Decreased Skeletal Muscle Mass After Neoadjuvant Therapy Correlates with Poor Prognosis in Patients with Esophageal Cancer

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Abstract. *Background: Loss of skeletal muscle is predictive of a poor prognosis in patients with various malignant lesions. Our aim was to determine whether changes in skeletal muscle after neo-adjuvant therapy (NAT) predict prognosis in patients with esophageal squamous cell carcinoma (ESCC) undergoing esophagectomy. Patients and Methods: The cross-sectional areas of the psoas muscles were measured on computed tomographic images collected at the initial visit, preoperatively and postoperatively in 84 patients. The psoas muscle index (PMI) was calculated by normalizing the cross-sectional areas to the patients' heights. Results: Low PMI at the initial visit was not associated with a poor prognosis. The majority of patients showed decreased PMI after NAT and surgery. The group in which the post-NAT PMI decreased had poorer overall survival than group without PMI decrease (p=0.025). Conclusion: Decreased PMI correlates well with a poor prognosis in patients with ESCC. Changes in PMI over a period of time may have greater sensitivity when evaluating prognosis than the PMI at any single time point.*

Esophageal squamous cell carcinoma (ESCC) is a highly aggressive malignant tumor with a poor prognosis (1). The operation for ESCC is one of the most challenging of digestive surgeries; it is highly invasive and requires a high degree of technical expertise. In addition, the operative and recovery times are both long, and the surgery is accompanied by frequent postoperative complications (2, 3). Although introduction of minimally-invasive esophagectomy has reduced surgical stress somewhat, preoperative chemotherapy or chemoradiotherapy is now standard treatment, which introduces a different kind of surgical stress into today's therapy for esophageal cancer. However, there have been few studies on the impact of preoperative conditions on the outcomes of patients with ESCC (4).

Sarcopenia is characterized by degenerative loss of skeletal muscle mass and strength. Loss of skeletal muscle has been identified as predictive of a poor prognosis in patients with many benign and malignant lesions, including liver cirrhosis (5), chronic obstructive pulmonary disease (6), lung cancer (7), cholangiocarcinoma (8), hepatocellular carcinoma (9), metastatic renal cell carcinoma (10), pancreatic cancer (11), colorectal cancer (12), melanoma (13), breast cancer (14), and diffuse large B-cell lymphoma (15), among others. In patients with ESCC without lymph-node involvement, skeletal muscle loss is associated with reduced overall survival (16), as well as postoperative respiratory complications, anastomotic insufficiency and toxicity during neoadjuvant chemotherapy (NAC) (16-18).

However, nearly all studies on sarcopenia to date have focused on the absolute amount of skeletal muscle mass at only a single time point (initial visit or preoperative condition), not the change of skeletal muscle mass over time. In this retrospective study, we examined the change in the psoas muscle index (PMI) during the period extending from the initial visit until after preoperative neoadjuvant therapy and then after surgery, and clarified the relationship between changes in PMI and clinical outcomes in patients with ESCC undergoing esophagectomy.

Patients and Methods

Patients. This study was approved by the Ethics Committee of Akita University (Approval number: 547) and was conducted in accordance with the Declaration of Helsinki of 1996. There were 84

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adult patients with cStage IB, II or III ESCC who underwent NAT [19 NAC and 65 NAC with radiotherapy (NACRT)] following esophagectomy at Akita University Hospital from Sep. 2008 to Jan. 2015. The 72 males and 12 females had a median age of 63 years (range=40-74 years). For all patients, tumor staging was based on the International Union against Cancer tumor-node-metastasis (TNM) Classification of Malignant Tumors (seventh edition) (19). Pretreatment diagnostic evaluation included esophagography, endoscopy, computed tomography (CT), and ^{18}F-fluorodeoxy-glucose positron-emission tomography CT.

PMI measurement. The cross-sectional areas of the right and left psoas muscles were measured by manually tracing them on CT images at the level of the middle of third lumbar vertebra (L3). Measurements were made using images taken on the initial visit, post-NAT and 3 months postoperatively. PMI was calculated by normalizing the cross-sectional areas to the patients' heights (cm^2/m^2) (20) (Figure 1A).

