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Association Between Sarcopenia and Clinical Outcomes in Patients With Esophageal Cancer Under Neoadjuvant Therapy

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Abstract. *Background/Aim: This study aimed to evaluate the association of sarcopenia and Clinical Outcomes with esophageal cancer under neoadjuvant chemoradiotherapy (CRT). Patients and Methods: A retrospective study assessing patients with esophageal cancer who underwent CRT between 2001 and 2014 was conducted in the medical center. Hospital patients' records on sarcopenia and treatment outcomes were statistically analyzed. Results: The sarcopenia group had significantly lower body mass index than the non-sarcopenia group. CRT-related severe adverse events with mucositis, fever, and neutropenic fever were greater in the sarcopenia group. Overall survival and disease-free survival were significantly better in the non-sarcopenia group. Sarcopenic patients who received nutritional support with enteral access had less severe mucositis. There was no difference in mortality of sarcopenia patients with nutritional support via enteral access or without. Moreover, sarcopenia and advanced tumor stage were independent factors for mortality outcome. Conclusion: Sarcopenia before CRT may be associated with increased toxicities and worse overall survival/ disease-free survival in esophageal cancer patients.*

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Approximately 400,000 deaths related to esophageal cancer (EC) were reported worldwide in 2012, with developing countries accounting for 75% of this number (1, 2). In Taiwan, the squamous cell carcinoma histological type accounts for >90% of cases and is more chemo-radiosensitive than adenocarcinoma (3). Preoperative neoadjuvant chemoradiotherapy (CRT) in patients with EC has been reported to improve survival. Unfortunately, the 5-year survival rate post-treatment is rarely greater than 30% (4, 5). Therefore, the development of a more precise risk stratification tool for EC is warranted.

Nutritional status plays a critical role in the development and progression of EC. A substantial deterioration in patients' nutritional status during aggressive treatments is common; the association between weight loss, low body mass index (BMI), and survival outcome is unclear (6-10). Sarcopenia appears to be a more accurate indicator of malnutrition than more conventional assessments such as BMI, albumin level, or prealbumin level (11). In recent decades, sarcopenia has been identified as a negative prognostic factor in various clinical cancer aspects, such as cancer treatment tolerance and overall survival (12-16). The etiology of sarcopenia is multifactorial, with contributions from physical inactivity, systemic inflammation, increased metabolic rate, and reduced nutrient intake (17, 18). In patients with EC, it has been reported that 25%-80% have sarcopenia at the time of diagnosis (18-22). However, few studies (10, 21, 22) have focused on patients with esophageal

squamous cell carcinoma (ESCC) with sarcopenia undergoing CRT, and the associated clinical outcomes remain to be elucidated. Thus, we designed the current study to investigate pretreatment sarcopenia and its association with neoadjuvant treatment tolerance, nutritional status, and survival of patients with ESCC.

Patients and Methods

Patients. The protocol employed in this retrospective study was approved by our local institutional review board and ethics committee. Patients included in the current analysis were the same patients as in our previous report (23), and included all consecutive patients who underwent CRT at Hualien Tzu Chi General Hospital between 2001 and 2014. Patients were confirmed as having 1) IA to IIIC ESCC; 2) completed radiotherapy and two cycles of chemotherapy with cisplatin combined with continuous infusion of fluorouracil for squamous cell carcinoma, prior to surgery. Patients were excluded if they 1) were missing pre-therapeutic computed tomography (CT) images; 2) had a previous history of cancer and concurrent uncontrolled medical illness; 3) had only surgery, only radiotherapy or supportive care. Patients were subsequently stratified based on the presence or absence of sarcopenia. This index was calculated on the day before CRT. A subset analysis was performed of sarcopenia patients with or without enteral access (EA) to improve their nutritional status before CRT. Patients received EA at the attending surgeon's discretion. The patients undergoing EA received adequate nutrition with an appropriate balance of carbohydrates, protein, and lipids. The formulas were not enriched with immunonutrients.

Body composition. CT images from whole-body ^{18}F-FDG positron emission tomographic-computed tomography (PET/CT) scans were used to assess skeletal muscle area (SMA). SMA was quantified at the axial slice nearest the inferior aspect of the third lumbar vertebra body (L3) by applying a threshold within −29 to +150 Hounsfield units (24). The region-growing algorithm (25) was used to facilitate the automatic segmentation of all skeletal muscle mass in the slice. Skeletal muscle contours on the CT image were modified when necessary. L3 was chosen because the cross-sectional area (cm^2) of skeletal muscle in this region has been found to be most correlated with whole-body skeletal muscle mass (26). The L3 skeletal muscle index (SMI, cm^2/m^2) was calculated as SMA normalized by the square of the height. All images were analyzed using open-source software OsiriX (Pixmeo, Geneva, Switzerland) (27). Sarcopenia was defined using previously determined thresholds of less than 52.4 cm^2/m^2 for men and less than 38.5 cm^2/m^2 for women (10, 16, 28).

