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Association between body composition, survival, and toxicity in advanced esophagogastric cancer patients receiving palliative chemotherapy

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Abstract

Background Palliative systemic treatment in patients with advanced or metastatic esophagogastric cancer may result in improved overall survival and quality of life but can also lead to considerable toxicity. In various cancer types, severe muscle mass depletion (sarcopenia) and poor muscle strength are associated with decreased survival and increased chemotherapy-related toxicity. The aim of this study is to determine the impact of body composition on survival and chemotherapy toxicity in esophagogastric cancer patients treated with first-line palliative chemotherapy.

Methods A total of 88 patients with advanced esophagogastric cancer treated with standard first-line palliative systemic therapy consisting of capecitabine and oxaliplatin (CapOx) between January 2010 and February 2017 were included. Skeletal muscle index (SMI), reflecting muscle mass, and skeletal muscle density (SMD), associated with muscle strength, were measured using pre-treatment of all patients and evaluation computed tomography scans after three treatment cycles of 65 patients and were used to determine sarcopenia and sarcopenic obesity (i.e. sarcopenia and body mass index >25 kg/m^2). The associations between body composition (SMI, SMD, sarcopenia, and sarcopenic obesity) and survival and toxicity were assessed using univariable and multivariable Cox and logistic regression analyses, respectively.

Results Of 88 patients, 75% was male, and median age was 63 (interquartile range 56–69) years. The majority of patients had an adenocarcinoma (83%). Before start of treatment, 49% of the patients were sarcopenic, and 20% had sarcopenic obesity. Low SMD was observed in 50% of patients. During three cycles CapOx, SMI significantly decreased, with a median decrease of 4% (interquartile range −8.6–−0.4). Median progression-free and overall survival were 6.9 and 10.1 months. SMI, SMD, sarcopenia, and sarcopenic obesity (both pre-treatment and after three cycles) were neither associated with progression-free nor overall survival. Pre-treatment SMD was independently associated with grade 3–4 toxicity (odds ratio 0.94; 95% confidence interval 0.89–1.00) and sarcopenic obesity with grade 2–4 neuropathy (odds ratio 3.82; 95% confidence interval 1.20–12.18).

Conclusions Sarcopenia was not associated with survival or treatment-related toxicity in advanced esophagogastric cancer patients treated with CapOx. Pre-treatment sarcopenic obesity was independently associated with the occurrence of grade 2–4 neurotoxicity and skeletal muscle density with grade 3–4 toxicity.

Keywords Esophageal cancer; Gastric cancer; Palliative treatment; Body composition; Skeletal muscle mass; Sarcopenia

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Introduction

Esophagogastric cancer is often diagnosed when curative treatment options are not available.[1,2] Palliative chemotherapy is considered standard treatment because it can improve survival and quality of life in incurable esophagogastric cancer patients.[3,4] Currently, doublet therapy with a fluoropyrimidine and platinum compound is recommended as first-line palliative chemotherapy, providing a survival benefit of several months.[5,6] Unfortunately, chemotherapy often causes toxicity, which may result in dose reductions, suspension, and discontinuation of chemotherapy and can thereby compromise treatment efficacy. Excess toxicity may also lead to a reduction in quality of life. The identification of patient or tumour characteristics that are related to toxicity and survival has the potential to improve quality of care by enabling more individually aligned treatment plans.

A characteristic of increasing interest is the loss of skeletal muscle mass. In various cancer types, the depletion of skeletal muscle mass (sarcopenia) is associated with decreased survival and increased risk of complications after surgery and systemic treatment-related toxicity.[7–10] Muscle mass can be easily determined by assessment of skeletal muscle index (SMI) using computed tomography (CT) scans that are routinely acquired for pre-treatment staging and treatment evaluation. Furthermore, muscle strength or quality is associated with skeletal muscle density (SMD), which can be measured then as well.[11–14]