Treatment strategy. For all patients, treatment strategies were defined at a conference attended by radiologists, physicians, and surgeons. In general, patients with locally advanced tumors or node-positive tumors underwent NACRT. Briefly, the radiotherapy consisted of 40 Gy in 20 fractions. The chemotherapy consisted of protracted infusion of 5-fluorouracil (800 mg/m^2/day) on days 1-5, combined with cisplatin or nedaplatin (80 mg/m^2/day) on day 1. This chemotherapy protocol was repeated twice with 3-4 week intervals in between. Our standard operative procedure was transthoracic or thoracoscopic esophagectomy with three-field lymphadenectomy of the mediastinal (involving the periesophageal region and areas around the trachea and bilateral main bronchus), abdominal (involving the perigastric region and areas around the celiac axis) and cervical (involving the bilateral periesophageal region and supraclavicular region) lymph nodes (21). Reconstruction commonly involved inserting a gastric tube or pedicled colon (22). A jejunostomy feeding tube was used for patients who needed reconstruction with a pedicled colon graft, or were in poor general condition.

Statistical analysis. Continuous variables are presented as medians (minimum-maximum) and differences between two groups were analyzed using the Mann–Whitney *U*-test. Categorized data were analyzed using the Pearson chi square test or Fisher exact probability test. The survival time distribution was determined using the Kaplan–Meier method with the log-rank test. The hazard ratios of PMI change for mortality were assessed using Cox's proportional hazards regression models. All statistical analyses were performed using the JMP10.0 (SAS Institute, Cary, NC, USA) and yielded two-sided *p*-values. Values of $p<0.05$ were considered statistically significant.

Results

PMI in patients with ESCC. Each patient's percentage PMI at the three time points (initial visit, post-NAT, and post-operation) is shown in Figure 1B. The median PMIs at the initial visit, post-NAT and post-operation were 4.63 (range=1.77-6.89), 4.54 (ange=1.59-6.89) and 3.99 (ange=1.53-7.17), respectively. Compared to PMI at the
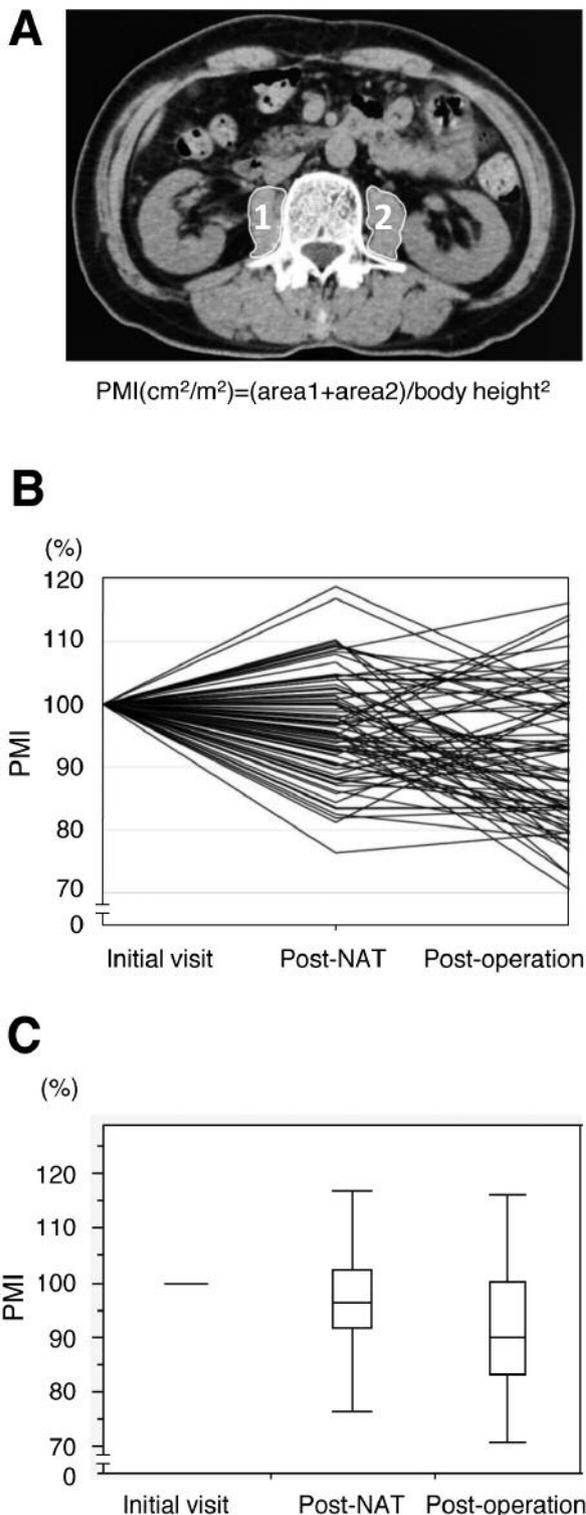
$$PMI(cm^2/m^2)=(area1+area2)/body\ height^2$$

