research article

Sarcopenia and myosteatosis at presentation adversely affect survival after esophagectomy for esophageal cancer

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Background. Esophageal cancer remains a disease with poor survival and many complications. Measuring muscle mass and quality can identify patients with diminished muscle mass (sarcopenia) and muscle fat infiltration (myosteatosis). We studied the impact of sarcopenia and myosteatosis in resectable esophageal cancer on overall survival and complications.

Patients and methods. 139 patients received a radical esophagectomy. Skeletal muscle area (SMA) and muscle attenuation (MA) in CT images at L3 level were recorded and groups with and without sarcopenia and myosteatosis were compared for overall survival (OS), perioperative mortality, conduit complications, pleuropulmonary complications, respiratory failure requiring mechanical ventilation and other significant complications.

Results. Prevalence of sarcopenia and myosteatosis at presentation was 16.5% and 51.8%, respectively. Both were associated with decreased OS. Median survival was 18.3 months (CI 5.4–31.1) *vs.* 31.0 months (CI 7.4–54.6) for sarcopenia/no sarcopenia (log rank p = 0.042) and 19.0 months (CI 13.3–24.7) *vs.* 57.1 months (CI 15.2–99.0) for myosteatosis (log rank p = 0.044), respectively. A relationship between sarcopenia and myosteatosis and other negative outcomes after esophagectomy could not be established.

Conclusions. Sarcopenia and myosteatosis before esophagectomy are associated with decreased overall survival but not with more frequent perioperative complications. Identification of patients at risk can guide therapeutic decisions and interventions aimed at replenishing muscle reserves.

Key words: sarcopenia; myosteatosis; esophagectomy; survival; esophageal cancer; muscle depletion

Introduction

Constant gradual improvements of operative techniques and perioperative care have reduced the dangers of esophagectomy, the cornerstone of radical treatment of resectable esophageal cancer, but it remains a major procedure burdened with high morbidity and mortality.[1] Overall 5-year survival in resectable esophageal cancer has improved in recent years by about 2–3 fold.[2] This improvement was attributed to centralization of surgical treatment and introduction of neoadjuvant chemoradiotherapy.[3] Advances were also made in perioperative care and better understanding and prevention of the detrimental effects of muscle depletion so typical of esophageal malignancies.[4]

Further improvement in outcomes can be achieved by tailoring the treatment to patients' ability to withstand the trauma of surgery and to return to a functional life after treatment. Adequate

fitness for treatment has traditionally been assessed from various performance scores, risk scores as well as more basic patients' characteristics like age and body mass index.[5] Body mass index (BMI) at presentation has proven to be an inaccurate predictor of outcomes since it does not correspond to body composition well.[6,7] Better methods to assess the most important parameter of body composition, the skeletal muscle content, have been introduced. They include functional tests like muscle strength measurements and measurements of muscle mass with dual energy x-ray imaging (DEXA), bioimpedance analysis or cross-sectional imaging (CT or MRI).[8] Cross-sectional imaging (or planimetry) has the advantage of being readily available in cancer patients for staging purposes. This has encouraged many studies to examine the relationship between overall muscle mass, its quality and their effect on outcomes. A reliable relationship between planimetrically determined muscle mass and quality and its function, determined by other methods available, has been established. Muscle area at the level of 3rd lumbal vertebra, normalized for height (skeletal muscle index (SMI)) is highly correlated with total body skeletal muscle mass.[9]

Estimating survival chances for a patient presenting with resectable esophageal cancer is important in planning appropriate treatment strategies and interventions aimed at improving survival and quality of life. Pronounced weight loss is a hallmark of malignant disease, especially pronounced in digestive tract tumors, among them in esophageal and pancreatic cancers in particular.[10] In their seminal work, the team from University of Alberta have shown that skeletal muscle depletion (sarcopenia and low muscle attenuation) is the real negative predictor of survival regardless of overall body weight in cancer patients.[6]

