Boffin Access

Open Access Journal | Volume: 1.4

Journal of Cancer Research and Oncobiology

ISSN 2517-7370

Impact of Sarcopenia in the Prognostic of Ressectable Esophageal Cancer

Sofia Pinheiro[1]
Teresa Carneiro[2]
Dina Luís[2]
António Gomes[2]
Ana Catarina Costa[3]
Sandra F Martins[1,4,5*]

[1]Life and Health Science Research Institute, School of Health Sciences, University of Minho, Braga, Portugal
[2]Esophagogastric Unit-Braga Hospital, Braga, Portugal
[3]Imaging Department, Braga Hospital, Braga, Portugal
[4]ICVS/3B's-PT Pt Government Associate Laboratory, Braga/Guimarães, Braga, Portugal
[5]Surgery Department, Coloproctology Unit, Braga Hospital, Braga, Portugal

Abstract

Background: Sarcopenia is an important prognostic factor in oncologic patients. In Esophageal Cancer, sarcopenia is associated with increased postoperative morbidity; however, there is no a clear association with mortality.

Purpose: To assess the impact of sarcopenia on morbidity and mortality, and evaluate the survival rates of patients who underwent curative esophagectomy for Esophageal Cancer.

Methods: Retrospective analysis of 71 patients with esophageal squamous cell carcinoma and esophageal adenocarcinoma, treated between 1st January 2004 and 30th September 2017. In order to obtain the skeletal muscle index, L3 muscle area was assessed through Computed Tomography. T test for independent samples, Mann-Whitney test, Qui-squared test and Fisher's test were used when pertinent, to compare the data from sarcopenic and non-sarcopenic groups. Disease-free survival and overall survival rates were calculated using Kaplan-Meier method and Cox regression modeling.

Results: Sarcopenia prevalence was 23.9% (17 patients). Patients with sarcopenia presented a mean muscle area of 138 cm^2 (± 11.7), significantly lower than the non-sarcopenic group (t (64.02)=5.84, p<.001, d=1.29), and a median skeletal muscle index of 49.3 cm^2/m^2 (3.46), significantly lower than the non-sarcopenic patients (U=58.0, p<.001, r=-.64). Sarcopenia was associated with a lower disease-free survival; however, it has not been a significant predictor when confounders were controlled.

Conclusions: In this study, sarcopenia was not associated with a higher postoperative morbimortality neither with a lower disease-free and overall survival.

Keywords

Esophageal cancer; Sarcopenia; Morbimortality; Disease-free survival; Overall survival

Introduction

Esophageal Cancer (EC) is the 8th most common malignancy in the world and its prevalence is expected to increase about 140% until 2025 [1-3]. EC has two main subtypes, Esophageal Squamous Cell Carcinoma (ESCC) and Esophageal Adenocarcinoma (AC). Regardless of histological type, this cancer is extremely aggressive, ranking 6th among all cancers in mortality [3-5], with an overall 5-year survival ranging between 15 and 20% [3].

The therapeutic and prognostic of EC patients are influenced by many factors, such as tumor stage and location, histological type, patient's performance status and comorbidities [6,7]. Furthermore, sarcopenia has been recognized as an important prognostic factor for oncological patients [8,9]. Irwin Rosenberg first described this condition in 1989 as a loss of muscular mass, yet presently it's considered both quantitative and qualitative criteria [10-12]. Currently, there is no general accepted definition for sarcopenia, but the European Working Group on Sarcopenia in Older People developed the consensus sets of definition and diagnostic criteria that require the loss of muscular mass in association with loss of muscular function [10].

Many studies have highlighted the importance of body composition evaluation in oncological patients, based on the fact that sarcopenia can negatively affect chemotherapy efficacy and toxicity, enhancing postoperative morbidities and in-hospital stay length, and also decreasing overall survival [9,13-15].

Cut-off values to define the presence of sarcopenia depends on the method selected for analysis [10]. Computed tomography (CT) and Magnetic resonance imaging (MRI) are considered the gold standard to estimate the lean muscle area, fat tissue and intramuscular fat infiltration [10,14,16]. At present, the majority of studies about sarcopenia in oncological patients use CT to analyze muscular area, given that these images are required to tumor staging [8,17].

Article Information

DOI: 10.31021/jcro.20181115
Article Type: Field of Vision
Journal Type: Research Article
Volume: 1 **Issue:** 4
Manuscript ID: JCRO-1-115
Publisher: Boffin Access Limited

Received Date: 05 July 2018
Accepted Date: 22 November 2018
Published Date: 31 November 2018

*Corresponding author:

Sandra F Martins, M.D., Phd
Life and Health Sciences Research Institute (ICVS)
School of Health Sciences, University of Minho
Campus de Gualtar, 4710-057 Braga, Portugal
Tel: + 351 253604827
Fax: +351 253604847
E-mail: Sandramartins@Med.Uminho.Pt

Citation: Pinheiro S, Carneiro T, Luís D, Gomes A, Costa AC, et al. Impact of Sarcopenia in the Prognostic of Ressectable Esophageal Cancer. A Systematic Review. J Cancer Res Oncobiol. 2018 Nov;1(4):115

Although recent studies about the impact of sarcopenia in many cancers, there are few reports about its importance in surgical resection of EC [18,19]. In these patients, sarcopenia is associated with a higher postoperative morbidity; however, there is no clear association with mortality [20,21].

