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Sarcopenia: Prevalence, and Impact on Operative and Oncologic Outcomes in the Multimodal Management of Locally Advanced Esophageal Cancer

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Objective: The aim of this article was to study the prevalence and significance of sarcopenia in the multimodal management of locally advanced esophageal cancer (LAEC), and to assess its independent impact on operative and oncologic outcomes.

Summary of Background Data: Sarcopenia in cancer may confer negative outcomes, but its prevalence and impact on modern multimodal regimens for LAEC have not been systematically studied.

Methods: Two hundred fifty-two consecutive patients were studied. Lean body mass (LBM), skeletal muscle index (SMI), and fat mass (FM) were determined pre-treatment, preoperatively, and 1 year postoperatively. Sarcopenia was defined by computed tomography (CT) at L3 as SMI $< 52.4\,cm^2/m^2$ for males and SMI $< 38.5\,cm^2/m^2$ for females. All complications were recorded prospectively, including comprehensive complications index (CCI), Clavien-Dindo complication (CDC), and pulmonary complications (PPCs). Multivariable linear, logistic, and Cox regression analysis was performed.

Results: In-hospital mortality was 1%, and CCI was 21 ± 19. Sarcopenia increased ($P = 0.02$) from 16% at diagnosis to 31% post-neoadjuvant therapy, with loss of LBM (-3.0 ± 5.4 kg, $P < 0.0001$), but not FM (-0.3 ± 2.7 kg, $P = 0.31$) during treatment. On multivariable analysis, preoperative sarcopenia was associated with CCI ($P = 0.043$), and CDC $\geq$IIIb ($P = 0.003$). PPCs occurred in 36% nonsarcopenic versus 55% sarcopenic patients ($P = 0.01$). Sarcopenia did not impact disease-specific ($P = 0.14$) or overall survival ($P = 0.11$) after resection. At 1 year, 35% had sarcopenia, significantly associated with pre-treatment BMI ($P = 0.013$) but not complications ($P = 0.20$).

Conclusions: Sarcopenia increases through multimodal therapy, is associated with an increased risk of major postoperative complications, and is prevalent in survivorship. These data highlight a potentially modifiable marker of risk that should be assessed and targeted in modern multimodal care pathways.

Keywords: body composition, body weight, CCI, chemoradiation, chemotherapy, comprehensive complications index, computed tomography, esophageal cancer, esophagectomy, fat mass, gastric conduit, morphometry, neoadjuvant therapy, nutrition, obesity, pulmonary complications, sarcopenia, skeletal muscle mass, subcutaneous fat, visceral fat

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Recent advances in multimodal therapy, surgery, and perioperative care have produced significant improvements in oncologic and operative outcome for patients with esophageal cancer treated with curative intent.[1,2] Even for patients with locally advanced cancer (LAEC), approximately half will now survive to 5 years, with the most recent published randomized clinical trial reporting a 47% 5-year survival in patients treated with multimodal therapy, and an in-hospital postoperative mortality of 4%.[3] This welcome progress notwithstanding, esophageal cancer surgery is associated with significant morbidity, and with short, medium, and long-term challenges to functional recovery and health-related quality of life (HR-QL).[4–6] In this context, the role of nutrition is paramount, with many patients losing weight at presentation, and myriad factors, including anorexia, early satiety, and persistent catabolism producing unintentional weight loss and associated functional limitations in the months following surgery or multimodal therapies.[7–10]

Sarcopenia, characterized by a reduction in skeletal muscle mass and function, is common in oncology, and is associated with adverse outcomes for numerous cancers, including melanoma, lung, and pancreas.[11–13] The drivers of sarcopenia are multifactorial, with physical inactivity, systemic inflammation, increased metabolic rate, and reduced nutrient intake all contributory. These risk factors are prevalent in esophageal cancer, and sarcopenia is reported in 26% to 75% of patients across the spectrum of disease at presentation.[14–19] Among patients with LAEC treated with curative intent, neoadjuvant therapy may additionally reduce lean body mass (LBM); however, whether this impacts oncologic and operative outcomes is unclear.[14,16,18,20–25] Furthermore, despite the prevalence of sarcopenia at presentation, and the weight loss trajectory observed among disease-free patients,[26] no study to date has assessed the impact of esophageal cancer surgery on LBM and sarcopenia in survivorship.

As such, this study aimed, first, to systematically examine changes in LBM among patients with LAEC treated with multimodal therapy and to investigate the impact of sarcopenia on operative and oncologic outcomes, in a high-volume European Center. Second, this study aimed to determine the incidence of sarcopenia among disease-free patients, and factors leading to loss of LBM in survivorship.

METHODS

Patient Selection and Study Design

The Esophageal and Gastric Centre at St. James's Hospital, Dublin, is a high-volume National Centre, and a detailed clinicopathologic database is prospectively maintained for all patients with

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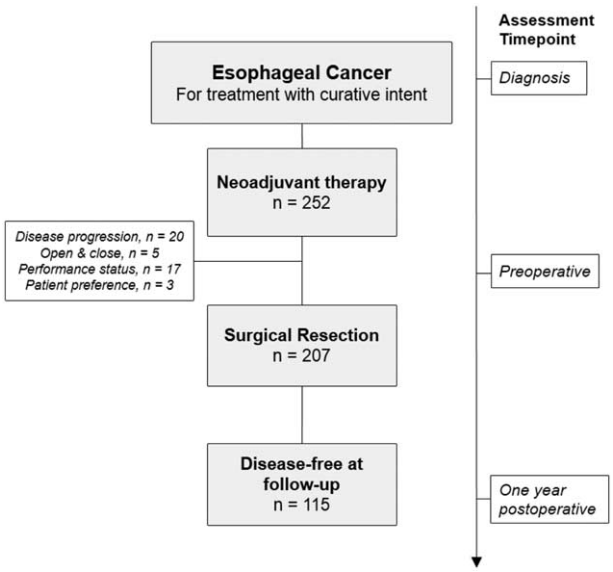

