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ORIGINAL PAPER

Skeletal muscle mass as a predictor of the response to neo-adjuvant chemotherapy in locally advanced esophageal cancer

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Abstract

Undernutrition and sarcopenia are associated with a higher incidence of chemotherapy-related toxicity and a poor prognosis in several kinds of cancer, but the impact of sarcopenia on the outcomes of chemotherapy for esophageal cancer remains unclear. Thus, the purpose of this retrospective study was to investigate whether sarcopenia affects the efficacy and toxicities of chemotherapy for advanced esophageal cancer patients. Data were collected from 31 esophageal cancer patients who underwent neo-adjuvant chemotherapy followed by surgery. Body composition was assessed at the start of chemotherapy by bioelectrical impedance analysis, and outcomes of chemotherapy were compared between sarcopenic and non-sarcopenic groups. Of the 31 patients, sarcopenia was observed in 16 (51.6%). The incidence of toxicities was not different between the two groups. However, as for pathologic response, a good therapeutic effect (Grade 2 or higher) was more common in the non-sarcopenic group than in the sarcopenic group (53.3% vs. 25.0%). Multivariate analysis showed that sarcopenia was an independent predictor of poor pathological response (odds ratio 8.02; $P=0.037$). The results of this study suggest the potential utility of sarcopenia assessment in neoadjuvant patient selection strategies.

Keywords Esophageal cancer · Sarcopenia · Chemotherapy · Bioelectrical impedance analysis

Introduction

Esophageal cancer is a highly aggressive malignant tumor, and the outcomes of patients with esophageal cancer remain poor, despite the development of multimodality therapies, including surgery, chemotherapy, and radiation therapy [1, 2]. Most patients are diagnosed in advanced stages, and chemotherapy plays a crucial role in the management of patients with not only metastatic, but also locally advanced, potentially operable esophageal cancer. Since the therapeutic index of chemotherapeutic drugs for esophageal cancer is narrow, it is important to identify factors that predict individual variations in toxicity and efficacy of chemotherapy. However, in esophageal cancer, predictors of toxicity and efficacy of chemotherapy have not been identified.

Sarcopenia is a clinical condition including loss of skeletal muscle mass and an associated decreased functional ability, due to aging or an induced catabolic state [3–5]. In addition, sarcopenia is prevalent in patients with various malignancies and has recently been recognized as indicating a poor prognosis in patients with various malignancies, such as lung and gastrointestinal cancers [6], pancreatic cancer [7], melanoma [8], and liver metastasis from colorectal cancer [9]. Profound weight loss and malnutrition subsequent to severe dysphagia are cardinal symptoms of esophageal cancer. It has been reported that 25–80% of patients with esophageal cancer were sarcopenic at the time of diagnosis [10–17]. Although alterations of body composition are

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associated with postoperative morbidity and mortality in patients with esophageal cancer [17–20], the clinical impact of sarcopenia on the outcomes of chemotherapy is unknown.

The present study focused on skeletal muscle mass evaluated by multifrequency bioelectrical impedance analysis (BIA) in esophageal cancer patients. The aim of this study was to determine whether sarcopenia defined by BIA could be used to predict the outcomes of neo-adjuvant chemotherapy in locally advanced esophageal cancer patients.

Patients and methods

Study subjects

This study retrospectively analyzed 89 consecutive esophageal cancer patients who received neoadjuvant chemotherapy followed by surgery at the Department of Molecular Gastroenterology and Hepatology, Kyoto Prefecture University of Medicine Hospital between April 2013 and December 2017. Of these 89 patients, 31 underwent body composition assessment by multifrequency bioelectrical impedance with eight tactile electrodes (InBody 720; Biospace Co., Ltd., Seoul, Korea) prior to neoadjuvant chemotherapy. This study was approved by the Medical Ethics Review Committee of the Kyoto Prefectural University of Medicine (Approval No. ERB-E-42-1).

Body composition assessment

Body composition was assessed prior to chemotherapy using the InBody 720. With this method, body weight, body mass index (BMI), body fat mass, and lean skeletal muscle mass were measured automatically and simultaneously. The skeletal muscle index (SMI) (kg/m^2) was calculated as the appendicular skeletal muscle mass divided by the square of the height. In the present study, sarcopenia was defined as an SMI less than the cut-off values of 7.0 kg/m^2 for men and 5.7 kg/m^2 for women based on the consensus report of the Asian Working Group for Sarcopenia [21].