The majority of patients with EC are diagnosed in advanced stages [20]; on the other hand, esophagectomy has a postoperative morbidity rate that could reach 60% [17]. Some studies carried out in EC patients showed a higher rate of postoperative complications, mainly pulmonary complications, in sarcopenic patients [17,22,23]; moreover, sarcopenia has influence in the toxic limiting dose of neoadjuvant chemotherapy and in overall survival time [20,23,24]. Therefore, sarcopenia evaluation by CT seems to bean essential tool that can be easily introduced in the clinical evaluation of cancer's patients; this would allow a better stratification of risks and a greater optimization of patient before surgery. Therefore, it seemed relevant to evaluate the impact of sarcopenia in morbidity and mortality of patients with EC treated surgically in Braga Hospital (BH).

Methods

It was performed a retrospective study of 141 patients with histological diagnosis of EC treated surgically in BH Surgery Department, between 1st January 2004 and 30th September 2017. After the application of inclusion criteria (histological diagnosis of SCC and AC, treated surgically, with preoperative abdominal CT staging and with preoperative CT with full visibility of L3 level) and exclusion criteria (patients with a distinct histological type or with palliative surgery or those who had a lack of information in the clinical process to the studied variables) an non-probabilistic sample of 71 patients were included.

The variables collected included:

- Demographic parameters: Age, Gender and Height.
- Body composition parameters: L3 muscular area and Skeletal muscle index (SMI).
- Clinicopathological parameters: Primary tumor location, Histological type and TNM classification Histological grade.
- Perioperative parameters: Postoperative hospital stay length, Postoperative morbidity, Clavien-Dindo classification and 30 days mortality [25].
- Survival parameters: Disease-free survival and Overall survival.

Image analyses

Preoperative abdominal CT was used to assess the muscular area at L3 level, as this level shows a great relation with the whole body muscular mass, which allows us to estimate about the total muscle area (TMA) [19]. National Institutes of Health (NIH) ImageJ® software was used to calculate muscular area in a single slice at L3 level [26]. At the 3rd lumbar vertebra psoas, paraspinal and abdominal wall muscles are accessed. A specific muscle tissue demarcation was performed using a Hounsfield Unit (HU) threshold of -29 to +150. Muscular area was manually delimited and automatically calculated by the software.

Sarcopenia's definition

Sarcopenia was defined to SMI values of less than 38.5 cm^2/m^2 for women and less than 52.4 cm^2/m^2 for men, according to previous studies of Prado et al. This index is measured as follows:

$$SMI = \frac{TMA(m^2)}{Height^2(m^2)}$$ [23]

Statistical analyze

Quantitative variables were analyzed in relation to the normality, based on values of skewness and kurtosis, Shapiro-Wilk test's results and in graph images [28,29]. For those which had no normal distribution, non-parametric tests were chosen.

For the descriptive analysis of categorical variables, absolute (n) and relative (%) frequencies were calculated. For normal quantitative variables, mean (M) and standard deviation (SD) were presented, instead of median (Mdn) and interquartile range (IQR) for those that didn't fulfill the normality assumptions.

Comparisons between the two groups, with and without sarcopenia, were performed through t test for independent samples (t), for normal quantitative variables, and Levene's test was used to assess variance homogeneity [30]. Cohen's D (d) was used as an effect size measure (.20, .50 e .80 values show low, mean and great differences, respectively) [31]. For quantitative not normal variables , Mann-Whitney test (U) was applied; for which r was used as the effect size (values of .10, .30 and .50 mean low, mean and great differences, respectively) [30,31]. For qualitative variables was realized Qui-squared (χ^2) or Fisher's Exact test, when more than 20% of cells expected counts less than 5 [32]. Effect size was analyzed through Phi (Φ) for dichotomous variables, and Cramér 's V (Φ_c), when at least one variable has more than two categories (values of .10, .30 and .50 show low, mean and great differences) [31]. Statistical significance was considered when p<.05.

Univariate and multivariate binary logistic regressions were used to analyze possible predictor of postoperative pulmonary complications, as well as the occurrence of complications with higher severity (Clavien-Dindo ≥ III) [33]. Assumptions were evaluated, namely the absence of multicollinearity and standardized residuals analyze, to check outliers that could affect the model results.

