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Influence of body composition and muscle strength on outcomes after multimodal oesophageal cancer treatment

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Abstract

Background Influence of sarcopenia in combination with other body composition parameters and muscle strength on outcomes after oesophageal surgery for oesophageal cancer remains unclear. The objectives were (i) to describe the incidence of sarcopenia in relation to adipose tissue quantity and distribution and muscle strength; (ii) to evaluate if neoadjuvant chemoradiation (nCRTx) influences body composition and muscle strength; and (iii) to evaluate the influence of body composition and muscle strength on post-operative morbidity and long-term survival.

Methods This retrospective study included patients with oesophageal cancer who received nCRTx followed by surgery between January 2011 and 2016. Skeletal muscle, visceral, and subcutaneous adipose tissue cross-sectional areas were calculated based on computed tomography scans, and muscle strength was measured using hand grip tests, 30 seconds chair stand tests, and maximal inspiratory and expiratory pressure tests prior to nCRTx and after nCRTx.

Results A total of 322 patients were included in this study. Sarcopenia was present in 55.6% of the patients prior to nCRTx and in 58.2% after nCRTx ($P = 0.082$). Patients with sarcopenia had a significantly lower muscle strength and higher fat percentage. The muscle strength and incidence of sarcopenia increased while the mean body mass index and fat percentage decreased during nCRTx. A body mass index above 25 kg/m^2 was associated with anastomotic leakage ($P = 0.032$). Other body composition parameters were not associated with post-operative morbidity. A lower handgrip strength prior to nCRTx was associated with pulmonary and cardiac complications ($P = 0.023$ and $P = 0.009$, respectively). In multivariable analysis, a lower number of stands during the 30 seconds chair stand test prior to nCRTx (hazard ratio 0.93, 95% confidence interval 0.87–0.99, $P = 0.017$) and visceral adipose tissue of >128 cm^2 after nCRTx (hazard ratio 1.81, 95% confidence interval 1.30–2.53, $P = 0.001$) were associated with worse overall survival.

Conclusions Sarcopenia occurs frequently in patients with oesophageal cancer and is associated with less muscle strength and a higher fat percentage. Body composition changes during nCRTx did not influence survival. Impaired muscle strength and a high amount of visceral adipose tissue are associated with worse survival. Therefore, patients with poor fitness might benefit from preoperative nutritional and muscle strengthening guidance, aiming to increase muscle strength and decrease visceral adipose tissue. However, this should be confirmed in a large prospective study.

Keywords Oesophageal cancer; Body composition; Sarcopenia; Muscle strength; Complications; Survival

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Introduction

The prognosis of oesophageal cancer remains poor, and the post-operative complication rate remains high.[1,2] Five years of survival rates following neoadjuvant chemoradiation (nCRTx) and oesophagectomy are reported to be 30–57%.[3–5] Up to 80% of patients with advanced oesophageal cancer are affected by cancer-induced cachexia, a clinical condition that results in skeletal muscle wasting with or without loss of body fat.[6–8] In patients with oesophageal cancer, cachexia is worsened by dysphagia, leading to malnutrition and a change in body composition.[9,10]

Current literature on the influence of body composition parameters [including body mass index (BMI), body fat percentage, skeletal muscle index, and sarcopenia] on post-operative morbidity and long-term survival in patients with oesophageal cancer after curative intent treatment is scarce, and literature on sarcopenia is often contradictory. Some studies show that sarcopenia is an independent predictor for development of post-operative complications and overall and disease-free survival while other studies did not find any correlation.[11–14] Few studies take other factors such as muscle strength and fat percentage or fat distribution into consideration. Sarcopenia reduces physical activity, which leads to decreased energy and an increased risk of obesity.[15] When sarcopenia is accompanied by a high fat mass, it is called sarcopenic obesity.[16] Both sarcopenia and obesity are associated with post-operative morbidity, mortality, and lower overall survival in patients with oesophageal cancer, and it is hypothesized that sarcopenic obesity may have a greater impact than either sarcopenia or obesity alone.[17–20] It is therefore of importance to evaluate influence of sarcopenia in combination with other body composition parameters and muscle strength on long-term and short-term outcomes in oesophageal cancer patients.

The objectives of the present study were to describe the incidence of sarcopenia and the relationship of sarcopenia with adipose tissue quantity and distribution and muscle strength, to evaluate the change in body composition, sarcopenia, and muscle strength during nCRTx, and to evaluate the influence of body composition and muscle strength on post-operative morbidity and long-term survival.

Methods

Study design and study population

A retrospective study was conducted using a prospectively maintained database containing consecutive patients with oesophageal cancer who have been treated with surgery between 1 January 2011 and 1 January 2016 in the Amsterdam UMC (location AMC), the Netherlands. The STROBE guidelines were used to ensure correct reporting of this study.[21] Study variables on baseline characteristics and post-operative complications were obtained from an existing prospectively maintained surgical database and medical records. Patients were included in this study if they had a resectable oesophageal carcinoma and were treated with nCRTx followed by surgery. Patients were excluded if diagnostic computed tomography (CT) images before and after nCRTx were missing or in case of insufficient quality for the assessment of body composition. CT images were considered of insufficient quality if tissue was cut off from the frame, and/or the CT scan was not in portal phase, and/or it was not a high-resolution scan.

Treatment of patients

In case of dysphagia and/or weight loss, patients were referred to a dietician. If indicated, patients were subscribed liquid oral nutritional supplements or tube feeding. All patients were screened for physical fitness by a physiotherapist, and if indicated, a training programme was advised.