FIGURE 1. Study design. All patients undergoing multimodal therapy for locally advanced esophageal cancer between January 2010 and March 2015 were considered for inclusion. Two hundred fifty-two of 261 patients met the inclusion criteria, of whom 207 proceeded to surgical resection upon completion of neoadjuvant therapy. Of 115 patients who were disease-free at last follow-up (median 26 months), 1-year body composition was available for 72 patients.

esophageal cancer (Fig. 1). Records for all patients with LAEC treated with multimodal therapy between January 2010 and March 2015 were reviewed for inclusion. Patients with a history of synchronous malignancy, eating disorder, or other illness or implant that might alter body composition or interpretation thereof, and those undergoing emergent surgery, salvage esophagectomy, upfront colonic, or jejunal interposition were excluded from the analysis. All eligible patients with at least 1 preoperative computed tomography (CT) scan capturing the level of the L3 vertebra conducted at our Centre and available for review were included for analysis of operative and/or oncologic outcome. To determine postoperative changes in LBM, only disease-free patients at most recent follow-up, for whom both preoperative and 1-year scans were available for analysis, were included. This study was approved by the Institutional Review Board and registered on ClinicalTrials.gov (NCT03061370).

During this period, patients with LAEC were treated with neoadjuvant chemoradiation (either Cisplatin/5-Fluorouracil, 40 Gy/15 Fr or Carboplatin/Paclitaxel, 41.4 Gy/23 Fr),[27–29] or perioperative chemotherapy (Etoposide, Cisplatin, Fluorouracil/Capecitabine).[30] During neoadjuvant therapy, tailored nutritional counseling was provided to all patients according to ESPEN best practice guidelines.[31] Patients were scheduled to undergo resection approximately 6 weeks after completion of preoperative therapy, and operative approach entailed en bloc esophagectomy with gastric conduit and thoracic or cervical anastomosis, or extended total gastrectomy with abdominal or thoracic Roux-en-Y reconstruction, as previously described.[1,7,32] An 8-Fr needle catheter jejunostomy was routinely placed at surgery, with feeding commenced on the first postoperative day and continued until at least postoperative day 21. All patients underwent assessment at a multidisciplinary clinic at diagnosis, before surgery, and at serial postoperative timepoints, as previously described.[10,33]

Postoperative complications were coded using the Clavien-Dindo classification (CD) and the comprehensive complications index (CCI).[34,35] Pneumonia was defined as per CDC guidelines and postoperative pulmonary complications (PPCs) according to ECCG criteria.[4,36] Prolonged intubation was defined as respiratory failure of any etiology requiring reintubation or mechanical ventilation >24 hours postoperatively.

Computed Tomography Assessment of Body Composition

Positron emission tomography with computed tomography (PET-CT)/CT scans were routinely obtained at diagnosis, post-neoadjuvant therapy, and 1 year postoperatively using a Discovery ST PET/CT scanner (GE Healthcare, Little Chalfont, UK) or multislice Somatom Sensation scanner (Siemens Healthcare, Erlangen, Germany) (Fig. 2). Images at L3 were analyzed by a single blinded investigator (SLD) to determine the cross-sectional area (cm^2) of each tissue compartment using a Siemens Leonardo PACS Workstation (Siemens Healthcare, Erlangen, Germany), applying an automated algorithm utilizing CT Hounsfield unit thresholds of −29 to 150 for skeletal muscle and −50 to −150 for adipose tissue.[37–39]

Skeletal muscle index (SMI) was derived as the ratio of lean tissue area to height as follows:

$$SMI\ (cm^2/m^2) = \frac{Lean\ Tissue\ Area_{[L3]}\ (cm^2)}{height\ (m^2)}$$

Sarcopenia was defined as SMI less than 52.4 cm^2/m^2 for men and less than 38.5 cm^2/m^2 for women.[37,39] LBM and fat mass (FM)

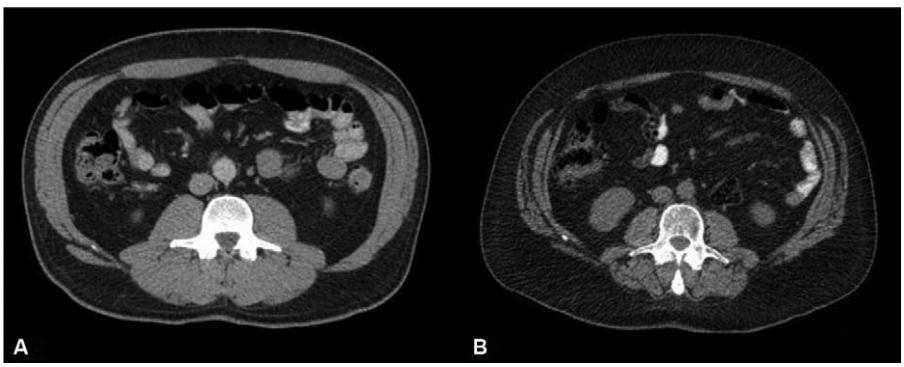

FIGURE 2. Computed tomography assessment of body composition. Abdominal computed tomography for 2 male patients with locally advanced esophageal cancer, of body mass index 31.5 kg/m^2 (A) and 32.4 kg/m^2 (B). Despite similar body mass indices, the patient in (A) has normal lean tissue and visceral fat areas, while the patient in (B) demonstrates both visceral obesity and sarcopenia.

were derived using the following formulae, which were developed and validated against DXA as standard:[37,39]

$$LBM\ (kg)\ =\ 0.30 \times [Lean\ Tissue\ Area_{[L3]}\ (cm^2)] + 6.06$$

$$FM\ (kg)\ =\ 0.042 \times [Total\ Fat\ Area_{[L3]}(cm^2)] + 11.2$$

Visceral obesity was defined as visceral fat area greater than 163.8 cm^2 for men and 80.1 cm^2 for women.[38]

Statistical Analysis

Data were analyzed using GraphPad Prism (v.6.0) for Windows, GraphPad software (San Diego, CA) and SPSS (v.23.0) software (SPSS, Chicago, IL). Univariable comparisons between groups were performed using the Student *t* or Mann-Whitney *U* tests for continuous or χ^2 or Fischer exact test for categorical variables. For the multivariable analyses, all clinically relevant variables were inputted into multivariable linear, logistic, or Cox proportional hazards regression models using a forward stepwise selection procedure. Data are reported as mean ± standard deviation unless otherwise specified. All statistical analyses were 2-tailed with the threshold of significance set at $P < 0.05$.