In order to investigate the presence of significant differences between groups in relation to survival, Kaplan-Meier method was

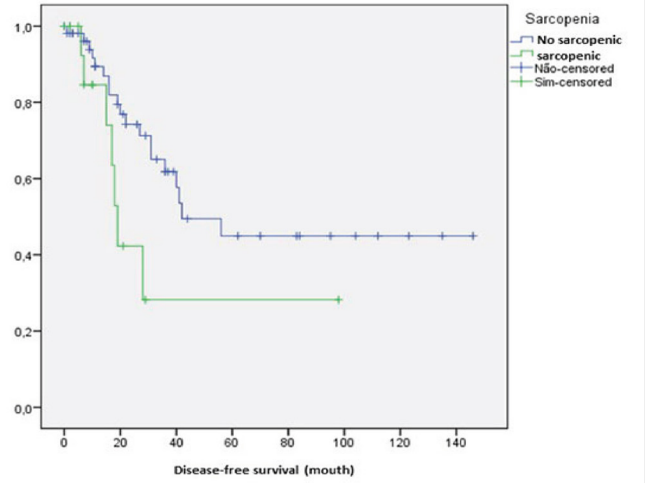

Figure 1: Disease-free survival of sarcopenic and non-sarcopenic patients

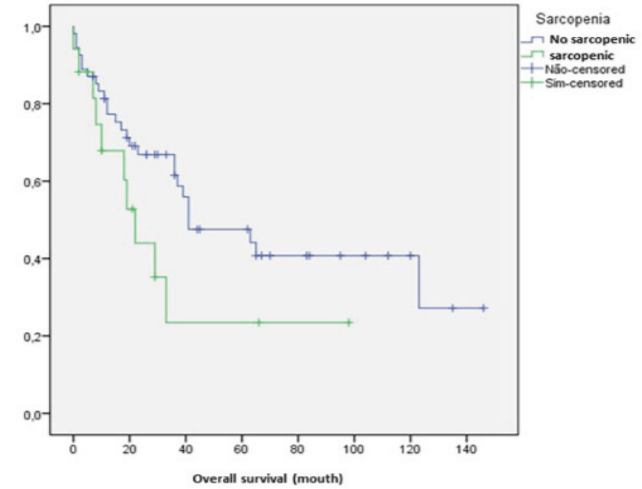

Figure 2: Overall survival of sarcopenic and non-sarcopenic patients

	Total (n=71)	Non Sarcopenic (n=54)	Sarcopenic (n=17)	
Gender *n (%)*				
Male	48 (88.9%)	17 (100.0%)	65 (91.5%)	*Fischer Test,*
Female	6 (11.1%)	0 (0.00%)	6 (8.50%)	p=0.324, Φ=-0.17
Age *M, (SD)*	63.1 (12.7)	63.2 (12.8)	62.9 (13.0)	t (69)=0.06 p=0.950, d=0.002
Height *M, (SD)*	1.66 (0.06)	1.66 (0.06)	1.68 (0.05)	t (69)=-1.64 p=0.106, d=0.36
L3 muscular Area *M, (SD)*	1.59 (28.0)	1.66 (28.3)	138 (11.7)	t (64.02)=5.84 *p<0.001, d=1.29*
SMI *(Mdn, IQR)*	55.6 (11.3)	58.5 (12.4)	49.3 (3.46)	*U=58.0, p<0.001, r =0.64*
Tumor Localisation *n (%)*				
Upper esophagus	0 (0.00)	0 (0.00)	0 (0.00)	
Middle esophagus	24 (33.8)	21 (38.9)	3 (17.6)	
Lower esophagus	27 (38.0)	20 (37.0.2)	7 (41.2)	*Fischer Test,*
Cardia ı	20 (28.2)	13 (24.1)	7 (41.1)	p=0.273, Φ_c=-0.22
Histological type *n (%)*				
SCC	38 (53.5%)	31 (57.4%)	7 (41.2%)	$\chi^2(1)$=1.37,
AC	33 (46.5%)	23 (42.6%)	10 (58.8%)	p=0.276, Φ=-0.14
T *n (%)*				
T1	25 (35.2%)	20 (37.0%)	5 (29.4%)	
T2	13 (18.3%)	10 (18.5%)	3 (17.6%)	$\chi^2(2)$ =0.420,
T3	33 (46.5%)	24 (44.4%)	9 (52.9%)	p=0.875, Φ_c=0.08
T4 a and b	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	
N *n (%)*				
N0	46 (64.8%)	37 (68.5%)	9 (52.9%)	
N1	14 (19.7%)	11 (20.4%)	3 (17.6%)	*Fischer Test,*
N2	6 (8.50%)	3 (5.60%)	3 (17.6%)	p=0.256, Φ_c=0.22
N3	5 (7.00%)	3 (5.60%)	2 (11.8%)	
M *n (%)*				
M0	71 (100.0%)	54 (100.0%)	17 (100.0%)	---
M1	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	
Histological grade n (%)				
G1	23 (32.4%)	16 (29.6%)	7 (41.2%)	$\chi^2(2)$=1.25,
G2	24 (33.8%)	20 (37.0%)	4 (23.5%)	p=0.540, Φ_c=0.13
G3	24 (33.8%)	18 (33.3%)	6 (35.3%)	
TNM stage n (%)				
ıA	13 (18.3%)	9 (16.7%)	4 (23.5%)	
ıIB	13 (18.3%)	12 (22.2%)	1 (5.90%)	
ıIIA	10 (14.1%)	8 (14.8%)	2 (11.8%)	
ıIB	15 (21.1%)	12 (22.2%)	3 (17.6%)	*Fischer Test,*
ıIIA	9 (12.7%)	8 (14.8%)	2 (11.8%)	p=0.334, Φ_c=0.31
ıIIB	5 (7.00%)	2 (3.70%)	3 (17.6%)	
ıIIC	5 (7.00%)	3 (5.60%)	2 (11.8%)	
ıv	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	

