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Research Article

Impact of Sarcopenia on the Survival of Patients with Lymph Nodes Metastasis of Esophageal Cancer

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Abstract

Introduction: Esophageal Cancer is a global concern due to its high incidence and persistent high mortality rates. At the time of diagnosis, more than 50% of patients have unresectable disease or distant metastasis. Sarcopenia is considered an independent risk factor for prognosis. Thus, it is relevant to assess the presence of sarcopenia and see if it is associated with decreased survival.

Objectives: To identify a possible correlation between the presence of sarcopenia and the survival of patients with lymph nodes metastasis of EC and to evaluate the prevalence of sarcopenia in these patients.

Methodology: Sample of 26 patients with histological diagnosis of Esophageal Adenocarcinoma or Squamous Cell Carcinoma with lymph nodes metastasis, submitted to surgical ressection. The patient's Muscle Mass Index (SMI) was measured using lumbar CT, at L3 level, in a single axial section, using appropriate software. The association of qualitative variables with the presence or absence of sarcopenia was assessed using the Pearson´s Chi-Square Test ($\chi 2$) or Fisher's Exact Test. For continuous variables the T test was used. Survival curves were determined for overall survival and disease-free survival using Kaplan-Meier method and the log-rank test. A Cox regression was also performed.

Results: The average age of patients was 64 years, the majority being male (88,5%). 9 (34,6%) patients had sarcopenia. Sarcopenia was not significantly associated with a decrease in DFS ($p = 0,1,75$) or a decrease in OS ($p = 0,113$). Staging was associated with lower overall survival ($p = 0,033$). There was not significant association between sarcopenia and clinical anatomopathological factors.

Conclusion: Sarcopenia has not been shown to have an impact on the survival of patients with esophageal lymph nodes metastasis.

Keywords: *Esophageal Cancer; Lymph Node Metastasis; Sarcopenia; Survival*

Abbreviations

AJCC: American Joint Committee on Cancer; HB: Hospital of Braga; CT: Computed Tomography; DICOM: Digital Imaging and Communications in Medicine; DFS: Disease Free Survival; EC: Esophageal Cancer; EWGSOP: European Working Group on Sarcopenia in Older People; HR: Hazard Ratio; MRI: Magnetic Resonance Imaging; OS: Overall Survival; QT: Quimioterapy; RT: Radiotherapy; SMI: Skeletal Muscle Index; SPSS: Statistical Package for the Social Science; TMN: Primary Tumor, Regional Lymph Nodes, Metastasis; UH: Unidades de Hounsfiel

Introduction

Esophageal cancer (EC) is the eighth most frequent cancer and the sixth leading cause of cancer related death worldwide [1-4]. It reaches a prevalence 3 to 4 times higher in males when compared to females [1,5] and is a global concern due to its high incidence and persistent high mortality rates [1].

Sarcopenia has been the target of several studies that indicate that it has negative effects on the survival of cancer patients. Sarcopenia was first defined in 1989 by Rosenberg as an age-related decline in muscle mass [6,7]. The recent improvement in techniques that allow access to body composition and access to representative epidemiological data have modified the initial concept of a simple decrease in muscle mass. The current definition of sarcopenia includes loss of muscle strength and a decline in functional quality [7], becoming recognized as a muscle disease in 2018 by the European Working Group on Sarcopenia in Older People (EWGSOP) [8].

The diagnostic methods for sarcopenia include measuring muscle mass and function, which includes muscle strength and physical performance. The non-invasive gold standard assessment of muscle mass is Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). CT has been used as a reference method as it is part of the diagnosis, staging and follow-up of the disease in most cancers. The most used evaluation method is the measurement of the musculoskeletal mass index by CT [8].

Sarcopenia is considered an independent risk factor for worse prognosis and survival in cancer patients [2,9]. Thus, considering the poor prognosis of patients with lymph node involvement, it is pertinent to assess the presence of sarcopenia and its impact on survival, since its presence is associated with reduced survival and poor response to chemotherapy [2,9].

Materials and Methods

For the elaboration of this project, a retrospective, descriptive and analytical study was carried out.