Sarcopenia is defined by the European Working Group on Sarcopenia in Older people as the presence of low muscle mass (under the 5th percentile) and low muscle function (strength or performance)[11] typically presenting in advanced age but also in cancer and other diseases. It is a well established predictor of poor survival and treatment outcomes in cancer patients.[6] Myosteatosis is defined as abnormal fat infiltration in skeletal muscle. It is negatively associated with muscle strength and quality and is brought on by aging[12], diabetes[13], obesity[14] and malignant disease.[6,15,16] Radiodensity of human muscle on CT scan (or muscle attenuation, MA) correlates well with its triglyceride content.[14] Measuring the attenuation values of muscle tissue corresponds well to the extent of myosteatosis, which is a sign of muscle wasting and again a predictor of poor outcome.[17]

By assessing muscle mass and quality before treatment an individualized risk assessment for overall survival and complications during treatment can be improved, patients at risk identified and appropriate interventions (mainly directed towards maintaining and gaining muscle mass) undertaken.[18] Our aim was to study the impact of muscle depletion (sarcopenia and myosteatosis) on outcomes (overall survival [OS], perioperative mortality and rate of complications) in resectable esophageal cancer.

Patients and methods

Study population

All patients who received an esophagectomy with curative intent for esophageal or esophago-gastric junction cancer at Clinical Department of Thoracic Surgery at University Medical Centre Ljubljana were eligible for inclusion in the study. Patients received either upfront surgery or neoadjuvant chemoradiotherapy followed by esophagectomy according to national guidelines. All patients received individualized nutritional support and counselling according to ESPEN best practice guidelines[19] and in all patients a catheter feeding jejunostomy was placed during esophagectomy. Clinical parameters were recorded prospectively in a database since 2003. Out of the 162 patients operated on consecutively between 2008 and 2018 CT images suitable for analysis of muscle mass and quality were available for 139 patients which were included in the study. Requirements for adequate images were the inclusion of L3 level and availability of non-contrast images for attenuation analysis. Only images recorded at presentation before the initiation of any treatment were considered.

Our study design was approved and the need for obtaining informed consent from participants waived by the Slovenian National medical ethics committee (approval number 0120–301/2016–2).

Definitions

We grouped complications into following groups. *Conduit complications* included clinically silent fistulae seen on esophagograms and/or CT scans, clinically important leaks that required interventions and frank gastric necroses. *Respiratory complications* included respiratory failure requiring mechanical ventilation and pneumonia, defined as the

presence of new infiltrates on chest radiography and a positive culture result from bronchoalveolar lavage or sputum requiring antibiotics. *Respiratory failure* requiring mechanical ventilation was recorded separately as well.

Other complications were defined as other serious complications (Dindo Clavien 2 or greater)[20] requiring intervention (*i.e.* early reoperation, cardioversion, endoscopic intervention) or directoscopically proven laryngeal nerve paralysis.[21]

OS was defined as the time interval between esophagectomy and death of any cause. Patients alive on 1.10.2018 as reported by Cancer registry of Slovenia were censored at that date.

BMI was calculated as patient weight [kg]/height [m]^2, recorded at admission one day before surgery.

CT body composition analysis (planimetry)

Pre-operative abdominal CT or whole body PET-CT scans were obtained. In each patient a single slice at the level of the 3rd lumbar vertebra (L3) was selected for automatic segmentation. CT scans were analyzed using the "Automated Body Composition Analyzer using Computed tomography image Segmentation" (ABACS) software[22,23], which uses a priori information about the skeletal muscle shape in the L3 region and predefined Hounsfield units (HU) values to recognize different tissues. HU values used to assess the total cross-sectional area for muscular tissue (SMA – skeletal muscle area) were −29 to +150 HU. Muscle attenuation (MA) was assessed by averaging HU of skeletal muscle. Additionally, SMI was calculated using the following formula: (SMA [cm2])/(patient height [m2]). All abdominal CT and PET-CT scans were analyzed by one blinded independent radiologist.

The following planimetry data were reported: number of days between CT and esophagectomy, SMA (skeletal muscle area) reported in cm^2, SMI (skeletal muscle index) is SMA corrected for height (*i.e.* divided by height squared) and expressed in cm^2/m^2. MA (muscle attenuation) was reported in Hounsfield units.