Figure 1. *A: Manual tracing of the areas of the bilateral psoas muscle. B: Psoas muscle index (PMI) in 84 patients at different time points. C: Box and whisker plot of PMI at different time points. The post-neo-adjuvant therapy (NAT) PMI significantly decreased (p=0.0213) compared to that at the initial visit and the postoperative PMI decreased even further (p=0.0001).*

Table I. *Psoas muscle index (PMI) in patients with esophageal squamous cell carcinoma.*

Clinical feature	No.	Initial visit PMI (cm^2/m^2)	*p*-Value	Post-NAT PMI (cm^2/m^2)	*p*-Value	Postoperative PMI (cm^2/m^2)	*p*-Value
ALL cases	84	4.63 (1.77-6.89)		4.54 (1.59-6.89)		3.99 (1.53-7.17)	
Age (years)			0.247		0.137		0.602
<65	51	4.70 (1.77-6.89)		4.62 (1.59-6.71)		4.17 (1.65-7.17)	
≥65	33	4.53 (2.06-6.40)		4.21 (1.95-5.96)		3.95 (1.71-6.60)	
Gender			<0.0001*		0.0001*		0.0016*
Male	72	4.77 (2.20-6.89)		4.63 (1.95-6.71)		4.19 (1.38-7.17)	
Female	12	3.55 (1.77-4.65)		3.23 (1.59-4.44)		3.34 (1.65-3.99)	
Clinical tumor depth			0.407		0.435		0.579
cT1-2	15	4.36 (2.69-6.18)		4.38 (2.80-6.71)		3.87 (2.39-7.17)	
cT3-4a	69	4.70 (1.77-6.89)		4.61 (1.59-6.58)		4.04 (1.65-6.60)	
Clinical LN involvement			0.706		0.562		0.796
cN0-1	58	4.57 (2.06-6.40)		4.49 (1.95-6.71)		3.99 (1.71-7.17)	
cN2-3	26	4.71 (1.77-6.89)		4.57 (1.59-6.58)		3.85 (1.65-6.57)	
NAT method			0.401		0.368		0.571
NAC	19	4.77 (2.78-6.40)		4.54 (2.65-6.49)		3.99 (2.93-6.60)	
NACRT	65	4.53 (1.77-6.89)		4.49 (1.59-6.71)		3.97 (1.65-7.17)	
Pathological tumor depth			0.491		0.369		0.179
pT0-2	47	4.53 (2.06-6.40)		4.45 (2.19-6.71)		3.82 (1.71-7.17)	
pT3-4a	37	4.83 (1.77-6.89)		4.83 (1.59-6.58)		4.56 (1.65-6.57)	
Pathological LN involvement			0.956		0.612		0.806
pN0-1	67	4.65 (2.06-6.89)		4.53 (1.95-6.71)		3.99 (1.71-7.17)	
pN2-3	17	4.61 (1.77-6.59)		4.49 (1.59-6.49)		4.22 (1.65-6.60)	
Histological response to NAT			0.160		0.180		0.155
Grade 0-1	33	4.77 (2.20-6.89)		4.66 (1.95-6.49)		4.41 (2.20-6.60)	
Grade 2-3	51	4.53 (1.77-6.40)		4.40 (1.59-6.71)		3.80 (1.65-7.17)	

Values are median (minimum-maximum). NAT: Neoadjuvant therapy; NAC: neoadjuvant chemotherapy; NACRT: neoadjuvant chemoradiotherapy; LN: lymph node. *Considered significant.

initial visit, the post-NAT PMI was significantly lower (*p*=0.0213), and the postoperative PMI was lower still (*p*=0.0001) (Figure 1C).