The target population under study consists of patients with a histological diagnosis of Esophageal Cancer with lymph node metastasis, who underwent surgical resection in the Surgery Service of the Hospital de Braga (HB), from 1st January 1st, 2004 to December 1st, 2019.

Non-probabilistic, convenience sample, with 26 patients selected, created from the population (Figure 1).

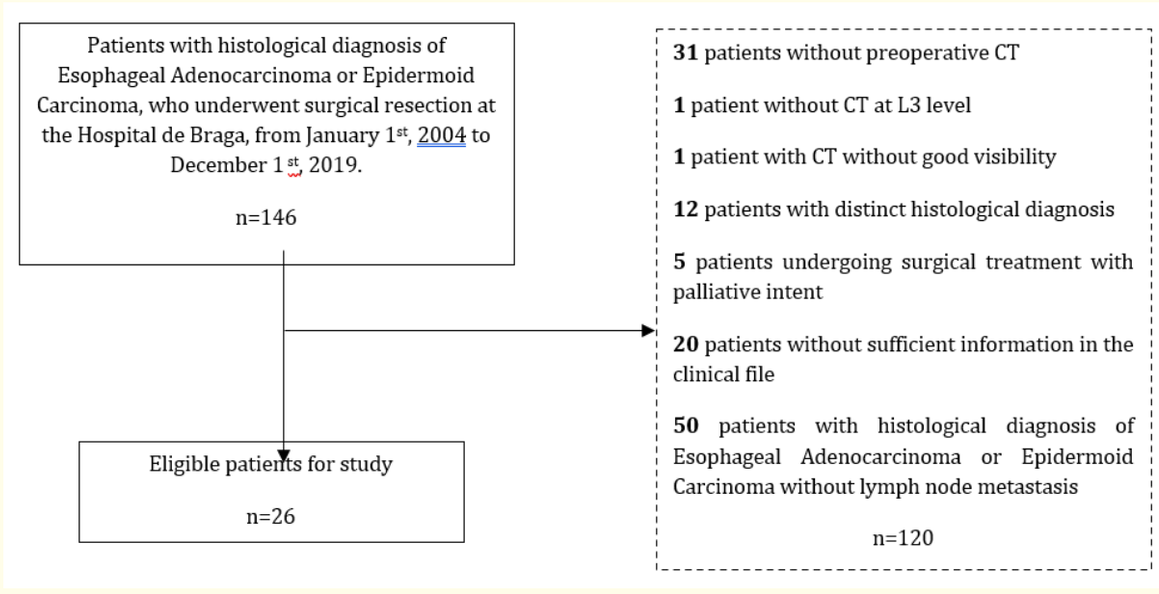

Figure 1: *Sample selection process, according to the inclusion and exclusion criteria.*

Patients who do not meet the inclusion criteria or meet any of the exclusion criteria mentioned below will be excluded from the study.

Inclusion criteria

Patients with histological diagnosis of Esophageal Adenocarcinoma or Epidermoid Carcinoma with lymph node metastasis, who underwent surgical resection at Hospital de Braga, between 1st January 1st, 2004 to December 1st, 2019.

Exclusion criteria

- Patients diagnosed with Esophageal Cancer with lymph node metastases undergoing surgical therapy with palliative purpose;
- Patients who do not have preoperative staging CT;
- Patients where imaging assessment at L3 level was not possible.

Data collection process

The characterization of the study sample was performed by collecting and analyzing information, according to the inclusion and exclusion criteria mentioned above. Two databases were used, already existing in the Surgery Department of the Hospital de Braga, and the data was later updated and complemented by consulting the computerized clinical files in Glintt®, having been organized and grouped in a document in Microsoft format Excel®.

The clinical data collected included time, date of relapse, place of relapse and date of death. Height was collected to calculate the Skeletal Muscle Index (SMI). The anatomopathological data of the primary tumor included the histological type, tumor location and staging of the primary tumor at the time of diagnosis. Data on the performance of treatment and, if so, what type of treatment was carried out were also included.

Patient follow-up data included the occurrence of recurrence, place of recurrence and death, as well as the respective dates. Subsequently, global survival and disease free survival were calculated using the time between the date of diagnosis and the date of death, regardless of the cause, or until the date of recurrence, respectively.