Previously defined muscle index cut-off values for sarcopenia in a healthy non-elderly Caucasian population were used to define limits for SMI in men at less than 43.1 cm^2/m^{2}and less than 32.7 cm^2/m^2 in women. Cutoff values for myosteatosis from the same study were used with myosteatosis defined as MA of less than 30.9 HU in men and 24.8 HU in women.[24]

Outcomes and statistical analysis

Standard descriptive statistics of demographic and clinical characteristics for patients with and without sarcopenia and myosteatosis were summarized. Differences in demographic and clinical characteristics between groups (sarcopenia/no sarcopenia and myosteatosis/no myosteatosis) were evaluated with Pearson's Chi-square tests for categorical and t-tests for parametric variables.

Primary outcome studied was overall survival. It was reported in each group with the Kaplan-Meier curve and the survival of groups with/without sarcopenia and with/without myosteatosis was compared using the log rank Mantel Cox test.

Secondary outcomes of interest were the incidences of complications in groups with/without sarcopenia and with/without myosteatosis. They were compared with Pearson's Chi-square test. P value of < 0.05 was considered significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, version 22.0, Armonk NY).

Results

Patient characterictics

One hundred and thirty-nine patients underwent esophagectomy with primary reconstruction with curative intent. Overall demographic, clinical and complication characterictics are summarized in Table 1. Mean BMI was 26.3 ± 4.8 with only 7 (5.0%) having a BMI less than 18.5. As many as 46 (33.1%) patients reported having lost 10% or more of their normal body weight prior to esophagectomy. Average time between CT and esophagectomy was 76.9 ± 52.3 days with a much shorter time in those receiving primary resection compared to those with neoadjuvant treatment. Sarcopenia was present in 23 (16.5%) patients and myosteatosis in 72 (51.8%).

Surgery and pathology

Eighty-seven (62.6%) patients received an open esophagectomy and 52 (37.4%) had a hybrid or completely minimally invasive procedure. Type of procedure data, radicality rates, numbers of lymph nodes harvested and histology and staging data are given in Table 1.

Complications and survival

9 patients died after esophagectomy during the initial hospitalization (in hospital mortality of 6.5%).

TABLE 1. Demographic, preoperative, procedure and outcome data in all patients (N = 139)

Demographic and preoperative data	
Age at Surgery (mean ± SD) [years]	63.9 ± 9.5
min-max	30–83
Gender (N, % female)	22 (15.8%)
BMI (mean ± SD) [kg/ m^2]	26.3 ± 4.8
Weight loss > 10% (N, %)	46 (33.1%)
Neoadjuvant therapy (N, %)	74 (53.2 %)
Planimetry data	
Days between CT and esophagectomy	
all (mean ± SD)	76.9 ± 52.3
min-max	6–192
median	84
Neoadjuvant (mean ± SD)	115.2 ± 36.0
min-max	14–192
median	125
No neoadjuvant (mean ± SD)	33.5 ± 28.5
min-max	6–141
median	23
SMA [cm^2] (mean ± SD)	
male	157.6 ± 28.0
female	103.9 ± 16.3
SMI [cm^2/m^2] (mean ± SD)	
male	52.1 ± 9.5
female	39.8 ± 6.8
Muscle attenuation [HU] (mean ± SD)	
male	31.2 ± 8.3
female	27.8 ± 8.7
sarcopenia (N, %)	23 (16.5%)
myosteatosis (N, %)	72 (51.8%)

Procedure data	
Surgical approach (N, %)	
open	87 (62.6%)
MIE	52 (37.4%)
Type of esophagectomy (N, %)	
Ivor-Lewis	109 (78.4%)
McKeown	26 (18.7%)
Transhiatal	4 (2.9%)
Radicality (N, %)	
R0	130 (93.5%)
R1	5 (3.6%)
R2	4 (2.9%)
Lymph nodes (mean ± SD) (N, %)	23.4 ± 12.3
min-max	0–76
median	21
Cancer type (N, %)	
Adenocarcinoma	74 (53.2%)
Squamous cell carcinoma	64 (46.0%)
GIST	1 (0.7%)
Pathological Stage (AJCC 2017) (N, %)	
I	51 (36.7%)
II	27 (19.4%)
III	36 (25.9%)
IVA	23 (16.5%)
IVB	2 (1.4%)
Complications (N, %)	
In hospital mortality	9 (6.5%)
Any complication	65 (46.8%)
Conduit complications	21 (15.1%)
Pleuropulmonary complications	37 (26.6%)
Respiratory failure	26 (18.7%)
Any other complications	42 (30.2%)
Median survival [months]	**26.8 (95% CI 8.1–45,7)**
1 year survival	73.7%
3 year survival	45.1%
5 year survival	40.3%