Patients were treated according to the national oesophageal cancer guidelines.[22] Resectable (cT2-4aN0-3M0 and cT0-1N+M0) patients were treated with nCRTx consisting of 23 fractions of 1.8 Gy (41.4 Gy) external beam radiotherapy combined with weekly administered carboplatin (AUC 2) and paclitaxel (50 mg/m^2). Six to 10 weeks after nCRTx (depending on patients' condition), patients had an open or minimally invasive transthoracic or transhiatal oesophagectomy with gastric tube reconstruction with either an intrathoracic or cervical anastomosis.[4] The choice for the surgical approach depended on patients (e.g. pulmonary function) and tumour (e.g. tumour location and invasion depth, location of lymph node metastases, and radiation field) characteristics.

Patients were screened for physical fitness, and if indicated, a training programme was advised.

Definition of post-operative morbidity

Post-operative complications were graded using the Clavien–Dindo classification system.[23] To classify the severity of post-operative complications, patients were divided into three groups: no complications, minor complications, and major complications (Clavien–Dindo IIIb–V). Definition of complications was scored according to the Esophagectomy Complications Consensus Group classification.[24]

Assessment of muscle strength

Muscle strength was measured by functional muscle tests by a physiotherapist, prior and after nCRTx as part of another

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study.[25] Hand grip strength was measured with the Jamar® grip strength dynamometer (Lafayette Instrument Company, USA), which is considered a reliable instrument to predict the total skeletal muscle mass.[26] Muscle strength of the lower extremities was assessed with the 30 seconds chair stand test. During this test, patients were asked to stand up from a chair without support of the arms and sit again, repeating this during 30 s.[27] Maximal inspiratory and expiratory pressure were measured as indicators of respiratory muscle strength with a micro-medical spirometer.[28]

Assessment of body composition

Variables describing body composition included skeletal muscle, visceral, subcutaneous, and total adipose tissue cross-sectional areas and indexes, presence of sarcopenia, body fat percentage, and BMI. In all patients, CT scans were acquired less than 6 weeks prior to nCRTx and 2 to 3 weeks after nCRTx as part of routine preoperative workup. Skeletal muscle, visceral, subcutaneous, and total adipose tissue cross-sectional areas were evaluated on CT images at a standard vertebral landmark (the midpoint of the third lumbar vertebrae; L3), because tissue areas in this region are significantly related to whole-body composition.[29,30]

Three independent researchers (E.H., M.F., and P.B.) measured the muscle surface area using Slice-O-Matic® software, and the mean of the three measurements was the final value. One researcher (P.B.) measured subcutaneous, visceral, and total adipose tissue areas because software add-on for these measurements was only available at his institute. Hounsfield unit thresholds of −29 to 150 for skeletal muscles (the psoas, paraspinal, transverse abdominal, internal and external oblique, and rectus abdominis muscles), −50 to −150 for visceral adipose tissue, and −190 to −30 for subcutaneous adipose tissue were used to differentiate muscle and adipose tissue from other tissues.[31]

Skeletal muscle index was calculated using the formula skeletal muscle surface index = skeletal muscle surface area / height^2, expressed in square centimetre per square metre. For women, sarcopenia was present if the skeletal muscle surface index was less than 41 cm^2/m^2. For men, sarcopenia was present when the skeletal muscle surface index was less than 53 cm^2/m^2 in case of a BMI of ≥25 kg/m^2 or the skeletal muscle surface index was less than 43 cm^2/m^2 in case of a BMI of <25 kg/m^2.[32] Subcutaneous, visceral, and total adipose tissue indexes were calculated the same way as skeletal muscle index.[33] Total fat mass was calculated using the formula fat mass = 0.042 × (visceral + adipose surface area) + 11.2, expressed in kilograms.[30,32] Body fat percentages were calculated, with a cut-off value for obesity for women of >44.4% and >35.7% for men.[30,34] Patients were considered to have sarcopenic obesity if they met the criteria for sarcopenia and obesity.

Statistical analysis

Patient, tumour, and treatment characteristics were presented using descriptive statistics. The mean (± standard deviation) was used in case of a normal distribution of variables, and the median (interquartile range) was used for variables with a skewed distribution. Categorical data were compared using a χ^2 or Fisher's exact test where appropriate or Wilcoxon signed rank test for paired data. Continuous data were compared using independent *t*-test. In case of paired data, the dependent *t*-test was used. Median and overall survival were calculated using Kaplan–Meier curves with subgroups being compared using the log-rank test. Cox proportional hazard model was used for multivariable analysis. Traditional clinical variables potentially influencing long-term survival (selected a priori: age, histology, ypT stage, ypN stage, resection margin, and Mandard score) were entered in a multivariable analysis of traditional clinical variables alone if they were significant in univariable analysis. Stepwise backwards elimination procedure ($P < 0.05$ to stay in the model) was used to reduce the number of predictors. Then body composition and muscle strength variables that were significant in univariate analysis were added to the models. Missing data were handled with complete case analysis. All analyses were executed in SPSS version 25.0 (SPSS Corp. Chicago, IL, USA). All tests were two-sided, and *P* values less than 0.05 were considered significant.

