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Preoperative Masseter Muscle Sarcopenia Predicts Mortality in Patients With Oesophageal Cancer

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Abstract. *Background/Aim: The impact of masseter muscle sarcopenia on the prognosis of patients with oesophageal cancer after oesophagectomy remains unclear. Patients and Methods: We retrospectively analysed data from 70 patients with oesophageal cancer who underwent oesophagectomy between 2013 and 2019. Overall survival and disease-free survival rates were analysed using Cox proportional hazards models and Kaplan–Meier curves with the log-rank test. Results: Masseter muscle sarcopenia was diagnosed in 36 patients. Multivariate analysis identified cytokeratin 19 fragment >1.1 (p=0.04); stage II, III, and IV cancer (p=0.01); and masseter muscle sarcopenia (p<0.01) as significant independent predictors of disease-free survival. Stage II, III, and IV cancer (p<0.01); masseter muscle sarcopenia (p<0.01); and postoperative pneumonia (p<0.01) were significant independent predictors of overall survival. Conclusion: Preoperative masseter muscle sarcopenia could be a strong predictor of long-term outcomes in patients who undergo oesophagectomy for oesophageal cancer.*

Oesophageal cancer is the eighth most commonly diagnosed cancer and the sixth leading cause of cancer-related deaths (1). Among all cancer types, patients with oesophageal cancer are the most prone to developing malnutrition due to its location. The 5-year survival rate is only approximately 20%, in spite of improved surgical outcomes in recent years (2).

Several prognostic factors have been reported for oesophageal cancers, such as histological type; tumour size; lymph node metastases; biomarkers, including vascular endothelial growth factor, p53, proliferating cell nuclear antigen, and human epidermal growth factor receptor 2; microvascular density (3-8); and inflammatory- and immunologic-based scores, such as neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and the Glasgow Prognostic Score (9, 10).

Recently, there has been growing interest in the relationship between prognosis and sarcopenia in patients with oesophageal cancer (11). Sarcopenia is defined as a decrease in skeletal muscle mass and loss of function caused by aging, disease, and malnutrition (12). The pathophysiological mechanisms underlying the association between sarcopenia and poor clinical outcomes in patients with cancer are multifactorial. Cancers cause skeletal muscle atrophy, which results in systemic inflammation, altered myokine production, mitochondrial dysfunction, altered insulin-dependent glucose handling, altered protein status, and altered pharmacokinetics of anticancer drugs (13).

Measurement of the psoas muscle mass area at the level of the third lumbar vertebra is widely recognized as an index for evaluating sarcopenia. Sarcopenia is a whole-body process that affects the muscles associated with chewing and swallowing (14, 15). In particular, the masseter muscle, which originates from the zygomatic arch bilaterally, are predominantly composed of type I muscle fibres known as slow muscle fibres, which are more strongly atrophied by disuse than aging (16). The measurement of masseter muscle thickness is a useful index of occlusal force and chewing ability, and its reduction can be a risk factor for malnutrition caused by a decrease in chewing ability (17).

Therefore, we hypothesized that a decrease in the preoperative masseter muscle area [masseter muscle sarcopenia (MMS)] would be significantly associated with poor prognosis in patients with oesophageal cancer. To our knowledge, there have been no reports in the field of digestive surgery suggesting an association between the masseter muscle area and prognosis of patients with cancer.

This study aimed to investigate the prognostic impact of MMS, along with other conventional prognostic factors,

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including psoas muscle sarcopenia (PMS), on the long-term outcomes of patients with oesophageal cancer following oesophagectomy.

Patients and Methods

Study design, setting, and participants. This retrospective cohort study analysed data from 70 patients who underwent oesophagectomy for oesophageal cancer at the International University of Health and Welfare Hospital (Nasushiobara, Tochigi Prefecture, Japan) between March 2013 and September 2019. The inclusion criteria were: 1) oesophageal cancer that was treated with oesophagectomy with three-field lymph node dissection; 2) complete enhanced cervical, thoracic, and abdominal computed tomography (CT) performed within 30 days of surgery; and 3) complete follow-up data and clinical details. Exclusion criteria included perioperative mortality, palliative surgery, and the presence of multiple cancers. The primary endpoint was overall survival (OS), and the secondary endpoints were disease-free survival (DFS) and postoperative complications.

As this was a retrospective study, the opt-out method was selected for obtaining consent from patients and their families. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the International University of Health and Welfare Hospital (approval no: 21-B-461).

Treatment and patient management. The oesophageal cancer practice guidelines (2017), edited by the Japan Oesophageal Society (18), were used to determine surgical indications for oesophageal cancer; the 11th edition of the Japanese Classification of Oesophageal Cancer (19) was used for staging and pathological diagnosis.