AC: Adenosarcinoma, absolute *(n)* relative (%) frequencies; Cohen's D (d): Effect size measure; Cramer's V (Φ_c): Effect size measure; IQR: Interquartile range; M: Mean; median; Phi (Φ): Effect size measure; SCC: Esophageal Squamous Cell Carcinoma; SD: Standard deviation; SMI: Skeletal Muscle Index; t: *t* test; U: Mann Whitney Test; χ^2 : Qui squared Test

Table 1: Demographic, Body composition and Clinicopathological parameters

performed, considering relapse in disease-free survival and death by any cause in overall survival [34]. To evaluate the interference of potential confounders, univariate Cox regression was used to determine Hazard coefficients for each variable. Multivariate Cox regression was performed to define which variables were independent predictors of survival [34]. These multivariate regression was preformed based on the statistical significant variables in univariate analyzes (p<.05) And those that were almost significant (p<.20) [35].

Results

The sample, demographic, body composition and clinicopathological parameters are depicted in Table 1. Sarcopenia prevalence was 23.9% (17 patients). Sarcopenic individuals showed a mean muscular area of 138 cm^2 (± 11.7), significantly lower than the non-sarcopenic group (t (64.02)=5.84, p<.001, d=1.29). Patients with sarcopenia had a median SMI of 49.3 cm^2/m^2 (3.46), significantly lower than those without sarcopenia (U=58.0, p <0.001, r=-.64). There were no differences between the groups concerning the other variables as described in Table 1.

Impact of sarcopenia in morbimortality

Postoperative morbidity occurred in 29 patients (40.8%). Pulmonary complications were the most common (65.5%), followed by anastomotic leakage (24.1%). It was found that 20 patients (69.0%) had minor complications (Clavien-Dindo ≤ II). The median in-hospital stay length was 13.0 days (6.00) and 30 days mortality occurred in 3 patients (4.20%). There were no significant differences between groups concerning morbidity and mortality (Table 2).

After univariate and multivariate logistic regressions, sarcopenia was not demonstrated to be an independent predictor of pulmonary complications or more severe complications (Clavien-Dindo ≥ III).

Impact of sarcopenia in disease-free survival

Disease relapse occurred in 26 patients (36.6%). There were no significant differences between the two groups, regarding the presence or site of relapse, as observed in Table 3.

In the survival analyzes, the Log Rank test demonstrated that there were significant differences in disease-free survival (χ^2 (1)=4.09, p=.043). Sarcopenic patients presented a lower disease-free survival time, than non-sarcopenic patients (medians of 19.0 (15.0) and 42.0 (31.0) months, respectively) (Figure 1).

To evaluate the effect of potential confounders defined in the literature, univariate and multivariate Cox regressions were depicted. Results are presented in Table 4.

Univariate analyzes showed that T (p=.003) and N (p=<.001) variables were significant predictors of disease-free survival. It was also revealed that G variable (p=.101) and sarcopenia (p=.051)

	Total (*n*=71)	Non Sarcopenic (*n*=54)	Sarcopenic (*n*=17)	
Morbility *n (%)*				
Without	42 (59.2%)	31 (57.4%)	11 (64.7%)	χ^2 (1)=0.29,
With	29 (40.8%)	23 (42.6%)	6 (35.3%)	*p*=0.778, Φ=-0.06
Respiratoty Mobility *n (%)*				
Without	10 (34.5%)	7 (30.4%)	3 (50.0%)	*Fisher test*
With	19 (65.5%)	16 (69.6%)	3 (50.0%)	*p*=0.633, Φ=-0.17
Others *n (%)*				
Without	22 (75.9%)	19 (82.6%)	3 (50.0%)	*Fisher test*
With	7 (24.1%)	4 (17.4%)	3 (50.0%)	*p*=0.131, Φ=-0.31
Clavien-Dindo Classification n (%)				
Without	24 (82.8%)	18 (78.3%)	6 (100.0%)	*Fisher test*
With	5 (17.2%)	5 (21.7%)	0 (0.00%)	*p*=0.553, Φ=-0.23
In hospital stay				
I	0 (0.00%)	0 (0.00%)	0 (0.00%)	
II	20 (69.0%)	16 (69.6%)	4 (66.7%)	
III a	0 (0.00%)	0 (0.00%)	0 (0.00%)	*Fisher test*
III b	4 (13.8%)	3 (13.0%)	1 (16.7%)	*p*=1.000, Φc=-0.04
IV a	0 (0.00%)	0 (0.00%)	0 (0.00%)	
IV b	0 (0.00%)	0 (0.00%)	0 (0.00%)	
V	5 (17.2%)	4 (17.4%)	1 (16.7%)	
(Mdn, AIQ)	13.0 (6.00)	13.0 (6.00)	14.0 (5.00)	*U*=443, *p*=0.828, r=-0.03
Mortality at 30 days				
Without	68 (95.8%)	52 (96.3%)	16 (94.1%)	*Fisher test*
With	3 (4.20%)	2 (3.70%)	1 (5.90%)	*p*=0.566, Φ=0.05