Follow-up. Nutritional parameters for both groups (with and without sarcopenia) were collected from the clinical documentation and included: 1) BMI evaluated in both groups at pre-CRT and recorded within one week of the second cycle chemotherapy (post-CRT). Post-CRT low BMI (BMI <18.5 kg/m^2) was defined by the European Society for Clinical Nutrition and Metabolism (ESPEN) malnutrition criteria (29). The blood data were collected within one week of the two-cycle chemotherapy. Severe adverse events (AEs ≥grade 3) and inflammatory status were assessed during the course of chemotherapy. AEs and laboratory abnormalities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0 (30). Survival analysis was performed for overall survival (OS) and disease-free survival (DFS). The OS was calculated from the date of diagnosis to the date of death or was censored at the date of the last follow-up for surviving patients. DFS was defined as the time between the end of treatment and the date of recurrence or the date of death or censoring at the date of the last follow-up.

Statistical analysis. The data were coded and analyzed using the SPSS statistical package, version 20 (SPSS, Chicago, IL, USA). The descriptive statistics such as frequency, percentage, mean, and standard deviation (SD) are provided by sarcopenia and non-sarcopenia groups. The Chi-square test or Fisher's exact test was performed for comparison between the two groups for categorical variables, and significant dependent variables were then further analyzed using binomial logistic regression. The Kaplan-Meier method was used to estimate the OS and DFS differences using the log-rank test. A Cox regression analysis was performed for significant findings regarding mortality.

Results

Patient characteristics. A total of 107 patients were assessed for eligibility for this study. Sarcopenia was identified on pre-CRT imaging in 65 patients (67%); none had sarcopenic obesity, *i.e.*, sarcopenia combined with BMI ≥25 kg/m^2 (27, 28). The presence of sarcopenia was associated with a lower BMI (19.7±2.8 *vs.* 24.5±4.1 kg/m^2, $p<0.001$) compared to patients without sarcopenia. There were no significant differences in age, sex, tumor factors, and the prevalence of smoking, alcohol consumption, and betel nut chewing between groups. The demographics of the study group are shown in Table I.

AEs, treatment tolerability, and nutritional status after CRT. The results are presented in Table II. Regarding gastrointestinal side effects, the frequency of grade 3 to 4 mucositis in the sarcopenia group was significantly greater than that in the non-sarcopenia group (27.6% *vs.* 9.5%, $p=0.016$). For hematologic AEs, anemia occurred more often (12.6%) in the group with sarcopenia than in the group without (4.8%), but the difference was not statistically significant ($p=0.052$). Regarding the inflammatory status, grade 3 to 4 fever and neutropenia fever were observed more frequently in the group with sarcopenia (21.5 % *vs.* 7.1%, $p=0.047$; 16.9% *vs.* 2.4%, $p=0.044$, respectively) than in the group without. There were no significant differences between the two groups in the biochemical evaluation, which included plasma creatinine, alanine aminotransferase, and aspartate aminotransferase (data not shown). The discontinuation of CRT rate was greater in the group with sarcopenia (18.5% *vs.* 2.4%, $p=0.013$). The most frequent AE leading to discontinuation was fever, accounting for 8 (61.5%) of 13 AEs, and 1 (100%) of 1 AEs in the two groups, respectively, and therapy was resumed when the symptoms resolved. Regarding the nutritional status after CRT, low BMI (≤18 kg/m^2) occurred more frequently in the group with sarcopenia (73.8 % *vs.* 52.4%, $p=0.032$) than in the group