The surgical procedure comprised thoracoscopic and laparoscopic oesophagectomy, and three-field lymphadenectomy. A feeding jejunostomy was placed in all cases. Neoadjuvant chemotherapy plus surgery (two cycles of 5-fluorouracil and cisplatin) was performed for patients with clinical stage II or III cancer, excluding those with severe stenosis. Chemoradiotherapy was performed in patients whose cancers were deemed unresectable at the initial visit. Surgery was indicated when the cancer was resectable. Postoperative adjuvant chemotherapy (tegafur/gimeracil/oteracil) was administered for 1 year after surgery in patients with stage II cancer or higher. Treatment for recurrent cases was either chemotherapy (5-fluorouracil plus cisplatin, docetaxel plus cisplatin plus 5-fluorouracil, docetaxel monotherapy, paclitaxel monotherapy, or nivolumab), radiation therapy (60 Gy), or a combination of chemotherapy and radiation therapy, depending on the performance status.

All surgeries were performed by an experienced surgeon, who was a licensed attending physician of laparoscopic surgery. All patients in this study underwent the following standard procedures: Thoracoscopic oesophagectomy with mediastinal lymph node dissection was performed in the prone position, after which patients were placed in a supine position and neck dissection, gastric mobilization with abdominal dissection, and gastric tube or ileocolic reconstruction were performed.

Postoperative complications including anastomotic leakage, recurrent nerve paralysis, and pneumonia, were diagnosed as complications if they were Clavien-Dindo grade II or higher and occurred within 3 months of surgery.

Basic surveillance after surgery was performed by tumour marker testing every 3 months. Neck, chest, and abdominal enhanced CT was performed every 6 months, and upper gastrointestinal endoscopy was performed every year.

Recurrences and metastases were defined as newly detected local or distant metastatic tumours after surgery on enhanced CT or positron emission tomography-CT, regardless of elevation of tumour markers such as squamous cell carcinoma-related antigen, cytokeratin 19 fragment (CYFRA), or carcinoembryonic antigen.

Data collection. The clinicopathological data collected included sex, age, body mass index, smoking, comorbidities, pre-and postoperative treatments, preoperative blood test results, tumour-node-metastasis stage, pathological diagnosis, tumour location, blood loss, operative time, postoperative complications (pneumonia, recurrent nerve paralysis, and anastomotic leakage), recurrence, and prognosis. The Glasgow Prognostic Score, based on the combination of C-reactive protein and serum albumin levels, was used for preoperative nutritional assessment (20).

Definition of MMS and PMS. MMS and PMS were diagnosed using cervical to abdominal enhanced CT performed within 1 month of surgery. The masseter muscle area was calculated as the sum of the left and right sides of the masseter muscle area (simple calculation formula: length of the major axis × length of the minor axis × π) 2 cm below the zygomatic arch in the axial plane (21, 22) (Figure 1). Given the absence of defined diagnostic thresholds for MMS and PMS, sex-specific cohort medians were chosen for dichotomization. MMS was defined as the masseter muscle area below the sex-specific median. The psoas muscle area was calculated as the sum of the left and right sides of the psoas muscle area (simple calculation formula: length of the major axis × length of the minor axis × π) at the third lumbar vertebra in the axial plane (23) (Figure 2). PMS was defined as the psoas muscle area below the sex-specific cohort median.

Statistical analysis. The Mann–Whitney *U*-test was used to compare continuous variables, and the chi-squared test was used to compare dichotomous variables. Univariate and multivariate analyses of DFS and OS were performed using the Cox proportional hazards model. The impact of MMS and PMS on the risk of recurrence and mortality was estimated using Kaplan–Meier curves with the log-rank test. Receiver operating characteristic curves and Youden's index were used to determine the optimal cut-off value of continuous variables in the Cox proportional hazards model. Stata/IC version 16.0 STATA Statistical Software (StataCorp, College Station, TX, USA) was used for statistical analysis. A p-value <0.05 was considered significant.

Results

Patient characteristics. Table I shows the patient demographic and clinicopathological characteristics. Seventy patients (65 men, 5 women) were enrolled in this study. The median age was 68.0 (range=46-91 years). The histological types were squamous cell carcinoma in 62 cases (88.5%), adenocarcinoma in 6 cases (8.6%), and other (undifferentiated large cell carcinoma, basaloid carcinoma) in 2 cases (2.9%). Fifty-five patients had thoracic oesophageal cancer (78.1%), 12 had