Previous studies in esophagogastric cancer patients during curative treatment found that sarcopenia was associated with increased chemoradiotherapy-related toxicity, increased post-operative complications, and decreased survival rates.[15–20] Furthermore, during neoadjuvant treatment, sarcopenic obesity has been associated with higher risk of dose reductions.[21] However, studies investigating the association between muscle mass and outcome in the palliative setting are limited. Only one study investigated SMD in a small study population in gastric cancer patients and found that low SMD is associated with poor survival.[11] No studies in the palliative have investigated the association between muscle mass depletion and toxicity. Investigating the relation between muscle mass loss and outcome in advanced esophagogastric cancer patients seems relevant because weight loss is common during palliative treatment (due to cancer-related cachexia and dysphagia resulting in malnutrition), which could lead to the loss of skeletal muscle mass.[22,23]

The aim of our study was to explore associations between skeletal muscle mass and density, sarcopenia and sarcopenic obesity, and survival and chemotherapy toxicity in esophagogastric cancer patients treated with first-line palliative chemotherapy.

Material and methods

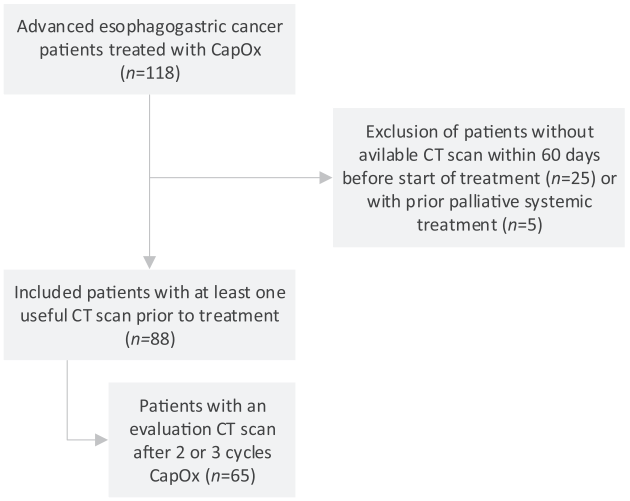
Study population

Between January 2010 and July 2017, all patients in the Academic Medical Center with incurable esophageal, gastroesophageal junction, or gastric cancer that received at least one cycle of standard first-line palliative systemic therapy consisting of capecitabine and oxaliplatin (CapOx) were included in the study (n = 118). Patients that did not have a CT scan or a positron emission tomography-CT scan containing images of the third lumbar vertebra within 60 days prior to start of treatment (n = 25) and patients that had palliative systemic treatment before a scan was made (n = 5) were excluded. A total of 88 patients with at least one useful CT scan were ultimately included, of which 65 had a second (evaluation) CT scan performed after three (n = 60) or two (n = 5) cycles of chemotherapy (*Figure* 1).

Treatment

Standard first-line palliative systemic therapy consisted of the fluoropyrimidine capecitabine (1000 mg/m^2, taken orally two times a day from Days 1–14) and platinum compound oxaliplatin (130 mg/m^2, administered intravenously on Day 1) in a three weekly cycle, with a maximum of six successive cycles followed by capecitabine monotherapy. Optionally, oxaliplatin could be reintroduced in case of progressive disease during capecitabine monotherapy. Treatment was discontinued in case of disease progression, inacceptable toxicity, or on patient's request. Toxicity was assessed using the Common Terminology Criteria for Adverse Events (version 4.03) by recording the highest Common Terminology Criteria for

Figure 1 Flowchart displaying patient selection. CT, computed tomography.



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Adverse Events grade of each adverse event throughout all cycles of first-line treatment.[24] Survival was calculated from the day metastatic disease was histologically confirmed or, if not available, diagnosed by imaging (n = 2), to date of death (overall survival), date of radiological progression according to Response Evaluation Criteria in Solid Tumors, clinical progression on CapOx or capecitabine monotherapy (progression-free survival; PFS), and lost-to-follow-up or end of follow-up (19 March 2018).