The PMIs at the three time points according to age, gender, clinical tumor depth, clinical LNs involvement, NAT method, pathological tumor depth, pathological lymph node involvement and histological response to NAT are summarized in Table I. The PMI recorded in female patients was significantly lower than in male patients at the initial visit (*p*<0.0001), post-NAT (*p*=0.0003) and post-operation (i=0.0016). Older patients tended to have lower PMIs than younger patients. The percentage PMI at the three time points according to these factors are shown in Figure 2. Patients with male gender, clinical or pathological tumor progression, NACRT, and lower histological response to NAT tended to have a greater post-NAT PMI decrease, although the effect was not significant.

Initial visit PMI and overall survival. Because female patients had obviously lower PMIs at their initial visits than male patients (median: 4.77 *vs*. 3.55, *p*<0.0001), we divided the male and female patients into high- and low-PMI groups using their respective medians as cutoff values. Each group consisted of 42 patients. The two groups had similar overall survival rates (*p*=0.814), and the group with low PMI did not have a significantly poorer prognosis (Figure 3A).

Post-NAT PMI change and overall survival. In 54 patients (64%), the post-NAT PMI was lower than that at the initial visit, whereas PMI was increased or unchanged in the remaining 30 patients (36%). Based on this result, we divided the patients into groups with and without PMI decrease. The backgrounds of the patients in the two groups are summarized in Table II. Age, gender, laboratory data (albumin, hemoglobin and C-reactive protein, tumor features (clinical or pathological tumor depth, lymph node involvement), NAT method and histological response to NAT were comparable between the two groups. However, the group with PMI decrease had a clearly poorer overall survival rate than the group without (*p*=0.025) (Figure 3C), and cancer was the main cause of death in group with PMI decrease (*p*=0.005) (Table II).

To further analyze the correlation between decreased PMI and overall survival, we divided the group with PMI
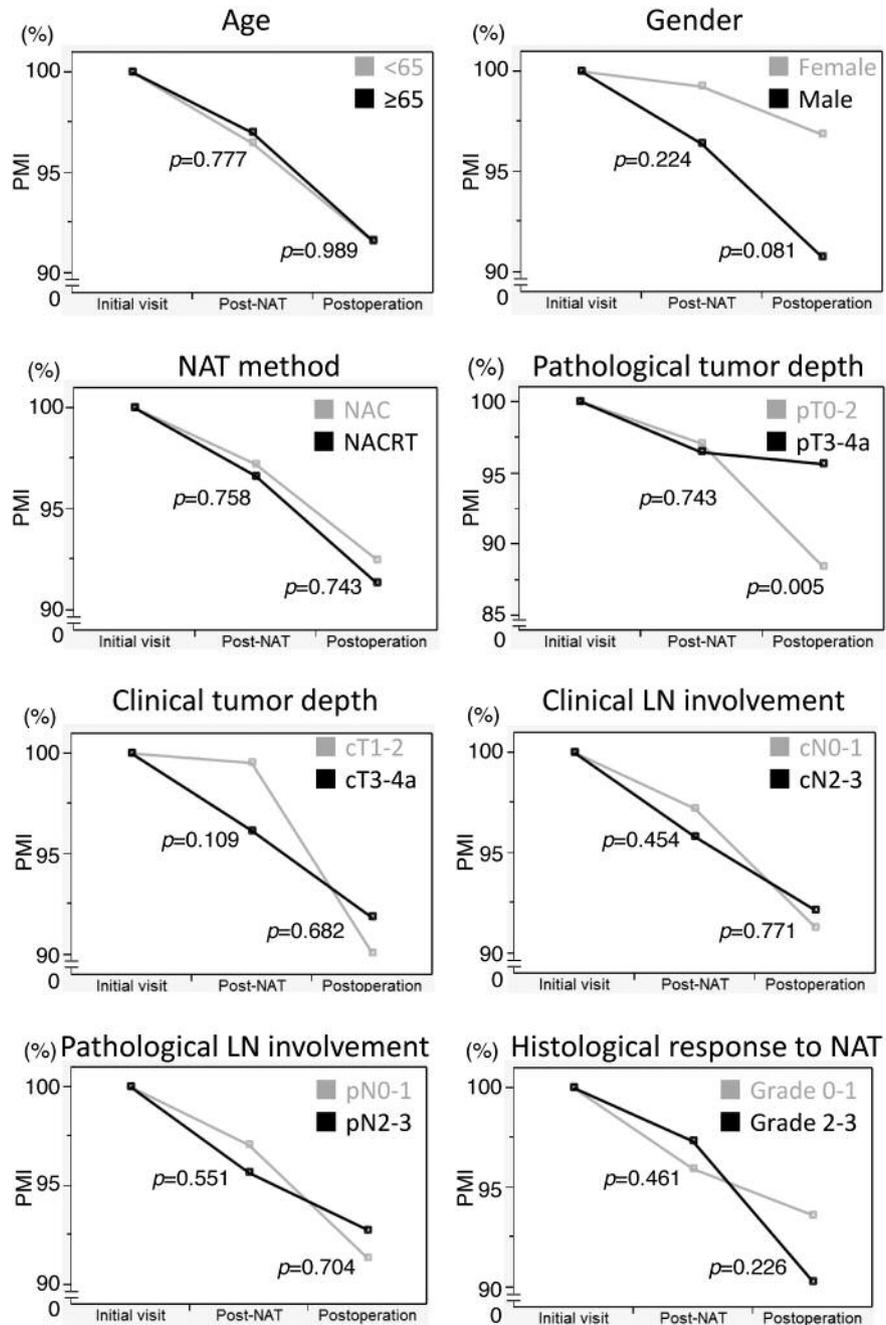
Figure 2. *Psoas muscle index (PMI) at initial visit, post-neo-adjuvant therapy (NAT) and postoperatively according to clinicopathological parameters. PMI is given as a percentage of the initial PMI. LN: Lymph node; NAC: neoadjuvant chemotherapy; NACRT: neoadjuvant chemoradiotherapy.*