Results

Patient characteristics

From January 2011 until January 2016, 362 patients underwent an oesophageal resection after nCRTx, of whom 322 patients were eligible for inclusion. In 175 patients, both the CT scans prior to nCRTx and after nCRTx were available and eligible for analysis. A flowchart of patient selection is shown in *Figure* 1. Baseline characteristics of all included patients are shown in *Table* 1. All patients in this cohort finished the planned nCRTx regimen.

Incidence of sarcopenia

Sarcopenia was present in 51.4% of the patients with adenocarcinoma and in 71.7% of the patients with squamous cell carcinoma based on the CT scan prior to nCRTx ($P = 0.013$). The mean age and proportion of women were higher in patients

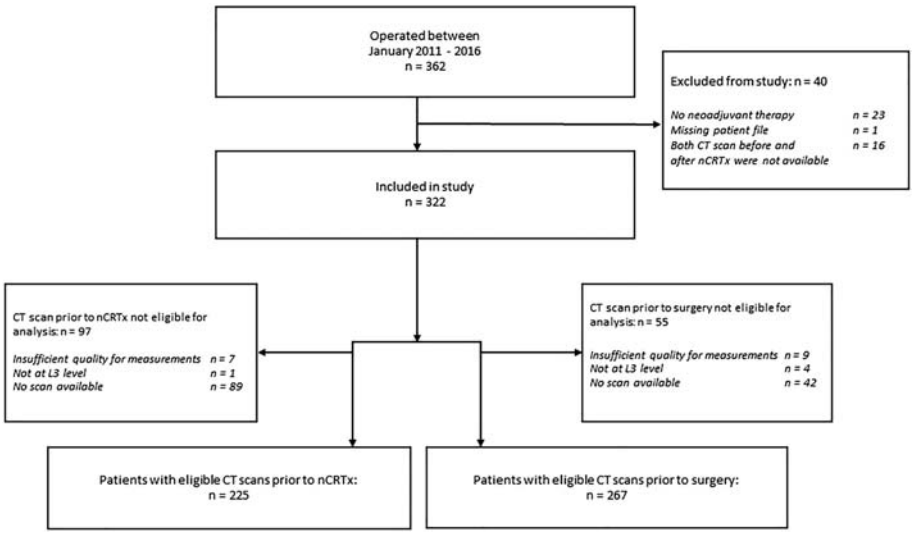

Figure 1 Flowchart patient selection. Insufficient quality for measurements includes the following: Tissue was cut off from the frame, and/or the CT scan was not in portal phase, and/or it was not a high-resolution scan. CT, computed tomography; nCRTx, neoadjuvant chemoradiation.

with sarcopenia ($P = 0.005$ and $P < 0.001$, respectively). Baseline characteristics of patients with and without sarcopenia prior to nCRTx and after nCRTx are shown in *Table* 1.

Relation between sarcopenia, body composition, and muscle strength

Table 2 shows the association between sarcopenia, body fat percentage, and muscle strength. Patients with sarcopenia both prior to nCRTx and after nCRTx had a significantly lower muscle strength and higher fat percentage compared with patients without sarcopenia. No association was seen between visceral and subcutaneous adipose tissue indexes and sarcopenia. Sarcopenic obesity was present in 11 (6.4%) sarcopenic patients prior to nCRTx and in 8 (3.0%) sarcopenic patients after nCRTx.

Influence of neoadjuvant chemoradiation on body composition and muscle strength

Most body composition parameters showed a significant change during nCRTx; the incidence of sarcopenia increased (55.6–58.2%, $P = 0.082$) while the mean BMI and fat percentage decreased [-0.4 kg/m^2, 95% confidence interval (CI) -0.3 to 0.5, $P < 0.001$, and -0.6%, 95% CI -0.04 to 1.2, $P = 0.036$, respectively].

All muscle strength tests showed an increase in muscle strength during nCRTx (data not shown). The strongest increase of muscle strength was seen in the maximal expiratory pressure (mean increase of 9.4 cmH_2O, 95% CI 3.7–15.1, $P = 0.001$) and grip strength of the non-dominant hand (mean increase of 1.4 kg, 95% CI 0.5–2.4, $P = 0.004$).

Influence of body composition and muscle strength on post-operative complications

Sarcopenia, sarcopenic obesity, and BMI, skeletal muscle index, body fat percentage, and muscle strength were measured as continuous variables, and all were not prior and after nCRTx significantly related to the incidence and severity of post-operative complications (*Table* 3).

A BMI of $\geq$26 kg/m^2 prior to nCRTx was associated with a higher incidence of anastomotic leakage (15.9% of the patients with a BMI between 18 and 25 kg/m^2 and 26.0% of the patients with a BMI of $\geq$26 kg/m^2 developed anastomotic leakage, $P = 0.032$). Obesity did not significantly influence the incidence of other complications (data not shown).

Figure 2 shows the correlation between BMI (as continuous variable), skeletal muscle index, body fat percentage, and hand grip strength and the incidence of anastomotic leakage, pulmonary complications, and cardiac complications. Pulmonary and cardiac complications were significantly associated with a lower handgrip strength when measured prior to nCRTx ($P = 0.023$ and $P = 0.009$, respectively).

