Surgery 166 (2019) 1041–1047

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Presented at the Academic Surgical Congress 2019

Impact of measurement of skeletal muscle mass on clinical outcomes in patients with esophageal cancer undergoing esophagectomy after neoadjuvant chemotherapy

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A R T I C L E I N F O

Article history:
Accepted 25 July 2019
Available online 11 October 2019

A B S T R A C T

Background: Some studies have reported that sarcopenia is linked to clinical outcomes in multiple types of malignancies, but this association has not been established in esophageal cancer. We assessed how sarcopenia affects clinical outcomes of multidisciplinary treatments for esophageal cancer.
Methods: We included 165 esophageal cancer patients who had undergone neoadjuvant chemotherapy followed by esophagectomy. Computed tomography was used for cross-sectional measurement of the psoas muscle at the third lumbar vertebra; we then calculated the height-adjusted psoas muscle index. Pre- and postneoadjuvant chemotherapy psoas muscle indices were evaluated for associations with neoadjuvant chemotherapy response and neoadjuvant chemotherapy -related adverse events and postoperative complications, in addition to survival. Psoas muscle index cutoffs were 6.36 cm^2/m^2 for men and 3.92 cm^2/m^2 for women.
Results: Psoas muscle index decreased after neoadjuvant chemotherapy (from 7.17 to 6.96 cm^2/m^2; $P = .0008$), and specifically in men (from 7.45 to 7.23 cm^2/m^2; $P = .0001$) but not in women (from 5.21 to 5.17 cm^2/m^2; $P = .810$). Preneoadjuvant chemotherapy psoas muscle index (low versus high) was associated with neoadjuvant chemotherapy response (response rate: 65.1% vs 80.3%; $P = .0494$) and neoadjuvant chemotherapy-related adverse events (neutropenia: 93.0% vs 78.7%; $P = .0337$; febrile neutropenia: 53.5% vs 34.3%; $P = .0278$; hyponatremia: 51.2% vs 31.2%; $P = .0190$). Post-neoadjuvant chemotherapy psoas muscle index correlated with postoperative rate of complications (56.9% vs 33.3%; $P = .0046$), especially pneumonia (31.4% vs 9.7% $P = .0008$). Psoas muscle index was not associated with survival.
Conclusion: Cross sectional measures of sarcopenia before and after neoadjuvant chemotherapy could predict tumor response, neoadjuvant chemotherapy -related adverse events, and postoperative complications in multidisciplinary treatments for esophageal cancer.

Introduction

Esophageal cancer (EC) is a highly aggressive, malignant neoplasm with an unfavorable prognosis.[1] In addition, esophagectomy is quite invasive and associated with a high rate of postoperative complications.[2,3] EC is also closely correlated with poor nutritional status because most patients present with dysphagia and weight loss, which can lead to intolerance to

Presented at the 14th Annual Academic Surgical Congress on February 6, 2019 in Houston, TX.

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https://doi.org/10.1016/j.surg.2019.07.033
0039-6060/

chemotherapy and poor postoperative outcomes.[4] Furthermore, neoadjuvant chemotherapy (NAC), which is recommended as a standard treatment for resectable, locally advanced EC in Japan,[5] may impair nutritional status in patients who need multimodal treatments.

Sarcopenia, characterized by decreases in both skeletal muscle mass and function related to aging or disease,[6] is associated with adverse clinical outcomes in several types of malignancies, including colorectal,[7] pancreatic,[8] and small cell lung cancers.[9] In EC, however, the impact of sarcopenia on clinical outcome remains unclear, especially with multidisciplinary treatments. Therefore, the aim of this study was to assess the importance of sarcopenia diagnosed by the measurement of psoas muscle mass using computed tomography (CT) in EC patients who had surgery after NAC.