Absolute (n) and relative (%) frequencies; Cramer's V (Φc): Effect size measure; IQR: Interquartile Range; M: Mean; Mdn: Median; Phi (Φ): Effect size measure; r: Effect size measure; U: Mann-Whitney Test; χ2: Quisquared Test

Table2: Sarcopenia impact in morbimortality

	Total (*n*=71)	Non-sarcopenic (*n*=54)	Sarcopenic (*n*=17)	
Relapse *n (%)*				
Without	45 (63.4%)	35 (64.8%)	10 (58.8%)	χ2 (1)=0.20
With	26 (36.6%)	19 (35.2%)	7 (41.2%)	*p*=0.774, Φ=0.05
Lymphnode *n (%)*				
Without	60 (84.5%)	47 (87.0%)	13 (76.5%)	*Fischer Test,*
With	11 (15.5%)	7 (13.0%)	4 (23.5%)	*p*=0.441, Φ=0.13
Anastomosis *n (%)*				
Without	66 (93.0%)	49 (90.7%)	17 (100.0%)	*Fischer Test,*
With	5 (7.00%)	5 (9.30%)	0 (0.00%)	*p*=0.328, Φ=-0.15
Lung *n (%)*				
Without	66 (93.0%)	49 (90.7%)	17 (100.0%)	*Fischer Test,*
With	5 (7.00%)	5 (9.30%)	0 (0.00%)	*p*=0.328, Φ=-0.15
Liver *n (%)*				
Without		53 (98.1%)	16 (94.1%)	*Fischer Test,*
With	2 (2.80%)	1 (1.90%)	1 (5.90%)	*p*=0.424, Φ=0.10
Peritoneal Carcinomatosis *n (%)*				
Without		51 (94.4%)	15 (88.2%)	*Fischer Test,*
With	5 (7.00%)	3 (5.60%)	2 (11.8%)	*p*=0.587, Φ=0.10
Bone *n (%)*				
Without	68 (95.8%)	51 (94.4%)	17 (100.0%)	*Fischer Test,*
With	3 (4.20%)	3 (5.60%)	0 (0.00%)	*p*=1.000, c=-0.12

Absolute (n) and relative (%) frequencies; Cramer's V (Φc): Effect size measure; Phi (Φ): Effect size measure; χ2: Qui squared test

Table3: Sarcopenia impact in disease relapse

	Univariate Analysis		Multivariate Analysis	
	p	*Hazard ratio (CI 95%)*	*p*	*Hazard ratio (CI 95%)*
Gender (male *vs.* female)	0.462	0.58 (0.14.2.47)	0.314	0.44 (0.09.2.17)
Age	0.954	1.00 (0.97.1.03)	0.597	1.01 (0.98.1.04)
Histological type (SCC *vs.* AC)	0.958	1.03 (0.48.2.32)	-	-
Tumour localization (middle				
third *vs.* Lower third and cardia I)	0.990	1.00 (0.43.2.30)	-	-
T (T ≤ 2 *vs.* T ≥ 3)	0.003	3.40 (1.52.7.60)	0.025	2.85 (1.14.7.11)
N (N0 *vs.* N ≥ 1)	<0.001	4.93 (2.18.11.17)	0.028	2.97 (1.13.7.84)
G (G ≤ 2 vs. ≥ G3	0.101	1.99 (0.87.4.55)	0.437	1.45 (0.57.3.66)
L3 muscular area	0.743	1.00 (0.98.1.01)		
Sarcopenia (without *vs.* with)	0.051	2.43 (1.00.5.91)	0.147	2.04 (0.78.5.36)

AC: Adenocarcinoma; CI: Confidence Interval; SCCs: Esophageal Squamous Cell Carcinoma

Table 4: Disease-free survival analyzes

were almost significant. All these predictors were included in the multivariate regression model, as well as control variables, such as gender and age.