The patient's muscle mass index was measured using lumbar CT. This measurement was made at the L3 level, in a single axial section, using a suitable software. The clinical data and records to be collected are anonymised, each clinical file analyzed has a unique code different from the case number. No data that allow the identification of participants will be collected or stored.

CT image analysis

Then, from the preoperative abdominal CTs of each patient, it was possible to obtain the images in cross-section, at the level of L3. These images were downloaded, with the help of a Graduated Imaging Assistant, under the definition Default Anonymization Profile, not containing any element identifying the patient.

Subsequently, they were recorded in DICOM (Digital Imaging and Communications in Medicine) format and stored in a folder that contained the pseudoanonymization code assigned to each patient at the beginning of the study. To calculate the SMI, the semi-automatic software National Institutes of Health ImageJ® was used. By manually contouring the external and internal limits of muscle mass and applying the threshold -29 and +150 HU (Hounsfield Units), to distinguish skeletal muscle from other tissues, the total abdominal muscle area was determined. The value of the total abdominal mass was obtained by subtracting the external limit by the internal limit and then dividing the result by 100 (Figure 2 and 3).

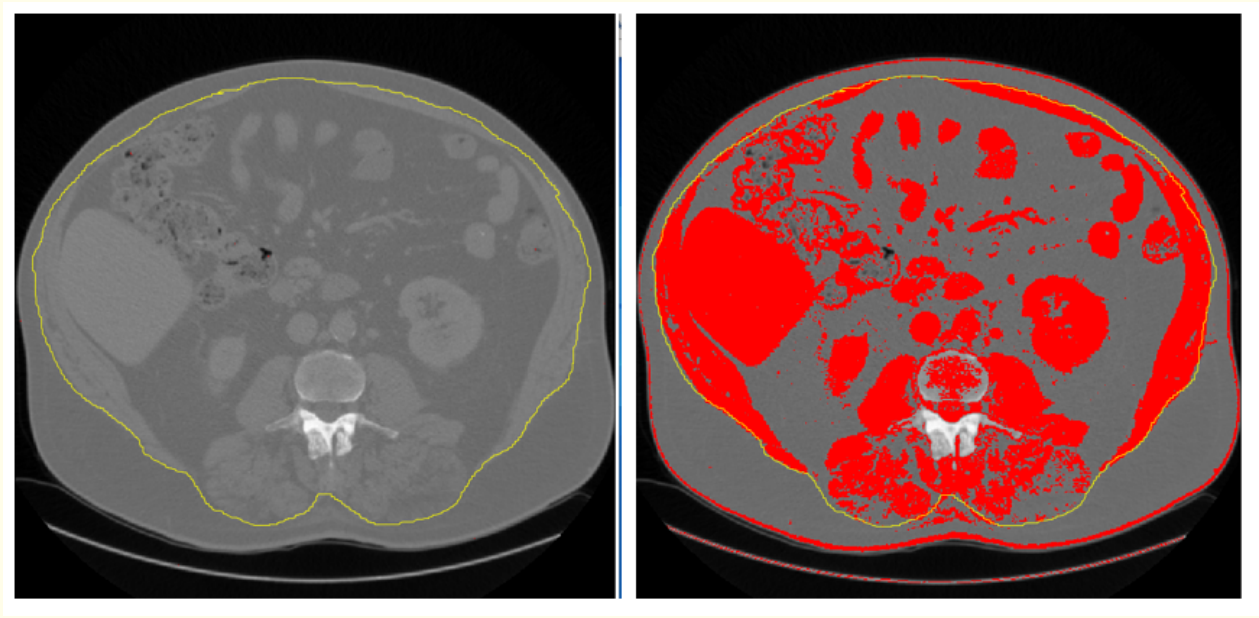

Figure 2: *Image of the L3 level with outline of the outer limit (yellow line) of muscle mass and application of the -250UH to -250UH threshold (left) and application of the -29UH to 150UH threshold (right).*