Methods

Patient eligibility

This retrospective study included 165 consecutive patients who underwent operative resections for EC after NAC at the Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University from January 2010 to December 2013. We collected data related to characteristics of the primary tumor and oncologic staging, other physical status, surgical and neoadjuvant treatment, NAC-related adverse events (AEs), response to NAC, postoperative complications, and prognostic factors. Clinico-pathologic factors were classified according to the Union for International Cancer Control TNM Classification of Malignant Tumors, 8th edition.[10] According to the Union for International Cancer Control classification, metastasis to supraclavicular lymph nodes (#104), which has been considered to be loco-regional lymph nodal disease by previous studies, is defined as “distant” lymph nodes metastasis. Therefore, by definition, patients with supraclavicular lymph nodes metastasis (but not any metastases to distant organs) were classified as stage IV in the present study. Patients underwent 1 of the following 2 NAC regimens: (1) the docetaxel, cisplatin, and 5-fluorouracil (DCF) regimen comprising 2 cycles of 70 mg/m^2 docetaxel and 70 mg/m^2 cisplatin administered by rapid intravenous infusion on day 1, along with 700 mg/m^2 5-FU by continuous intravenous infusion for 5 days (days 1–5) and (2) the adriamycin, cisplatin, and 5-fluorouracil (ACF) regimen, comprising 2 cycles of 35 mg/m^2 adriamycin and 70 mg/m^2 cisplatin by rapid intravenous infusion on day 1, along with 700 mg/m^2 5-FU in the same manner as DCF.[11–14]

Patients who received preoperative radiotherapy were excluded. Total body computed tomography (CT) before NAC (pre-NAC) and after NAC (post-NAC) were performed as routine care for all eligible patients.[15,16] All patients underwent radical subtotal esophagectomy with either 2- or 3-field lymphadenectomy followed by reconstruction with a gastric conduit or a pedicaled jejunum or colon 3 to 4 weeks after completion of 2 cycles of NAC as described previously.[17,18] NAC-related AEs were classified by Common Terminology Criteria for Adverse Events, version 4.0,[19] whereas postoperative complications were classified using the Clavien-Dindo classification.[3,20] The Human Ethics Review Committee of Osaka University Graduate School of Medicine approved the protocol for this retrospective study, and each participant provided signed consent.

Measurement of psoas muscle index measurement by CT before and after NAC

Psoas muscle mass was measured by CT using the Synapse Vincent system (Fuji Film Co. Ltd., Tokyo, Japan). The cross-sectional area of the psoas muscle (cm^2) was measured at the level of the third lumbar vertebra (L3) with automated selection of both sides of the psoas muscle. The psoas muscle index (PMI) was calculated by adjustment for height (PMI [cm^2/m^2] = total psoas area at L3 [cm^2] / height ^{2} [m^2]). The cutoff values for PMI were set at 6.36 cm^2/m^2 for men and 3.92 cm^2/m^2 for women based on the average −2 standard deviations in healthy Japanese individuals under age 50.[21] Patients with PMI less than the cutoff were diagnosed as having sarcopenia.

Evaluation of clinical response to NAC

All patients underwent restaging by CT, endoscopy, and positron emission tomography/CT to evaluate the clinical response at 2 to 3 weeks after NAC. Clinical tumor responses were evaluated using esophagoscopy and CT after each cycle of chemotherapy[17,22,23] in accordance with the criteria of the Japanese Society for Esophageal Disease.[24] The detailed criteria of clinical response is as follows. A complete response (CR) was defined as complete regression of disease diagnosed by CT and endoscopy findings. The patient was not considered to have achieved a CR if the presence of cancer cells in biopsy samples were confirmed by endoscopy. A partial response (PR) was defined as a >50% decrease in the size of the primary tumor and lymph node metastases as confirmed by CT and endoscopy. Progressive disease (PD) was defined as a >25% increase in the size of the primary tumor or the appearance of new lesions. Cases that did not meet the criteria for either PR or PD were defined as stable disease. The histopathologic tumor response was evaluated according to Japanese Society for Esophageal Disease histologic criteria.[12,24]

Statistical analysis

Data were analyzed using JMP13 software (SAS Institute Inc., Cary, NC). Continuous data are reported as means and standard deviations. Differences between groups were analyzed with the Pearson χ^2 test for categorical variables. The Mann-Whitney *U* test was used for group comparisons of continuous data on a single time point. Kaplan-Meier survival curves and log-rank analysis were used to demonstrate possible survival differences between the groups. Comparisons showing significance in univariate analysis were entered into multivariate analysis in logistic regression models. P values < .05 were considered to be statistically significant.