Skeletal muscle index and skeletal muscle density assessment

Pre-treatment CT scans (CT 1) and evaluation CT scans after the second or third treatment cycle (CT 2) with administration of intravenous contrast were assessed for body composition. According to the CT protocol in our centre, patients were scanned in the late portal venous phase, as routinely performed in cancer patients, with a tube voltage of 120 kV, regularly used in contrast-enhanced scans. The medical imaging software Slice-O-Matic® (version 5.0; Tomovision, Montreal, Quebec, Canada) was used to identify and demarcate the skeletal muscle compartments at the L3 level using predetermined cut-off points for Hounsfield units (HU) (−29 to +150).[8,14,25] Using two single-slice axial images, the average surface areas of the psoas muscles, abdominal wall muscles, and paraspinal muscles, in which transverse and spinous processes were visible, were used to determine muscle area. CT scans were analysed by a trained investigator (M. P.). SMI (cm^2/m^2) was determined by normalizing the obtained muscle area (cm^2) for squared body height (m^2). SMD was expressed as mean HU-value of the skeletal muscle cross sectional areas.

We used specific cut-off values for SMI and SMD that are correlated with reduced survival in a large cohort consisting of patients with solid tumours, taking into account BMI and sex as defined by Martin *et al*.[8] Sarcopenia was defined as SMI <43 cm^2/m^2 in male patients with BMI <25 kg/m^2 and SMI <53 cm^2/m^2 if BMI >25 kg/m^2; in female patients, sarcopenia was set at SMI <41 kg/m^2 irrespective of BMI. Cut-off values for SMD were $<$ 41 HU in non-overweight patients (BMI <25 kg/m^2) and <33 HU if BMI >25 kg/m^2 for both sexes. Sarcopenic obesity was defined as sarcopenia combined with overweight or obesity (BMI >25 kg/m^2).

Statistical analysis

Patient and tumour characteristics are presented as mean with standard deviation, median with interquartile range (IQR), or counts and percentages. SMI and SMD of CT 1 and CT 2 were compared using the paired t-test or Wilcoxon signed rank test, whichever was appropriate. Correlations between continuous variables were determined using Pearson's correlation coefficient in case of normally distributed data and Spearman in non-normally distributed data. The association of SMI and SMD with survival, toxicity, and response on chemotherapy was tested using Cox proportional hazard and logistic regression, respectively. Variables were added as confounders to multivariable regression analyses if the association/correlation of the variable with both the determinant and the outcome had a P value lower than 0.2.

For all other analyses, a P value lower than 0.05 was regarded as statistically significant. Statistical analyses were performed with IBM SPSS Statistics for Windows (Version 24.0 IBM Corp. Armonk, NY, USA).

Results

Patient characteristics

Characteristics of the 88 included patients are displayed in *Table* 1. Seventy-five percent of the patients were male,

Table 1. Patient characteristics and body composition

	All patients (n = 88)
Baseline characteristics	
Men—no (%)	66 (75.0%)
Age in years—median (IQR)	63.0 (56–69)
Tumour location—no (%)	
Oesophagus	47 (53.4%)
Gastro-esophageal junction	25 (28.4%)
Stomach	16 (18.2%)
Histology—no (%)	
Adenocarcinoma	73 (83.0%)
Squamous cell carcinoma	15 (17.0%)
WHO performance status—no (%)	
0 or 1	78 (88.6%)
≥2	10 (11.4%)
Reported weight loss before start of treatment—no (%)	
<8%	49 (55.7%)
≥8%	38 (43.2%)
Unknown	1 (1.1%)
Prior curative treatment—no (%)	40 (45.5%)
Metastatic dissemination—no (%)	
Only lymphatic	29 (33.0%)
Hematogenous	59 (67.0%)
Number of metastatic sites—no (%)	
0 or 1	37 (42.0%)
≥2	51 (58.0%)
Treatment and toxicity	
Days between CT 1 and start of CapOx—median (IQR)	18 (7.3–29.0%)
Days between CT 1 and CT 2—median (IQR)	79 (66.5–89.0%)
Number of completed CapOx cycles—no (%)	
1–3	39 (44.3%)
4–6	40 (45.5%)
>6	9 (10.2%)
Capecitabine monotherapy—no (%)	37 (42.0%)
Toxicity grade 3 or 4—no (%)	32 (36.4%)
Neuropathy grade 2–4—no (%)	18 (20.5%)
Hematologic toxicity grade 3–4—no (%)	21 (23.9%)
Dose reduction or delay—no (%)	56 (63.3%)

CapOx, capecitabine/oxaliplatin; IQR, interquartile range.

