Impact of Sarcopenia in the Prognostic of Ressectable Esophageal Cancer

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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, Quiz-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 cm² (± 11.7), significantly lower than the non-sarcopenic group (164.02±5.84, p<.001, d=.29), and a median skeletal muscle index of 49.3 cm²/m² (3.46), significantly lower than the non-sarcopenic patients (Us=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].


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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 be an 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 psosas, 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 cm²/m² for women and less than 52.4 cm²/m² for men, according to previous studies of Prado et al. This index is measured as follows:

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

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 ($\chi^2$) or Fisher’s Exact test, when more than 20% of cells expected counts less than 5 [32]. Effect size was analyzed through Phi ($\phi$) for dichotomous variables, and Cramér’s V ($\phi$), 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<0.05.

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
### Table 1: Demographic, Body composition and Clinicopathological parameters

<table>
<thead>
<tr>
<th>Gender a (%)</th>
<th>Total (n=71)</th>
<th>Non Sarcopenic (n=54)</th>
<th>Sarcopenic (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>48 (88.9%)</td>
<td>17 (100.0%)</td>
<td>65 (91.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (11.1%)</td>
<td>0 (0.00%)</td>
<td>6 (8.50%)</td>
</tr>
</tbody>
</table>

**Age M, (SD)**

- Total (n=71): 63.1 (12.7)
- Non Sarcopenic (n=54): 63.2 (12.8)
- Sarcopenic (n=17): 62.9 (13.0)

**Height M, (SD)**

- Total (n=71): 1.66 (0.06)
- Non Sarcopenic (n=54): 1.66 (0.06)
- Sarcopenic (n=17): 1.68 (0.05)

**L3 muscular Area M, (SD)**

- Total (n=71): 1.59 (28.0)
- Non Sarcopenic (n=54): 1.66 (28.3)
- Sarcopenic (n=17): 138 (11.7)

**SMI (Mdn, IQR)**

- Total (n=71): 55.6 (11.3)
- Non Sarcopenic (n=54): 58.5 (12.4)
- Sarcopenic (n=17): 49.3 (3.46)

**Tumor Localisation n (%)**

- Upper esophagus: 0 (0.00%)
- Middle esophagus: 24 (33.8%)
- Lower esophagus: 27 (38.0%)
- Cardia: 20 (28.2%)

**Histological type n (%)**

- SCC: 38 (53.5%)
- AC: 33 (46.5%)

**T n (%)**

- T1: 25 (35.2%)
- T2: 13 (18.3%)
- T3: 33 (46.5%)
- T4 a and b: 0 (0.00 %)

**N n (%)**

- N0: 46 (64.8%)
- N1: 14 (19.7%)
- N2: 6 (8.50%)
- N3: 5 (7.00%)

**M n (%)**

- M0: 71 (100.0%)
- M1: 0 (0.00 %)

**Histological grade n (%)**

- G1: 23 (32.4%)
- G2: 24 (33.8%)
- G3: 24 (33.8%)

**TNM stage n (%)**

- T1A: 13 (18.3%)
- T1B: 13 (18.3%)
- T1A: 10 (14.1%)
- T1B: 15 (21.1%)
- T1A: 9 (12.7%)
- T1B: 5 (7.00%)
- T1C: 5 (7.00%)
- T4: 0 (0.00 %)

- N0: 46 (64.8%)
- N1: 14 (19.7%)
- N2: 6 (8.50%)
- N3: 5 (7.00%)

| AC: Adenosarcoma, absolute (n) relative (%) frequencies; Cohen’s D (d): Effect size measure; Cramer’s V (Φ): 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; χ²: Qui squared Test |
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 ($\chi^2(1)=4.09$, 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) were not significant predictors of disease-free survival. It was also revealed that G variable (p=.101) and sarcopenia (p=.051) were not significant predictors of disease-free survival.