decrease into mildly and severely decreased groups using the median decrease in PMI ($\Delta=0.283$) as the cut-off value. Both groups contained 27 patients (50%). Interestingly, the severely-decreased group had significantly poorer overall survival than the mildly-decreased group ($p=0.003$) (Figure 3D).

Post-NAT PMI changes and short-term surgical outcome. As shown in Table III, patients in the groups with and without PMI decrease had similar operative times (553 (383-776) *vs.* 515 (417-804) min; $p=0.365$) and blood loss (635 (143-3217) *vs.* 553 (115-2,099) ml; $p=0.254$). The overall incidence of complications was 41.7%, and there was no
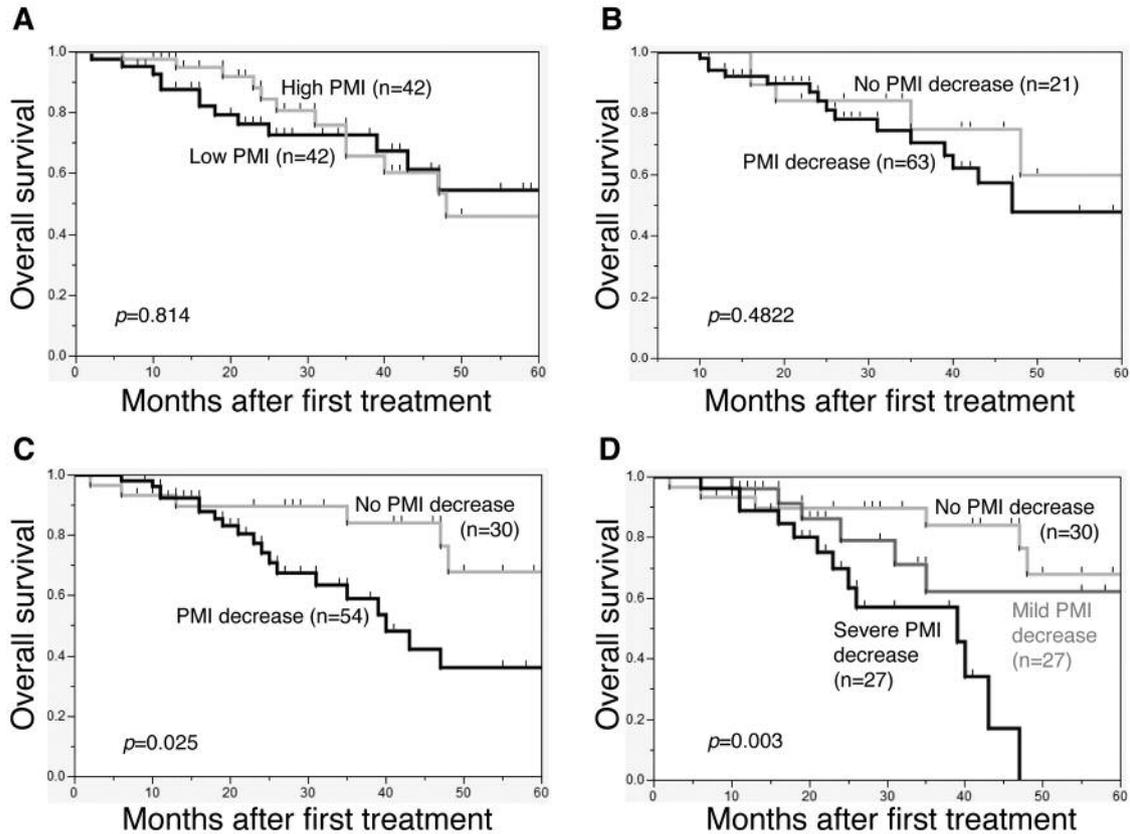
Figure 3. *Overall survival stratified according to psoas muscle index (PMI) at initial visit (A), whether or not PMI decreased between the initial visit and postoperatively (B), whether or not PMI decreased between the initial visit and post-neoadjuvant therapy (NAT) (C), and according to severity of PMI decrease (D).*