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and median age at diagnosis of metastatic disease was 62.2 years (IQR 56–69). The majority of the patients had an adenocarcinoma (83% vs. 17% squamous cell carcinoma), and 47 (53%) of the tumours were localized in the oesophagus, 25 (28%) around the gastro-esophageal junction, and 16 (18%) in the stomach, respectively. A total of 143 (93%) scans were performed in our centre; all scans were assessed by expert radiologists from our centre. Median time between the baseline CT (CT 1) and start of the first CapOx cycle was 18 days (IQR 7.5–32).

The majority of the patients had one to three (n = 39, 44%) or four to six cycles (n = 40, 46%) of CapOx, and 42% of the patients continued with capecitabine monotherapy after CapOx. In 56 patients (63%), doses of capecitabine and/or oxaliplatin were reduced or postponed due to toxicity. Thirty-two patients (36%) had grade 3–4 toxicity (including hematologic toxicity); 18 patients (21%) experienced peripheral sensory neuropathy grade 2 or higher.

Body composition

Table 2 shows SMI, SMD, BMI, and the number of sarcopenic and sarcopenic obese patients in CT 1 and CT 2 for all patients, men and women. Mean pre-treatment SMI was 46.9 cm^2/m^2 for all patients, and 48.0 and 38.4 cm^2/m^2 for male and female patients, respectively, which differed significantly ($P < 0.001$; *Table* 2). Mean pre-treatment SMD for the entire group was 37.8 HU and did not differ between men and women in CT 1 (P = 0.265). Fifty percent of all patients had a SMD below cut-off value (*Table* 2), reflecting poor quality of muscle tissue. Nearly half of the patients had sarcopenia before start of treatment (48.9%), and 19.7% had sarcopenic obesity.

Skeletal muscle index was significantly lower on the second CT scan in the whole group and for male and female patients independently ($P < 0.001$, $P < 0.001$, and P = 0.011, respectively), with a median difference of −4.0% (IQR −8.6–−0.4%) for all patients. SMD and BMI were comparable in CT 1 and CT 2 (P = 0.840 and P = 0.122, respectively). The proportion of patients with sarcopenia increased over time (CT 1 49% vs. CT 2 55%) in all patients (*Table* 2). The amount of sarcopenic obese patients increased from 19% in CT 1 to 22% in CT 2 ($P < 0.001$).

Survival

One patient was excluded for survival analyses because trastuzumab was added to CapOx after the third treatment cycle. Median progression-free survival of remaining patients (n = 87) was 6.9 months (IQR 3.7–10.3), and overall survival was 10.1 months (IQR 5.0–16.1).

Table 2. Comparison of body composition between CT 1 and CT 2 and between men and women (CT 1)