AJCC = American joint committee on cancer; BMI = body mass index; CI = confidence interval; CT = computed tomography; GIST = gastrointestinal stromal tumor; HU = Hounsfield units; MIE = minimally invasive esophagectomy; SD = standard deviation; SMA = skeletal muscle area; SMI = skeletal muscle index

Almost half or 65 patients (46.8%) experienced a complication of Dindo-Clavien grade 2 severity or greater[20] after the procedure. Rates of other complications and survival rates are shown in Table 1. Survival is shown as a Kaplan-Meier curve in Figure 1. Median follow up was 18.1 months (range 0–115). 72 patients (51.8%) died during the observation period and 67 (48.1%) were censored.

Sarcopenia and myosteatosis subgroups

Demographic and clinical data was compared between patients with and without sarcopenia and with and without myosteatosis (Table 2). Patients with myosteatosis were significantly older than patients without it whereas in patients with or without sarcopenia age difference didn't reach statistical significance. BMI was significantly lower in sarcopenic patients but significantly higher in patients with myosteatosis.

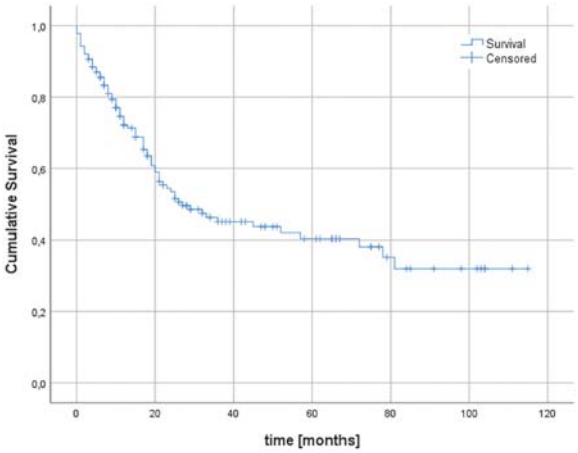

FIGURE 1. Cumulative survival Kaplan-Meier curve.

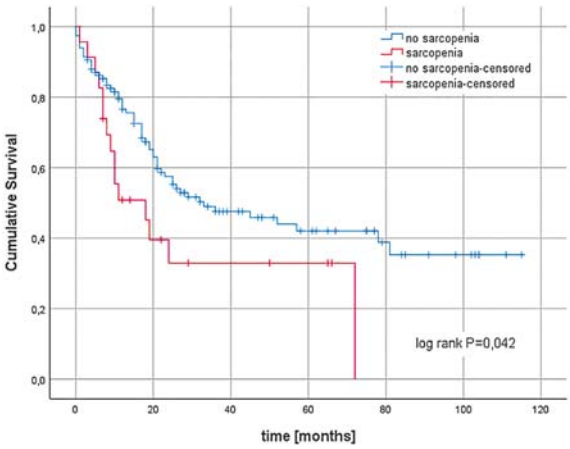

FIGURE 2. Kaplan-Meier survival curves for sarcopenia.

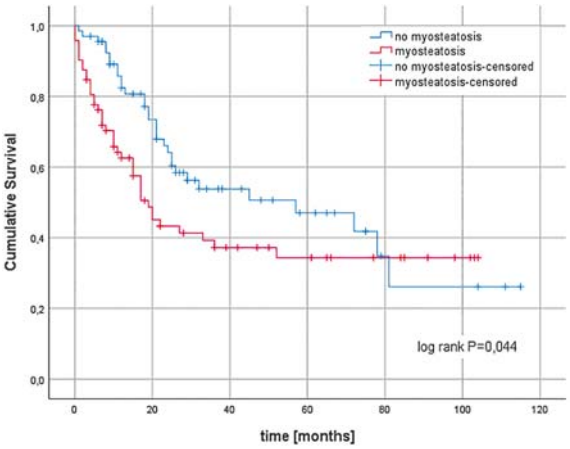

FIGURE 3. Kaplan-Meier survival curves for myosteatosis.