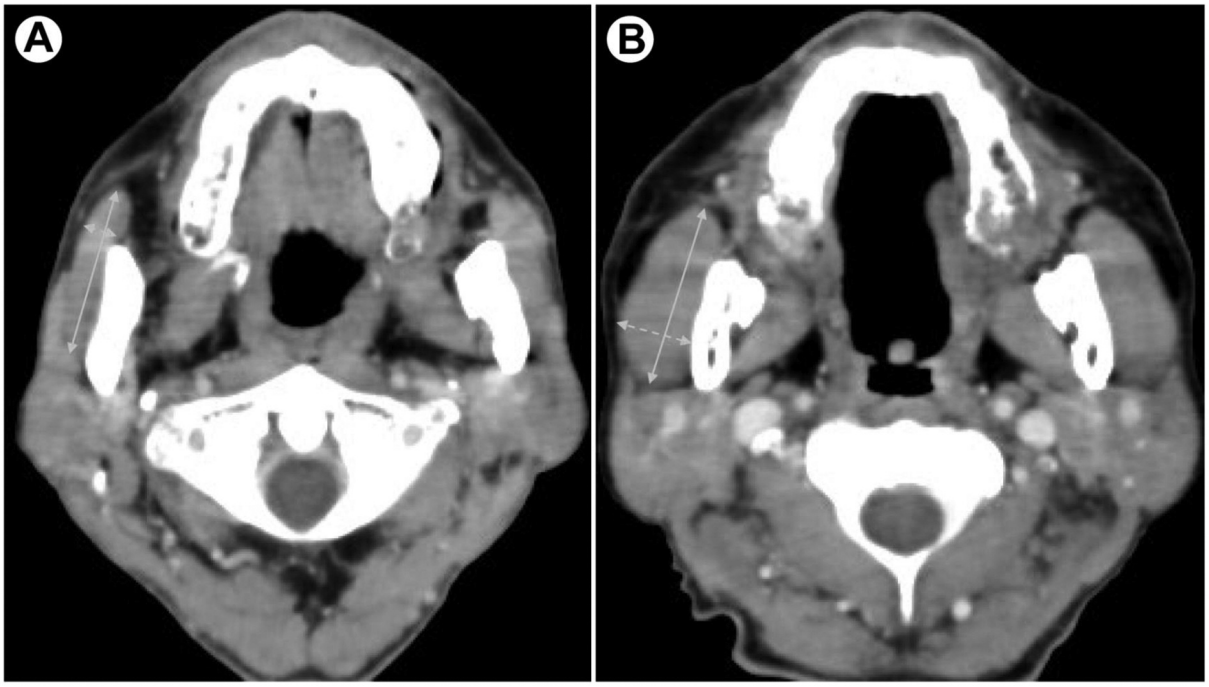

Figure 1. *Masseter muscle cross-sectional area calculation measured in the axial plane 2 cm below the inferior edge of the zygomatic arch. Formula: length of major axes (continuous line) × length of minor axes (dotted line) × π. (A) Masseter muscle sarcopenia and (B) non-masseter muscle sarcopenia.*

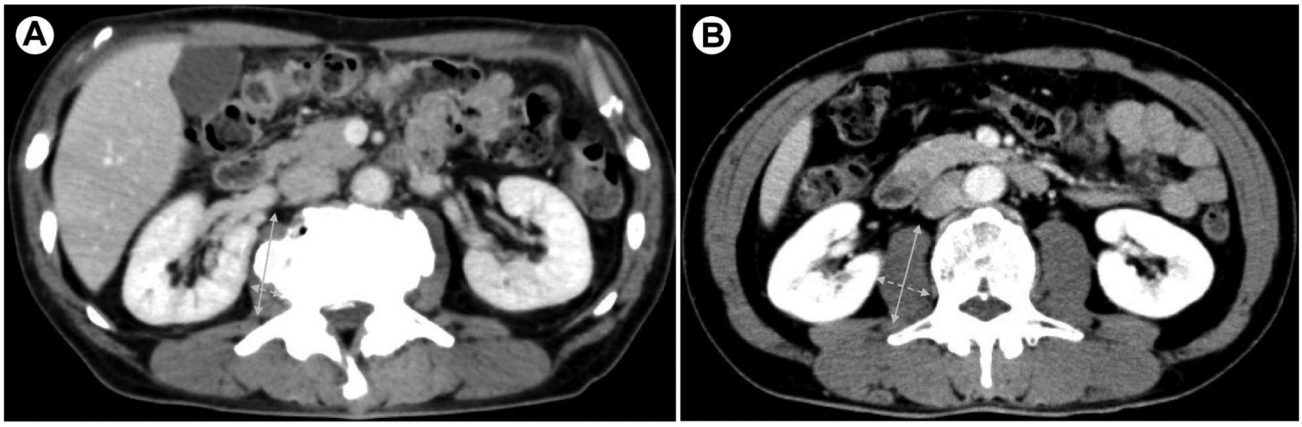

Figure 2. *Psoas muscle mass area calculation measured at the level of the third lumbar vertebra. Formula: length of the major axes (continuous line) × length of the minor axes (dotted line) × π. (A) Psoas muscle sarcopenia and (B) non-psoas muscle sarcopenia.*

abdominal oesophageal cancer (17.1%), and 3 had cervical oesophageal cancer (4.3%). Pathological diagnosis of oesophageal cancer showed that 23 patients had stage I cancer (32.8%), 19 had stage II cancer (27.1%), 26 had stage III cancer (37.1%), and 2 had stage IV cancer (3.0%). Neoadjuvant chemotherapy was administered to 14 patients (20%), preoperative radiation therapy to 4 patients (5.7%), and postoperative adjuvant chemotherapy to 50 patients (71.4%). Postoperative pneumonia was observed in 20 patients (28.5%), anastomotic leakage in 12 patients (17.1%), and recurrent nerve paralysis in 18 patients (25.7%). MMS was diagnosed in 36 patients (51.4%), and PMS was diagnosed in 35 patients (50.0%). The median masseter muscle area was 24.3 cm^2 (range=10.2-60.9 cm^2) for men and 26.2 cm^2 (range=11.9-41.2