RESULTS

Patient Characteristics

Of 261 patients undergoing multimodal therapy during the study period, 252 met the inclusion criteria (Fig. 1, Table 1). Clinicopathologic characteristics of the 207 patients who proceeded to surgical resection are detailed in Table 1. For the entire study population, the prevalence of sarcopenia at diagnosis was 15.9%, while 43.0% were viscerally obese, and 6.3% demonstrated both sarcopenia and visceral obesity. Sarcopenia was significantly associated with lower body weight ($P < 0.001$) and BMI ($P < 0.001$), and was present in 25.3% of normal weight and 10.8% of overweight patients (Supplementary Table 1, http://links.lww.com/SLA/B284). Sarcopenia was significantly associated with pre-treatment BMI and SCC ($P < 0.05$).

Sarcopenia During Neoadjuvant Therapy

Significant LBM loss occurred during neoadjuvant therapy (56.4 ± 10.1 vs 53.5 ± 9.7, -3.0 ± 5.4 kg, $P < 0.0001$), with an increase in sarcopenia from 15.9% at baseline to 30.8% preoperatively ($P = 0.02$). No change in FM ($P = 0.31$) was observed following neoadjuvant therapy. LBM loss was unrelated to dysphagia score at presentation ($P = 0.90$), cT ($P = 0.27$), and cN stage ($P = 0.76$). Baseline sarcopenia was not significantly associated with disease progression (16.7 vs 7.9%, $P = 0.41$) or impaired performance status (8.3% vs 4.7%, $P = 0.11$); however, post-neoadjuvant therapy, sarcopenia was associated with disease progression (19.6% vs 4.6%, $P = 0.001$) and performance status precluding surgery (12.5% vs 2.1%, $P = 0.005$).

Sarcopenia and Operative Outcome

At resection, 49 patients (25.5%) were sarcopenic, while 84 (44.0%) were viscerally obese (Table 2, Supplementary Figure 1, http://links.lww.com/SLA/B285). Preoperative sarcopenia was associated with CCI ($P = 0.008$), major postoperative complications [≥IIIb, 24.5% vs 11.8%, odds ratio (OR) 2.41, 95% confidence interval (95% CI) 1.05–5.48, $P = 0.028$], and pulmonary complications (55.1% vs 35.7%, OR 2.21, 95% CI 1.15–4.28, $P = 0.01$). Postoperative pneumonia as per the CDC definition occurred in 44.8% and 27.3% of patients with and without sarcopenia, respectively (OR 2.17 95% CI 1.11–4.26, $P = 0.01$).

On multivariable analysis (Supplementary Tables 2 and 3, http://links.lww.com/SLA/B284), preoperative sarcopenia was independently predictive of increased CCI ($P = 0.004$), inpatient LOS ($P = 0.009$), major postoperative complications (≥IIIb, OR 5.30, 95% CI 1.94–14.45, $P = 0.001$), PPCs (OR 2.17, 95% CI 1.12–4.23, $P = 0.023$), pneumonia (OR 2.33, 95% CI 1.18–4.61, $P = 0.015$), and prolonged intubation (OR 3.83, 95% CI 1.24–11.79, $P = 0.019$). Sarcopenia was not associated with in-hospital mortality ($P = 0.43$), which was 1.0% across the study population.

Sarcopenia and Oncologic Outcome

For all patients with LAEC treated with curative intent, sarcopenia was associated with reduced disease-specific survival (5-year DSS, 34.2% vs 47.5%, $P = 0.0002$), and on multivariable analysis relative loss of LBM during treatment [hazard ratio (HR) 6.31, 95% CI 2.02–10.95] was predictive of DSS, with baseline BMI (HR 0.92, 95% CI 0.87–0.97, $P = 0.002$), histologic type [squamous cell carcinoma (SCC), HR 0.29, 95% CI 0.14–0.63], cT3–4 (HR 4.78, 95% CI 1.48–15.44, $P = 0.009$), and cN+ (HR 2.98, 95% CI 1.63–5.45) (Fig. 3).

Sarcopenia was not associated with ypT, ypN, pCR, or TRG, but tended to be associated with reduced probability of R0 resection (92.3 vs 81.6%, $P = 0.054$). On multivariable analysis, independent predictors of non-R0 resection were ypT stage (OR 5.53, 95% CI 1.98 – 15.44, $P = 0.001$) and visceral obesity, which was protective (OR 0.24, 95% CI 0.08–0.77, $P = 0.02$), suggesting that the relationship between sarcopenia and R0 resection is mediated by reduced visceral fat planes. Despite this, sarcopenia did not significantly impact survival outcome on univariable (5-year DSS, 46.5% vs 52.3%, $P = 0.14$) or multivariable analysis among resected patients (Supplementary Table 4, http://links.lww.com/SLA/B284).