There was no statistically significant difference in sex distribution, days between CT and esophagectomy, weight loss, neoadjuvant therapy, cancer type, pathological stage, lymph nodes harvested or surgical approach between sarcopenia/no sarcopenia and myosteatosis/no myosteatosis groups.

Complications and survival were compared between sarcopenia/no sarcopenia and myosteatosis/no myosteatosis groups as shown in Table 3 and Figure 2 and 3.

No statistically significant difference in in hospital mortality, any complications, pleuropulmonary complications, respiratory failure or any other complications was found between sarcopenia/no sarcopenia and myosteatosis/no myosteatosis groups. Conduit complications were however significantly less common in the myosteatosis group (5/72 (6.9%) *vs.* 16/67 (23.9%) in patients without myosteatosis (OR 0.238 (0.082–0.692), p = 0.005).

Survival for sarcopenia/no sarcopenia and myosteatosis/no myosteatosis is given in two Kaplan Meier plots in Figures 2 and 3. Survival curves were compared with the log rank Mantel Cox test and differences in survival between each pair were statistically significant (p = 0.042 for sarcopenia/no sarcopenia and p = 0.044 for myosteatosis/no myosteatosis).

Discussion

Our prospective cohort study shows that diminished muscle reserves, measured as sarcopenia (loss of muscle mass) and myosteatosis (infiltration of muscle with fat), are associated with decreased overall survival in patients receiving esophagectomy as part of radical esophageal cancer treatment. A relationship between sarcopenia and myosteatosis and other negative outcomes after esophagectomy (perioperative mortality and incidence of complications) could not be established.

Effects of muscle mass loss have been studied in numerous other malignancies as well as non malignant diseases[25-27] but studies reporting myosteatosis as well as sarcopenia are still rare.[28] Prevalence of sarcopenia in studies on correlation between muscle area and survival in esophageal cancer can range widely from 16%–80%.[29-31] Choosing the right cutoff values for defining sarcopenia and myosteatosis can be challenging. In keeping with the definition of sarcopenia as absolute muscle mass below the 5th percentile of the population[32] we chose recently published cutoff values for a population closely resembling ours. Van der Werf *et al.* have published sex specific percentiles for SMI and MA for a healthy Caucasian population.[24] They

TABLE 2. Demographic, preoperative, pathological and procedure data compared between sarcopenia/no sarcopenia and myosteatosis/no myosteatosis groups

	Sarcopenia (N = 23 (16.5%))	No Sarcopenia (N = 116 (83.5%))	p	Myosteatosis (N = 72 (51.8%))	No Myosteatosis (N = 67 (48.2%))	p
Age at Surgery (mean ± SD)	67.1 ± 7.8	63.3 ± 9.7	0.076	67.1 ± 7.7	60.5 ± 10.0	*< 0.001*
Female sex (n (%))	3 (13.0%)	19 (16.4%)	0.689	10 (13.9%)	12 (17.9%)	0.516
BMI (mean ± SD)	23.8 ± 5.9	26.7 ± 4.4	*0.006*	27.3 ± 4.9	25.2 ± 4.4	*0.006*
Days between CT and esophagectomy (mean ± SD)	81.4 ± 57.6	76.1 ± 51.4	0.654	78.8 ± 52.8	75.0 ± 52.1	0.666
Weight loss > 10% (n (%))	11 (47.8%)	35 (30.2%)	0.100	25 (34.7%)	21 (31.3%)	0.672
Neoadjuvant Therapy (n (%))	14 (60.9%)	60 (51.7%)	0.422	34 (47.2%)	40 (59.7%)	0.141
Cancer Type (n (%))			0.864			0.500
Adenocarcinoma	13 (56.6%)	61 (52.6%)		37 (51.4%)	37 (55.2%)	
Squamous cell carcinoma	10 (43.4%)	54 (46.6%)		35 (48.6%)	29 (43.3%)	
GIST		1 (0.8%)			1 (1.5%)	
Pathological Stage (AJCC 2017) (n (%))			0.650			0.546
I	8 (34.8%)	43 (37.1%)		26 (36.1%)	25 (37.3%)	
II	6 (26.1%)	21 (18.1%)		11 (15.3%)	16 (23.9%)	
III	4 (17.4%)	32 (27.6%)		21 (29.2%)	15 (22.4%)	
IVA	4 (17.4%)	19 (16.4%)		12 (16.7%)	11 (16.4%)	
IVB	1 (4.3%)	1 (0.8%)		2 (2.8%)	0	
Lymph nodes (mean ± SD)	28.8 ± 10.5	23.9 ± 12.6	0.266	24.4 ± 11.1	22.4 ± 13.5	0.337
Surgical approach			0.258			0.167
open	12 (52.2%)	75 (64.7%)		49 (68.1%)	38 (56.7%)	
MIE	11 (47.8%)	41 (35.3%)		23 (31.9%)	29 (43.3%)	