Neo-adjuvant chemotherapy and pre-chemotherapy data collection

The drugs administered during cycle 1 chemotherapy were cisplatin and 5-fluorouracil (5-FU) in the doublet regimen (FP regimen), and cisplatin, 5-FU, and docetaxel in the triplet regimen (DCF regimen). The FP regimen consisted of cisplatin 80 mg/m^2 on day 1 and 5-FU 800 mg/m^2 infusions days 1–5, and the DCF regimen consisted of docetaxel 70 mg/m^2 on day 1, cisplatin 70 mg/m^2 on day 1, and 5-FU 700 mg/m^2 infusions on days 1–5. The length of one chemotherapy cycle of each regimen was 21 days.

Data from blood tests before neo-adjuvant chemotherapy, including neutrophil count, total lymphocyte count, C-reactive protein (CRP), and albumin, were collected from the patients' records. The modified Glasgow prognostic score (mGPS) was scored as 0, 1, or 2 based on CRP (> 1.0 mg/dL) and hypoalbuminemia (< 3.5 g/dL), as previously described [22]. To summarize, patients with both increased CRP and hypoalbuminemia were given a score of 2, patients with either increased CRP or hypoalbuminemia were given a score of 1, and those with normal CRP and without hypoalbuminemia were given a score of 0.

Outcome evaluation

Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Objective tumor response was assessed by computed tomography scans in accordance with the Response Evaluation Criteria in Solid Tumor

Table 1 Patients' characteristics

	No. of patients $n = 31$
Gender, *n*[%]	
Male	27[87.1]
Female	4[12.9]
Age, median [range]	66[41–75]
Tumor location, *n*[%]	
Upperesophagus	9[29.0]
Middle esophagus	16[51.6]
Distal esophagus	6[19.4]
Stage (UICC, 7th ed.), *n*[%]	
II	3[9.7]
III	28[90.3]
Tumor depth, *n*[%]	
cT1	2[6.5]
cT2	5[16.1]
cT3	22[71.0]
cT4	2[6.5]
Histology, *n*[%]	
Squamous cell carcinoma	31[100]
Adenocarcinoma	0[0]
Chemotherapy, *n*[%]	
Doublet (5-FU + CDDP)	7[22.6]
Triplet (5-FU + CDDP + DTX)	24[77.4]
BMI, mean ± SD	21.31 ± 3.29
Body fat weight, mean ± SD	13.38 ± 5.38
SMI, mean ± SD	6.773 ± 0.961
Sarcopenic, *n*[%]	16[51.6]
Sarcopenic obesity, *n*[%]	0[0]

SMI skeletal muscle mass index

(RECIST version 1.1) criteria. Pathological response was evaluated according to the Japanese Classification of Esophageal Cancer (11th ed.) [23] that categorizes tumors into four levels of response (Grades 0–3). Grade 3 indicates no viable cancer cells. Grade 2 indicates viable cancer cells accounting for less than 1/3 of tumor tissue, while other cancer cells are severely degenerated or necrotic. Grade 1 is classified as Grades 1a and 1b. Grade 1a indicates viable cancer cells accounting for 2/3 or more tumor tissue, while Grade 1b indicates viable cancer cells accounting for 1/3 or more, but less than 2/3, of tumor tissue. Grade 0 indicates no recognizable cytological or histological therapeutic effect.

Statistical analysis

The categorical variables were analyzed by χ^2 tests to evaluate the correlations between sarcopenia and the clinical and pathological variables. The numerical variables were analyzed with Student's *t*-test or with the Mann–Whitney *U* test, as appropriate. A Cochran–Armitage trend test was used to evaluate the association between the prevalence of