The multivariate model was significant (χ^2 (6)=25.1, p<.001) and showed that despite sarcopenia is associated with a lower disease-free survival, it was not an independent predictor, when other variables were controlled. T ≥ 3 (B=1.05, Wald=5.02, p=.025) and N ≥ 1 (B=1.09, Wald=4.85, p=.028) variables revealed to be independent predictors of a lower disease-free survival (Table 4).

Impact of sarcopenia in overall Survival

Median overall survival of sarcopenic patients was 22.0 months (23.0), whereas patients without sarcopenia presented a median overall survival of 41,0 months (53.0). There were no significant differences between those groups (χ^2 (1)=2.97, p=.085) (Figure 2).

Concerning to univariate Cox regressions, T (p=.002), N (p =.001), M (p=.047), anastomosis leakage (p=.001) and Clavien-Dindo ≥ III (p=.001) variables showed to be significant predictors of overall survival. It was also found that G (p=.086), gender (p=.144) and

sarcopenia (p=.092) variables were very close to significance. Thus, those predictors were included in a multivariate Cox regression model, using gender as control variables. The multivariate model was significant (χ^2 (8)=48,9, p<.001) and showed that sarcopenia was not a predictor of overall survival. Age (B=0.03, Wald=5.00, p=.025), T ≥ 3 (B=0.80, Wald=4.51, p=.034) and N ≥ 1 (B=1.15, Wald=6.45, p =.01) demonstrated to be independent predictors of a lower overall survival. Anastomotic leakage (B=1.11, Wald=4,77, p=.029) and Clavien-Dindo ≥ III (B=2.34, Wald=17.40, p<.001) also revealed to be independent predictors of poorer overall survival (Table 5).

Discussion

The promoting factors of sarcopenia are multifactorial, including physical inactivity, systemic inflammation, increased metabolic rate and reduced nutrient intake. All these drivers are prevalent in EC patients, in which sarcopenia has been reported between 26.0% to 75.0% [36,37].

In this study, sarcopenia was documented in 23.9% of cases; this lower value may result of the analysis methods and the different cutoff values that can be used to define sarcopenia, making literature results inconsistent.

Patients with sarcopenia had a mean muscular area of 138 cm^2 (± 11.7) and a median SMI of 49.3 cm^2/m^2 (3.46), values significantly lower than those of non-sarcopenic patients. Data from literature support the differences between these variables, namely regarding to SMI, reporting a similar median value (46.6 cm^2/m^2) [20]. This finding was expected, as SMI is the index is used to distinguish patients with or without sarcopenia.

When evaluating the impact of sarcopenia in morbidity, we concluded that postoperative morbidity rate was identical between sarcopenic and non-sarcopenic patients, showing no significant differences between both groups, even when we analyze the subgroups of commodities. These results are partially similar to those found in literature. Paireder M. et al. [23] performed a study in patients submitted to esophagectomy after neoadjuvant therapy. They concluded that there were no differences between morbidity rates between the two groups, not even concerning to pulmonary complications or anastomotic leakage. Otherwise, a study performed in patients with thoracic EC who underwent esophagectomy showed a significant higher incidence of pulmonary complications in patients with preoperative sarcopenia (32.0%), than in non-sarcopenic patients (12.0%) [17]. Multivariate analysis of that study demonstrated that sarcopenia was an independent predictor of the onset of respiratory postoperative complications [17]. Furthermore, Elliott JA et al. [36] looked into the impact of sarcopenia in the multimodal approach of locally advanced EC and concluded that sarcopenia was also an independent predictor of more severe complications (Clavien-Dindo ≥ IIIb).

As it turned out for many other cancers, sarcopenia can impair in-hospital stay length and 30 days mortality [14]. In the present study, there were no significant differences for these variables; similar results are documented in literature [18,36].

Concerning survival, disease-free survival time was significantly inferior in patients with sarcopenia (median of 19,0 months), which was consistent with other described studies, one of them reporting a median disease-free survival of 15,8 months in sarcopenic patients [23,36]. Although sarcopenia seemed to be associated with a lower disease-free survival, it was not an independent predictor when other variables were included and controlled. Thereby, in the multivariate analysis, T ≥ 3 and N ≥ 1 variables showed to be the only independent predictors of an impaired disease-free survival.

Regarding to the overall survival, there were no significant differences between both groups. Some studies demonstrated the absence of significant differences in overall survival, but others reported a lower overall survival in sarcopenic patients [18,20,21,23]. Tamandl D et al. [20] documented a significant decrease in overall survival of patients with sarcopenia (median of 31,5 months), in a study performed in patients treated with potentially curative esophagectomy. Despite overall survival in our study was similar between the two groups, we performed a Cox regression modeling to check the impact of sarcopenia when controlled for confounders. Our results showed that T ≥ 3, N ≥ 1, anastomotic leakage and Clavien-Dindo ≥ III variables independently predicted a lower overall survival, unlike sarcopenia that presented no significant differences. Some data from literature confirm that sarcopenia is an independent predictor of overall survival [18,20,21,23].

