this study, should be associated with long-term morbidity from pneumonia caused by subclinical aspiration.

In this study, we demonstrated that a reduction of skeletal muscle volume until 6 months after esophagectomy affected the morbidity from pneumonia 6 months after surgery, suggesting that long-term nutritional support may be necessary to prevent postoperative pneumonia. An intervention of long-term nutritional care may represent a potential treatment and prevention strategy for a reduction of skeletal muscle and postoperative pneumonia.

We also found that the lowest PI and the incidence of presarcopenia were highest at 6 months after esophagectomy and that the decrease of PI until 6 months after surgery and older age were significantly associated with the incidence of pneumonia 6 months after esophagectomy. In addition, this study showed that patients with pneumonia 6 months after esophagectomy had poorer OS but not RFS, compared to those without pneumonia. These results suggest that extensive nutritional support until, at least, 6 months after surgery is important and pneumonia

6 months after surgery may be associated with non-cancer-related mortality after esophagectomy for esophageal cancer.

This study has certain limitations. This study was single institutional retrospective design and had relatively small number of patients. The incidence of pneumonia may induce the reduced the skeletal muscle volume, and vice versa. In this study, we did not indicate that the adequate nutritional supports and kinesitherapy may reduce the morbidity from pneumonia after esophagectomy. Thus, it is necessary to conduct a multicenter, prospective, randomized study to verify our hypothesis that intensive and prolonged postoperative nutritional support based on PI may be useful to prevent long-term morbidity from pneumonia after esophagectomy and improve outcomes after resection for esophageal cancer.

In conclusion, skeletal muscle volume reduction until 6 months after esophagectomy was independently associated with the incidence of pneumonia 6 months after resection for esophageal cancer, suggesting prolonged postoperative nutritional support may prevent long-term morbidity from pneumonia after esophagectomy and improve outcomes after resection for esophageal cancer.

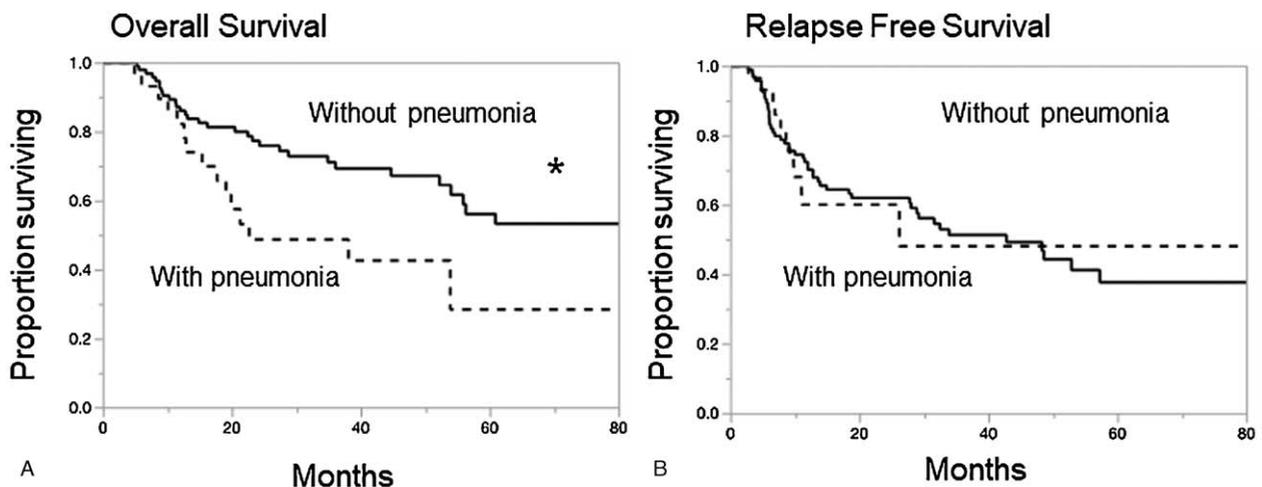


Figure 3. Overall survival and relapse-free survival in patients with and without pneumonia 6 months after esophagectomy. Bold lines: patients without pneumonia. Dotted lines: patients with pneumonia. * $P < .05$ via the log-rank test.

Table 3**Univariate and multivariate analysis of factors affecting the incidence of pneumonia 6 months after esophagectomy.**

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Age, >70 y	2.68	1.12–6.39	.02	2.92	1.16–7.32	.02
Male sex	2.98	0.65–13.9	.15	–	–	–
Body mass index, <22 kg/m ²	3.40	1.19–9.70	.02	4.29	1.43–12.87	.01
Total protein, <6.5 g/dL	0.49	0.20–1.19	.11	–	–	–
Albumin, <3.5 g/dL	1.10	0.36–3.33	.87	–	–	–
Total lymphocyte count, <1500 /mL	1.22	0.53–2.80	.64	–	–	–
Prognostic nutritional index, <47	1.42	0.61–3.29	.42	–	–	–
Preoperative respiratory function	–	–	–	–	–	–
Predicted VC (%), <80%	1.43	0.35–5.94	.62	–	–	–
FEV1.0%, <70%	0.85	0.34–2.15	.74	–	–	–
Preoperative therapy	1.03	0.45–2.36	.95	–	–	–
Thoracic surgery, open	1.35	0.54–3.40	.52	–	–	–
Lymph node dissection, 3FL	0.97	0.41–2.33	.95	–	–	–
Anastomosis, cervical	1.20	0.49–2.93	.69	–	–	–
Operation time, min, >456 min	1.35	0.57–3.17	.49	–	–	–
Thoracic surgery time, min, >142 min	0.65	0.27–1.55	.33	–	–	–
Preoperative PSP	2.08	0.83–5.19	.11	–	–	–
Change of PI between preoperative and 6M after surgery	2.84	1.06–7.62	.03	3.25	1.15–9.15	.03

CI=confidence interval, FEV=forced expiratory volume, FL=field, M=month, PI=psaos muscle volume index, PSP=presarcopenia, VC=vital capacity.

Table 4**Survival rates of patients with and without reduction of PI.**

Survival rates	1 y	2 y	3 y	4 y	5 y
Without reduction of PI	88%	77%	67%	58%	39%
With reduction of PI	82%	57%	48%	37%	28%
P	.402	.047	.100	.089	.354

PI = psaos muscle volume index, y=year.

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