AJCC = American joint committee on cancer; BMI = body mass index; CT = computed tomography; GIST-gastrointestinal stromal tumor; HU = Hounsfield units; MIE = minimally invasive esophagectomy; SD = standard deviation; SMA = skeletal muscle area; SMI = skeletal muscle index

proposed using the 5th percentile for cutoff values for SMI and MA in non-elderly (age 20–60) to avoid age related muscle loss. These values (SMI 43.1 cm^2/m^2 for men and 32.7 cm^2/m^2 for women) are markedly lower then ones used in most previous studies. Consequently, the prevalence of sarcopenia in our study (16.5%) is also lower than 26–75% reported in other studies in resectable esophageal cancer. Mean SMA and SMI was 157.6 ± 28.0 cm^2 and 52.1 ± 9.5 cm^2/m^2 in males and 103.9 ± 16.3 cm^2 and 39.8 ± 6.8 cm^2/m^2 in females (both significantly different between sexes with $p < 0.001$) which correlates well with studies in similar populations. We believe that choosing the right population with which patients are compared is crucial in determining the real prevalence of sarcopenia (*e.g.*, the study by Nishigori *et al.* in Japanese esophageal cancer patients[33] used the cutoff points obtained in Canadian obese patients[34] and reported sarcopenia in 75% of patients).

Defining myosteatosis is even more difficult, since the term is not used much yet and reports are scarcer. We chose cutoffs according to the same principle, *i.e.* at the 5th percentile of a healthy population. We did not find a statistically significant difference in muscle attenuation between males and females (31.2 ± 8.3 HU *vs.* 27.8 ± 8.7 HU, p = 0.082), but with small numbers in our groups and the availability of sex-specific cutoff values for attenuation we opted for those. Myosteatosis was present in 51.8% of our patients and there was no significant relationship between sarcopenia and myosteatosis (OR 1.256 (CI 0.510–3.093, p = 0.620)). This is in contrast with the study by Stretch *et al.* where the proportions of patients with sarcopenia and myosteatosis were inverse (40.7% *vs.* 25.2%) but they similarly reported no correlation between muscle mass and muscle radiodensity. A possible reason for this are the higher cutoffs they used for sarcopenia (40th percentile of their patients or 47.7 cm^2/m^2 and 36.5 cm^2/m^2).[28]

On univariate analysis sarcopenia and myosteatosis were associated with lower overall survival in our study group (Kaplan Meier log rank p = 0.042

TABLE 3. Complication and survival data compared between sarcopenia/no sarcopenia and myosteatosis/no myosteatosis groups

	Sarcopenia (N = 23 (16.5%))	No Sarcopenia (N = 116 (83.5%))	Odds Ratio (OR. 95% CI)	p
Complications (n (%))				
In hospital mortality	1 (4.3%)	8 (6.9%)	0.614 (0.073–5.158)	0.650
Any complication	11 (47.8%)	54 (46.6%)	1.052 (0.430–2.578)	0.911
Conduit complications	4 (17.4%)	17 (14.7%)	1.226 (0.371–4.049)	0.738
Pleuropulmonary complications	8 (34.8%)	29 (25.0%)	1.600 (0.615–4.160)	0.332
Respiratory failure	5 (21.7%)	21 (18.1%)	1.230 (0.410–3.689)	0.711
Any other complications	4 (17.4%)	38 (32.8%)	0.432 (0.137–1.359)	0.143
Median survival [months]	18.3 (CI 5.4–31.1)	31.0 (CI 7.4–54.6)		*0.042*
1 year survival	50.8%	78.5%		
3 year survival	32.9%	47.7%		
5 year survival	32.9%	42.2%		