Table 2 Clinical characteristics according to the presence of sarcopenia

	Sarcopenic $n=16$	Non-sarcopenic $n=15$	*P*-values
Gender, *n*[%]			0.015
Male	12[75]	15[100]	
Female	4[25]	0[0]	
Age, median [range]	64[41–75]	70[55–75]	0.126
Tumor location, *n*[%]			0.262
Upper	4[25]	2[13.3]	
Mid	6[37.5]	10[66.7]	
Distal	6[37.5]	3[20]	
Stage (UICC, 7th ed.), *n*[%]			0.502
II	1[6.3]	2[13.3]	
III	15[93.4]	13[86.7]	
Tumor depth, *n*[%]			0.373
cT1	1[6.3]	1[6.7]	
cT2	3[18.8]	2[13.3]	
cT3	10[62.5]	12[80]	
cT4	2[12.5]	0[0]	
Chemotherapy, *n*[%]			0.598
Doublet	3[18.8]	4[26.7]	
Triplet	13[81.2]	11[73.3]	
BMI, mean ± SD	19.11 ± 1.258	23.65 ± 1.298	0.001
Body fat weight, mean ± SD	11.32 ± 2.59	15.59 ± 2.687	0.026
SMI, mean ± SD	6.03 ± 0.305	7.57 ± 0.316	0.001
Hematologica adverse events			
Neutropenia (Grade ≥ 3), *n*[%]	9[56.3]	9[60]	0.833
Thrombocytopenia (Grade ≥ 3), *n*[%]	1[6.3]	1[6.7]	0.962
Non-hematologica adverse events			
Febrile neutropenia, *n*[%]	4[25.0]	5[33.3]	0.609
Diarrhea (Grade ≥ 3), *n*[%]	1[6.3]	0[0]	0.221
Nausea (Grade ≥ 3), *n*[%]	1[6.3]	0[0]	0.221
Heart failure (Grade ≥ 3), *n*[%]	0[0]	1[6.7]	0.222
Objective response, *n*[%]			0.605
PR	10[62.5]	8[53.3]	
SD	6[37.5]	7[46.7]	
Pathological response, *n*[%]			0.103
Grade < 2	12[75]	7[46.7]	
Grade ≥ 2	4[25]	8[53.3]	

SMI skeletal muscle mass index, *PR* partial response, *SD* stable disease

sarcopenia and the pathological response grade. Multivariate logistic analysis was performed to evaluate the effects of clinical variables on the pathologic response. Results of the logistic regression analysis are given as adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and *P* values. Differences were considered significant when the two-sided *P* value was less than 0.05. All statistical analyses were performed using JMP 13 software (SAS Institute, Inc., Cary, NC, USA).

Results

Patients' characteristics

The clinical and pathological characteristics of the 31 patients included in the study are shown in Table 1. Patients' ages ranged from 41 to 75 years, and there was a male predominance (87.1%). The histological subtype was squamous cell carcinoma in all cases. The average BMI was 21.31 kg/m^2, and 13 patients (41.9%) had a BMI < 20 kg/m^2. Although sarcopenia was observed in 16 patients (51.6%) prior to neoadjuvant chemotherapy, none had sarcopenic obesity, i.e., sarcopenia combined with BMI ≥ 25 kg/m^2.

Sarcopenia and clinical outcomes

There were no significant differences in age, tumor location and depth, stage, chemotherapy regimen, and best objective response between the sarcopenic and non-sarcopenic groups (Table 2). The proportion of females was higher in the sarcopenic group (25% vs. 0%). A comparison of the pre-chemotherapy laboratory data showed that the differences in albumin levels, CRP values, mGPS scores, and neutrophil-to-lymphocyte ratios (NLRs) were not significant (data not shown). BMI and body fat weight were significantly lower in the sarcopenic group than in the non-sarcopenic group.

The incidences of both Grade 3/4 hematological and non-hematological (i.e., febrile neutropenia and gastrointestinal complications) toxicities were not different between the two groups. With respect to the pathological response, 2 patients were classified as Grade 0, 14 patients as Grade 1a, 3 patients as Grade 1b, 9 patients as Grade 2, and 3 patients as Grade 3. The prevalence of sarcopenia showed a significant trend to decrease according to the pathological response grade ($P = 0.038$, Fig. 1). In the sarcopenic group, the rate of Grade 2 or higher, which is judged as having a therapeutic effect, was 25%, and it showed a tendency to be lower than 53.3% in the non-sarcopenic group (Table 2, $P = 0.103$).