Sarcopenia in Survivorship

One hundred fifteen of 207 resected patients were disease-free after a median of 26 months of follow-up. One-year CT was available for 72 patients (63%) (Supplementary Figure 2, http://links.lww.com/SLA/B285). Further loss of LBM occurred during the first postoperative year (baseline: 58.0 ± 10.3, preoperative: 55.9 ± 10.1, 1 year: 52.7 ± 9.3 kg, -5.3 ± 4.5 kg LBM, $P < 0.0001$), with increased prevalence of sarcopenia, from 6.9% at baseline, to 21.1% preoperatively, and 34.7% at 1 year ($P < 0.0001$). Significant loss of FM also occurred during the first postoperative year (baseline: 24.7 ± 6.0, preoperative: 24.7 ± 5.5, 1 year: 19.7 ± 5.5 kg, -5.5 ± 5.9 kg FM, $P < 0.0001$).

At 1 year, sarcopenia was independently associated with lower baseline BMI (HR 0.85, 95% CI 0.74–0.97, $P = 0.013$) but not CCI ($P = 0.20$), major postoperative complication ($P = 0.96$), anastomotic leak ($P = 0.15$), prolonged intubation ($P = 0.45$), operative approach ($P = 0.83$), histologic type ($P = 0.67$), pT ($P = 0.59$), or pN stage ($P = 0.66$), while only baseline LBM independently predicted LBM loss ($P < 0.001$). Similarly, only greater baseline FM ($P = 0.004$) and age ($P = 0.02$) independently predicted loss of FM at 1 year.

DISCUSSION

This study characterized the evolution of sarcopenia through multimodal treatment of LAEC, and in survivorship, providing novel data suggesting that sarcopenia should be measured and recorded as a potentially modifiable marker of risk. Sarcopenia was associated with risk of progression during multimodal therapy, and adverse oncologic outcomes. Moreover, muscle mass declined during

TABLE 1. Clinicopathologic Characteristics and Preoperative Sarcopenia in Resected Population

	All patients n = 207	No Sarcopenia n = 143	Sarcopenia n = 49	*P*
Clinical characteristics				
Age, mean (SD)	61.6 (9.3)	60.6 (8.9)	64.4 (10.1)	0.013
Sex, N (%)				
Female	42 (20.3)	32 (22.4)	4 (8.2)	0.03
Male	165 (79.7)	111 (77.6)	45 (91.8)	
Body weight, kg, mean (SD)	77.7 (16.0)	78.9 (15.7)	74.7 (14.7)	0.11
BMI, mean (SD)	26.9 (4.7)	27.7 (4.5)	24.9 (4.6)	<0.001
Obesity, N (%)	54 (26.5)	46 (32.2)	6 (12.2)	0.008
Morbid obesity, N (%)	7 (3.4)	6 (4.2)	1 (2.0)	0.68
Ever smoker, N (%)	142 (68.6)	103 (72.0)	32 (65.3)	0.37
Current smoker, N (%)	59 (28.5)	43 (30.0)	13 (26.5)	0.72
Diabetes, N (%)	13 (6.3)	10 (7.0)	1 (2.0)	0.30
Cardiovascular comorbidity, N (%)	31 (15.0)	16 (11.2)	11 (22.4)	0.059
Respiratory comorbidity, N (%)	34 (16.4)	20 (14.0)	12 (24.5)	0.12
ASA grade, N (%)				
Grade I	121 (58.5)	83 (58.0)	30 (61.2)	0.88
Grade II	75 (36.2)	52 (36.4)	17 (34.7)	
Grade III	11 (5.3)	8 (5.6)	2 (4.1)	
Neoadjuvant therapy, N (%)				
Chemotherapy	67 (32.4)	42 (29.4)	20 (40.8)	0.14
Chemoradiation	140 (67.6)	101 (70.6)	29 (59.2)	
Operation type, N (%)				
Extended total gastrectomy	33 (15.9)	20 (14.0)	7 (14.3)	0.89
2-stage esophagectomy	114 (55.1)	82 (57.3)	26 (53.1)	
3-stage esophagectomy	44 (21.3)	31 (21.7)	11 (22.4)	
Transhiatal esophagectomy	16 (7.7)	10 (7.0)	5 (10.2)	
Pathologic characteristics				
Histologic type, N (%)				
Adenocarcinoma	168 (81.2)	120 (83.9)	34 (69.4)	0.037
Squamous cell carcinoma	39 (18.8)	23 (16.1)	15 (30.6)	
Clinical stage, N (%)				
T1	2 (1.0)	1 (0.7)	0 (0.0)	0.08
T2	28 (13.5)	22 (15.4)	5 (10.2)	
T3	175 (84.5)	120 (83.9)	42 (85.7)	0.13
T4	2 (1.0)	0 (0.0)	2 (4.1)	
N0	79 (38.2)	60 (42.0)	13 (26.5)	
N1	99 (47.8)	64 (44.8)	26 (53.1)	
N2	27 (13.0)	17 (11.9)	10 (20.4)	
N3	2 (1.0)	2 (1.4)	0 (0.0)	
Pathologic stage, N (%)				
T0	35 (16.9)	22 (15.4)	7 (14.3)	0.75
T1	28 (13.5)	20 (14.0)	6 (12.2)	
T2	29 (14.0)	22 (15.4)	5 (10.2)	
T3	105 (50.7)	72 (50.3)	28 (57.1)	
T4	10 (4.8)	7 (4.9)	3 (6.1)	
N0	113 (54.6)	82 (57.3)	23 (46.9)	0.25
N1	52 (25.1)	34 (23.8)	17 (34.7)	
N2	24 (11.6)	16 (11.2)	3 (6.1)	
N3	18 (8.7)	11 (7.7)	6 (12.2)	
Tumor regression grade, N (%)				
TRG 1	37 (18.5)	24 (16.8)	7 (14.3)	0.12
TRG 2	43 (21.5)	30 (22.4)	12 (24.5)	
TRG 3	50 (25.0)	40 (30.0)	7 (14.3)	
TRG 4	49 (24.5)	35 (24.5)	11 (22.4)	
TRG 5	21 (10.5)	11 (7.7)	9 (18.4)	
Not applicable	7 (3.4)	3 (2.1)	3 (6.1)	
pCR, N (%)	33 (15.9)	22 (15.4)	6 (12.2)	0.82
R0 resection, N (%)	186 (90)	132 (92.3)	40 (81.6)	0.054

Obesity, BMI >30 kg/m^2; morbid obesity, BMI >40 kg/m^2 or >35 kg/m^2 with obesity-related comorbidity.
ASA indicates American Society for Anesthesiologists; BMI, body mass index (kg/m^2); CCI, comprehensive complications index; SD, standard deviation.

neoadjuvant therapy and preoperative sarcopenia was associated with an increased overall burden of postoperative complications, a 5-fold increased risk of major morbidity, and a 2-fold increased risk of pulmonary complications. In disease-free survivors, the incidence of sarcopenia continued to increase, highlighting the complexity of unintentional weight loss in these patients.