Results

Association between pre-therapeutic PMI and background parameters

Clinico-pathologic characteristics of patients classified as having pre-NAC PMI are detailed in Table I. Low compared to high PMI was associated with older age (respectively 68.3 vs 65.1 years, P = .0323), a lesser body mass index (19.6 vs 22.1 kg/m^2, P < .001), a lesser serum albumin concentration (3.57 vs 3.78, P = .0069), and a lesser prognostic nutrition index (45.1 vs 45.7, P = .0121). No differences were identified in other parameters, including sex, tumor location, cT, cN, cStage, pT, pN, pStage, comorbidity, American Society for Anesthesiologists Physical Status, NAC regimen, serum levels of C-reactive protein, neutrophil-to-lymphocyte ratio, or modified Glasgow Prognostic Scale.

Changes in PMI during NAC for EC

In all patients, average values for PMI decreased from 7.17 to 6.97 cm^2/m^2 during NAC (P = .0008). Of note, men showed a statistically

Table I
Patients and treatment characteristics classified by pre-NAC PMI

Factors		PMI		*P* value
		Low PMI ($n = 43$)	High PMI ($n = 122$)	
Age	Average (±SD)	68.3 ± 6.4	65.1 ± 9.0	.0323
Sex	Male ($n = 144$)	40 (93%)	104 (85.3%)	.1647
	Female ($n = 21$)	3 (7%)	18 (14.8%)	
Location	Ut	6 (14%)	14 (11.5%)	.6686
	Mt/Lt	37 (86%)	108 (88.5%)	
cT	cT1-2	7 (16%)	33 (27.1%)	.1565
	cT3-4	36 (84%)	89 (73.0%)	
cN	cN0	14 (33%)	24 (19.7%)	.0844
	cN1–3	29 (67%)	98 (80.3%)	
Clinical stage	cStage I/II	14 (33%)	36 (29.5%)	.7082
	cStage III/IV*	29 (67%)	86 (70.5%)	
Comorbidity	Total	13 (30%)	38 (31.2%)	.9110
	Respiratory	3 (7%)	15 (12.3%)	.3159
	Cardiovascular	5 (12%)	13 (11.6%)	.8613
	Cerebrovascular	1	10 (8.2%)	.1433
	Diabetes mellitus	5 (12%)	9 (7.4%)	.4041
ASA-PS	0–1	15 (36%)	32 (26.2%)	.2410
	2–3	27 (64%)	90 (73.8%)	
NAC regimen	DCF	32 (74%)	75 (61.5%)	.1199
	ACF	11 (26%)	47 (38.5%)	
BMI (kg/m^2)	Average (±SD)	19.6 ± 2.5	22.1 ± 2.7	< .001
Serum Alb (mg/dL)	Average (±SD)	3.57 ± 0.44	3.78 ± 0.44	.0069
CRP (mg/dL)	Average (±SD)	0.73 ± 1.27	0.42 ± 0.81	.0663
PNI	Average (±SD)	45.1 ± 5.2	45.7 ± 5.26	.0121
NLR	Average (±SD)	3.14 ± 1.99	3.02 ± 1.66	.1121
mGPS	0	21 (49%)	79 (64.8%)	.1357
	1	20 (47%)	36 (29.5%)	
	2	2	7 (%)	
Operation time (minutes)	Average (± SD)	466 (± 11)	471.7 (± 87.8)	.7189
Blood loss (mL)	Average (± SD)	612 (± 444)	683.9 (± 443.5)	.3336
Route of reconstruction	Posterior mediastinal	39 (91%)	117 (95.9%)	.0999
	Subcutaneous	4 (9%)	5 (4.1%)	
Reconstruction organ	Gastric tube	40 (93%)	119 (97.5%)	.1819
	Pediculate jejunum	3 (%)	3	
Operative approach	Open	40 (78%)	83 (72.8%)	.4434
	VATS	11 (22%)	31 (27.2%)	
Range of lymph node dissection	3-field	33 (65%)	66 (57.9%)	.4092
	2-field	18 (35%)	48 (42.1%)	