To further evaluate the clinical significance of sarcopenia in neo-adjuvant chemotherapy for locally advanced esophageal cancer patients, whether the presence of sarcopenia could serve as a predictor of therapeutic effect was

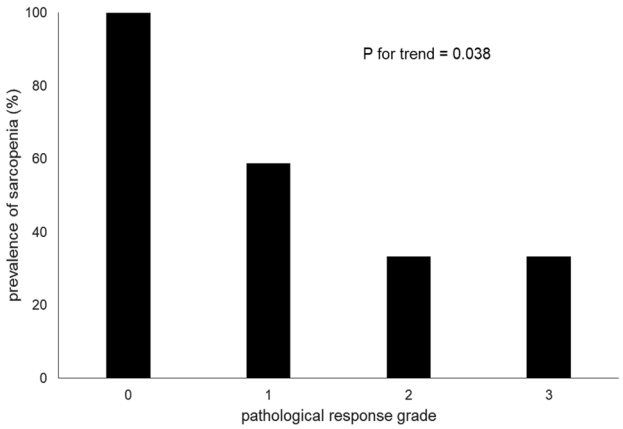

Fig. 1 The prevalence of sarcopenia according to the grade of pathological response. The Cochran–Armitage trend test shows a significant decrease in the prevalence of sarcopenia with increasing grades of pathological response ($P = 0.038$)

investigated. On univariate analyses, higher levels of mGPS ($P = 0.0385$) were related to a poor therapeutic response (under Grade 2), and advanced age (≥ 65) ($P = 0.141$) and the presence of sarcopenia ($P = 0.103$) tended to be related to a poor therapeutic response, but not significantly. In a multiple logistic regression model for pathological response grade, three explanatory variables showing a univariate association ($P < 0.20$) with poor therapeutic response were included (mGPS, age, and sarcopenia). Multivariable analysis demonstrated that sarcopenia (OR 8.02; 95% CI 1.122 = 165.41; $P = 0.037$) and advanced age (9.73; 95% CI 1.344 = 202.18; $P = 0.022$) were independent predictors of a poor therapeutic response to neo-adjuvant chemotherapy in locally advanced esophageal cancer patients (Table 3).

Discussion

The present study showed that 51.6% of locally advanced esophageal cancer patients were considered sarcopenic prior to neoadjuvant chemotherapy, and the presence of sarcopenia and advanced age (≥ 65 years) were independent predictors of a poor pathological response to neo-adjuvant chemotherapy. The present report is the first showing the association between sarcopenia and the efficacy of neo-adjuvant chemotherapy in esophageal cancer. On the other hand, the presence of sarcopenia did not show any association with hematological or non-hematological toxicities in this study.

There is mounting evidence that sarcopenia or sarcopenic obesity is independently associated with a poor response to cancer therapy in various malignancies, such as melanoma [8] and renal cell [24], hepatic [25], colorectal [26], pancreatic [7], breast [27], and lung cancers [6]. However, there

has been a paucity of literature exploring the effects of sarcopenia on the toxicity of and the response to chemotherapy for esophageal cancer. The clinical impact of sarcopenia on toxicity of neo-adjuvant chemotherapy in esophageal cancer patients has been investigated in a few previous studies with variable conclusions (Table 4). Several studies have reported that sarcopenia or sarcopenic obesity was associated with increased toxicity of neo-adjuvant chemotherapy in locally advanced esophageal cancer patients [11, 12, 16]. On the other hand, Yip et al. showed that the presence of sarcopenia prior to neo-adjuvant chemotherapy was not associated with chemotherapy dose reduction [13]. In the present study, the presence of sarcopenia was not associated with adverse events and dose reduction of neo-adjuvant chemotherapy. One reason why there was no association between the presence of sarcopenia and dose-limiting toxicity (DLT), such as neutropenia and febrile neutropenia, in the present study was that most patients (especially 92% of DCF therapy cases) were given prophylactic G-CSF.

In esophageal cancer, few reports have evaluated the impact of sarcopenia on the efficacy of chemotherapy. Two previous reports showed that the presence of sarcopenia was not associated with clinical or pathological response to chemotherapy or chemoradiotherapy [13, 16]. In contrast, the present study showed the association between the presence of sarcopenia and the pathologic response to neo-adjuvant chemotherapy. Different results among reports may be due to differences in treatments

Table 3 Odds ratios for pathological response of clinical variables and body composition