Table I. *Demographic and clinicopathological characteristics of the patient cohort.*

Variable	Total	Masseter muscle sarcopenia	Non-masseter muscle sarcopenia	*p*-Value
Patients	70	36	34	
Age, years	68.0 (46-91)	68.5 (52-91)	67.5 (46-88)	0.19
Gender				0.69
Male	65 (92.8%)	33 (91.7%)	32 (94.1%)	
Female	5 (7.2%)	3 (8.3%)	2 (5.9%)	
Body mass index, kg/m^2	18.6 (12.0-34.0)	17.1 (12.0-34.0)	19.3 (14.7-24.7)	<0.01*
Histopathology				0.40
Squamous cell carcinoma	62 (88.5%)	33 (91.6%)	29 (85.3%)	
Adenocarcinoma	6 (8.6%)	2 (5.6%)	4 (11.8%)	
Other	2 (2.9%)	1 (2.8%)	1 (2.9%)	
Primary tumour location				0.286
Cervical	3 (4.3%)	1 (2.8%)	2 (5.9%)	
Thoracic	55 (78.6%)	31 (86.1%)	24 (70.6%)	
Abdominal	12 (17.1%)	4 (11.1%)	8 (23.5%)	
Pathological stage				0.02*
I	23 (32.8%)	6 (16.6%)	17 (50.0%)	
II	19 (27.1%)	11 (30.6%)	8 (23.5%)	
III	26 (37.1%)	18 (50.0%)	8 (23.5%)	
IV	2 (3.0%)	1 (2.8%)	1 (3.0%)	
Preoperative chemotherapy	14 (20.0%)	10 (27.8%)	4 (11.8%)	0.09
Preoperative radiotherapy	4 (5.7%)	3 (8.3%)	1 (2.9%)	0.33
Adjuvant chemotherapy	50 (71.4%)	29 (80.6%)	21 (61.8%)	0.08
Operation time, min	451 (309-613)	439 (309-571)	480 (384-613)	0.09
Intraoperative blood loss, ml	119 (1-1,030)	122 (1-650)	90 (5-1,030)	0.74
Postoperative pneumonia	20 (28.5%)	14 (38.9%)	6 (17.7%)	0.04*
Anastomotic leakage	12 (17.1%)	8 (22.2%)	4 (11.8%)	0.246
Recurrent nerve paralysis	18 (25.7%)	6 (16.6%)	12 (35.3%)	0.08
Masseter muscle area, cm2	25.3 (10.2-60.9)	17.4 (10.2-26.2)	41.2 (28.0-60.9)	<0.01*
Psoas muscle area, cm2	48.3 (12.0-92.5)	39.9 (12.0-82.5)	59.8 (20.9-92.5)	<0.01*

Values are presented as n (%) or median (range). *p-values <0.05 are considered statistically significant.

cm^2) for women. The median psoas muscle area was 51.7 cm^2 (range=12.0-92.5 cm^2) for men and 21.5 cm^2 (range=17.2-41.1 cm^2) for women. The median follow-up duration was 36.0 months (range=1.2-91.3 months). During follow-up, 31 patients (44.3%) experienced recurrence, and 38 (54.3%) died.

In the univariate analysis, the MMS group was significantly associated with a lower body mass index (p<0.01), higher pathological stage (p=0.02), higher rate of postoperative pneumonia (p=0.04), and lower psoas muscle area (p<0.01) than the non-MMS group.

Univariate and multivariate DFS analyses. Table II shows the relationship between the clinicopathological characteristics and DFS after oesophagectomy for oesophageal cancer. In the univariate analysis, DFS was significantly lower in patients with the following: postoperative adjuvant chemotherapy (p<0.01); tumour size >60 mm (p=0.05); vascular invasion (p=0.03); CYFRA >1.1 (p=0.02); stage II, III, and IV cancer (p<0.01); and MMS (p<0.01). In the multivariate analysis, CYFRA >1.1 [odds ratio (OR)=2.88, 95% confidence interval (CI)=1.07-7.72, p=0.04]; stage II, III, and IV cancer (OR=5.82, 95%CI=1.50-22.6, p=0.01); and MMS (OR=5.60, 95%CI=2.24-14.0, p<0.01) were significant independent predictors of DFS.