	myosteatosis (N = 72 (51.8%))	no myosteatosis (N = 67 (48.2%))	odds ratio (OR. 95% CI)	p
Complications (n (%))				
In hospital mortality	7 (9.7%)	2 (3.0%)	3.500 (0.701–17.486)	0.107
Any complication	32 (44.4%)	33 (49.3%)	0.824 (0.423–1.607)	0.570
Conduit complications	5 (6.9%)	16 (23.9%)	0.238 (0.082–0.692)	*0.005*
Pleuropulmonary complications	17 (23.6%)	20 (30.0%)	0.726 (0.341–1.545)	0.406
Respiratory failure	14 (19.4%)	12 (17.9%)	1.066 (0.453–2.510)	0.884
Any other complications	24 (33.3%)	18 (26.9%)	1.361 (0.656–2.822)	0.407
Median survival [months]	19.0 (CI 13.3–24.7)	57.1 (CI 15.2–99.0)		*0.044*
1 year survival	64.2%	84.0%		
3 year survival	36.9%	53.7%		
5 year survival	33.9%	46.9%		

CI = confidence interval; OR = odds ratio

and p = 0.044, respectively). For sarcopenia this is in accordance with previously published data and for myosteatosis this is one of the first published reports. Dijksterhuis *et al.* have published a report on body composition, survival and toxicity in advanced esophagogastric cancer patients receiving palliative chemotherapy where they used BMI-specific cutoff values to define myosteatosis (< 41 HU in non obese (BMI < 25) and < 33 HU in overweight patients). Prevalence of myosteatosis in their group was 50% and they found a lower risk of grade III and IV toxicity in patients with higher muscular density but no association between sarcopenia or myosteatosis and survival was found.[35] Tamandl *et al.* published a study with 200 patients receiving an esophagectomy. They stratified patients in low- and high-muscle attenuation groups with a cutoff of 40HU in a population similar to ours. Average MA was 36 HU (31–41) and patients with MA < 40 HU had significantly poorer overall survival.[36] The percentage of patients with MA over and under 40 HU is not given, so we cannot compare the prevalence to our results but this definition of reduced muscle attenuation uses a cutoff considerably higher than ours.

On the other hand, a study by Gabiatti *et al.* in patients with locally advanced esophageal cancer receiving definitive chemoradiotherapy demonstrated favorable progression free survival and overall survival in a subgroup of patients with myosteatosis but without systemic inflammation.[37]

Sarcopenia has been studied extensively as a predictive factor in esophageal cancer. A recently published meta-analysis by Boshier *et al.* reviewed

29 studies with 3193 patients (38% sarcopenic) in which various methods were used to diagnose sarcopenia.[38] Sarcopenic patients had more pulmonary complications and lower overall survival. A similar meta-analysis by Deng *et al.* reviewed 11 cohort studies including 1520 patients (52.3% sarcopenic). Patients with sarcopenia had lower 3-year and 5-year survival after resection.[39]

Complications and perioperative mortality were compared in our study between sarcopenia/no sarcopenia and myosteatosis/no myosteatosis groups and no statistically significant negative effect of muscle depletion was found. This is in concordance with most other studies who failed to show a connection even in studies who showed differences in long term survival.[29,40] Insufficient statistical power in most studies including ours to detect a potential difference in complication rates is no doubt a strong factor. For conduit complications however, the incidence in our cohort was significantly lower in the myosteatosis group (5/72 (6.9%) *vs.* 16/67 (23.9%) in patients without myosteatosis, (OR 0.238 (0.082–0.692), p = 0.005). It is difficult to explain the reason for this observation. A higher BMI in patients with myosteatosis could indicate a better nutritional status at presentation. Despite the lower incidence of this dangerous complication perioperative mortality in patients with myosteatosis was not different than in patients without it.