Influence of body composition and muscle strength on long-term survival

The median follow-up time was 37.6 months (95% CI 28.1–47.2). Patients with sarcopenia prior to nCRTx had a median

Table 1 Baseline characteristics of all included patients

		Prior to nCRTx			After nCRTx		
	All patients	Sarcopenia	No sarcopenia	*P* value	Sarcopenia	No sarcopenia	
	n = 322	*n* = 125	*n* = 100		*n* = 155	*n* = 112	*P* value
Age, mean ± *SD*	63.7 ± 8.7	64.9 ± 8.4	61.6 ± 8.9	**0.005**	65.6 ± 7.7	61.1 ± 9.0	**<0.001**
Female gender	78 (24.2)	42 (33.6)	16 (16.0)	**0.003**	53 (34.2)	11 (9.8)	**<0.001**
BMI, mean ± *SD*	25.6 ± 4.0[a]	25.1 ± 3.7	26.3 ± 4.5	**0.044**	25.2 ± 3.6	26.1 ± 4.1	**0.044**
BMI <18.5	4 (1.3)[a]	3 (2.4)	0	0.249	1 (0.6)	2 (1.8)	**0.035**
BMI 18.5–24.9	142 (44.4)[a]	52 (41.6)	48 (48.0)		66 (42.6)	53 (47.3)	
BMI 25–39.9	121 (37.8)[a]	53 (42.4)	35 (35.0)		73 (47.1)	36 (32.1)	
BMI >30	48 (15.0)[a]	17 (13.6)	17 (17.0)		15 (9.7)	21 (18.8)	
Co-morbidities							
Diabetes	31 (9.7)	11 (8.8)	7 (7.0)	0.621	15 (9.7)	11 (6.4)	0.950
Cardiovascular co-morbidity	118 (37.6)	52 (41.6)	30 (30.0)	0.104	69 (44.5)	33 (19.2)	**0.014**
COPD	20 (6.2)	6 (4.8)	9 (9.0)	0.209	10 (6.5)	6 (5.4)	0.710
ASA score							
I	60 (18.6)	18 (14.4)	20 (20.0)	0.212	26 (16.8)	25 (22.3)	0.382
II	173 (53.7)	77 (61.6)	50 (50.0)		84 (54.2)	52 (46.4)	
III	89 (27.6)	30 (24.0)	30 (30.0)		45 (29.0)	35 (31.1)	
Oesophagectomy							
Transhiatal	58 (18.0)	19 (15.2)	20 (20.0)	0.345	25 (16.1)	17 (15.2)	0.833
Transthoracic	264 (82.0)	106 (84.8)	80 (80.0)		130 (83.9)	95 (84.8)	
Cervical anastomosis	160 (60.6)	59 (55.7)	53 (66.3)	0.144	74 (56.9)	54 (56.8)	0.990
Intrathoracic anastomosis	104 (39.4)	47 (44.3)	27 (33.7)		56 (43.1)	41 (43.2)	
Approach							
Minimally invasive	260 (80.7)	106 (84.8)	82 (82.0)	0.573	133 (85.8)	92 (82.1)	0.417
Open	62 (19.3)	19 (15.2)	18 (18.0)		22 (14.2)	20 (17.9)	
Histology							
Adenocarcinoma	257 (79.8)	91 (72.8)	88 (88.0)	**0.005**	110 (71.0)	99 (88.4)	**0.001**
Squamous cell carcinoma	65 (20.2)	34 (27.2)	12 (12.0)		45 (29.0)	13 (11.6)	
R0 resection	301 (94.1)	114 (91.2)	96 (96.0)	0.151	145 (93.5)	107 (62.2)	0.405
Clinical T category							
T1–2	68 (21.3)	29 (23.2)	22 (22.0)	0.366	29 (18.7)	27 (15.7)	0.528
T3–4	235 (73.4)	89 (71.2)	76 (76.0)		118 (76.1)	78 (45.3)	
Tx	17 (5.3)	7 (5.6)	2 (2.0)		8 (5.2)	6 (3.5)	
Clinical N category							
N0	86 (27.0)	40 (32.3)	26 (26.0)	0.397	45 (29.0)	27 (15.7)	0.249
N1	155 (48.6)	57 (46.0)	55 (55.0)		65 (41.9)	58 (33.7)	
N2–3	78 (24.5)	27 (21.8)	19 (19.0)		45 (29.0)	26 (15.1)	
ypT category							
T0	58 (18.1)	29 (23.6)	13 (13.0)	0.200	32 (20.6)	16 (14.3)	0.580
T1–2	108 (33.8)	40 (32.5)	33 (33.0)		52 (33.5)	40 (35.7)	
T3–4	145 (45.3)	50 (40.7)	51 (51.0)		69 (44.5)	55 (49.1)	
Tx	8 (2.5)				1 (0.6)	1 (0.9)	
ypN category							
N0	191 (59.5)	79 (63.7)	54 (54.0)	0.131	93 (60)	65 (58.0)	0.944
N1	64 (19.9)	27 (21.8)	21 (21.0)		91 (58.7)	24 (21.4)	
N2–3	66 (20.5)	18 (14.5)	25 (25.0)		31 (20.0)	23 (20.5)	
Mandard							
TRG 1–2	120 (38.4)	57 (48.7)	30 (30.9)	**0.008**	68 (43.9)	32 (18.6)	**0.007**
TRG 3–5	188 (60.3)	60 (51.3)	67 (69.1)		82 (52.9)	79 (45.9)	

Numbers are presented as *n* (%) unless otherwise indicated. cTN and ypTN categories are according to AJCC 8th edition. Bold values represent statistical significant *P* values. ASA, American Society of Anaesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; nCRTx, neoadjuvant chemoradiation; SD, standard deviation; TRG, tumour regression grade.
[a]BMI prior to nCRTx; may not add up to 100% because not all patients have known BMI values prior to nCRTx.

overall survival of 48.4 months (95% CI 37.7–59.1), and patients without sarcopenia had a median overall survival of 31.8 months (95% CI 21.1–42.4, *P* = 0.148). The median overall survival was 37.6 months (95% CI 23.3–52.0) in the group of patients with sarcopenia and 39.2 months (95% CI 21.1–57.3) in the group of patients without sarcopenia based on CT scans after nCRTx (*P* = 0.805).