Esophageal cancer resection is associated with significant risk of major morbidity.[5] Although a 1% in-hospital mortality reflects a

TABLE 2. Postoperative Morbidity and Preoperative Body Composition in Resected Population

	All patients n = 207	No Visceral Obesity n = 107	Visceral Obesity n = 84	*P*	No Sarcopenia n = 143	Sarcopenia n = 49	*P*
Comprehensive complications index, mean (SD)	20.6 (18.7)	20.1 (20.5)	21.4 (17.2)	0.64	18.6 (18.2)	26.6 (20.8)	0.008
Clavien-Dindo ≥3b, N (%)	30 (14.5)	16 (15.0)	12 (14.3)	0.90	17 (11.8)	12 (24.5)	0.028
Clavien-Dindo grade, N (%)							
No complication	57 (27.5)	30 (28.0)	23 (27.4)	0.037	44 (30.8)	10 (20.4)	0.13
Grade I	26 (12.6)	20 (18.7)	5 (6.0)		20 (14.0)	5 (10.2)	
Grade II	69 (33.3)	25 (23.4)	34 (40.5)		45 (31.5)	15 (30.6)	
Grade III							
Grade IIIa	25 (12.1)	16 (14.9)	9 (10.7)		17 (11.8)	7 (14.3)	
Grade IIIb	6 (2.9)	4 (3.7)	1 (1.2)		1 (0.7)	4 (8.2)	
Grade IV							
Grade IVa	11 (5.3)	5 (4.7)	5 (6.0)		8 (5.6)	3 (6.1)	
Grade IVb	11 (5.3)	5 (4.7)	6 (7.1)		7 (4.9)	4 (8.2)	
Grade V	2 (1.0)	2 (1.9)	0 (0.0)		1 (0.7)	1 (2.0)	
Anastomotic leak, N (%)	10 (4.8)	3 (2.8)	6 (7.1)	0.16	9 (6.3)	0 (0.0)	0.12
Postoperative pulmonary complications, N (%)	84 (40.6)	40 (37.4)	38 (45.2)	0.27	51 (35.7)	27 (55.1)	0.01
Pneumonia, N (%)	66 (31.9)	29 (27.1)	31 (36.9)	0.16	39 (27.3)	22 (44.8)	0.01
Prolonged intubation, N (%)	22 (10.6)	12 (11.2)	9 (10.7)	0.91	14 (9.8)	8 (16.3)	0.22
Atrial fibrillation, N (%)	41 (19.9)	14 (13.1)	21 (29.8)	0.037	26 (18.2)	10 (20.4)	0.68
Major cardiac morbidity, N (%)	4 (1.9)	2 (1.9)	2 (2.4)	0.81	3 (2.1)	1 (2.0)	0.98
In-hospital mortality, N (%)	2 (1.0)	2 (1.9)	0 (0.0)	0.21	1 (0.7)	1 (2.0)	0.43

Sarcopenia and visceral obesity defined by preoperative computed tomography.
SD indicates standard deviation.