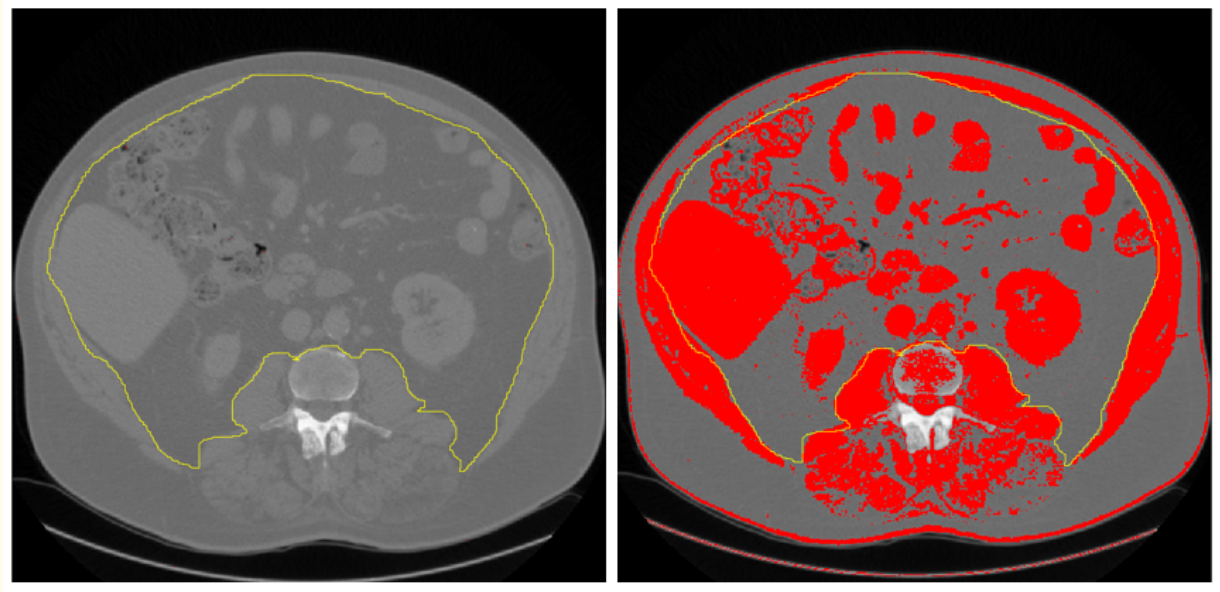

Figure 3: *Image of the L3 level with contour of the inner limit (yellow line) of muscle mass and application of the -250UH to -250UH threshold (left) and application of the -29UH to 150UH threshold (right).*

After obtaining the value of the total muscle area, the skeletal muscle mass index was calculated, using the height of each one (SMI-total abdominal muscle area/height^2).

Definition of sarcopenia

Sarcopenia was defined as SMI values lower than 38.5 cm^2/m^2 in females and lower than 52.4 cm^2/m^2 in males, according to previous studies by Prado., *et al* [10].

Statistical analysis

The data obtained were registered in an Excel database (Microsoft Office Excel 2013) and statistically analyzed using the Statistical Package for Social Sciences program (SPSS Inc., Chicago IL, USA), version 26.0.

For the descriptive study of the population, the absolute (n) and relative (%) frequencies were determined for all variables. For quantitative variables, means (M) and standard deviations (SD) were presented for those with normal distribution and medians (Mdn) for those that did not meet normality assumptions.

The comparison between the groups, with and without sarcopenia, was performed using the t test for independent samples (t) in quantitative variables with normal distribution, and the assumption of homogeneity of the variables was evaluated using the Levene test.

The association of qualitative variables with the presence or absence of sarcopenia was assessed using the Pearson Chi-Square Test (χ^2) or Fisher's Exact Test (when $n < 5$), considering the results to be significant for significance values (p) less than 0.05.

In order to assess the existence of significant differences between the groups in terms of survival, survival curves for overall survival and for disease-free survival were determined using the Kaplan-Meier method using the log-rank test. relapse event, in disease-free survival, and the death event, in overall survival.

A univariate Cox regression was performed with determination of the Hazard coefficients for each variable. To assess which variables were independent predictors of survival, a multivariate Cox regression was performed. In the regression models, the multivariate analysis was performed from the variables with statistical significance obtained by the univariate regression ($p < 0.05$).

Results

Sample characterization

This study included 26 patients with EC with lymph node metastases undergoing surgical treatment, 3 (11.5%) female and 23 (88.5%) male, aged between 39 and 85 years (Mean = 64.31 and Standard deviation = 12.98). The prevalence of sarcopenia was 34.6% (9 patients).