	All patients			Male			Female			
Body composition	CT 1 (n = 88)	CT 2 (n = 65)	P value	CT 1 (n = 66)	CT 2 (n = 50)	P value*	CT 1 (n = 22)	CT 2 (n = 15)	P value*	P value#
SMI cm^2/m^2—mean (SD)	46.9 (9.9)	44.4 (10.0)	<0.001[a]	48.0 (9.3)	46.6 (9.8)	<0.001[a]	39.9 (4.6)	37.0 (6.3)	0.011[a]	<0.001[b]
SMD, HU—mean (SD)	37.8 (8.9)	38.6 (9.0)	0.840[a]	38.4 (9.0)	39.5 (8.7)	0.851[a]	35.9 (8.5)	35.4 (9.9)	0.942[a]	0.265[b]
BMI, kg/m^2—median (IQR)	23.4 (21.6–26.1)	23.2 (21.7–26.1)	0.122[c]	23.4 (21.4–26.1)	23.2 (21.7–26.1)	0.265[c]	24.1 (22.6–26.4)	23.2 (22.0–26.3)	0.120[c]	0.512[d]
BMI category—no (%)			<0.001[e]			<0.001[e]			<0.001[e]	0.629[e]
Underweight (<18.5 kg/m^2)	5 (5.7%)	3 (4.6%)		3 (4.5%)	2 (4.0%)		2 (9.1%)	1 (6.7%)		
Normal weight (20–24.9 kg/m^2)	54 (61.4%)	43 (66.2%)		42 (63.6%)	33 (66.0%)		12 (54.4%)	10 (66.7%)		
Overweight (≥25 kg/m^2)	29 (32.9%)	19 (29.2%)		21 (31.8%)	15 (30.0%)		8 (36.4%)	4 (26.7%)		
Sarcopenia—no (%)	43 (48.9%)	36 (55.4%)	<0.001[e]	29 (43.9%)	25 (50.0%)	<0.001[e]	14 (63.6%)	11 (73.3%)	0.033[f]	0.109[e]
Sarcopenic obesity—no (%)	17 (19.3%)	14 (21.5%)	<0.001[f]	13 (19.7%)	12 (24.0%)	<0.001[f]	4 (18.2%)	2 (13.3%)	0.029[f]	0.574[f]
Low SMD—no (%)	44 (50.0%)	30 (46.2%)	<0.001[f]	28 (42.4%)	21 (42.0%)	<0.001[e]	16 (72.7%)	9 (60.0%)	0.011[f]	0.014[e]

BMI, body mass index; CT, computed tomography; HU, Houndsfield units; IQR, interquartile range; SD, standard deviation; SMD, skeletal muscle density; SMI, skeletal muscle index.
*Comparison between CT 1 and CT 2 in male and female patients.
#Comparison between male and female patients in CT 1.
[a]Paired t-test.
[b]Unpaired t-test.
[c]Wilcoxon signed rank test.
[d]Mann–Whitney U-test.
[e]χ^2 test.
[f]Fisher's exact test.

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In both univariable and multivariable regression analyses, SMI and SMD (pre-treatment and after three cycles) were not independently associated with progression-free or overall survival. Sarcopenia in CT 2 was significantly associated with progression-free survival in univariable analysis [hazard ratio 0.56; 95% confidence interval (CI) 0.33–0.95] but not in multivariable analysis. Sarcopenia (pre-treatment), sarcopenic obesity, low SMD, and BMI did not impact PFS and overall survival, neither did the difference in SMI (ΔSMI), SMD (ΔSMD), or BMI (ΔBMI) between CT 2 and CT 1 (*Table* 3).

Toxicity

Univariable and multivariable logistic regression analyses for grade 3–4 toxicity and grade 2–4 peripheral sensory neuropathy are presented in *Table* 4.

Pre-treatment SMD (CT 1) was associated with the occurrence of grade 3–4 toxicity [odds ratio (OR) 0.94; 95% CI 0.89–1.00] in both univariable and multivariable logistic regression analyses, and sarcopenic obesity (CT 1) with grade 2 or more peripheral sensory neuropathy (OR 3.82; 95% CI 1.20–12.18). All other parameters were not independently related to (neuro)toxicity.

Discussion

In this first study exploring skeletal muscle features of incurable esophagogastric cancer patients treated with first-line palliative systemic therapy with CapOx, sarcopenia and low muscle density were observed in (nearly) half of our patients (48.9% and 50.0%, respectively). SMI, SMD, sarcopenia, sarcopenic obesity, or BMI (pre-treatment and after three cycles of CapOx) and change in SMI were not related to progression-free or overall survival, whereas a higher SMD was independently associated with a lower risk of grade 3–4 toxicity. Sarcopenic obesity was significantly related with neuropathy.