difference in the incidence of any complication (anastomosis leakage, pneumonia, recurrent nerve paralysis, chylothorax) between the two groups. Postoperative mortality and hospital stay duration were also comparable. These results suggest the post-NAT change in PMI is not related to the short-term surgical outcomes.

Cox's proportional hazards regression models. We used Cox's proportional hazards regression models to further investigate which factors independently contribute to overall survival in these patients with ESCC. In the univariate analysis, male gender ($p=0.002$), decrease in PMI ($p=0.021$), pathological lymph node involvement ($p=0.030$), and histological response to NAT ($p=0.026$) were significant factors. Multivariate analysis showed that male gender ($p=0.005$) and decreased PMI ($p=0.050$) were independent risk factors for poorer overall survival. The hazard ratio for decrease in PMI and reduced overall survival was more than 2.4 (Table IV). In the crude, age- and gender-adjusted, and multivariate-adjusted models, the hazard ratios were more than 2.7 for a decrease in PMI (Table V).

Postoperative PMI changes and overall survival. Finally, by comparing the initial visit PMI with the postoperative PMI, the patients were divided into groups with and without postoperative PMI decrease. The group with postoperative PMI decrease included 63 patients (75%), while the group without postoperative PMI decrease included 21 patients (25%). The group with postoperative PMI decrease tended to have poorer overall survival than the group without, although the difference was not significant ($p=0.482$) (Figure 3B).

Discussion

The results of this study show that in patients with ESCC, post-NAT PMI decrease is predictive of a poorer prognosis, and the more PMI decreases the worse overall survival appears to be. This observation was confirmed by a Cox's proportional hazards regression analysis in which decreased PMI was an independent risk factor for poorer survival. On the other hand, low PMI at the initial visit or 3 months after esophagectomy was not associated with a poor prognosis.

Table II. *Background of patients with esophageal squamous cell carcinoma in this study.*

Clinical feature	No PMI decrease (N=30)	PMI decrease (N=54)	p-Value
Age (years)	63.5 (47-72)	62 (40-74)	0.846
Gender			
Female	5 (16.7%)	7 (13.0%)	0.642
Male	25 (83.3%)	47 (87.0%)	
Clinical tumor depth			0.317
cT1	3 (10.0%)	2 (3.7%)	
cT2	5 (16.7%)	5 (9.26%)	
cT3	22 (73.3%)	45 (83.33%)	
c4a	0 (0.0%)	2 (3.7%)	
Clinical lymph node involvement			0.056
cN0	1 (3.3%)	8 (14.8%)	
cN1	23 (76.7%)	26 (48.2%)	
cN2	5 (16.7%)	19 (35.2%)	
cN3	1 (3.3%)	1 (1.9%)	
Albumin (g/dl)	4.2 (3.2-5.1)	4.1 (2.9-4.9)	0.154
Hemoglobin (g/dl)	14.0 (10.5-16.0)	13.8 (10.1-17.0)	0.929
CRP (g/dl)	0.08 (0.01-5.79)	0.13 (0.01-5.88)	0.212
NAT method			
NAC	6 (20.0)	13 (24.1)	0.669
NACRT	24 (80.0)	41 (75.9)	
Pathological tumor depth			0.710
pT0	6 (20.0%)	15 (27.8%)	
pT1	7 (23.3%)	9 (16.7%)	
pT2	4 (13.3%)	6 (11.1%)	
pT3	13 (43.3%)	22 (40.7%)	
pT4a	0 (0.0%)	2 (3.7%)	
Pathological LN involvement			0.389
pN0	14 (46.7%)	30 (55.6%)	
pN1	11 (36.7%)	12 (22.2%)	
pN2	3 (10.0%)	10 (18.5%)	
pN3	2 (6.7%)	2 (3.7%)	
Histological response to NAT			0.194
Grade 0-1	9 (30.0%)	24 (44.4%)	
Grade 2-3	21 (70.0%)	30 (55.6%)	
Prognosis			0.005*
Cancer death	3 (10.0%)	19 (35.2%)	
Death from other disease	3 (10.0%)	0 (0.0%)	
Alive	24 (80.0%)	35 (64.8%)	