Adenocarcinoma was the most common histological type in 15 (57.7%) patients and epidermoid was present in 11 (42.3%) patients. In these patients, the tumor was located in the middle esophagus in 7 (26.9%) patients, in the lower esophagus in 8 (30.8%) patients, in cardia I in 8 (30.8%) patients and in the cardia II in 3 (11.5%) patients.

At diagnosis, the most frequent stage was stage III, with 21 (80.8%) patients and the remaining 5 (19.2) patients in stage II. Most patients present in T3 (76.9%) and the most prevalent lymph node involvement was N1 with 14 (53.8%) patients. In this sample, 7 (26.9%) patients underwent neoadjuvant therapy.

During the 120-month follow-up, disease relapse was observed in 56.7% (15 patients) and there were 20 (76.9%) deaths. No deaths were observed within 30 days after surgery. The characterization of the patients included in the study is described in table 1.

	n (%)
Clinical data	
Age	64,31 (12,98) (a)
Gender	
Female	3 (11,5)
Male	23 (88,5)
Clinical - pathological characterization	
Location	
Middle esophagus	7 (26,9)
Lower esophagus	8 (30,8)
Cardia I	8 (30,8)
Cardia II	3 (11,5)
Histological type	
Adenocarcinoma	15 (57,7)
Epidermoid	11 (42,3)
T	
T1	2 (7,7)
T2	4 (15,4)
T3	20 (76,9)
T4	0 (0,0)
N	
N1	14 (53,8)
N2	6 (23,1)
N3	6 (23,1)
Histologic grade	
G1	6 (23,1)
G2	8 (33,3)
G3	12 (46,2)
G4	0 (0,0)
TMN	
I	0 (0,0)
II	5 (19,2)
III	21 (80,8)
IV	0 (0,0)
Relapse	
Yes	15 (56,7)
No	11 (42,3)
Neoadjuvant treatment	
Yes	7 (26,9)
No	19 (73,1)
Morto	
Yes	20 (76,9)
No	6 (23,1)
30 day mortality	
Yes	0 (0,0)
No	26 (100)
Sarcopenia	
Yes	9 (34,6)
No	17 (65,4)

Table 1: *Characterization of patients included in the study.*

The mean SMI observed in males was 56.45 cm^2/m^2 and the mean in females was 43.41 cm^2/m^2. The median total abdominal muscle area in L3 in males was 156.81 cm^2 and in females it was 110.28 cm^2. The description of body composition data can be seen in table 2.

	Min-Max	M	SP
Total abdominal muscle area L3 (cm^2)	85,71 - 217,51	151,44	28,38
Female	85,71 - 125,91	110,28	21,54
Male	108,84 - 217,51	156,81	24,73
Skeletal muscle mass index, SMI, (cm^2/m^2)	32,26 - 79,89	54,95	10,11
Female	32,26 - 55,22	43,41	11,49
Male	41,47- 79,89	56,45	9,15

Table 2: *Description of the sample's body composition.*
Mdn- Median; P25-P75- Percentil 25 e percentil 75; Mín-Máx- minimum and maximum

The median disease-free survival was 15.5 months and the median overall survival was 18.5 months (Table 3).

	Min-Max	Mdn	P25-P75
Disease free survival (months)	1 - 56	15,50	8,50 - 21,25
Overall survival (months)	1 - 120	18,50	9,75 - 33,75

Table 3: *Disease free survival and overall sample survival.*
M- Mean; P25-P75- Percentil 25 e percentil 75; Mín-Máx- minimum and maximum.

Relationship between sarcopenia and clinical-antomopathological factors

Individuals with sarcopenia had a mean muscle area of 151.44 cm^2 (SD = 28.4), significantly lower than the group of patients without sarcopenia ($p < 0.001$). Sarcopenic patients had SMI values with a median of 54.94 cm^2/m^2, significantly lower than those without sarcopenia ($p < 0.001$) (Table 5). No significant differences were found for the remaining variables referred to in table 4.