Impact of MMS and PMS on DFS after oesophagectomy. The Kaplan–Meier curve of MMS and DFS showed that patients with MMS had significantly lower DFS than those without MMS (3-year survival, 31.3% *vs*. 78.7%; log-rank test, p=0.01) (Figure 3A). The Kaplan–Meier curve of PMS and DFS showed that patients with PMS did not have significantly lower DFS than those without PMS (3-year survival, 49.1% *vs*. 62.0%, respectively; log-rank test, p=0.21) (Figure 4A).

Univariate and multivariate OS analyses. Table III shows the relationship between patient clinicopathological characteristics and OS after oesophagectomy for oesophageal cancer. In the univariate analysis, OS was significantly lower in patients who received postoperative adjuvant chemotherapy (p=0.04) and in those with CYFRA >1.1 (p=0.04); stage II, III, and IV cancer

Table II. *Univariate and multivariate analyses of clinicopathological variables in relation to disease-free survival after oesophagectomy for oesophageal cancers.*

Variables		DFS univariate analysis		DFS multivariate analysis	
	n	Hazard ratio (95%CI)	*p*-Value	Hazard ratio (95%CI)	*p*-Value
Male					
Yes	65	1.44	0.619		
No	5	(0.34-6.03)			
Preoperative chemotherapy					
Yes	14	1.49	0.352		
No	56	(0.64-3.49)			
Adjuvant chemotherapy					
Yes	50	4.92	<0.01*	3.32	0.07
No	20	(1.49-16.23)		(0.92-11.9)	
Preoperative radiotherapy					
Yes	4	1.58	0.527		
No	66	(0.38–6.67)			
GPS					
1 or 2	15	1.92	0.10		
0	55	(0.88-4.17)			
Tumour size >60 mm					
Yes	16	2.14	0.05	2.29	0.06
No	54	(1.01-4.57)		(0.98-5.36)	
Squamous cell carcinoma					
Yes	62	2.19	0.282		
No	8	(0.52-9.19)			
Vascular invasion					
Yes	54	3.65	0.03*	0.93	0.927
No	16	(1.11-12.0)		(0.24-3.70)	
SCC >1.4					
Yes	30	2.22	0.03*	1.72	0.226
No	40	(1.09-4.54)		(0.71-4.13)	
CYFRA >1.1					
Yes	43	2.53	0.02*	2.88	0.04*
No	27	(1.12-5.68)		(1.07-7.72)	
CEA >2.1					
Yes	48	1.62	0.243		
No	22	(0.72-3.62)			
Stage II, III, IV cancer					
Yes	47	8.50	<0.01*	5.82	0.01*
No	23	(2.56-28.2)		(1.50-22.6)	
Masseter muscle sarcopenia					
Yes	36	4.96	<0.01*	5.60	<0.01*
No	34	(2.19-11.2)		(2.24-14.0)	
Psoas muscle sarcopenia					
Yes	35	1.58	0.21		
No	35	(0.77-3.21)			
Current smoker					
Yes	40	0.99	0.701		
No	30	(0.97-1.02)			
Anastomotic leakage					
Yes	12	1.33	0.527		
No	58	(0.54-3.25)			
Recurrent nerve paralysis					
Yes	18	0.49	0.144		
No	52	(0.19-1.28)			
Postoperative pneumonia					
Yes	20	0.87	0.736		
No	50	(0.29-1.95)			

CEA: Carcinoembryonic antigen; CI: confidence interval; CYFRA: cytokeratin 19 fragment; DFS: disease-free survival; GPS: Glasgow Prognostic Score; SCC: squamous cell carcinoma-related antigen. **p*-values <0.05 are considered statistically significant.