Values are median (minimum-maximum) or frequency (%). CRP: C-reactive protein; NAT: neoadjuvant therapy; NAC: neoadjuvant chemotherapy; NACRT: neoadjuvant chemoradiotherapy; LN: lymph node. *Considered significant.

Skeletal muscle loss in patients with cancer may result from fasting, disuse, malnutrition, systemic inflammatory responses or cachexia, a well-known predictor of poor prognosis (23, 24). In patients with ESCC, skeletal muscle loss can also be exacerbated by esophageal obstruction, depending on the stage and location of the tumor. Because ESCC often responds well to chemotherapy and radiotherapy, patients with ESSC often receive more preoperative NAT than other cancer patients. The adverse effects of NAT and the subsequent anatomical changes caused by the surgery can also lead to eating difficulties and severe postoperative malnutrition. In the present study, PMI decreased after NAT in most patients. Interestingly, however, in some patients (35%) PMI did not decrease, and these patients had a significantly better prognosis. Analysis of the differences between patients who experienced a decrease in PMI and those who did not, revealed that age, gender, laboratory data (albumin, hemoglobin and C-reactive protein), tumor features (clinical or pathological tumor depth, lymph node involvement), NAT method (NAC, NACRT) and histological response to NAT did not account for different responses. Compromised nutritional status may be one explanation for the decrease in PMI, but obviously not the only one, as there was no significant difference in nutritional markers (*e.g.* albumin and hemoglobin) between the two groups. Genetic factors may also contribute to the different individual responses to NAT (25-27). At present, however, there is no clear explanation and further study will be required to resolve this issue.

One limitation of this study is that we did not collect data on oral ingestion, esophageal obstruction, fasting duration or use of total parenteral nutrition. Moreover, although no differences were found in the tumor features or effect of therapy between patients whose PMI decreased and those whose PMI was unchanged, cancer remained the main reason for death in the group with decreased PMI.

Skeletal muscle loss has been identified as a factor contributing to a poor prognosis in patients with various benign and malignant lesions (28). However, most of those studies focused on the absolute value of the PMI (or other indices) at only a single time point. Likewise, although skeletal muscle loss is associated with a poor prognosis in patients with ESCC (16), few studies have evaluated the change in PMI over time. In fact, because patients with ESCC require multimodal treatment, and there are a variety of factors that may affect nutritional condition during treatment, the nutritional condition of patients with ESCC is in a continuous state of change. Consequently, the changes in PMI during the treatment period likely better reflect the change of state in the patient than the PMI at any one time point. In our patients, all of whom underwent NAT and surgery, an increase or decrease in PMI from the initial visit to post-NAT was a better predictor of prognosis. To the best of our knowledge, this is the first time that change in PMI has been identified as a valuable prognostic factor in ESCC. Given the association between a decrease in PMI and a poor prognosis, preoperative nutritional support may be especially important for patients whose PMI decreased. Through oral nutrient supplementation, and total parenteral nutrition, nutritional management is being improved for patients with ESCC but nutritional intervention remains insufficient.