Univariable analysis of body composition and muscle strength variables showed a significant association with lower number of stands during the 30 seconds chair stand test prior to nCRTx and survival (hazard ratio 0.94, 95% CI 0.88–1.00, *P* = 0.038) and visceral adipose tissue of >128 cm^2 after nCRTx with impaired survival (hazard ratio 1.41, 95% CI 1.03–1.92, *P* = 0.34; Supporting Information, *Table S1*). *Table* 4 shows the final multivariable survival analysis. A lower number of stands during the 30 seconds chair stand test prior to nCRTx and visceral adipose tissue of >128 cm^2 after nCRTx remained significantly associated with worse overall survival.

Table 2 Association between sarcopenia and fat mass and muscle strength

	Prior to nCRTx			After nCRTx		
	Sarcopenia	No sarcopenia	*P* value	Sarcopenia	No sarcopenia	*P* value
	n = 125	*n* = 100		*n* = 155	*n* = 112	
Adipose tissue						
Visceral adipose tissue index (cm^2/m^2)	51.8 ± 34.8	50.6 ± 32.0	0.798	44.2 ± 29.0	46.2 ± 29.3	0.587
Subcutaneous adipose tissue index (cm^2/m^2)	54.4 ± 26.9	52.8 ± 31.6	0.687	53.7 ± 23.8	51.2 ± 31.8	0.492
Total adipose tissue index[a] (cm^2/m^2)	106.2 ± 48.3	203.4 ± 54.7	0.692	97.9 ± 43.7	97.4 ± 53.1	0.924
Fat percentage	31.6 ± 5.5 *n* = 36	29.6 ± 5.3 *n* = 35	**0.006**	30.6 ± 4.5 *n* = 44	29.1 ± 5.4 *n* = 35	**0.017**
Muscle strength						
Hand grip strength, dom (kg)	40.1 ± 11.7	44.1 ± 8.2	0.108	40.2 ± 9.8	47.3 ± 8.1	**0.001**
Hand grip strength, ndom (kg)	37.9 ± 10.6	42.7 ± 8.3	**0.037**	37.5 ± 9.7	44.6 ± 7.8	**0.001**
30 s chair stand test (number of stands)	17.5 ± 4.2	20.11 ± 4.8	**0.016**	16.6 ± 5.6	22.1 ± 8.2	**0.001**
Maximal inspiratory pressure (cmH_2O)	84.4 ± 28.5	108.6 ± 31.8	**0.001**	86.7 ± 24.2	113.7 ± 26.5	**<0.001**
Maximal expiratory pressure (cmH_2O)	117.7 ± 37.4	144.1 ± 43.2	**0.008**	124.3 ± 40.6	155.9 ± 37.0	**0.001**

Values are presented as mean ± standard deviation. Bold values represent statistical significance. dom, dominant hand; nCRTx, neoadjuvant chemoradiation; ndom, non-dominant hand.
[a]Total adipose tissue index based on the sum of visceral and subcutaneous adipose tissue surface areas.

Finally, change in body composition during nCRTx was not significantly associated with survival, but Kaplan–Meier curves show lower cumulative survival rates for patients who had a decline in fat percentage and skeletal muscle index and who had an increase in BMI (*Figure* 3).

Discussion

This study evaluated sarcopenia, body composition, and muscle strength before and after nCRTx and the influence on post-operative complications and long-term survival in oesophageal cancer patients. We found that sarcopenia is associated with lower muscle strength and a higher fat percentage. An impaired muscle strength and a BMI of ≥26 kg/m^2, but not sarcopenia itself, were associated with more post-operative complications and a higher incidence of anastomotic leakage. Moreover, impaired muscle strength and increased visceral adipose tissue were associated with worse long-term survival. Body composition did alter during nCRTx, but these changes did not influence survival. To our knowledge, this is the first study reviewing the change of multiple components of body composition together with muscle strength during preoperative treatment and the influence on short-term and long-term post-operative outcomes in oesophageal cancer patients.

During nCRTx, the fat percentage, skeletal muscle index, and BMI decreased in most patients, which is also seen in other studies.[35] It is not clear whether this decrease is related to the nCRTx or the ongoing situation of oesophageal obstruction and decreased food intake. Recent studies have demonstrated that a low skeletal muscle index increases the toxicity of nCRTx and nCRTx itself increases the risk of losing muscle mass.[13,36,37] Consequently, nCRTx seems to have a negative impact on muscle strength as well.[35] Despite this, we found an improvement of muscle strength during nCRTx. This might be explained by the fact that each patient received personalized physiotherapy and dietary treatment in our centre on indication. A possible explanation for the decrease in skeletal muscle index while muscle strength increased is change in muscle quality.[38] Muscle quantity might have decreased during neoadjuvant treatment, but muscle quality might have been improved due to physiotherapy and dietary care.