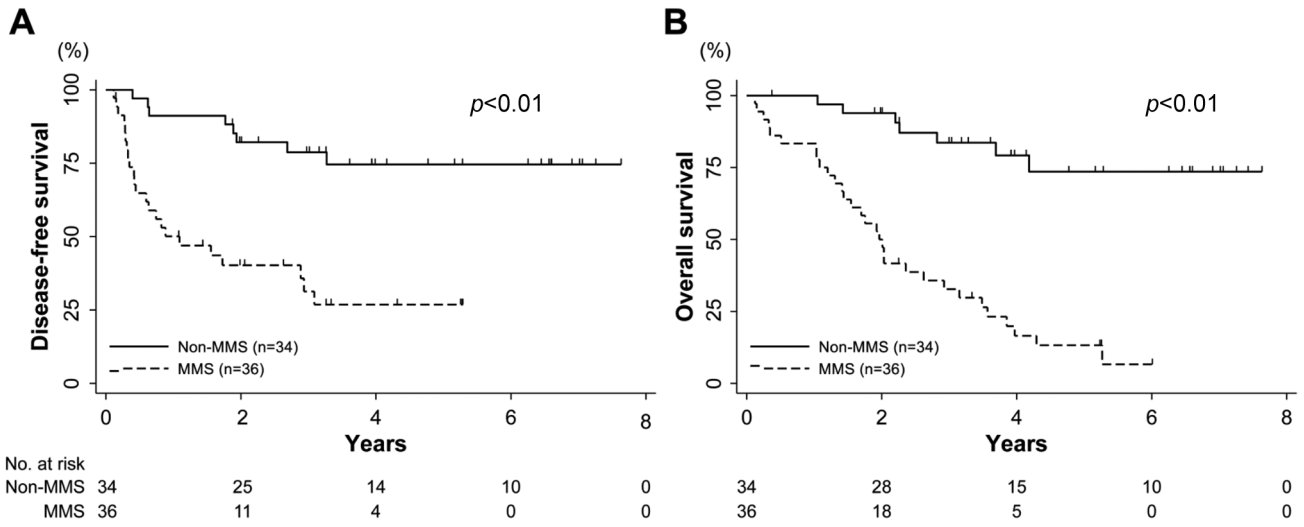

Figure 3. *Kaplan–Meier curves of survival after oesophageal cancer operation in patients with and without masseter muscle sarcopenia (MMS). (A) Kaplan–Meier curves of disease-free survival. (B) Kaplan–Meier curves of overall survival.*

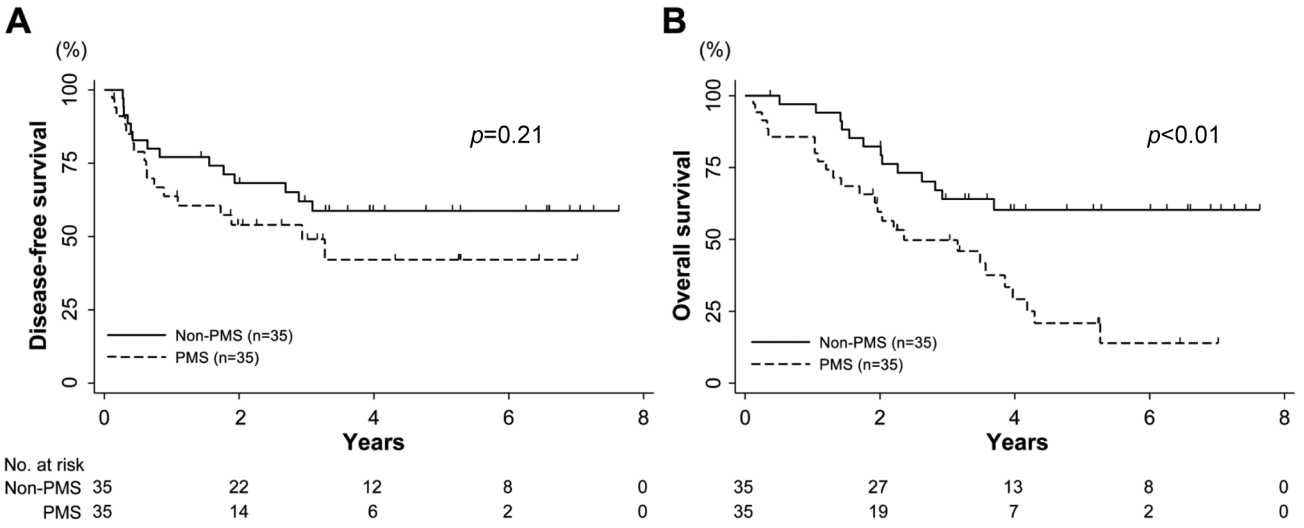

Figure 4. *Kaplan–Meier curves of survival after oesophageal cancer operation in patients with and without psoas muscle sarcopenia (PMS). (A) Kaplan–Meier curves of disease-free survival. (B) Kaplan–Meier curves of overall survival.*

(p<0.01); MMS (p<0.01); PMS (p<0.01); and postoperative pneumonia (p=0.02). In the multivariate analysis, stage II, III, and IV cancer (OR=4.76, 95%CI=1.78-12.7, p<0.01); MMS (OR=5.72, 95%CI=2.30-14.2, p<0.01); and postoperative pneumonia (OR=2.77, 95%CI=1.33-5.74, p<0.01) were significant independent predictors of OS.

Impact of MMS and PMS on OS after oesophagectomy. The Kaplan–Meier curve of MMS and OS showed that patients with MMS had significantly lower OS than those without MMS (3-year survival, 32.7% *vs.* 83.6%; log-rank test, p<0.01) (Figure 3B). Similarly, the Kaplan–Meier curve of PMS and OS showed that patients with PMS had lower OS than those without PMS (3-year survival, 49.8% *vs.* 64.1%; log-rank test, p<0.01) (Figure 4B).

Discussion

This study examined the prognosis of patients with oesophageal cancer using preoperative masseter muscle area.

Table III. *Univariate and multivariate analyses of clinicopathological variables in relation to overall survival after oesophagectomy for oesophageal cancers*.