ASA-PS, American Society of Anesthesiologists–physical status; *CRP*, C-reactive protein; *mGPS*, modified Glasgow Prognostic Scale; *NLR*, neutrophil–lymphocyte ratio; *PNI*, prognostic nutritional index; *SD*, standard deviation; *VATS*, video-assisted thoracic surgery.
* A total of 31 patients with supraclavicular lymph nodes metastasis are classified as stage IV according to the Union for International Cancer Control, 8th edition.

significant decrease in PMI during NAC (from 7.45 to 7.23 cm^2/m^2, $P = .0001$), but women did not show any difference (from 5.21 to 5.17 cm^2/m^2, $P = .810$; Table II). Using the cutoff value, 43 (26.1%) of 165 patients were classified into the low-PMI group before NAC. After NAC, the number of patients categorized as low PMI slightly increased to 51 (30.9%; Table II). No difference in the decreased rate of PMI was identified between the 2 NAC regimens: 3.7% (range; −23.2–28.5%) in the DCF group and 3.7% (range; −18.9–36.2) in the ACF group ($P = .1765$).

Correlation between pre-NAC PMI and NAC-related AEs

Table III shows the details of NAC-related AEs in the 2 groups. Rates of neutropenia (93.0% vs 78.7%, $P = .0337$), febrile neutropenia (53.5% vs 34.3%, $P = .0278$), and hyponatremia (51.2% vs 31.2%, $P = .0190$) were greater in the low-PMI group, as was the rate of overall AEs (97.7% vs 82.0%, $P = .0033$) (Table III). Notably, because of severe adverse effects, the low-PMI group had a greater need for reduction in the dose of chemotherapy on the second NAC cycle (51.2% vs 33.6%, $P = .0416$). In univariate analysis, age ($P = .0251$) and NAC regimen ($P \leq .0001$) were risk factors for overall AEs in addition to low PMI. Multivariate analysis revealed that all of these measures were independent risk factors for overall AEs (Table III).

Impact of pre-NAC PMI on tumor response to NAC

The comparison of the response to NAC between 2 two groups is summarized in Table IV. The clinical response rate was less in the low-PMI compared with the high-PMI group (65.1% vs 80.3%, $P = .0494$); however, pathologic response did not differ between the 2 groups (grade1b–3: 53.5% vs 60.7%, $P = .4116$) (Table IV). In univariate and multivariate analyses of favorable clinical response to NAC, low PMI (odds ratio [OR] 3.16; 95% confidence interval [CI], 1.39–7.32; $P = .0062$) was identified as an independent predictive parameter along with the NAC regimen (ACF) (OR 3.72; 95% CI, 1.70–8.12; $P = .0010$; Table IV). Tumor response was not associated with a decrease in PMI during NAC (data not shown).

The association between post-NAC PMI and postoperative complications

Table V shows the postoperative morbidity rate classified by post-NAC PMI. The rates of overall complications (56.9% vs 33.3%, $P = .004$)

Table II
Changes in PMI during preoperative chemotherapy

		PMI		P value
		Pre-NAC	Post-NAC	
Overall (*N* = 165)	Average (± SD)	7.17 (±2.01) cm^2/m^2	6.97 (±1.86) cm^2/m^2	.0008
Male (*n* = 144)	Average (± SD)	7.46 (±1.96) cm^2/m^2	7.23 (±1.80) cm^2/m^2	.0001
Female (*n* = 21)	Average (± SD)	5.21 (±1.03) cm^2/m^2	5.17 (±1.17) cm^2/m^2	.8100

	Pre-NAC (%)		Post-NAC (%)	
	Low PMI	High PMI	Low PMI	High PMI
Overall (*N* = 165)	43 (26.1)	122 (73.9)	51 (30.9)	114 (69.1)
Male (*n* = 144)	40 (27.8)	104 (72.2)	45 (31.3)	99 (68.1)
Female (*n* = 21)	3 (14.3)	18 (85.7)	6 (28.6)	15 (61.4)

SD, standard deviation.