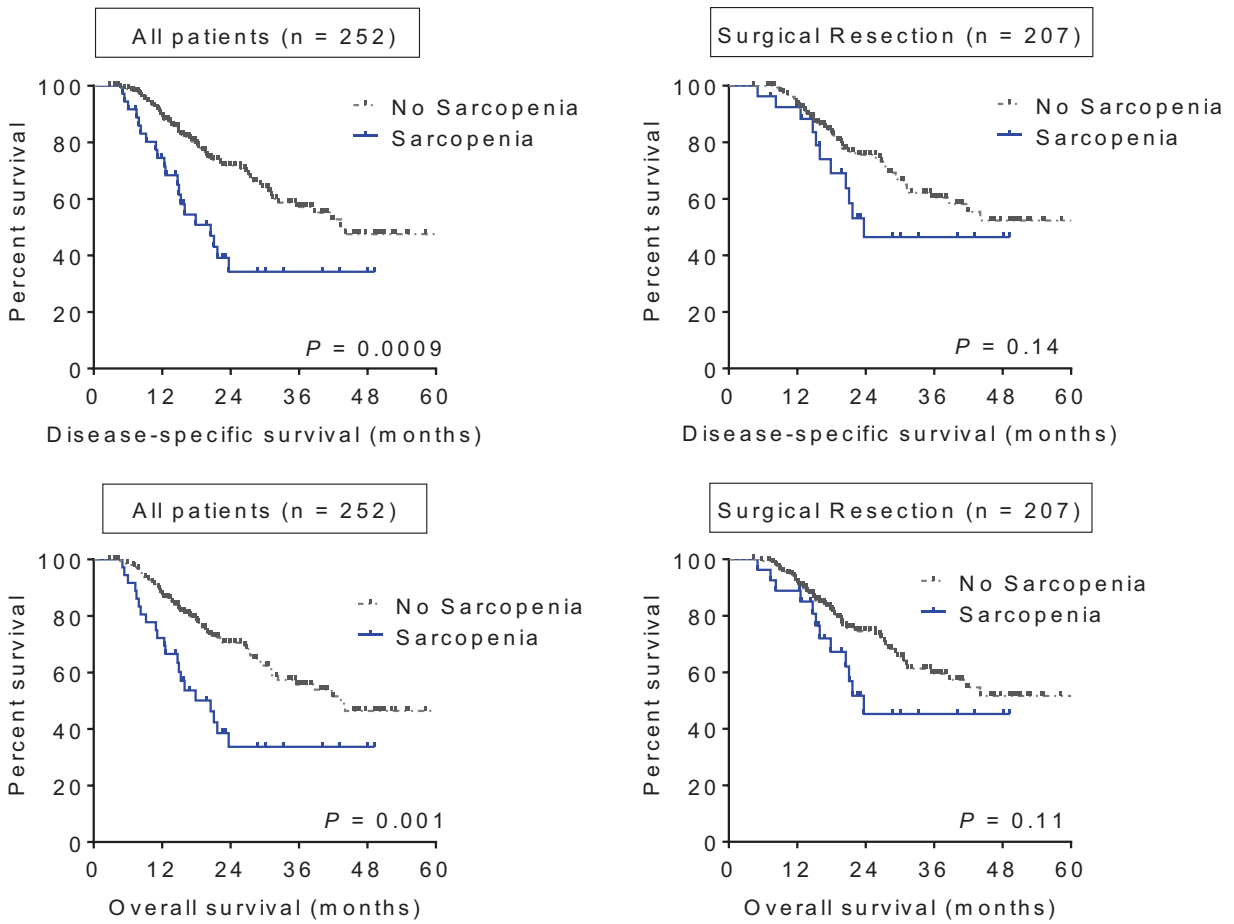

FIGURE 3. Sarcopenia at presentation and disease-specific survival, Among all patients treated with neoadjuvant therapy, baseline sarcopenia was associated with reduced disease-specific survival ($P = 0.0009$, left); however, sarcopenia did not impact survival outcome among those who proceeded to planned surgical resection following completion of neoadjuvant treatment ($P = 0.14$, right). Log-rank test.

high-volume experience, consistent with others,[40] pulmonary morbidity when accurately and prospectively documented remains high. Using the CDC clinical definition of pneumonia, with radiologic, laboratory, and clinical features as criteria, irrespective of sputum or blood culture,[36] the overall incidence is high at 32%, but significantly more prevalent among patients with preoperative sarcopenia, at 45% compared with 27%. This is consistent with Japanese series: Nishigori et al[14] reported an approximate 3-fold increase in PPCs among patients with sarcopenia, and Ida et al[15] reported a 5-fold increased risk of PPCs with lower LBM. These series were exclusively SCC, with mean BMIs of 21 and 22 kg/m^2 and preoperative sarcopenia rates of 75% and 44%, respectively, compared with 27 kg/m^2 and 31% herein. Conversely, in a study of 120 patients treated with neoadjuvant CROSS, 45% with baseline sarcopenia, Grotenhuis et al[16] identified no significant impact of sarcopenia at presentation on operative outcome, although analysis of only the pre-chemoradiation CT may have meant that LBM measures did not reflect muscle mass at operation, something acknowledged by the authors as a limitaton. In the present study, sarcopenia was not associated with anastomotic complications or atrial fibrillation, the latter more common among patients with visceral obesity. Notably, sarcopenia was associated with increased operative morbidity independent of body weight or BMI, something not previously reported.

The mechanism linking reduced muscle mass to postoperative respiratory morbidity is unclear. Sarcopenia reduces maximum inspiratory pressure, forced expiratory volume 1 second, and forced vital capacity in older adults, theoretically increasing risk of mucus plugging and atelectasis.[23,41,42] Sarcopenia is also associated with increased insulin resistance and higher circulating levels of proinflammatory cytokines, possibly contributing to risk of postoperative acute lung injury,[14] while globally impaired muscle function may additionally impact oropharyngeal motility, resulting in impaired swallow function and increased aspiration risk.[43,44] Prehabilitation programs in esophageal cancer targeting inspiratory muscle training, aiming to achieve a reduction in PPCs, hence have considerable theoretical rationale.[45]

Neoadjuvant therapy in esophageal cancer is generally associated with clinical improvement in dysphagia, yet paradoxically the incidence of sarcopenia significantly increased, from 16% to 31%, with mean loss of 3 kg LBM. Awad et al,[18] in 47 patients undergoing preoperative chemotherapy for esophageal and gastric cancers, demonstrated an LBM loss of 2.9 ± 4.7 kg, and Yip et al[25] reported an increase in sarcopenia from 26% to 43% following chemotherapy in LAEC. Although the physiologic drivers of this significant decline in muscle mass are unclear, the relative preservation of FM suggests a direct effect with respect to skeletal muscle. In this regard, cytotoxic agents may impair myocellular proliferation and protein synthesis by disrupting the mammalian target of rapamycin (mTOR) kinase signaling pathway,[46] while cisplatin also promotes muscle wasting through a number of mechanisms including impaired Akt phosphorylation, leading to sustained activation of the degradative proteasome and autophagy systems, and altered NF-kB signaling.[47,48] Sarcopenia was associated with worsened performance status and disease progression, precluding surgical resection. Whether this reflects reduced volume of effective distribution of chemotherapy, enabling increased toxicity, is unclear, but is an important question for further study, particularly in the context of recent data demonstrating an almost 3-fold increased rate of dose-limiting chemotoxicity with sarcopenia in esophageal cancer.[18,20,24] The complex interplay between baseline sarcopenia and oncologic outcome is highlighted by reduced DSS with sarcopenia among all LAEC patients, but not among those proceeding to surgery post-neoadjuvant therapy. Future studies assessing the role of LBM-based dosing, versus conventional BSA-based calculations, are consequently of great interest in this context (eg, NCT01624051).