	With sarcopenia n = 9	Without sarcopenia n = 17	Statistic
Age, M (DP)	64,35 (13,16)	63,66 (12,93)	p = 0,8
Gender (n,%)			
Female	1 (11,1)	2 (11,8)	Fisher test p = 0,732
Male	8 (88,9)	15 (88,2)	
Location (n,%)			
Middle esophagus	1 (11,1)	6 (35,3)	Fisher test P = 0,298
Lower esophagus	4 (44,4)	4 (23,5)	
Cardia I	2 (22,2)	6 (35,3)	
Cardia II	2 (22,2)	1 (5,9)	
Histological type (n,%)			

Epidermoid	4 (44,4)	7 (41,2)	Fisher test
Adenocarcinoma	5 (55,5)	10 (58,8)	p = 0,598
T (n,%)			
T1	0 (0,0)	2 (11,8)	Fisher test
T2	1 (11,1)	3 (17,6)	p = 0,504
T3	8 (88,9)	12 (70,6)	
N (n,%)			
N1	3 (33,3)	11 (64,7)	Fisher test
N2	3 (33,3)	3 (17,6)	p = 0,337
N3	3 (33,3)	3 (17,6)	
Histological Grade (n,%)			
G1	3 (33,3)	3 (17,6)	Fisher test
G2	2 (22,2)	6 (35,3)	p = 0,760
G3	4 (44,4)	8 (47,1)	
TMN (n,%)			
I	0 (0,0)	0 (0,0)	Fisher test
II	1 (11,1)	4 (23,5)	p = 0,628
III	8 (88,9)	13 (76,5)	
Relapse (n,%)			
Sim	6 (66,6)	9 (52,9)	Fisher test
Não	3 (33,3)	8 (47,1)	p = 0,683

***Table 4**: Relationship between sarcopenia and clinical and pathological factors.*

		Statistic
Age (M,DP)	64,31 (12,98)	p = 0,8
Height (M, SP)	1,66 (0,05)	p = 0,549
Muscular area (M,SP)	151,44 (28,38)	p <0,001
SMI (Mdn)	54,94	p < 0,001

***Table 5:** Relationship between sarcopenia and age, height, muscle area in L3 and SMI.*
M- Mean; SP- Standard Deviation; Mdn- Median; p- Significance Level.

Relationship between sarcopenia and disease free survival

During the follow-up, there were 15 (56.7%) disease recurrences; 6 (40%) in sarcopenic and 9 (60%) in non-sarcopenic. The median disease-free survival was higher in the group without sarcopenia (Mdn = 22 months) compared to patients with sarcopenia (Mdn = 17 months). The Log-Rank Test indicated the absence of significant differences between groups (χ^2 (1) = 1.843, p = 0.175) (Figure 4).

Univariate analysis showed no significant associations between variables and lower disease-free survival (Table 6).

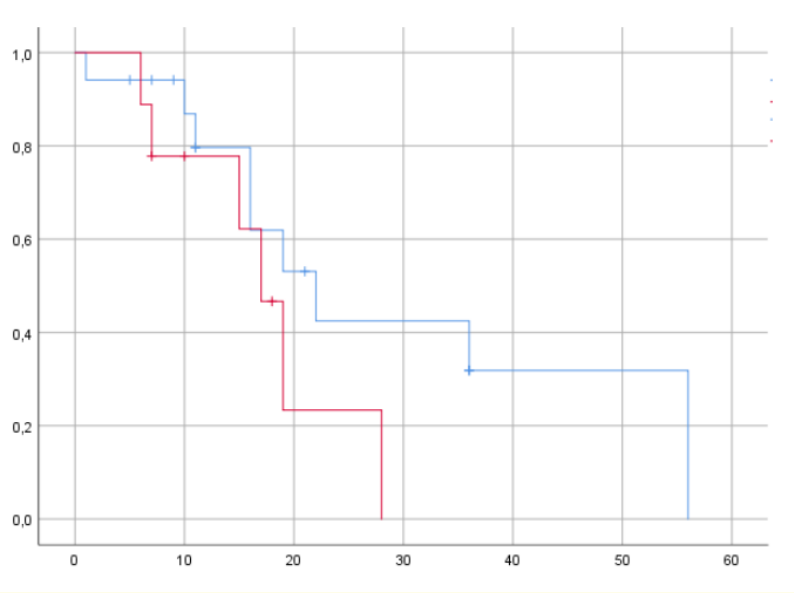

Figure 4: *Disease-free survival in patients with (red line) and without (blue line) sarcopenia (in months).*