Table III
Adverse events (≧grade 3) of neoadjuvant chemotherapy classified by pre-NAC PMI and univariate and multivariate analysis on overall adverse events

Factors	Total (*N* = 165)	PMI (%)		P value
		Low PMI (*n* = 43)	High PMI (*n* = 122)	
Overall adverse events	142 (86.1)	42 (98)	100 (82.0)	.0033
Leukopenia	117 (70.9)	35 (81)	82 (67.2)	.0783
Neutropenia	136 (82.4)	40 (93)	96 (78.7)	.0337
Febrile neutropenia	65 (39.3)	23 (54)	42 (34.3)	.0278
Thrombocytopenia	15 (9.1)	3 (7)	12 (9.8)	.5750
Hyponatremia	60 (36.4)	22 (51)	38 (31.2)	.0190
Anorexia	26 (15.8)	6 (14)	20 (16.4)	.7057
Diarrhea	39 (23.6)	12 (28)	27 (22.1)	.4433
Stomatitis	19 (11.5)	5 (12)	14 (11.5)	.9785

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex (female)	1.62 (0.35–7.48)	.5317		
Age (>65)	2.71 (1.11–6.65)	.0251	4.28 (1.40–13.0)	.0106
ASA-PS (≥2)	0.33 (0.09–1.17)	.0741		
BMI (<19)	1.12 (0.35–3.55)	.8534		
Comorbidity	0.81 (0.32–2.06)	.6648		
Low PMI	9.24 (1.21–70.7)	.0106	9.53 (1.09–83.1)	.0413
Low PNI	4.70 (0.61–36.5)	.1055		
NLR (>2.5)	0.69 (0.27–1.79)	.4459		
NAC regimen (ACF)	18.2 (5.13–64.9)	< .0001	23.7 (6.05–93.2)	< .001

ASA-PS, American Society of Anesthesiologists–physical status; *BMI*, body mass index; *NLR*, neutrophil–lymphocyte ratio; *PNI*, prognostic nutritional index.
All adverse events are diagnosed with Common Terminology Criteria for Adverse Events version 4.0 (Grade >3)

and postoperative pneumonia (31.4% vs 9.7%, *P* = .0008) were greater in the low-PMI compared with the high-PMI group (Table V). Univariate logistic regression analysis of overall complications revealed that age (*P* = .0085), preoperative comorbidity (*P* = .0124), low PMI (*P* = .0045), and blood loss (*P* = .0039) were statistically significant. Among these factors, low PMI (OR 3.15; 95% CI, 1.48–6.70; *P* = .0023), comorbidity (OR 2.37; 95% CI, 1.13–4.95; *P* = .0207), and blood loss (OR 3.20; 95% CI, 1.57–6.49; *P* = .0009) were also shown to be independent predictive parameters by multivariate analysis (Table V). Similarly, univariate and multivariate analyses of postoperative pneumonia identified low PMI (OR 7.02; 95% CI, 2.60–19.0; *P* = .0001) as an independent predictive parameter with the greatest OR along with comorbidity (OR 3.07; 95% CI, 1.18–7.99; *P* = .0215) and blood loss (OR 4.12; 95% CI, 0.99–7.91; *P* = .0099; Table V).

Influence of PMI before and after NAC on long-term survival

Kaplan-Meier curves of overall survival (OS) and recurrence-free survival classified by pre- or post-NAC PMI were not different in the 2 groups as shown in Supplemental Fig 1. The 2-year survival rates were 71% vs 72% for low vs high pre-NAC PMI and 74% vs 71% for low vs high post-NAC PMI. The 2-year recurrence-free survival was 59% vs 63% for low vs high pre-NAC PMI and 60% vs 63% for low vs high post-NAC PMI. Survival did not differ with low versus high PMI pre- or post-NAC. Similarly, a decrease in PMI did not correlate with long-term survival (data not shown).