The association between a BMI of ≥26 kg/m^2 and higher incidence of anastomotic leakage was also found in other studies and could be explained by a higher rate of intraoperative complications such as accidental injury and ischaemia.[17,39,40]

Although in our study no significant differences in post-operative complication incidence and severity between patients with and without sarcopenia were seen, another study showed in a cohort of 207 adenocarcinoma patients that sarcopenia was associated with a five-fold increased risk of major morbidity and a two-fold increased risk of pulmonary complications.[41] While the sample sizes and treatment of patients in both studies were similar, patients in the present study have a higher American Society of Anaesthesiologists score, and almost double the number of patients had cardiovascular co-morbidities and/or type 1 diabetes, which might have contributed to the much higher overall incidence of major complications in the present study. Furthermore, the difference in applied chemotherapy schedules is likely to have impact on complications of the patients, because paclitaxel/carbotaxol has been described less toxic compared with cisplatinum/5-FU.[42] Consequently, because of the different characteristics and different nCRTx schedules, these studies cannot be compared.

Table 3 Influence of body composition and muscle strength on no, minor, and major complications

	Prior to nCRTx				After nCRTx			
	No complication	Minor complication	Major complication	*P* value	No complication	Minor complication	Major complication	*P* value
	n = 86	*n* = 95	*n* = 44		*n* = 94	*n* = 107	*n* = 66	
Body composition								
Sarcopenia, *n* (%)	50 (58.1)	53 (55.8)	22 (50.0)	0.675	52 (55.3)	64 (59.8)	39 (59.1)	0.797
Sarcopenic obesity, *n* (%)	8 (9.3)	6 (6.3)	2 (4.5)	n/a	3 (3.2)	4 (3.7)	1 (1.5)	n/a
Skeletal muscle index (cm^2/m^2)	46.2 ± 9.3	46.1 ± 8.6	46.9 ± 10.1	0.866	46.3 ± 8.7	45.0 ± 8.5	46.3 ± 9.2	0.479
BMI (kg/m^2)	25.9 ± 4.0	25.9 ± 4.0	26.5 ± 4.7	0.710	25.6 ± 3.6	25.4 ± 3.9	25.9 ± 4.2	0.756
Fat percentage	30.7 ± 58	30.8 ± 5.7	30.6 ± 4.4	0.965	30.0 ± 4.8	29.9 ± 5.4	30.5 ± 4.4	0.570
Visceral adipose tissue index (cm^2/m^2)	52.8 ± 34.8	50.8 ± 32.5	48.0 ± 32.9	0.773	44.5 ± 27.8	43.9 ± 29.2	47.8 ± 43.8	0.648
Subcutaneous adipose tissue index (cm^2/m^2)	51.5 ± 28.0	53.4 ± 30.3	58.1 ± 29.8	0.592	52.8 ± 26.8	51.4 ± 27.2	56.3 ± 32.4	0.478
Total adipose tissue index[a] (cm^2/m^2)	104.4 ± 53.3	104.2 ± 51.7	106.1 ± 48.4	0.984	96.3 ± 45.9	95.4 ± 48.8	104.6 ± 53.3	0.471
	n = 86	*n* = 95	*n* = 44		*n* = 86	*n* = 95	*n* = 44	
Muscle strength								
Hand grip strength, dom (kg)	40.3 ± 10.0	43.4 ± 8.7	43.9 ± 13.6	0.405	41.5 ± 8.1	44.1 ± 9.5	45.4 ± 12.6	0.376
Hand grip strength, ndom (kg)	39.1 ± 8.4	41.3 ± 8.4	41.2 ± 11.9	0.659	40.2 ± 9.4	41.8 ± 8.7	39.8 ± 11.3	0.747
30 s chair stand test (number of stands)	39.1 ± 8.4	17.7 ± 4.7	20.2 ± 5.1	0.264	18.6 ± 8.4	18.4 ± 6.0	20.8 ± 7.3	0.569
Maximal inspiratory pressure (cmH_2O)	97.3 ± 31.1	98.0 ± 35.4	89.3 ± 30.1	0.724	98.0 ± 29.2	99.0 ± 26.6	99.2 ± 31.8	0.761
Maximal expiratory pressure (cmH_2O)	128.9 ± 44.1	133.5 ± 39.9	128.3 ± 45.0	0.904	133 ± 38.7	140.7 ± 41.1	143.3 ± 49.4	0.675

Values are presented as mean ± standard deviation unless otherwise indicated; major complications are defined as complications of Clavien–Dindo grade IIIB or higher. BMI, body mass index; dom, dominant hand; n/a, not applicable; nCRTx, neoadjuvant chemoradiation; ndom, non-dominant hand.
[a]Total adipose tissue index based on the sum of visceral and subcutaneous adipose tissue surface areas.