Conclusion

Sarcopenia impact on malignancy is well documented in literature; however, it's role in tumour surgical resection is more controversial.

The diagnosis of sarcopenia can be easily implemented in the context of tumour staging, namely EC, insofar that the patients already have CT for preoperative staging. Sarcopenia evaluation, will allow a better risk stratification and a greater optimization of patient before surgery such as appropriate nutritional care and physical exercise. Although, in the present study, sarcopenia was not associated with a

	Univariate Analysis		Multivariate Analysis	
		Hazard ratio		*Hazard ratio*
	p	*(CI 95%)*	*p*	*(CI 95%)*
Gender (male *vs.* female)	0.144	0.23 (0.03. 1.67)	0.104	0.18 (0.02. 1.42)
Age	0.84	1.00 (0.98. 1.03)	0.025	1.03 (1.00. 1.06)
Histological type (SCC *vs* AC)	0.242	0.68 (0.35. 1.31)		
Tumour localisation (middle third *vs.* Lower third and cardia ı)	0.688	0.87 (0.44. 1.71)		
T (T ≤ 2 *vs.* T ≥ 3)	0.002	2.89 (1.46. 5.72)	0.034	2.22 (1.06. 4.62)
N (N0 *vs.* N ≥ 1**)**	0.001	3.03 (1.54. 5.99)	0.011	3.17 (1.30. 7.72)
G (≤ G2 *vs.* ≥ G3**)**	0.086	1.84 (0.92. 3.68)	0.123	1.81 (0.85. 3.85)
L3 Muscular area	0.847	1.00 (0.99. 1.01)		
Morbility (without *vs.* With)	0.463	1.29 (0.66. 2.52)		
Respiratory Morbility (without *vs.* with)	0.503	0.74 (0.30. 1.79)		
Anastomatic leakage (without vs. with)	0.001	4.89 (1.94. 12. 19)	0.029	3.03 (1.12. 8.20)
Clavien - Dindo (≤ II *vs.* ≥ III)	0.001	3.97 (1.79. 8.81)	<0.001	10.22 (3.43. 30.48)
Sarcopenia (without *vs.* with)	0.092	1.89 (0.90. 3.96)	0.51	1.32 (0.58. 3.03)

Table 5: Overall survival analyzes

higher postoperative morbimortality, neither with a lower disease-free and overall survival.

Ethical Considerations

The protocol of this study was submitted to the appreciation and approval of the Sub commission of Ethics for Health and Life Sciences of Minho University and of Ethical Commission of Braga Hospital.