General clinical data in our cohort does not differ significantly from similar published series in resectable esophageal cancer. Patients with myosteatosis were significantly older than patients without it (67.1 ± 7.7 *vs.* 60.5 ± 10.0 (p < 0.001)) whereas in patients with or without sarcopenia age difference didn't reach statistical significance (67.1 ± 7.8 *vs.* 63.3 ± 9.7 (p = 0.076)). BMI was significantly lower in sarcopenic patients (23.8 ± 5.9 *vs.* 26.7 ± 4.4 (p = 0.006)) but significantly higher in patients with myosteatosis (27.3 ± 4.9 *vs.* 25.2 ± 4.4 (p = 0.006)). 13 patients (9.4%) had both sarcopenia and myosteatosis, their BMI was 25.5 ± 6.1 (range 18.1–37.1). 33.1% of our patients lost 10% or more of their body weight but this did not confer a greater risk of having sarcopenia (OR 2.12 (CI 0.855–5.266), p = 0.100) or myosteatosis (OR 1.165 (CI 0.574–2.366), p = 0.672). As suggested elsewhere[28] sarcopenia and myosteatosis are probably two separate entities with different causes and effects reflecting different disturbances in metabolic processes.

Underlying causes of sarcopenia and myosteatosis are most likely overlapping to some extent. Possible mechanisms, through which they negatively affect survival, are various. Diminished food intake due to dysphagia and loss of appetite as well as a chronic inflammation state in esophageal cancer lead to sarcopenia. This in turn causes diminished mobility and rehabilitation after surgery[41], respiratory complications[33], inferior wound healing[42] and diminished tolerance of chemo and radiotherapy.[35] Skeletal muscle has been described as an endocrine organ[43] and it is the derangement of this function that is also a possible cause of inferior survival. Carefully designed studies are needed to corroborate this hypothesis.

The inclusion of myosteatosis assessment is in our opinion a strength of our study. We see that myosteatosis is more prevalent than sarcopenia and is a more sensitive marker of muscle degradation which precedes muscle mass and overall body mass loss. It is nevertheless at least as detrimental to prognosis as sarcopenia. Our study also uses recently published cut-off values that in our opinion assess the incidence of sarcopenia better than previous studies. However, this hinders the comparability of our results with others. It is not without weaknesses either. All CT images were recorded at staging with approximately half the patients going straight to resection and the other half receiving neoadjuvant treatment first. No repeat CT images were taken after neoadjuvant treatment if there were no clinical signs of progression according to our group's guidelines. The distribution of intervals from CT to esophagectomy is therefore bimodal and the planimetric data reflects patients' muscle reserves at beginning of any treatment and not necessarily at esophagectomy. This is a shortcoming when assessing the impact on perioperative mortality and complications since muscle mass loss is a well known process during neoadjuvant therapy.[44-47] The large variation in times between CT and esophagectomy should in our opinion however not be regarded as a weakness when assessing the impact on overall survival of radical esophageal cancer treatment. Our study also lacks statistical power to detect a potential difference in mortality and complications, an issue that has fraught all previous studies as well. With growing numbers of cases in which CT images are available for analysis and with potential pooling of data these statistical issues can be overcome in the future.

Lastly, due to the univariate nature of our analysis no causal effect between survival and muscle depletion markers can be established, but the association shown can serve as an incentive for further research.

Conclusions

In a prospective cohort study from a dedicated database on esophagectomies we studied the association of sarcopenia and myosteatosis with outcomes after curative esophagectomies with or without neoadjuvant chemoradiotherapy. Prevalence of sarcopenia and myosteatosis at presentation was 16.5% and 51.8%, respectively. Both sarcopenia and myosteatosis were associated with decreased overall survival. For sarcopenia this is in accordance with previously published data and for myosteatosis this is one of the first published reports. Identifying novel predictors of outcomes can be beneficial for tailoring treatment options in patients with esophageal cancer as well as for planning intervention strategies targeted at improving functional body reserves.

Authors' contributions

MSr and MSo designed the study. MSr collected, analyzed and interpreted the data and was the major contributor in writing the manuscript. TJ collected the imaging data and was a minor contributor in writing the manuscript. TJ and KP analyzed and interpreted the imaging data. MSo designed the data collecting database. All authors read and approved the final manuscript.

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