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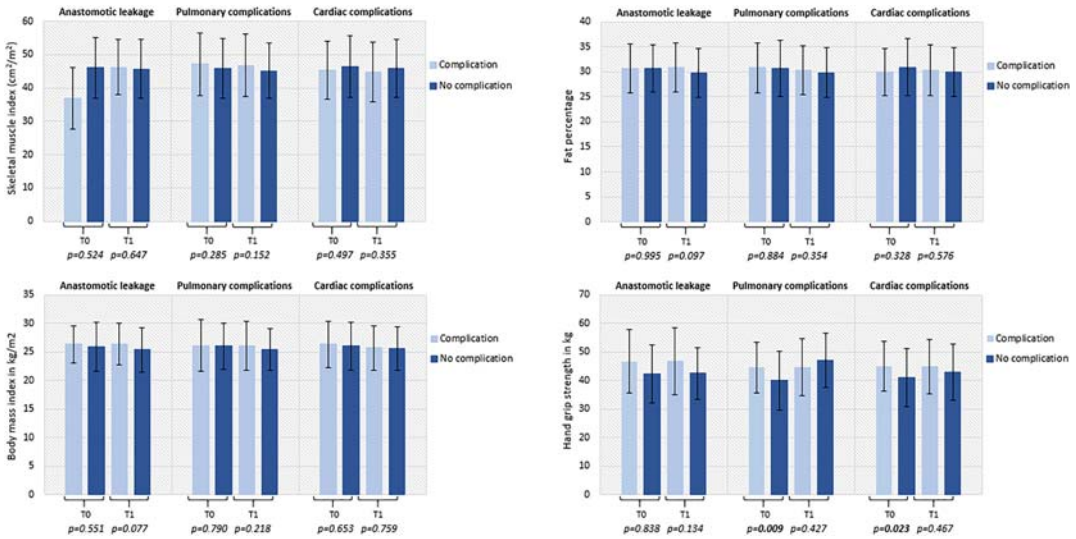

Figure 2 Influence of body composition and muscle strength on post-operative complications. T0 is prior to neoadjuvant therapy, and T1 is after neoadjuvant therapy and prior to surgery.

Table 4 Multivariable analysis on the influence of traditional clinical factors, body composition, and muscle strength on overall survival according to the Cox proportional hazard model

	Prior to nCRTx		After nCRTx	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Traditional clinical variables				
ypN category[a]				
N1	0.95 (1.02–3.73)	0.096	1.85 (1.23–2.79)	<**0.001**
N2–3	1.77 (0.83–3.81)			
Mandard score				
TRG 3–5[b]	1.66 (0.90–3.04)	0.102	1.81 (1.22–2.67)	**0.003**
Muscle strength prior to nCRTx				
30 s chair stand test	0.93 (0.87–0.99)	**0.017**		
Body composition after nCRTx				
VAT[c] > 128 cm^2			1.81 (1.30–2.53)	**0.001**

Results are based on fitting separate univariate Cox models for each factor followed by stepwise variable selection (Supporting Information, *Table S1*); bold values represent statistical significance. CI, confidence interval; HR, hazard ratio; nCRTx, neoadjuvant chemoradiation; TRG, tumour regression grade; VAT, visceral adipose tissue surface area.
[a]ypN stage based on AJCC 8th, reference group is N0.
[b]Reference group is TRG 1–2.
[c]There was no linearity between VAT and log hazard; therefore, VAT has been dichomatized by median split.

A Japanese study, including patients with mostly squamous cell carcinoma, found a significant difference in post-operative complications and mortality in older patients with and without sarcopenia. They did not find this effect in younger patients.[43] This suggests that not only the amount of muscle but also the quality of the muscle is of influence, and younger patients might have better muscle quality.[44,45] A recent study on the influence on skeletal muscle surface index and skeletal muscle quality showed that preoperative skeletal muscle quantity does not influence post-operative outcomes after a pancreatoduodenectomy but showed that the muscle quality, determined as muscle attenuation index, does have a major effect on post-operative complications.[46]

The present study showed a relation between visceral adipose tissue area and long-term survival, but not between long-term survival and subcutaneous adipose tissue or body fat percentage. This indicates that the distribution of adipose tissue might play a role in long-term survival. Other studies suggest that visceral adipose tissue surface area is related to a higher inflammation and an adverse cardiometabolic risk profile. These conditions may directly promote tumour progression or predict other co-morbid conditions such as cardiovascular disease that can further impair survival.[47–49] On the other hand, subcutaneous adipose tissue might play a protective role in overall survival in cancer patients as it may provide protective nutritional reserves.[50] Therefore, if