<table>
<thead>
<tr>
<th>Morbility n (%)</th>
<th>Total (n=71)</th>
<th>Non Sarcopenic (n=54)</th>
<th>Sarcopenic (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without</td>
<td>42 (59.2%)</td>
<td>31 (57.4%)</td>
<td>11 (64.7%)</td>
</tr>
<tr>
<td>With</td>
<td>29 (40.8%)</td>
<td>23 (42.6%)</td>
<td>6 (35.3%)</td>
</tr>
<tr>
<td><strong>Respiratory Mobility n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without</td>
<td>10 (34.5%)</td>
<td>7 (30.4%)</td>
<td>3 (50.0%)</td>
</tr>
<tr>
<td>With</td>
<td>19 (65.5%)</td>
<td>16 (69.6%)</td>
<td>3 (50.0%)</td>
</tr>
<tr>
<td><strong>Others n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without</td>
<td>22 (75.9%)</td>
<td>19 (82.6%)</td>
<td>3 (50.0%)</td>
</tr>
<tr>
<td>With</td>
<td>7 (24.1%)</td>
<td>4 (17.4%)</td>
<td>3 (50.0%)</td>
</tr>
<tr>
<td><strong>Clavien-Dindo Classification n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without</td>
<td>24 (82.8%)</td>
<td>18 (78.3%)</td>
<td>6 (100.0%)</td>
</tr>
<tr>
<td>With</td>
<td>5 (17.2%)</td>
<td>5 (21.7%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td><strong>In hospital stay</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>ii</td>
<td>20 (69.0%)</td>
<td>16 (69.6%)</td>
<td>4 (66.7%)</td>
</tr>
<tr>
<td>iii a</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>iii b</td>
<td>4 (13.8%)</td>
<td>3 (13.0%)</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>iv a</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>iv b</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>v</td>
<td>5 (17.2%)</td>
<td>4 (17.4%)</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>(Mdn, AIQ)</td>
<td>13.0 (6.00)</td>
<td>13.0 (6.00)</td>
<td>14.0 (5.00)</td>
</tr>
<tr>
<td><strong>Mortality at 30 days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without</td>
<td>68 (95.8%)</td>
<td>52 (96.3%)</td>
<td>16 (94.1%)</td>
</tr>
<tr>
<td>With</td>
<td>3 (4.20%)</td>
<td>2 (3.70%)</td>
<td>1 (5.90%)</td>
</tr>
</tbody>
</table>

Absolute (n) and relative (%) frequencies; Cramer’s V ($\Phi_c$): Effect size measure; IQR: Interquartile Range; M: Mean; Mdn: Median; Phi (ϕ): Effect size measure; ρ: Effect size measure; U: Mann-Whitney Test; $\chi^2$: Quisquared Test

**Table 2**: Sarcopenia impact in morbimortality
Table 3: Sarcopenia impact in disease relapse

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

Table 4: Disease-free survival analyzes

<table>
<thead>
<tr>
<th></th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
<th>p</th>
<th>Hazard ratio (CI 95%)</th>
<th>p</th>
<th>Hazard ratio (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender (male vs. female)</strong></td>
<td>0.462</td>
<td>0.58 (0.14.2.47)</td>
<td>0.314</td>
<td>0.44 (0.09.2.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>0.954</td>
<td>1.00 (0.97.1.03)</td>
<td>0.597</td>
<td>1.01 (0.98.1.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Histological type</strong> (SCC vs. AC)</td>
<td>0.958</td>
<td>1.03 (0.48.2.32)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tumour localization</strong> (middle)</td>
<td>0.990</td>
<td>1.00 (0.43.2.30)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T (T ≤ 2 vs. T ≥ 3)</td>
<td>0.003</td>
<td>3.40 (1.52.7.60)</td>
<td>0.025</td>
<td>2.85 (1.14.7.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (N0 vs. N ≥ 1)</td>
<td>&lt;0.001</td>
<td>4.93 (2.18.11.17)</td>
<td>0.028</td>
<td>2.97 (1.13.7.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G (G ≤ 2 vs. ≥ G3)</td>
<td>0.101</td>
<td>1.99 (0.87.4.55)</td>
<td>0.437</td>
<td>1.45 (0.57.3.66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L3 muscular area</td>
<td>0.743</td>
<td>1.00 (0.98.1.01)</td>
<td>0.147</td>
<td>2.04 (0.78.5.36)</td>
<td></td>
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</tr>
<tr>
<td><strong>Sarcopenia</strong> (without vs. with)</td>
<td>0.051</td>
<td>2.43 (1.00.5.91)</td>
<td>0.147</td>
<td>2.04 (0.78.5.36)</td>
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AC: Adenocarcinoma; CI: Confidence Interval; SCCs: Esophageal Squamous Cell Carcinoma

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 (\( \chi^2(1)=297. p=.005 \) (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=0.092) 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 (χ²(8)=48.9, p<0.001) and showed that sarcopenia was not a predictor of overall survival. Age (B=0.03, Wald=5.00, p=0.25), T ≥ 3 (B=0.80, Wald=4.51, p=0.034) and N ≥ 1 (B=1.15, Wald=6.45, p =0.01) demonstrated to be independent predictors of a lower overall survival. Anastomotic leakage (B=1.11, Wald=4.77, p=0.029) and Clavien-Dindo ≥ III (B=2.34, Wald=17.40, p<0.001) 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 cm² (± 11.7) and a median SMI of 49.3 cm²/m² (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 cm²/m²) [20]. This finding was expected, as SMI is the index 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 submitted to esophagectomy. Despite overall survival in our study was similar to results are documented in literature [18,36].

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### 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
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