Table I. *Patient characteristics classified by pretreatment sarcopenia.*

Variable	Total	Sarcopenia	Non-sarcopenia	*p*-Value
Number	107	65	42	
Age, years				
Mean±SD	54.1±7.5	52.2±7.1	54.4±8.0	0.142
Gender, n (%)				
Male	101 (94.4)	63 (96.9)	38 (90.5)	0.157
Female	6 (5.6)	2 (3.1)	4 (9.5)	
Alcohol, n (%)				
Never drinker	0	0	0	N/A
Ever drinker	107 (100)	65 (100)	42 (100)	
Smoking, n (%)				
Never drinker	1 (0.9)	0	1 (2.4)	0.393
Ever drinker	106 (99.1)	65 (100)	41 (97.6)	
Betel nut, n (%)				
Never chewing	12 (11.2)	5 (7.7)	7 (16.7)	0.151
Ever chewing	95 (88.8)	60 (92.3)	35 (83.3)	
BMI, kg/m^2				
Mean±SD	21.6±4.12	19.7±2.8	24.5±4.1	<0.001
Albumin g/dl				
Mean±SD	3.7±1.4	3.7±1.6	3.6±0.9	0.843
SMI, cm^2/m^2				
Mean±SD	49.1±10.2	43.3±6.4	51.2±8.3	<0.001
Tumor site, n (%)				
Upper	22 (20.5)	15 (23.1)	7 (16.7)	0.889
Middle	45 (42.0)	28 (43.1)	17 (40.5)	
Lower	24 (22.4)	13 (20.0)	11 (26.1)	
Overlapping	16 (15.1)	9 (13.8)	7 (16.7)	
Stage, n (%)				
I	2 (1.9)	1 (1.5)	1 (2.4)	0.880
II	36 (33.6)	21 (32.3)	15 (35.7)	
III	69 (64.5)	43 (66.2)	26 (61.9)	
EA, n (%)				
Without	50 (46.7)	29 (44.6)	21 (50.0)	0.586
With	57 (53.3)	36 (55.4)	21 (50.0)	

BMI: Body mass index; SMI: skeletal muscle index; EA: enteral access; N/A: not applicable.

Table II. *Adverse events, treatment and nutritional status between sarcopenia and non-sarcopenia groups after neoadjuvant chemoradiotherapy (N=107).*

	Sarcopenia (n=65) n (%)	Non-sarcopenia (n=42) n (%)	*p*-Value
Adverse events ≥ grade 3*			
Mucositis	18 (27.6)	4 (9.5)	0.016
Diarrhea	0 (0)	1 (2.4)	0.862
Anemia	8 (12.6)	2 (4.8)	0.052
Thrombocytopenia	2 (3.1)	0 (0)	0.587
Fever	14 (21.5)	3 (7.1)	0.047
Infection	6 (9.2)	3 (7.1)	0.456
Neutropenic fever	11 (16.9)	1 (2.4)	0.044
Discontinuation of CRT			0.013
No	52 (81.5)	41 (97.6)	
Yes	13 (18.5)	1 (2.4)	
Low BMI (<18.5 kg/m^2)			0.032
No	17 (26.2)	20 (47.6)	
Yes	48 (73.8)	22 (52.4)	

CRT: Chemoradiotherapy; BMI: body mass index; *By Common Terminology Criteria for Adverse Events, version 4.0 (30).

Table III. *Subgroup analysis of serious adverse events (grade ≥3), treatment tolerability and nutritional status of the sarcopenia group after neoadjuvant chemoradiotherapy stratified by use of enteral access (n=65).*

Variable	Sarcopenia (n=65)		*p*-Value
	EA (n=36)	No EA (n=29)	
Mucositis	6 (16.2)	12 (41.5)	0.029
Fever	7 (19.4)	9 (31.0)	0.062
Neutropenic fever	6 (16.3)	5 (17.2)	1.000
Discontinuation of CRT			0.540
No	26 (72.2)	23 (79.3)	
Yes	10 (27.8)	6 (20.7)	
Low BMI (<18.5 kg/m^2)			0.540
No	8 (22.2)	9 (31.0)	
Yes	28 (77.8)	20 (69.0)	

CRT: Chemoradiotherapy; BMI: body mass index.

without. A subset analysis of patients with sarcopenia stratified by EA was also performed (Table III). The patients' baseline characteristics were no significantly different between the groups with and without EA regarding most variables. However, the BMI was lower in the group with EA than in the group without (19.0±0.48 kg/m^2 *vs.* 20.6±2.66 kg/m^2, p=0.029) (data not shown). Regarding AEs, the sarcopenic patients who received EA had less grade 3 to 4 mucositis than those who did not receive EA (16.2% *vs.* 41.5%, p=0.029). There were no significant differences between sarcopenia with EA or without EA groups regarding inflammation status, treatment tolerability, laboratory data, or nutritional status after CRT.