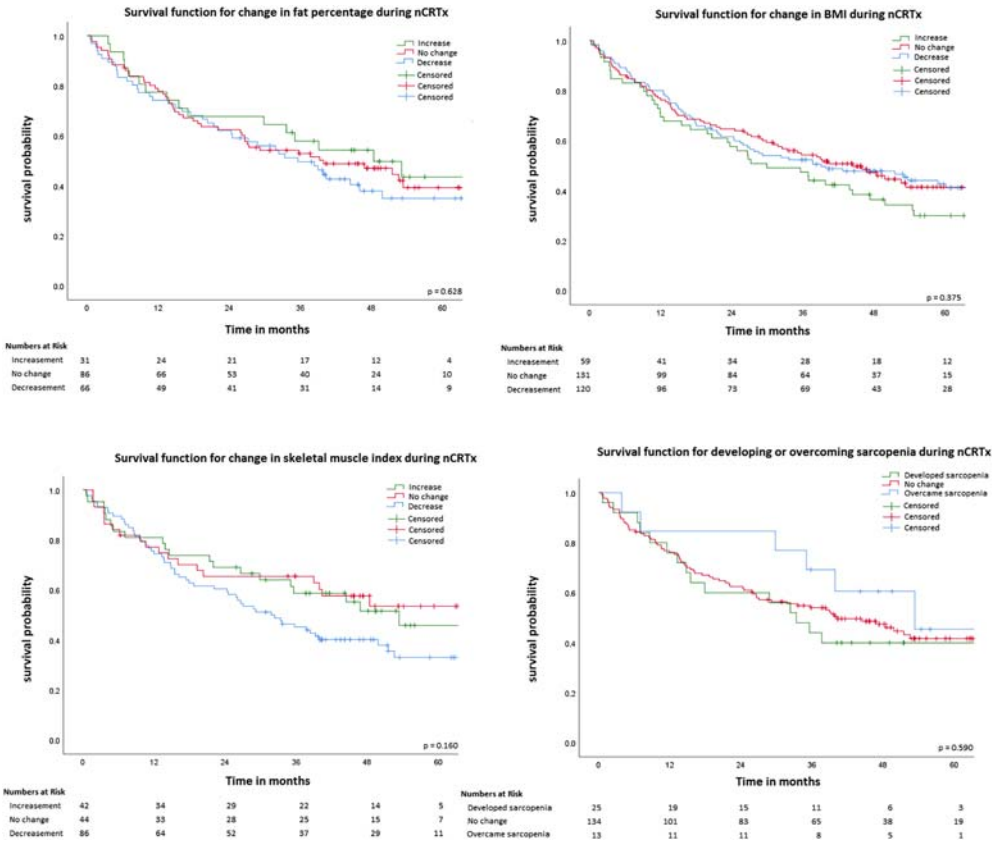

Figure 3 Kaplan–Meier survival curves. Change in fat percentage defined as at least 2% change, change in BMI defined as at least 1 unit change, change in skeletal muscle index defined as at least 1.5 cm^2/m^2 change. *P* values based on log-rank test. BMI, body mass index; nCRTx, neoadjuvant chemoradiation.

possible, the amount of visceral adipose tissue should be aimed to be decreased in oesophageal cancer patients.

Furthermore, two reviews showed that patients with a high BMI have a better overall 5 years of survival, which was not encountered in the present study.[17,39] This phenomenon is also seen in other types of cancer and is called the BMI paradox. The BMI paradox is a hypothesis that holds that BMI is, counterintuitively, associated with higher survival in certain groups of people, such as patients with cancer. A theory behind the BMI paradox is that BMI cannot be regarded a proxy for the amount or location of adipose tissue, nor for muscle mass and muscle quality. A healthy BMI can mask excess adiposity, which is associated with worse survival, and patients with a high BMI do not necessarily have a high amount of adipose tissue.[51] A wide amount of other theories behind the BMI paradox such as methodological explanations and other clinical explanations exist.[52]

Our study has some limitations. Skeletal muscle strength was only assessed in patients who were also included in another study.[25] Patients' characteristics of this cohort were comparable with the total population in the study but were much smaller than the total number of patients in the present study. This might have contributed to selection bias, together with the retrospective nature of the study. Moreover, the influence of sarcopenic obesity on post-operative complications or long-term survival could not be assessed properly because the incidence of sarcopenic obesity in this cohort was very low. Sarcopenic obesity has been reported as one of the most powerful independent predictors of poor survival for patients with cancer.[16,53] It should also be mentioned that handgrip strength is less reliable in older patients and the chair stand test can be influenced by co-morbidities. The cohort in this study has a median age of 65 years, and almost half of the patients have co-morbidities; this might have made the muscle strength outcomes less reliable.

Also, no standardized cut-off values for sarcopenia exist. Most of the oncological studies use sex-specific cut-off values determined by Prado *et al*.[54] This was a study in obese patients with, aside from gastrointestinal tumours, also tumours in the respiratory tract. This population differs systematically from patients with oesophageal cancer, and therefore, these cut-off values might not be applicable. The present study used the cut-off values by Martin *et al*., which are more applicable to patients in our cohort.[32] Strengths of this study were that the measurements on the CT scans were performed by different researchers and then the mean surface area was

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calculated, reducing the intra-observer variability. Only CT scans of sufficient quality were included. Studies show that CT scan quality influences measurements of surface areas on CT slices, especially portal phase and slice thickness.[30,55] Furthermore, we did not only focus on skeletal muscle surface or sarcopenia, but we also focused on other parameters of body composition and muscle strength.

In order to determine the precise influence of body composition and muscle strength on short-term and long-term outcomes, future studies should use a uniform method of measuring body composition. A large prospective study is necessary to not only study muscle mass but also at muscle quality, muscle strength, BMI, and adipose tissue distribution and quantity.

In conclusion, sarcopenia occurs frequently in patients with oesophageal cancer and is associated with less muscle strength and a higher fat percentage. Impaired muscle strength and a high amount of visceral adipose tissue are associated with worse short-term outcomes and worse survival. Therefore, patients with poor fitness might benefit from preoperative nutritional and muscle strengthening guidance, aiming to increase muscle strength and decrease visceral adipose tissue. However, this hypothesis should be confirmed in a large prospective study.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Univariable and multivariable analysis of traditional clinical factors and body composition and muscle strength for predicting overall risk of mortality

Conflict of interest

E.H., M.F., M.E., M.H., P.B., and D.L. have nothing to declare. H.V.L. has served as a consultant for BMS, Celgene, Lilly, and Nordic and has received unrestricted research funding from Bayer, BMS, Celgene, Lilly, Merck Serono, MSD, Nordic, Philips, and Roche. M.V.B.H. is consultant for Mylan and Medtronic and Johnson & Johnson and has received research/travel grants from Olympus, Medtronic, and Stryker. S.G. is consultant for Medtronic and has received a research grant from Olympus. The authors certify that they comply with the ethical guidelines for publishing in the *Journal of Cachexia, Sarcopenia and Muscle*: update 2019.[56]

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