	Univariate analysis	
	P-valor	**HR**
Age	0,930	0,988 (0,963-1,036)
Gender	0,416	2,334 (0,303-17,949)
Location	0,056	0,523 (0,269-1,017)
Histological type	0,970	1,022 (0,338-3,086)
Neoadjuvant treatment	0,363	0,368 (0,05-3)
T	0,428	1,463 (0,571-3,751)
N	0,189	1,552 (0,805-2,991)
Histological grade	0,696	0,877 (0,455-1,692)
Staging	0,124	1,535 (0,889-2,648)
Stage	0,774	1,208 (0,333-4,375)
Sarcopenia	0,190	2,093 (0,693-6,324)

Table 6: *Univariate Cox regression for disease-free survival.*

Multivariate Cox regression was not performed, as no significant values were obtained in the univariate analysis.

Relationship between sarcopenia and global survival

During follow-up there were 20 (76.9%) deaths, 8 (40%) in sarcopenic patients and 12 (60%) in non-sarcopenic patients. The median overall disease survival was higher in the group without sarcopenia (Mdn = 23 months) compared to patients with sarcopenia (Mdn = 19 months). The Log-Rank Test indicated the absence of significant differences between groups (χ^2 (1) = 2.51, p = 0.113) (Figure 5).

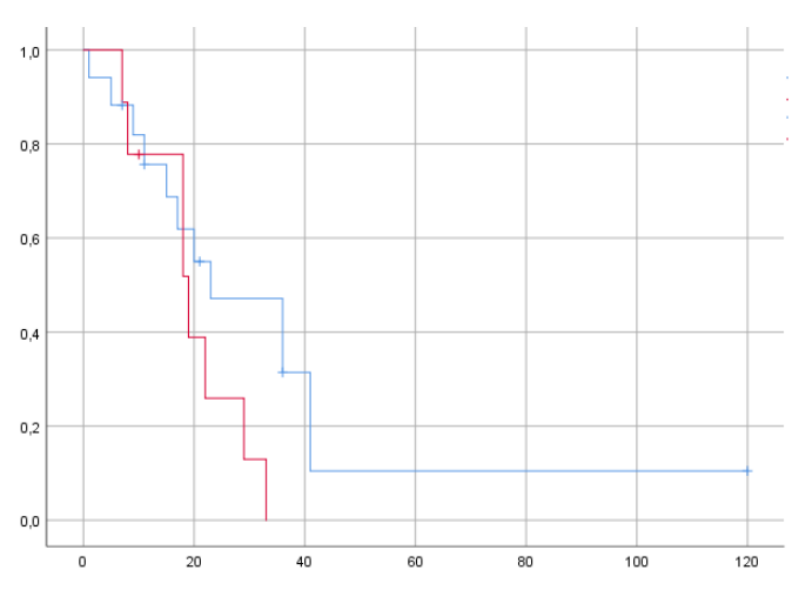

Figure 5: *Overall survival in patients with (red line) and without (blue line) sarcopenia (in months).*

Univariate analysis using Cox regression revealed that staging is associated with lower overall survival (p = 0.033) (Table 7).

	Analyse univariada	
	P-value	**HR**
Age	0,725	1,006 (0,974-1,038)
Gender	0,812	0,836 (0,192-3,652)
Location	0,065	0,633 (0,389-1,029)
Histological type	0,810	0,96 (0,365-2,196)
Neoadjuvant treatment	0,765	1,186 (0,387-3,633)
T	0,085	2,303 (0,892-5,946)
N	0,121	1,526 (0,894-2,603)
Histological grade	0,897	0,963 (0,542-1,712)
Staging	0,033	1,595 (1,039-2,449)
Stage	0,309	1,815 (0,576-5,718)
Sarcopenia	0,124	2,184 (0,808-5,904)

Table 7: *Univariate Cox regression for overall survival.*

Multivariate Cox regression was not performed, as only staging obtained significant results in univariate Cox regression.