Although several studies in lung cancer, gastrointestinal cancer, and lymphoma patients, both pre-treatment SMI[7,8,26] and SMD[8,11,27–30] were associated with overall survival. We did not observe this association, either due to limited power of our study or the relatively large number of overweight patients in our population with baseline sarcopenia [17 of 43 (39.5%); *Table* 2] that could have been a protective factor for survival, a phenomenon that is referred to as the obesity paradox.[8,31] Other causes of the specifics of esophagogastric cancer patients have to be identified in future studies. In addition, the difference in skeletal muscle mass index pre-treatment and after three cycles of CapOx (ΔSMI) was not associated with survival, in contrast to earlier findings in metastatic colorectal patients who received first-line treatment with CapOx.[30] However, ΔSMI tended towards statistical significance in multivariable analysis for PFS (hazard ratio 0.94; 95% CI 0.86–1.02), indicating increase of muscle mass could prolong PFS. Possibly, either the limited time between the two CT scans and duration of treatment or the small group of patients resulted in these differences in outcome.

A decrease in SMD was independently associated with a higher chance of grade 3 or 4 toxicity. SMD is associated with strength or quality of muscle mass: a lower SMD is related to fat infiltration in muscles or myosteatosis, which is a

Table 3. Univariable and multivariable Cox regression analysis

	Progression-free survival						Overall survival					
	Univariable analysis			Multivariable analysis[a]			Univariable analysis			Multivariable analysis[b]		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
SMI CT 1, cm^2/m^2	1.01	0.99–1.03	0.243	0.99	0.97–1.02	0.647	1.02	0.99–1.04	0.231	0.99	0.97–1.02	0.588
SMI CT 2, cm^2/m^2	1.02	1.00–1.04	0.060	1.00	0.97–1.04	0.900	1.03	1.00–1.05	*0.049*	1.00	0.97–1.03	0.862
ΔSMI, cm^2/m^2	1.02	0.94–1.11	0.601	0.94	0.86–1.02	0.116	0.97	0.90–1.05	0.544	0.97	0.88–1.06	0.481
Sarcopenia CT 1	0.72	0.47–1.11	0.136	0.78	0.47–1.30	0.343	0.70	0.44–1.10	0.123	0.94	0.59–1.50	0.787
Sarcopenia CT 2	0.56	0.33–0.95	*0.031*	0.76	0.41–1.41	0.385	0.53	0.30–0.91	*0.022*	0.88	0.47–1.64	0.686
Sarcopenic obesity CT 1	0.90	0.52–1.56	0.703	0.61	0.32–1.16	0.133	0.79	0.45–1.40	0.424	0.88	0.50–1.54	0.656
Sarcopenic obesity CT 2	0.87	0.47–1.62	0.663	0.95	0.49–1.86	0.890	0.98	0.52–1.84	0.940	0.90	0.45–1.79	0.765
SMD CT 1, HU	1.01	0.98–1.03	0.562	1.01	0.98–1.04	0.588	1.00	0.98–1.03	0.609	1.00	0.97–1.03	0.754
SMD CT 2, HU	1.01	0.98–1.04	0.540	0.99	0.96–1.02	0.528	1.00	0.98–1.03	0.765	0.98	0.95–1.01	0.255
ΔSMD, HU	1.02	0.99–1.06	0.213	0.98	0.94–1.01	0.198	1.00	0.97–1.04	0.852	1.00	0.96–1.04	0.839
Low SMD CT 1	1.04	0.68–1.61	0.850	1.05	0.64–1.73	0.835	0.94	0.60–1.47	0.789	1.40	0.85–2.31	0.193
BMI CT 1, kg/m^2	0.99	0.95–1.04	0.719	0.95	0.90–1.01	0.100	0.99	0.95–1.04	0.809	0.97	0.92–1.02	0.181
BMI CT 2, kg/m^2	1.01	0.95–1.06	0.828	1.00	0.94–1.07	0.862	1.03	0.98–1.10	0.237	0.98	0.92–1.04	0.417
ΔBMI, kg/m^2	0.93	0.73–1.17	0.533	0.84	0.64–1.10	0.205	0.91	0.70–1.17	0.460	0.86	0.67–1.09	0.204
Overweight (BMI ≥25 kg/m^2)	1.03	0.65–1.64	0.890	0.84	0.50–1.42	0.513	1.03	0.64–1.67	0.895	0.96	0.60–1.55	0.868

BMI, body mass index; CI, confidence interval; CT, computed tomography; HR, hazard ratio; HU, Houndsfield units; SMD, skeletal muscle density; SMI, skeletal muscle index. Confounders multivariable analyses.
[a]Sex, age, WHO performance status ≥2, number of metastatic sites ≥2.
[b]Sex, age, WHO performance status ≥2, number of metastatic sites ≥2, hematogenous metastatic dissemination.