Overall survival and disease-free survival. The median OS was 21.9 (3.8-36.9) months compared to 30.5 (4.8-83.6) months, and the DFS was 12.6 (1.1-35.8) months compared to 23.5 (3.4-77.8), in the sarcopenia and the non-sarcopenia groups. A Kaplan–Meier analysis was performed for patients with and without sarcopenia. As shown in Figure 1, OS (p<0.001) and DFS (p=0.020) were significantly better in patients without sarcopenia. A subset analysis of patients with sarcopenia stratified by EA or without EA was also performed. The findings demonstrated no significant difference in OS and DFS in patients with sarcopenia who had EA or not (OS, p=0.713;

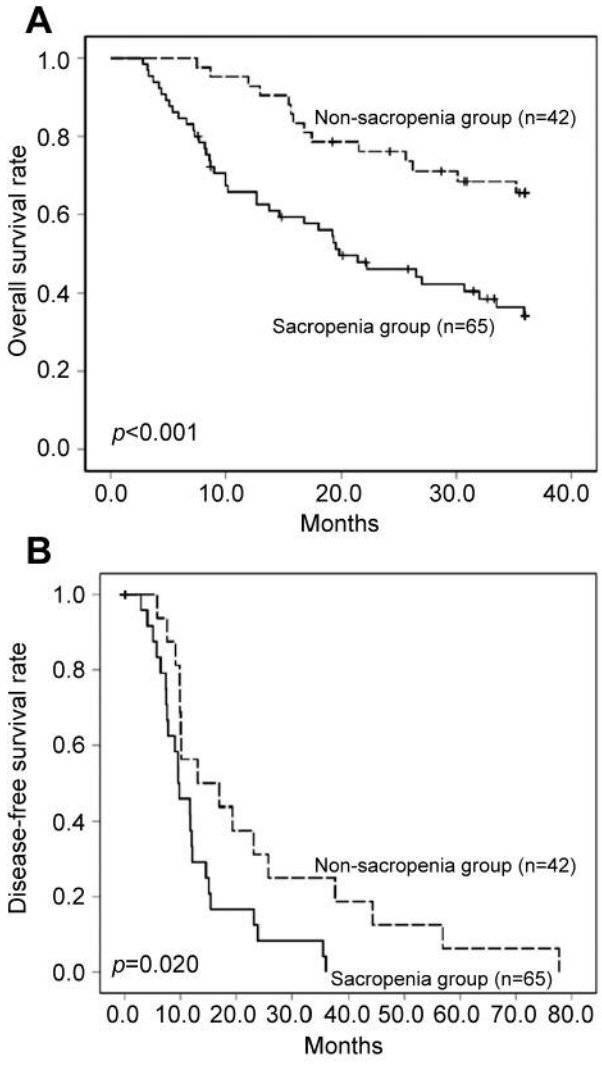

Figure 1. *Kaplan–Meier curves presenting overall survival (A) and disease-free survival (B) in patients with esophageal squamous cell carcinoma undergoing neoadjuvant therapy stratified according to sarcopenia status.*

DFS, p=0.510). A further multivariate analysis with the Cox proportional hazard regression model including age, tumor stage, sarcopenia, lower BMI (BMI<18.5 kg/m^2), EA, and discontinuation of CRT (Table IV) demonstrated that sarcopenia (HR=2.45, 95%CI=1.30-4.63) and advanced tumor stage (HR=2.69, 95%CI=1.39-5.19) were the predictors of mortality in these patients.

Discussion

Although sarcopenia is relatively well established as a negative predictor of clinical outcomes in a wide range of cancers (10, 16, 33-35), the impact of sarcopenia on patients with ESCC and the optimal strategies to improve sarcopenia in cancer patients undergoing treatment are unknown. The present study analyzed 107 ESCC patients undergoing neoadjuvant therapy among which 60.7% (n=65) had sarcopenia. We found sarcopenia to be a significant predictor of poorer OS and DFS after treatment. At three years after treatment, sarcopenia and initial staging of III were independent risk factors for shorter survival according to multivariate Cox regression analysis model. These results highlight the importance of pretreatment for sarcopenia and the potential clinical utility of sarcopenia assessment. About 25%-80% of patients with EC have been reported to present with sarcopenia at the time of diagnosis (14-18). In addition, sarcopenia is a common indicator of malnutrition due to cancer progression (6, 36). EA is a standing recommendation to prevent BW loss and esophageal obstruction in patients undergoing CRT and surgery (37). In our current data set, there was no significant difference in patients with sarcopenia receiving EA or not in terms of OS and DFS. The results are consistent with Sato *et al.* who have revealed that nutritional support of unresectable sarcopenic EC patients prior to definitive chemoradiotherapy was not associated with OS (10).