References

1. Mao WM, Zheng WH, Ling ZQ. Epidemiologic risk factors for esophageal cancer development. Asian Pac J Cancer Prev. 2011;12(10):2461-2466.
2. Rasool S, A Ganai B, Syed Sameer A, Masood A. Esophageal cancer: Associated factors with special reference to the Kashmir Valley. Tumori. 2012;98(2):191-203.
3. Napier KJ, Scheerer M, Misra S. Esophageal cancer: A Review of epidemiology, pathogenesis, staging workup and treatment modalities. World J Gastrointest Oncol. 2014 May;6(5):112-120.
4. Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol. 2013 Sep;19(34):5598-5606.
5. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet. 2013;381(9864):400-412.
6. Berry MF. Esophageal cancer: Staging system and guidelines for staging and treatment. J Thorac Dis. 2014 May;6(Suppl 3):289-297.
7. Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016 Sep;27(Suppl 5):v50-v57.
8. Boutin RD, Yao L, Canter RJ, Lenchik L. Sarcopenia: Current Concepts and Imaging Implications. AJR Am J Roentgenol. 2015 Sep;205(3):W255-W266.
9. Miyata H, Sugimura K, Motoori M, Fujiwara Y, Omori T, et al. Clinical Assessment of Sarcopenia and Changes in Body Composition During Neoadjuvant Chemotherapy for Esophageal Cancer. Anticancer Res. 2017 Jun;37(6):3053-3059.
10. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, et al. Sarcopenia: European consensus on definition and diagnosis. Age Ageing. 2010 Jul;39(4):412-423.
11. Kim TN, Choi KM. Sarcopenia: Definition, Epidemiology, and Pathophysiology. J Bone Metab. 2013;20:1-10.
12. Dodds RM, Uk M, Roberts HC, Cooper C, Sayer AA. The Epidemiology of Sarcopenia. J Clin Densitom. 2015 Oct-Dec; 18(4):461-466.
13. Calcagno C, Lobatto ME, Robson PM, Millon A. Three dimensional (3D) dynamic contrast enhanced (DCE)MRI for the accurate, extensive quantification of microvascular permeability in atherosclerotic plaques. HHS Public Access. 2016 Oct;28(10):1304-1314.
14. Yip C, Dinkel C, Mahajan A, Siddique M, Cook GJR, et al. Imaging body composition in cancer patients: visceral obesity, sarcopenia and sarcopenic obesity may impact on clinical outcome. Insights Imaging. 2015 Aug;6(4):489-497.
15. Zhang G, Li X, Sui C, Zhao H, Zhao J. Incidence and risk factor analysis for sarcopenia in patients with cancer. 2016;1230-1234.
16. Pahor M, Manini MC. Sarcopenia: clinical evaluation, biological markers and other evaluation tools. J Nutr Health Aging. 2009 Oct;13(8):724-728.
17. Nishigori T, Okabe H, Tanaka E, Tsunoda S, Hisamori S, et al. Sarcopenia as a predictor of pulmonary complications after esophagectomy for thoracic esophageal cancer. J Surg Oncol. 2016 May;113(6):678-684.
18. Grotenhuis BA, Shapiro J, van Adrichem S, de Vries M, Koek M, et al. Sarcopenia/Muscle Mass is not a Prognostic Factor for Short- and Long-Term Outcome After Esophagectomy for Cancer. World J Surg 2016;40(11):2698-2704.
19. Harada K, Ida S, Baba Y, Ishimoto T, Kosumi K, et al. Prognostic and clinical impact of sarcopenia in esophageal squamous cell carcinoma. Dis Esophagus. 2016 Aug;29(6):627-633.
20. Tamandl D, Paireder M, Asari R, Baltzer PA, Schoppmann SF, et al. Markers of sarcopenia quantified by computed tomography predict adverse long-term outcome in patients with resected esophageal or gastro-oesophageal junction cancer. Eur Radiol. 2016 May;26(5):1359-1367.
21. Black D, Mackay C, Ramsay G, Hamoodi Z, Nanthakumaran S, et al. Prognostic Value of Computed Tomography : Measured Parameters of Body Composition in Primary Operable Gastrointestinal Cancers. Ann Surg Oncol. 2017 Aug;24(8):2241-2251.
22. Joglekar S, Nau PN, Mezhir JJ. The impact of sarcopenia on survival and complications in surgical oncology: A review of the current literature--Author response. J Surg Oncol. 2015 Dec;112(8):910.
23. Paireder M, Asari R, Kristo I, Rieder E, Tamandl D, et al. Impact of sarcopenia on outcome in patients with esophageal resection following neoadjuvant chemotherapy for esophageal cancer. Eur J Surg Oncol. 2017;43(2):478-484.
24. Tan BHL, Brammer K, Randhawa N, Welch NT, Parsons SL, et al. Sarcopenia is associated with toxicity in patients undergoing neo-adjuvant chemotherapy for oesophago-gastric cancer. Eur J Surg Oncol. 2015;41(3):333-338.
25. Dindo D, Demartines N, Clavien P. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. 2004 Aug;240(2):205-213.
26. Gomez-perez SL, Haus JM, Sheean P, Patel B, Mar W, et al. Measuring abdominal circumference and skeletal muscle from a single cross-sectional computed tomography image: a step-by-step guide for clinicians using National Institutes of Health ImageJ. J Parenter Enteral Nutr. 2016 May;40(3):308-318.
27. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory gastrointestinal tracts : a population-based study. Lancet Oncol. 2008 Jul;9(7):629-635.
28. Kim H. Statistical notes for clinical researchers : assessing normal distribution (2) using skewness and kurtosis. Restor Dent Endod. 2013 Feb;38(1): 52-54.
29. Razali NM, Wah YB, Sciences M. Power comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors and Anderson-Darling tests. 2011;2(1):21-33.
30. Chan YH. Biostatistics 102: quantitative data--parametric & non-parametric tests. Singapore Med J. 2003 Aug;44(8):391-396.
31. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. New York (NY): Lawrence Erlbaum Associates; 1998.
32. Chan YH. Biostatistics 103 : Qualitative Data - tests of independence. Singapore Med J. 2003 Oct;44(10):498-503.
33. Chan YH. Biostatistics 202: logistic regression analysis. Singapore Med J. 2004 Apr;45(4):149-153.
34. Chan YH. Biostatistics 203. Survival analysis. Singapore Med J. 2004 Jun;45(6):249-256.
35. Maldonado G, Greenland S. Simulation Study of Confounder-Selection Strategies. Am J Epidemiol. 1993 Dec;138(11):923-936.
36. Elliott JA, Doyle SL, Guinan EM, Elliott JA, Doyle ÃSL, et al. Sarcopenia: Prevalence, and Impact on Operative and Oncologic Outcomes in the Multimodal Management of Locally Advanced Esophageal Cancer. Ann Surg. 2017 Nov;266(5):822-830.
37. Shafiee G, Keshtkar A, Soltani A, Ahadi Z, Larijani B, et al. Prevalence of sarcopenia in the world : a systematic review and meta- analysis of general population studies. J Diabetes Metab Disord. 2017 May;16:21.