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Table 4. Univariable and multivariable logistic regression analysis.

	Toxicity grade 3 or 4						Peripheral sensory neuropathy grade ≥ 2		
	Univariable analysis			Multivariable analysis[a]			Univariable analysis[b]		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
SMI CT 1, cm^2/m^2	1.01	0.97–1.06	0.600	1.00	0.96–1.06	0.734	0.99	0.93–1.05	0.645
SMI CT 2, cm^2/m^2	1.00	0.95–1.06	0.930	1.00	0.95–1.05	0.924	0.97	0.91–1.04	0.376
ΔSMI, cm^2/m^2	0.96	0.83–1.10	0.521	0.97	0.84–1.11	0.633	0.98	0.84–1.14	0.784
Sarcopenia CT 1	0.88	0.37–2.11	0.778	0.87	0.36–2.11	0.764	1.87	0.65–5.38	0.248
Sarcopenia CT 2	1.59	0.57–4.44	0.379	1.48	0.52–4.23	0.462	0.75	0.24–2.32	0.618
Sarcopenic obesity CT 1	1.29	0.44–3.80	0.647	1.19	0.39–3.60	0.760	3.82	1.20–12.18	*0.024*
Sarcopenic obesity CT 2	0.94	0.27–3.21	0.916	0.91	0.26–3.22	0.886	1.30	0.35–4.91	0.699
SMD CT 1, HU	0.94	0.89–0.99	*0.019*	0.94	0.89–1.00	*0.037*	1.02	0.97–1.09	0.435
SMD CT 2, HU	0.95	0.89–1.00	0.080	0.95	0.90–1.01	0.109	1.07	0.99–1.14	0.074
ΔSMD, HU	0.99	0.93–1.05	0.724	0.99	0.93–1.06	0.741	0.98	0.91–1.04	0.464
Low SMD CT1	1.81	0.75–4.37	0.186	1.75	0.72–4.28	0.219	0.57	0.20–1.63	0.294
BMI CT 1, kg/m^2	1.06	0.96–1.17	0.243	1.04	0.95–1.15	0.403	0.97	0.86–1.10	0.675
BMI CT 2, kg/m^2	1.03	0.92–1.15	0.611	1.03	0.92–1.15	0.649	0.85	0.71–1.03	0.099
ΔBMI, kg/m^2	0.80	0.52–1.22	0.306	0.88	0.56–1.38	0.567	1.03	0.64–1.65	0.902
Overweight (BMI ≥25 kg/m^2)	1.11	0.44–2.78	0.830	0.87	0.33–2.35	0.790	1.87	0.65–5.39	0.249

BMI, body mass index; CI, confidence interval; CT, computed tomography; HU, Houndsfield units; OR, odds ratio; SMD, skeletal muscle density; SMI, skeletal muscle index. Confounders multivariable analyses.
[a]WHO performance status ≥2.
[b]There were no confounders, so only univariable analysis was performed.

pathological condition.[9,27,32,33] Myosteatosis is hypothesized to be a preliminary state for sarcopenia and therefore a more accurate representative of muscle function than the SMI.[27] Half of our patients had a pre-treatment SMD that was beyond cut-off values, which is in line with the 58.5% of low SMD in the study with metastatic gastric cancer patients in which the same cut-off values of Martin *et al*. were used.[11]