Discussion

This study characterized the diagnosis of sarcopenia by performing PMI measurement using CT scans before and after NAC and revealed that PMI significantly decreased after NAC, in men but not in women. In addition, low PMI before NAC was associated with poor response to chemotherapy and more severe NAC-related AEs, whereas a low PMI post-NAC was associated with more postoperative complications, especially pneumonia. These results imply that PMI measured by CT during NAC could be useful in predicting

Table IV
Response to NAC classified by pre-NAC PMI and univariate and multivariate analysis of poor clinical response to NAC (nonresponders)

Factors		PMI (%)		P value
		Low PMI (n = 43)	High PMI (n = 122)	
Clinical response	Responders*	28 (65)	98 (80.3)	.0494
	Nonresponders†	15 (35)	24 (19.7)	
Pathological response	pCR	6 (14%)	9 (7.4%)	.1971
	Non-pCR	37 (86%)	113 (92.6%)	

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex (Female)	0.97 (0.33–2.86)	.9605		
Age (>65)	0.91 (0.43–1.89)	.7917		
ASA-PS (≥2)	1.52 (0.66–3.45)	.3219		
BMI (<19)	1.64 (0.70–3.84)	.2478		
cT3–4	1.04 (0.43–2.50)	.9301		
cN ≥1	1.41 (0.57–3.45)	.4548		
cStage 3–4	0.96 (0.43–2.13)	.9266		
Comorbidity	1.28 (0.60–2.70)	.5201		
Low PMI	2.44 (1.12–3.45)	.0210	3.16 (1.39–7.32)	.0062
Low PNI	0.93 (0.34–2.50)	.8799		
NLR (>2.5)	0.76 (0.37–1.56)	.4600		
mGPS = 2	0.27 (0.03–2.08)	.1817		
NAC regimen (ACF)	3.03 (1.45–6.25)	.0025	3.72 (1.70–8.12)	.0010
Dose reduction	0.83 (0.40–1.79)	.6342		

ASA-PS, American Society of Anesthesiologists–physical status; *mGPS*, modified Glasgow Prognostic Scale; *NLR*, neutrophil–lymphocyte ratio; *pCR*, pathological CR; *PNI*, prognostic nutritional index.
* CR and PR
† Stable disease and PD

clinical outcomes of EC patients who will undergo multidisciplinary treatments.

In 2010, the European Working Group on Sarcopenia in Older People established a consensus on the evaluation of sarcopenia, recommending a set of approaches including measurements of muscle mass, muscle strength (handgrip strength), and physical performance (gait speed).[6] Because CTs are performed in routine care for all eligible EC patients before and after NAC in our department, measurement of muscle mass by CT required no additional examinations and is a reasonable way to diagnose sarcopenia in cases involving multimodal treatment for EC. Although several studies have reported CT-based diagnosis of sarcopenia, no consensus exists regarding PMI cutoff values. In the present study, we adopted cutoffs of 6.36 cm^2/m^2 for men and 3.92 cm^2/m^2 for women, based on the average −2 standard deviations for healthy Japanese subjects younger than age 50 years.[21] Because few women were diagnosed with sarcopenia using this criterion, establishment of an optimal cutoff for PMI remains to be determined.

Several studies have reported an association between sarcopenia and chemotherapy AEs.[25–27] Murimwa et al[25] reported a greater risk of developing grade 3 or 4 toxicity of chemoradiotherapy (radiotherapy with concurrent cisplatin and continuous infusion of 5-FU chemotherapy) in sarcopenic patients in EC. Tan et al[26] reported a 3-fold increased risk of dose-limiting toxicity owing to chemotherapy with sarcopenia in esophagogastric cancer. Our study reports the association of sarcopenia and AEs specifically associated with NAC in EC patients. In contrast, few studies have found that sarcopenia is an independent risk factor for poor response to anticancer therapy. In EC patients, Sato et al[28] reported that response rates of chemoradiotherapy for unresectable EC patients were less in the group with sarcopenia than those without sarcopenia (43.8% vs 78.6%, P = .025). They assumed that sarcopenia was the most relevant phenotypic feature of cancer cachexia, which is derived from high malignancy potential and thus related to poor response to chemoradiotherapy. The present study identified PMI as an independent predictive factor for tumor response to chemotherapy alone in EC patients.