A number of studies have demonstrated that sarcopenia is associated with increased AEs in patients receiving neoadjuvant therapy (18, 19, 22, 38). Tan *et al.* (18) have reported that the prevalence of dose-limiting toxicity was more common in patients with sarcopenia compared with those without sarcopenia (54.5% *vs.* 28.9%, p=0.015). Murimwa *et al.* (22) have reported that sarcopenia was significantly associated with grade 3 or 4 toxicity of CRT in patients with EC (p=0.004). Consistent with these reports, our results demonstrated that CRT-related AEs such as mucositis (p=0.016), fever (p=0.047), and neutropenic fever (p=0.044) were more likely to develop in the sarcopenia group. However, Yip *et al.* have reported that sarcopenia was not associated with chemotherapy dose reductions (19). Ota *et al.* (38) have reported that the presence of sarcopenia was

Table IV. *Cox proportional model for identifying the relationship between clinical features and mortality (N=107).*

Variable	HR (95%CI)	p-Value
Age	1.02 (0.98-1.06)	0.256
Stage III	2.69 (1.39-5.19)	0.003
Sarcopenia	2.45 (1.30-4.63)	0.001
Low BMI	1.49 (0.81-2.73)	0.193
Enteral access	0.96 (0.55-1.65)	0.883
Discontinuation of CRT	1.84 (0.98-3.42)	0.051

BMI: Body mass index.

not associated with AEs of neoadjuvant chemotherapy. This discrepancy may be due to the fact that most of their patients (especially 92% of docetaxel, cisplatin, and 5-fluorouracil therapy cases) were given prophylactic G-CSF (34). In addition, a treatment modality, which combined platinum base-chemotherapy and radiotherapy, has been associated with a higher incidence of bone marrow suppression and gastrointestinal mucositis (39). Cisplatin promotes muscle wasting through a number of mechanisms, including impaired Akt phosphorylation, which leads to sustained activation of the degradative proteasome and autophagy systems and altered NF-kB signaling (40, 41). Skeletal muscle mass is known to decrease with advanced cancer stage and is defined as secondary sarcopenia (6). Ali *et al*. (42) have demonstrated that sarcopenia induces upregulation of pro-inflammatory agents, which might alter the immune system and tumor microenvironment, leading to poorer clinical outcomes including a poor response to chemotherapy and higher rates of AEs. However, the significance of sarcopenia's impact on AEs and nutritional status in patients with EC remains unclear. Further investigations into AEs during CRT in sarcopenia patients are necessary to understand these aspects fully.

Although nutritional support by EA of patients with sarcopenia did not affect survival, it appears that EA intervention during CRT may be associated with a reduction in the occurrence of mucositis. In the present study, sarcopenia patients with EA had significantly lower BMI at baseline under CRT than those without EA. However, the sarcopenia patients in the EA group had similar OS/DFS to patients with normal nutritional status and no EA. The clinical implication of these findings is to improve the outcome of CRT-related mucositis and maintain OS/DFS. We also identified that the sarcopenia and advance tumor stage as an independent prognostic factors of mortality. Sarcopenia appears to be a more accurate marker for malnutrition than more conventional assessments, such as BMI. This is consistent with a previous study by Stone *et al*. demonstrating that sarcopenia is a negative predictor of outcomes regardless of BMI (28). Weight loss and low BMI are often used as prognostic factors for patients with cancer (7, 8, 29). However, these parameters do not provide reliable information on body composition, in particular, muscle mass and quality (8, 43). Thus, pretreatment sarcopenia assessments might be useful to identify a high-risk negative prognostic factor not identified *via* other clinical assessments.

This study has certain limitations. First, CT imaging is often obtained as part of PET/CT. However, many patients were excluded due to a lack of available images for this analysis, which might have led to a selection bias. Second, the study was retrospective. Therefore, bias generated from the retrospective review could not be avoided. Finally, the study results are based solely on the experience of a medical center. Although it would be ideal for an external cohort to validate our results, future multicenter studies are warranted to fully elucidate the most effective nutritional supplements and other interventions to improve the clinical outcome of patients with ESCC and sarcopenia who are undergoing treatment.

In conclusion, sarcopenia was present in 60.7% of the patients with ESCC and might be a significant predictor of reduced OS and DFS under CRT. These data suggest that sarcopenia assessment would be a useful prognostic tool for patients with ESCC and might help target patients for positive nutritional support or other interventions to improve their outcomes.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Huang, Wang and Peng have full access to all the data in the study. Huang, Wang, Peng, Lue, and Hsieh designed the study. Lue and Liu contributed to the image analysis. Huang, Wang, Lue, Liu and Hsieh contributed to the data and statistical analysis. Huang, Wang and Peng contributed to the drafting of the manuscript together.

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