Patients with sarcopenic obesity had greater risk of grade 2–4 peripheral sensory neuropathy (OR 3.82; 95% CI 1.20–12.18). A possible explanation is that oxaliplatin is a lipophilic agent and accumulates in the fat tissue compartments. In patients with excess fat, this may result in longer exposure to the drug that could lead to increased risk of neuropathy in sarcopenic obesity patients.[34,35] Currently, dosing chemotherapy is performed base on body surface area, which is based on a patient's height and weight and used as an index for chemotherapy dosing, without taken body composition into account. This could result in overdosing in patients with sarcopenic obesity because of their high body surface area and decreased muscle mass, as reported in previous studies.[10,20,34,36]

In our study, we found that BMI did not differ between CT 1 and CT 2 although muscle mass decreased significantly, which supports earlier findings stating that muscle mass is not necessarily associated with BMI and that loss of muscle mass could be accompanied by growth of adipose tissue.[13,35]

Accordingly, there were significantly more patients with sarcopenia and sarcopenic obesity at the time of the evaluation CT scan than at the pre-treatment scan. Given the observed relation with sarcopenic obesity and neurotoxicity and SMD and toxicity grade 2–4, interventions to prevent decrease of SMI and SMD during palliative systemic treatment could prevent toxicity. Given the complex pathologic process of cachexia and sarcopenia and according to increasing evidence, these interventions should ideally be multimodal and at least consist of nutritional support, physical exercise perhaps combined with pharmacological interventions. This could prevent (pre) cachectic patients from developing refractory cachexia, a stage of cancer cachexia associated with progressive cancer not responding to anticancer treatment, low performance status, and short life expectancy.[23,37] In our study, we observed a median decrease of 4% in SMI and an increase of sarcopenic (obese) patients after only three cycles of chemotherapy, stressing the urgency that these preventive measures need to be applied in an early stage of treatment.

We are aware of several limitations in our study. Firstly, our study comprised a limited number of patients; nevertheless, it is the largest cohort esophagogastric cancer patients treated with palliative systemic therapy in which these analyses are performed. Secondly, patients without available CT scans were excluded from the analysis, which could lead to a possible selection bias created due to exclusion of patients without available CT scans. Furthermore, sample size was too small to perform subanalyses between sarcopenic patients with overweight and obesity, because obese sarcopenic patients may have a worse survival.[38] Moreover, we could not determine the relation between skeletal muscle features and quality of life, clinical outcomes, or muscle function or strength because these data were not prospectively collected in our study. In metastatic lung cancer patients treated with first-line systemic therapy, clinical outcomes and global quality of life were positively associated with skeletal muscle features.[39] This deserves further study in esophagogastric cancer patients. Lastly, approximately 7% of included CT scans were not performed in our centre. Although in all CT

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scans intravenous contrast was used, differences in contrast-enhancement phases and tube voltages might affect calculations of determinants used in our study.[40,41]

In conclusion, skeletal muscle mass and density, sarcopenia, and sarcopenic obesity are not associated with survival in advanced esophagogastric cancer patients treated with first-line chemotherapy. However, low SMD is independently associated with the occurrence of grade 3–4 toxicities and sarcopenic obesity with grade 2–4 peripheral sensory neuropathy. Research focusing on interventions to increase or prevent decrease of muscle mass index and density and adjustment of chemotherapy doses to muscle mass could be valuable in preventing chemotherapy toxicity in these patients in the future.

Ethical standards

Our study was considered Medical Research Involving Human Subjects Act (WMO) exempt by the Medical Ethics Committee of the Amsterdam UMC. Therefore, formal approval of the Medical Ethics Committee was not necessary. The authors certify that they comply with the ethical guidelines for publishing in the *Journal of Cachexia, Sarcopenia and Muscle*: update 2017.[42]

Conflicts of interest

M.G.H.v.O. has received unrestricted research grants from Bayer, Lilly, Merck Serono, and Roche. H.W.M.v.L. has served as a consultant for Celgene, Lilly, and Nordic and has received unrestricted research funding from Bayer, Celgene, Lilly, Merck Serono, MSD, Nordic, and Roche. The other authors have nothing to disclose.

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