The detailed mechanisms linking sarcopenia to AEs or tumor response are unclear. Prado et al[29] reported that sarcopenia was an impressive predictor of toxicity, including diarrhea (29.0% vs 2.4%, P = .01) and stomatitis (36.0% vs 4.9%, P = .008) in patients with metastatic breast cancer treated with capecitabine. They also reported that sarcopenia was not exclusively associated with body surface area (BSA) (1.7 m^2 vs 1.8 m^2, P = .42) but was linked also to lean body mass (34.0 kg vs 42.5 kg, P < .0001). Therefore, these authors concluded that lean body mass is a better predictor than BSA of 5-FU pharmacokinetics (clearance and volume of distribution). Because doses of chemotherapy drugs were adjusted according to BSA in the present study, doses of chemotherapy drugs in patients with sarcopenia may have been overestimated. This possibility in turn could explain why the severities of NAC-related AEs were worse in the sarcopenic group. Regarding the association between sarcopenia and clinical response to NAC, the frequency of dose reduction related to AEs was greater in the sarcopenic group in this study, in agreement with the findings of Tan et al,[26] and could partly explain why sarcopenia impaired the clinical response to NAC. Skeletal muscle is not only a locomotive organ but also plays a fundamental homeostatic role through secretion of metabolic mediators such as myokines. Ali et al[30] proposed that the sarcopenic state induces an upregulation of pro-inflammatory agents, including tumor necrosis factor and interleukins 1 and 6. These mediators may disturb the immune system and tumor microenvironment, leading to poor clinical outcomes, including a poor response to chemotherapy and greater rates of AEs.

Esophagectomy is highly invasive and associated with considerable risk for major morbidity.[1] Although both pre- and post-NAC PMI were associated with a high frequency of postoperative pneumonia, only post-NAC PMI was an independent risk factor in multivariate analysis (data not shown), implying that post-PMI is more appropriate than pre-PMI for predicting postoperative

Table V
Postoperative complications and surgical outcomes classified by post-NAC PMI and univariate and multivariate analysis on overall complications and pneumonia

Factors (≥grade 2)	Total (*N* = 165) (%)	Low PMI (*n* = 51) (%)	High PMI (*n* = 114) (%)	*P* value
Overall complications	67 (40.6)	29 (57)	38 (33.3)	.0046
Pneumonia	27 (16.4)	16 (31)	11 (9.7)	.0008
Anastomotic leak	7 (4.2)	3 (6)	4 (3.5)	.4845
Expectoration disorder	12 (7.3)	10 (22)	14 (12.7)	.1380
Arrhythmia	18 (10.9)	7 (14)	11 (9.7)	.4376
Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Sex (Female)	1.43 (0.54–3.75)	.4676		
Age (>65)	2.49 (1.25–4.96)	.0085	1.97 (0.94–4.13)	.0712
ASA (≥2)	0.68 (0.35–1.36)	.2772		
BMI (<19)	0.81 (0.38–1.72)	.5902		
Comorbidity	2.34 (1.19–4.59)	.0124	2.37 (1.13–4.95)	.0207
Low PMI	2.64 (1.34–5.19)	.0045	3.15 (1.48–6.70)	.0023
Low PNI	1.22 (0.58–2.58)	.5959		
NLR (>2.5)	1.11 (0.56–2.21)	.7557		
mGPS = 2	1.39 (0.34–5.77)	.6477		
Operation time (>median)	1.23 (0.66–2.30)	.5036		
Blood loss (>median)	2.54 (1.34–4.82)	.0039	3.20 (1.57–6.49)	.0009
NAC regimen (DCF)	1.88 (0.96–3.68)	.0653		
Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Sex (Female)	0.23 (0.03–1.77)	.1240		
Age (>65)	2.18 (0.83–5.76)	.1086		
ASA (≥2)	0.72 (0.29–1.75)	.4640		
BMI (<19)	0.95 (0.35–2.55)	.9132		
Comorbidity	2.44 (1.05–5.67)	.0340	3.07 (1.18–7.99)	.0215
Low PMI	4.28 (1.81–10.1)	.0005	7.02 (2.60–19.0)	.0001
Low PNI	1.65 (0.66–4.17)	.2825		
NLR (>2.5)	1.23 (0.51–2.96)	.6511		
mGPS = 2	1.50 (0.29–7.63)	.6251		
Operation time (>median)	2.91 (1.19–7.10)	.0156	2.80 (0.99–7.91)	.0520
Blood loss (>median)	3.61 (1.43–9.09)	.0045	4.12 (0.99–7.91)	.0099
NAC regimen (DCF)	0.91 (0.39–2.13)	.8225		