With improved oncologic outcomes, and low operative mortality, there is currently a major focus on survivorship and quality of life.[6–10] Weight loss is a significant issue, and seminal papers from Sweden highlighted that over two-thirds of patients experience >10% body weight at 6 months, while one-third of patients lose ≥15% body weight at 5-year follow-up.[26,49] Although clearly linked to sarcopenia, no previous study has described the underlying changes in body composition in survivorship. In the current study, continued loss of muscle mass was observed, with a 5-fold increase compared with initial presentation, while in a cohort of 50 patients who had surgery only (data not shown), the prevalence of sarcopenia at 1 year was 37.5%, hence ongoing muscle loss appears independent of neoadjuvant therapy. Although loss of LBM may reduce strength and mobility, corroborating measures of functional performance were not conducted, which we acknowledge as a limitation.[43] In the context of a survivorship program recently established at this Center, a feasibility project demonstrated that a 12-week multimodal rehabilitation program, including supervised exercise, dietetic counseling, and multidisciplinary education, was associated with increased indices of physical function and HR-QL, and reduced circulating inflammatory markers among disease-free patients post-esophagectomy;[50] an RCT examining this approach is ongoing.

In conclusion, sarcopenia, very simply diagnosed by routine staging CT, is common in LAEC, increased by neoadjuvant therapy, and independently associated with postoperative morbidity. Sarcopenia is prevalent in survivorship. Measures of muscle mass and function, and targeted approaches through multimodal protocols and in survivorship, have appeal in the evolving goals to optimize a complex attritional cancer treatment protocol and improve survivorship.

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DISCUSSANTS

Bruno Walther (Lund, Sweden):

Thank you for the opportunity to discuss this interesting paper. It is well known that esophageal cancer patients lose weight, but sarcopenia is previously not described in detail from diagnosis to

1 year after oncological and surgical therapy. I have the following questions and remarks: First, please rank the importance of the different factors inducing sarcopenia in the resected patients? Second, in your study, 16% of the patients had sarcopenia at study start and 35% after 1 year. We have found that there is a strong correlation between anastomotic diameter and gain in weight. No matter how you define it, was sarcopenia more common in patients with strictures? In our study comparing neck and chest anastomoses after esophagectomy in radio-chemonaive patients (*Ann Surg* 2003; 238: 803–812), the weight loss leveled away after 3 months and the patients start to gain weight.

Third, enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass (LBM) following esophageal cancer surgery, as your group wrote in Annals of Surgery (*Ann Surg* 2009; 249: 355–363). In the present study, there is a loss of LBM during the first postoperative year. Please clarify the difference between the studies. Do you still use EPA in the nutritional support?

Fourth, do you use full stomach as a substitute, proposed by Collard and others, or do you modify the stomach to a gastric tube used for morbid obesity? This is because the weight reduction and sarcopenia seen in your surgical patients might to some extent be explained by the way the stomach is modified to substitute the resected esophagus. Finally, congratulations to an important study and an excellent presentation.

Response from Jessie A. Elliott (Dublin, Ireland):

Thank you, Professor Walther for your comments and your questions, which I will address in sequence. First, in terms of sarcopenia before resection, we found that sarcopenia was associated with older age, male sex, lower body mass index, and LBM at diagnosis, SCC, and tended to be associated with a cardiovascular comorbidity. We did also identify a significant association between sarcopenia and clinically node-positive disease at the preoperative time point. And, then looking forward into survivorship in the resected population, among disease-free patients at 1 year postoperatively, the only independent factor tested that predicted sarcopenia in that cohort was baseline LBM. Interestingly, even though we assessed factors such as length of stay, critical care length of stay, and perioperative complications in a multivariate model, none of these predicted long-term change in LBM in these patients. For this reason, we are suggesting that not only other mechanisms, for example, as you mentioned anastomotic stricture, but also changes in appetite, gut hormones, and gut function might underline the long-term changes in body composition observed in this cohort. I think this is something that requires further study.

The second question you had was about the prevalence of anastomotic stricture in the sarcopenic patients at follow-up. We did not identify any statistically significant difference in the prevalence of strictures between sarcopenic and nonsarcopenic patients. However, this needs to be examined in a dedicated study to determine the role of anastomotic strictures in the postoperative loss of LBM after esophagectomy.

Third, you asked us about whether we were still using EPA-supplemented feeds in our patient cohort. The answer is no, and the rationale for this has been discussed earlier this morning. A proportion of the patients in the study may have received EPA-supplemented feed, but given our recent data, this should not have impacted their LBM at the time of surgery, or postoperatively.

The final question was in relation to the gastric conduit that we use. So, this is a 5 cm greater curvature gastric conduit, which has been described in detail in a number of our studies (*World J Surg* 2017; 41:487–497 and *Ann Surg* 2017; 266:82–90). It is certainly possible that this reconstruction may be contributing to a bariatric-like mechanism in our patient cohort. The other possible operative factor that may contribute to a bariatric-like mechanism is pyloric management. In our center, pyloroplasty is performed as routine. We have shown that these patients demonstrate a greatly exaggerated postprandial satiety gut hormone response, which may be related to rapid gastric conduit emptying. However, no study so far has looked at the differences in gut hormone physiology and appetite among patients with gastric conduit versus whole stomach reconstruction, and I think that is something that could be very interesting to assess in the future.

P. Ronan O'Connell (Dublin, Ireland):

Thank you chairman. Jessie, congratulations on a wonderful presentation. I have 3 quick questions: First, was there a difference in the complication rates between those who were sarcopenic ab initio and those who developed sarcopenia as a result of chemoradiotherapy? Second, did the sarcopenia progress in those who were sarcopenic ab initio and if so did they have a worse outcome? This leads me to the last point, if you identify somebody with sarcopenia pre-chemoradiotherapy is that a diagnosis that would make you think that the patient should go directly to surgery and not have chemoradiotherapy?