Table III. *Short-term surgical outcomes of patients with esophageal squamous cell carcinoma in this study.*

Surgical outcome	No PMI decrease (N=30)	PMI decrease (N=54)	*p*-Value
Operation time (min)	553 (383-776)	515 (417-804)	0.365
Blood loss (ml)	635 (143-3217)	553 (115-2099)	0.254
Complications			0.248
Present	15 (50.0%)	20 (37.0%)	
Absent	15 (50.0%)	34 (63.0%)	
Anastomotic leakage	2 (6.7%)	6 (11.1%)	0.506
Pneumonia	3 (10.0%)	6 (11.1%)	0.875
Recurrent nerve paralysis	10 (33.3%)	17 (31.5%)	0.862
Chylothorax	3 (10.0%)	2 (3.7%)	0.243
Postoperative mortality	1 (3.3%)	1 (1.9%)	0.670
Hospital stay (days)	26.5 (16-89)	25 (16-101)	0.444

Values are median (minimum-maximum) or frequency (%). PMI: Psoas muscle index. *Considered significant.

Table IV. *Univariate and multivariate analyses for 5-year-survival (Cox's proportional hazards regression models)*

Factor	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*p*-Value	Hazard ratio	95% CI	*p*-Value
Age (<65 *vs.* ≥65 years)	–	0.8902-4.6268	0.0901			
Gender (female *vs.* male)	1.8109×10^9	2.6405- –	0.0020*	1.6198×10^9	2.2113- –	0.0048*
Initial visit PMI (high *vs.* low)	–	0.8041-4.1407	0.1549			
cT (1-2 *vs.* 3-4)	–	0.6430-13.5551	0.2398			
cN (0-1 *vs.* 2-3)	–	0.6058-3.0766	0.4217			
NAT (NAC *vs.* NACRT)	–	0.7812-4.0802	0.1591			
PMI change (increase *vs.* decrease)	2.7790	1.1560-7.7210	0.0214*	2.4353	1.0000-6.8347	0.0500*
ypT (0-2 *vs.* 3-4a)	–	0.9744-5.1350	0.0580			
ypN (0-1 *vs.* 2-3)	2.5417	1.0986-5.6331	0.0302*	–	0.9465-5.4561	0.0653
Histological response to NAT (grade 2-3 *vs.* 0-1)	2.4757	1.1117-5.8693	0.0263*	–	0.7618-4.1438	0.1931
Complication (negative *vs.* positive)	–	0.7119-3.5398	0.2634			

PMI: Psoas muscle index; NAT: neoadjuvant therapy; NAC: neoadjuvant chemotherapy; NACRT: neoadjuvant chemoradiotherapy; ypT: post-therapy pathological tumor depth; ypN: post-therapy pathological lymph node involvement. *Considered significant.

Table V. *Hazard ratios per PMI decrease for 5-year-survival (Cox's proportional hazards regression models).*

	Hazard ratio	95% CI		*p*-Value
Crude (PMI decrease only)	2.7790	1.1560	7.7210	0.0214*
Adjusted for age, gender	2.8251	1.1677	7.8874	0.0202*
Adjusted for age, gender, ypT, ypN and histological response to NAT	2.8266	1.0204	8.9323	0.0454*
Adjusted for age, gender, ypT, ypN, histological response to NAT and complication	3.1406	1.0761	10.6169	0.0356*

We found that male patients had significantly higher PMIs than did female patients (Table I), which is consistent with other past findings (16, 17). Notably, however, our 12 female patients all survived 5 years. This is significantly better than the male patients, although the males and females had comparable tumor features at their initial visits. Different pathogenic mechanisms in different genders may be responsible for the different prognoses. Discovering the mechanisms by which gender affects prognosis is imperative in future projects.

Compared to the post-NAT decrease in PMI, the postoperative PMI decrease showed more individual variation. As a result, postoperative PMI changes did not correlate with prognosis. This is consistent with the features of surgery for ESCC (highly invasive, long operation and recovery times, more complications). But if a minimally-invasive operation can be performed well and totally, individual variation may improve, and postoperative PMI changes may correlate with prognosis.

There have been several reports showing that loss of skeletal muscle mass is associated with an increased risk of anastomotic leak (17), postoperative respiratory complications (16), perioperative infection, longer hospital stays, and prolonged rehabilitation in patients with cancer (29). However, we found no correlation between PMI change and short-term surgical outcomes in the present study. That said, the small number of patients is a limitation of our study, and our findings require confirmation in independent cohort studies in the future.

We found that a decrease of PMI post-NAT is well correlated with a poor prognosis in patients with ESCC. Moreover, the greater the decrease in PMI, the worse overall survival appears to be. In evaluating patients with ESCC, changes in PMI during a particular period may provide greater sensitivity than a single measurement of PMI at one time point.

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