All complications are classified by Clavien-Dindo classification (Grade >2).
ASA, American Society of Anesthesiologists; *BMI*, body mass index; *mGPS*, modified Glasgow Prognostic Scale; *NLR*, neutrophil−lymphocyte ratio; *PNI*, prognostic nutritional index;

pneumonia. Boshier et al[31] found in a systematic review of 27 studies that sarcopenic patients with EC have a greater incidence of postoperative pulmonary complications (OR 2.03; 95% CI, 1.32–3.11; *P* = .001), particularly pneumonia.[32–35] Sarcopenia is also reported to be associated with a deterioration of the strength of respiratory[36] and swallowing muscles[37], which might increase the risk for morbidities, including dysphagia, septum plugging, and atelectasis, and thus contribute to the development of postoperative pneumonia. Therefore, our results could point to the clinical importance of aggressive intervention with rehabilitation and nutritional support throughout multidisciplinary treatments for EC patients to improve outcome. In contrast, some studies have reported the impact of sarcopenia on prognosis; Paireder et al,[38] in 130 patients undergoing esophageal resection after NAC for EC, found poor OS in the sarcopenic group (*P* = .036). Liu et al[39] also reported that decreased PMI during NAC was associated with poorer OS compared to no decrease in PMI (*P* = .025), but that low PMI at the initial visit was not associated with prognosis. In contrast to these findings, we did not identify an impact of sarcopenia on prognosis. The differences of background factors between the 2 groups related to patient characteristics, such as cN stage and NAC regimen, might have masked potential prognostic impact of sarcopenia in the present study.

Several limitations of this study should be acknowledged. First, it is a retrospective, cohort study at a single institution with the potential for increased selection bias. Second, although sarcopenia was diagnosed by PMI with a cutoff value based on data for healthy Japanese men and women according to previous findings, a standard PMI cutoff for diagnosing sarcopenia has not been established. Because the optimal cutoff value may vary by ethnicity, nationality, lifestyle, and clinical setting, the values used here may not be applicable universally. Third, we diagnosed sarcopenia using only PMI similar to previous studies. As mentioned, the European Working Group on Sarcopenia in Older People recommends a set of approaches for diagnosing sarcopenia, including muscle mass, handgrip strength, and gait speed.[6] Further study is necessary to identify the necessary measures of grip strength and walking speed in addition to muscle mass.

In conclusion, sarcopenia as diagnosed by measurement of psoas muscle mass via CT ¥ occurs at an increased rate after chemotherapy and is associated with the success of clinical response to chemotherapy, chemotherapy-related AEs, and postoperative complications, including pneumonia in EC patients. Although a prospective study with a larger number of patients is essential to validate the importance of these findings, the present report offers important information that may lead to improved clinical outcomes in EC patients undergoing multimodal treatments.

Funding/Support

None.

Conflict of interest/Disclosure

There are no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2019.07.033.

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