Response from Jessie A. Elliott (Dublin, Ireland):

Thank you, Professor O'Connell for these interesting questions. We did look at the role of baseline sarcopenia for predicting postoperative complications. Baseline sarcopenia tended to be associated with increased postoperative complications ($P = 0.095$), and was associated with an increased risk of pulmonary complications ($P = 0.02$). However, preoperative sarcopenia measures were more accurate than baseline measures for prediction of postoperative outcomes.

We also looked at patients who were sarcopenic at presentation versus patients who became sarcopenic during neoadjuvant therapy. We did not see any difference in the overall burden of complications experienced by incident sarcopenic patients versus baseline sarcopenic patients. Patients who were sarcopenic at baseline continued to lose LBM (-1.1 ± 1.4 kg), but this was less pronounced compared with nonsarcopenic patients (-5.7 ± 0.8 kg, $P = 0.02$), and the overall burden of complications was similar among all patients with sarcopenia (whether progressive or stable during neoadjuvant therapy, $P = 0.80$).

The third question was should sarcopenic patients be considered for surgery upfront? I think the answer to that is no – We know that these patients have a much better oncologic outcome after neoadjuvant therapy. The way I see it, we have this great therapeutic window to intervene among patients undergoing neoadjuvant therapy, to try and improve their performance status and achieve a better postoperative outcome. Therefore, I think the main message arising from these data is that there is a potential opportunity to improve outcomes through preoperative prehabilitation in this cohort, and the efficacy of such an approach requires further assessment.

Christophe Mariette (Lille, France):

Thanks a lot Jessie, definitely a very nice presentation, so congratulations. I have 2 short questions based on the methodology. My first question is regarding the multivariable model. Do you think it is useful to put so many variables in the model that may have some interactions altogether? My recommendation would have been to put in the multivariable model (i) clinically relevant variables (and not all the statistically significant in univariable analysis), and (ii) the variables without strong known interactions.

The second question is why were the reoperations excluded from the analysis? It could have been a good marker of the negative impact of sarcopenia on outcomes.

In addition, I just want to highlight that in general in medicine, statistically significant does not always mean clinically relevant.

Response from Jessie A. Elliott (Dublin, Ireland):

Thank you, Professor Mariette for your questions and comments. In terms of the multivariable models, we endeavor to avoid issues with collinearity. There are a couple of important things to note about the multivariable models we used. First, for this study, our models used a forward stepwise selection procedure, so that means that the model selects the first variable based on the variable with the strongest univariable correlation to the outcome, thereafter further variables are inputted into the model based on the residual variability in the outcome. So, the number of variables first presented to the model is less problematic, because only the variables that are significant on univariable analysis are actually inputted into the model in a stepwise approach. Rules of thumb regarding sample size and covariate count in regression oversimplify the issue considerably. In fact, the sample size required in terms of number of covariates depends on the expected effect size, the required power, and the output of interest.

Second, the aim of our multivariable analysis was to probe for variables that were most strongly predictive of operative outcome, rather than choosing known factors and feeding them into the model. We were interested in identifying which factors most strongly impacted outcome in our cohort, rather than controlling for certain factors and looking at the impact of another. So, it is a different analytical approach.

With respect to reoperation, we did include patients with Clavien-Dindo grade IIIb. So, patients who returned to theater for a complication were included. We did not include salvage esophagectomy because we felt that this cohort was likely at a great risk of baseline sarcopenia and they are likely at an increased risk of complications – We felt that it would increase the heterogenity of the cohort and dilute the message. Our numbers for salvage would also be quite small, so we would not have the power to analyze them separately from our main study population.

Richard van Hillegersberg (Utrecht, The Netherlands):

Thank you very much for a well-conducted important study on this topic. I have a question about the neoadjuvant chemoradiotherapy or chemotherapy. Do you have an explanation why these patients deteriorate under this neoadjuvant treatment? In our experience during the neoadjuvant chemoradiotherapy, a lot of patients who respond well get into an anabolic state because they are allowed to eat again or have nutritional support. Furthermore, did you look into the toxicity profiles of chemotherapy versus chemoradiotherapy and did you look into the group that responded well to the neoadjuvant treatment?

Response from Jessie A. Elliott (Dublin, Ireland):

Thank you for these questions. What is very interesting, I think, about the changes in body composition during neoadjuvant therapy is that it was a very specific loss of LBM that occurred and actually the fat mass was completely stable, which would sort of imply that this is some kind of specific myotoxic effect. In that regard, it is known that a number of the chemotherapeutic agents used in esophageal cancer can have a direct effect on muscle proliferation and myocyte protein synthesis, through various pathways including mTor and NFKB signaling. It is possible that there is a direct myotoxic effect of the chemotherapeutic agents.

In that regard, interestingly in other malignancies, some groups are now looking at the use of LBM-based calculations for chemotherapy dosing, rather than basing it on body surface area, which is the current standard. It may be that patients who are sarcopenic will accumulate a higher dose of these hydrophilic drugs in their muscle and therefore be at an increased risk of chemotherapy toxicity. The toxicity profiles were not specifically captured in this particular study. It is certainly something that could be studied further. There are 2 previous studies (*Eur J Surg Oncol* 2015; 41:333–338 and *Clin Nutr* 2016; 35:724–730), one from Sweden and one from the UK looking at the role of sarcopenia in terms of risk from chemotherapy toxicity in the neoadjuvant context in esophageal and gastric cancer, and both showed that patients with sarcopenia at baseline are at an increased risk of toxicity. Certainly, it is something that warrants more study going forward.

On multivariable analysis, we did not find any difference between chemotherapy and chemoradiation in terms of risk of sarcopenia either in the population overall, or in adenocarcinoma patients alone. It is certainly something that could be looked at in the ongoing trials.

In terms of sarcopenia in responders versus nonresponders, there was no difference in prevalence of preoperative sarcopenia according to the presence of pCR among all patients (21% vs 26%, $P = 0.82$), and pCR was not independently predictive of preoperative sarcopenia on multivariable analysis.