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*P*-values	Odds ratio	95% CI	*P*-values
Age (≥ 65 vs. < 65)			0.141			0.022
< 65	1			1		
≥ 65	3.03	0.67–13.61		9.73	1.344–202.180	
Gender (male vs. female)			0.623			
Male	1					
Female	1.7	0.20–14.02				
Tumor depth (cT1 or cT2 vs. cT3 or cT4)			0.525			
cT1 or cT2	1					
cT3 or cT4	0.56	0.089–3.489				
Stage (II vs. III)			0.839			
I	1					
II	0.77	0.062–9.579				
Chemotherapy (doublet vs. triplet)			0.525			
Doublet	1					
Triplet	0.56	0.089–3.489				
Pre-chemotherapy						
Serum albumin (≥ 3.5 vs. < 3.5)		0.528–48.860	0.111			
≥ 3.5	1					
< 3.5	5.07					
CRP (> 1.0 vs. ≤ 1.0)			0.195			
≤ 1.0	1					
> 1.0	3.92	0.399–38.700				
NLR (> 2.5 vs. ≤ 2.5)			0.789			
> 2.5	1					
≤ 2.5	1.22	0.279–5.371				
mGPS (0 or 1 vs. 2)			0.038			0.057
0 or 1						
2						
Sarcopenia (yes vs. no)			0.103			0.037
No	1			1		
Yes	3.42	0.750–15.670		8.02	1.122–165.410	

NLR neutrophil-to-lymphocyte ratio, *mGPS* modified Glasgow prognostic score

Table 4 Summary of studies on the impact of sarcopenia on the outcomes of chemo(radio)therapy in patients with esophageal cancer

Study	Disease status	No. of patients	Method of measuring skeletal muscle mass	Percentage of sarcopenia (sarcopenic obese)	Findings
Awad et al. [10]	Resectable (T1 11%, T2 21%, T3 20%, T4 2%)	47 (Adeno 100%)	CT (L3 skeletal muscle index)	57 (15)	NAC was associated with an increase in the proportion of patients becoming sarcopenia
Yip et al. [13]	Resectable (stage 0, 6%; I, 3%; II, 51%; III, 40%)	35 (Adeno 86%, SqCC 14%)	CT (L3 skeletal muscle index)	26 (3)	Sarcopenia was not associated with DLT and chemotherapy response
Anandavadivelan et al. [11]	Resectable (T1 3%, T2 28%; T3 69%)	72 (Adeno 67%, SqCC 33%)	CT (L3 skeletal muscle index)	43 (14)	Sarcopenia and sarcopenic obese were associated with DLT during NAC and OS
Tan et al. [12]	Resectable (stage I, 23.6%; II, 30.3%; III, 46.1%)	89 (Esophago-gastric cancer) (Adeno 80.9%, SqCC 19.1%)	CT (L3 skeletal muscle index)	49.40	Sarcopenia was associated with DLT during NAC
Murimwa et al. [16]	Resectable (stage I, 5.4%; II, 37.5%; III, 55.4%)	56	CT (L4 skeletal muscle index)	41	Sarcopenia was associated with acute Grade $\geq$ 3 toxicity with chemoradiation
Our study	Resectable (stage II, 9.7%; III, 90.3%)	31 (SqCC 100%)	BIA	51.60	Sarcopenia was associated with pathological response in patients undergoing NAC

Adeno adenocarcinoma, *SqCC* squamous carcinoma, *DLT* dose-limiting toxicity, *NAC* neo-adjuvant chemotherapy

(chemoradiotherapy vs. chemotherapy), the race of the subjects (Western vs. Eastern populations), histological type of esophageal cancer (adenocarcinoma vs. squamous cell carcinoma), muscle mass measurement methods (computerized tomography vs. BIA), and so on (Table 4).

Several limitations of this study should be acknowledged. First, this was a retrospective study with a relatively small sample size. Therefore, the results of this study should be validated in a larger prospective study. In addition, only skeletal muscle mass could be evaluated for sarcopenia assessment due to the retrospective nature of the study. Assessing function through handgrip strength and the timed get up and go test would add validity to the assessment of sarcopenia. Future studies should evaluate both muscle mass and function for the assessment of sarcopenia.

In conclusion, the presence of sarcopenia prior to neoadjuvant chemotherapy was an independent predictor of a poor pathologic response in the present study. This result suggests the potential utility of sarcopenia assessment in neoadjuvant patient selection strategies. Moreover, the result of the present study also suggests the need for a future study to verify whether nutritional intervention can improve the efficacy of neo-adjuvant chemotherapy. Further studies are needed to define the clinical significance of sarcopenia in chemotherapy for esophageal cancer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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