Variables		OS univariate analysis		OS multivariate analysis	
	n	Hazard ratio (95%CI)	*p*-Value	Hazard ratio (95%CI)	*p*-Value
Male					
Yes	65	1.01	0.986		
No	5	(0.31-3.29)			
Preoperative chemotherapy					
Yes	14	2.09	0.06		
No	56	(0.97-4.49)			
Adjuvant chemotherapy					
Yes	50	2.47	0.04*	1.96	0.187
No	20	(1.03-5.91)		(0.72-5.31)	
Preoperative radiotherapy					
Yes	4	2.25	0.182		
No	66	(0.68-7.41)			
GPS					
1 or 2	15	1.55	0.224		
0	55	(0.77-3.12)			
Tumour size >60 mm					
Yes	16	1.64	0.166		
No	54	(0.81-3.32)			
Squamous cell carcinoma					
Yes	62	1.08	0.882		
No	8	(0.38-3.05)			
Vascular invasion					
Yes	54	2.04	0.110		
No	16	(0.85-4.89)			
SCC >1.4					
Yes	30	1.18	0.607		
No	40	(0.622-2.25)			
CYFRA >1.1					
Yes	43	2.09	0.04*	2.04	0.06
No	27	(1.05-4.19)		(0.99-4.24)	
CEA >2.1					
Yes	48	2.11	0.061		
No	22	(0.96-4.61)			
Stage II, III, IV cancer					
Yes	47	5.17	<0.01*	4.76	<0.01*
No	23	(2.14-12.5)		(1.78-12.7)	
Masseter muscle sarcopenia					
Yes	36	7.34	<0.01*	5.72	<0.01*
No	34	(3.22-16.9)		(2.30-14.2)	
Psoas muscle sarcopenia					
Yes	35	2.69	<0.01*	0.994	0.988
No	35	(1.37-5.29)		(0.48-2.06)	
Current smoker					
Yes	40	0.98	0.942		
No	30	(0.51-1.86)			
Anastomotic leakage					
Yes	12	1.33	0.500		
No	58	(0.58-3.02)			
Recurrent nerve paralysis					
Yes	18	0.85	0.67		
No	52	(0.40-1.79)			
Postoperative pneumonia					
Yes	20	2.13	0.02*	2.77	<0.01*
No	50	(1.12-4.07)		(1.33-5.74)	

CEA: Carcinoembryonic antigen; CI: confidence interval; CYFRA: cytokeratin 19 fragment; GPS: Glasgow Prognostic Score; OS: overall survival; SCC: squamous cell carcinoma-related antigen. **p*-values <0.05 are considered statistically significant.

Few studies have examined the significance of MMS in the field of digestive surgery. The DFS and OS of patients with oesophageal cancer with MMS were significantly lower than those of patients without MMS. To our knowledge, this is the first study to demonstrate an association between MMS and poor prognosis in patients with oesophageal cancer.

Several studies have discussed the relationship between PMS and short- and long-term outcomes in patients with oesophageal cancer (24, 25). Nakashima *et al*. (24) performed an examination of 341 patients with oesophageal cancer who underwent oesophagectomy using the cross-sectional area of the total skeletal muscle at the level of the third lumbar vertebra calculated by preoperative CT. The rates of anastomotic leakage and in-hospital mortality were significantly higher in the group of older adults with sarcopenia than in those without sarcopenia (anastomotic leakage: 31.5% *vs*. 15.2%, p=0.015; in-hospital mortality: 6.8% *vs*. 0.0%, p=0.037), and the OS of patients with sarcopenia was significantly associated with a poor prognosis in the older adult group (p<0.001). Nishigori *et al*. (25) conducted a study on 199 patients with thoracic oesophageal cancer. They assessed skeletal muscle mass using preoperative CT scans by measuring the cross-sectional muscle area at the level of the third lumbar vertebra. Their study found no significant differences in overall complications between the sarcopenia and non-sarcopenia groups (risk ratio=1.10, 95%CI=0.80-1.53, p=0.54); however, pulmonary complications were significantly more frequent in the sarcopenia group than in the non-sarcopenia group (risk ratio=2.63, 95%CI=1.20-5.77, p=0.007).

Sarcopenia assessed by the skeletal muscle mass area at the level of the third lumbar vertebra has recently been shown to be associated with poor prognosis of malignant disease (24, 25). Sarcopenia is also closely associated with aging, and it is irreversible. In some cases, improvement of sarcopenia cannot be achieved even with early physical interventions.

Recently, the concept of frailty has been proposed to also include sarcopenia. Frailty is defined as a state in which an individual's vulnerability increases when exposed to a stressor due to an age-related decrease in standby capacity (26). Frailty is considered a condition not yet requiring nursing care. Nonetheless, frailty is a high-risk state in which patients are prone to health problems due to multifaceted factors including social, mental, psychological, and physical vulnerabilities (26).

Sarcopenia is a key component of physical frailty (27) and the two should be considered as different concepts with different outcomes, as evidenced by the International Classification of Diseases (ICD) including a new code for sarcopenia (ICD-10-CM code M62.84) in 2016. Frailty is reported to first manifest as a weakening of oral function, which results in decreased social interaction followed by declining physical function, such as decreased muscle strength (28). Oral frailty refers to the vulnerability of oral function, which occurs in the early and reversible stages of frailty; therefore, early diagnosis and intervention are crucial (26). Oral frailty was proposed in Japan to highlight the importance of maintaining and improving oral function as a factor influencing physical frailty.

Watanabe *et al*. (17) reported that the risk of frailty was significantly associated with lower occlusal force, masseter muscle thickness, and oral diadochokinesis rate. In particular, the masseter muscle was reported to be an important skeletal muscle for maintaining oral function.

There are a few reports showing an association between MMS and the long-term prognosis of patients undergoing neurosurgery and vascular surgery (21, 22). Tanabe *et al*. (21) investigated the association of masseter sarcopenia and brain atrophy with 1-year mortality among 327 trauma patients over 65 years of age using CT. They reported that masseter sarcopenia [hazard ratio (HR)=2.0, 95%CI=1.2-3.1, p=0.005] and brain atrophy (HR=2.0, 95%CI=1.1-3.5, p=0.02) were both independently and cumulatively associated with mortality. Furthermore, Oksala *et al*. (22) measured the masseter muscle area using preoperative brain CT in 242 patients who underwent carotid endarterectomy. They found that increased masseter muscle area was significantly associated with lower mortality (HR=0.76, 95%CI=0.61-0.96, p=0.023). However, few studies have been published on the association between MMS and prognosis in the gastrointestinal field. Therefore, head and neck CT is not routinely performed preoperatively in this field.

In our institution, it was possible to evaluate the masseter muscle area in the preoperative evaluation of oesophageal cancer because the imaging range of CT was expanded to the head and neck to evaluate the carotid artery prior to cervical dissection. Previous studies have measured the masseter muscle area using software (21, 22), but this method incurs additional costs, is more time-consuming, and requires more effort. Therefore, we simply analysed the masseter muscle area using CT with the following formula: length of the major axes × the length of the minor axes × π; this formula is usually utilized in measuring the psoas muscle area (23). We believe that our new method of measuring the masseter muscle area is useful, simple, and minimally invasive.

Remarkably, MMS and PMS in this study were both significantly associated with poorer OS, but only MMS was significantly associated with poorer DFS (MMS, p<0.01; PMS, p=0.21). The reason why MMS was significantly associated with poor DFS remains unknown. However, it is possible that the decrease in oral function due to MMS resulted in a decrease in medication compliance or that adjuvant chemotherapy was intermittent.

In addition, the MMS group in this study had a significantly higher occurrence of postoperative pneumonia than the non-MMS group. Aspiration pneumonia due to decreased oral function leads to poor OS and long-term

hospital stays. Preoperative evaluation of MMS may be useful in predicting pneumonia as a short-term complication.

The most important implication of this study is that preoperative evaluation of MMS may allow early diagnosis of frailty and thus early intervention during the reversible stage. MMS correlates with oral frailty and may reflect a decrease in systemic skeletal muscle mass earlier than PMS. Preoperative physical intervention [regular oral care, denture adjustment, rehabilitation for occlusal force (oral exercises, etc.)], promotion of social participation, and psychological intervention in the frail phase (the stage preceding sarcopenia) may improve the prognosis of patients with malignancies (29, 30). In the field of digestive surgery, oesophageal, gastric, and colorectal cancers may be related to prognosis by a similar mechanism. In the future, further evaluation of other organs is required.

This study has some limitations. First, it was a retrospective study with a small number of cases from a single institution. In addition, masseter sarcopenia is a novel concept, and diagnostic criteria have not yet been established. Furthermore, the MMS group was significantly more likely to have stage II, III, or IV cancer than the non-MMS group, which suggests that the patient backgrounds were not completely unified. The MMS group may have had a higher cancer stage progression because interaction with others, such as social participation and medical examinations, decreases during the frail period. Subsequently, the disease progresses and becomes symptomatic without patients going to the hospital.

This study is the first report to suggest MMS as a useful prognostic indicator in the field of digestive surgery. Sarcopenia intervention and early frailty intervention *via* preoperative evaluation of oral function may improve the prognosis of gastrointestinal cancers. We are currently conducting a prospective study on early intervention before surgery for gastrointestinal cancers in patients with oral frailty.

Conclusion

This retrospective study showed that preoperative MMS was significantly associated with poorer DFS and OS in patients who underwent oesophagectomy for oesophageal cancer. Preoperative masseter muscle area measurement may be a useful prognostic indicator for patients with oesophageal cancer.

Conflicts of Interest

The Authors declare no conflicts of interest for this article.

Authors' Contributions

Study conception and design: Kamada; Acquisition of data: Kamada, Fuse, Takahashi, Nakashima, Nakaseko, Yoshida, Eto; Analysis and interpretation of data: Kamada, Ito; Drafting of manuscript: Kamada; Critical revision: Ito, Ohdaira, Suzuki.

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