Discussion

Despite advances in therapeutic strategies, patients with Esophageal cancer globally maintain a poor prognosis [1]. The advanced stage at the time of diagnosis and the severe malnutrition characteristic of these patients contribute to the high mortality rate [11]. Thus, the identification of factors that negatively influence survival becomes essential. There has been a growing interest in evaluating the influence of sarcopenia as a predictor of shorter survival, both disease-free and global [1,12].

Sarcopenia has a multifactorial etiology, which includes physical inactivity, systemic inflammation and inadequate protein intake [13]. All these factors are prevalent in patients with EC, with sarcopenia being reported in 16-79% patients [12].

The presence of lymph node metastasis is very frequent in the EC and negatively contributes to patient survival, being associated with greater tumor invasion with potential distant metastasis [14]. The study by Rice., *et al*. suggests that the presence of lymph node involvement is associated with locally more invasive and less differentiated tumors [15]. Node metastasis is estimated to decrease 5-year survival from 63% to 30% when compared to patients without nodal involvement [16]. Given the frequency of lymph node involvement at the time of diagnosis, and considering that this variable confers a worse prognosis, it is pertinent to assess the influence that sarcopenia may have on the survival of these patients. Thus, in this study, which includes patients with a histological diagnosis of adenocarcinoma or squamous cell carcinoma with lymph node metastasis undergoing surgical resection, it was decided to analyze the impact of sarcopenia on survival.

In the sample, the mean age was approximately 64 years, with the majority of patients being male (88.9%). These data are consistent with the literature that states that EC is more frequent in the 6th decade of life, with a predominance of males [1,5].

Most tumors were located in the lower esophagus (30.8%) and in Cardia I (30.8%), with the majority (57.7%) being adenocarcinomas. Literature data suggest that currently the most frequent histological type worldwide is the epidermoid, however adenocarcinoma is the most frequent histological type in developed countries, including Europe [17,18].

Sarcopenia was present in 34.6% of patients. Patients with sarcopenia had a mean muscle area of 151.44 cm^2 (28,38) and SMI values with a median of 54.94 cm^2/m^2, values significantly lower ($p < 0,001$) than patients without sarcopenia. Literature data support the existence of these significant differences in both variables [19]. These findings were expected since these values allow us to distinguish between patients with and without sarcopenia.

Disease-free survival time was shorter in sarcopenic patients (median 17 months). However, there were no significant differences between groups with and without sarcopenia ($p = 0.175$). Univariate analysis did not obtain statistically significant results. Sarcopenia was included in the analysis and was not shown to be an independent predictor of lower disease-free survival. Some studies suggest that sarcopenia is related to a lower disease free survival, however data in the literature are inconsistent. A study by Siegal., *et al*. concluded that sarcopenia is associated with higher mortality and lower disease free survival in patients undergoing surgical resection [20]. However, some studies conclude that there is no association [21].

Regarding overall survival, the group with sarcopenia had a lower survival (median of 19 months), however, there were no significant differences between the two groups. Although there were no significant differences in overall survival between the two groups, a Cox regression was also performed to analyze the effect of sarcopenia on overall survival. Staging has been shown to be associated with lower overall survival in patients with nodal metastases. Sarcopenia did not prove to be an independent predictor of lower overall survival. If on the one hand there are studies that revealed no significant differences in overall survival, others found the existence of a lower overall survival. Some data in the literature confirm that sarcopenia is not an independent predictor of survival. A study performed in patients undergoing surgical resection concluded that sarcopenia is an independent predictor of lower OS ($HR = 1.58$; $p < 0.001$) and lower SLD

(HR = 1.46; p = 0.005) [22]. On the other hand, one study found that sarcopenia is not significantly associated with a worse prognosis or worse DFS or OS [23].

In a study that correlates sarcopenia and lymph node involvement, it was concluded that both predict a worse prognosis and a lower OS [24]. In contrast, a study by Harada., *et al*. demonstrates that although sarcopenia significantly reduces OS in patients without lymph node involvement (log rank = 0.035), the same is not true in patients with lymph node metastasis (log rank = 0.31) [25].

It is important to emphasize that this study has several limitations. First, a larger sample size could have contributed to the existence of a statistically relevant group analysis. Second, the fact that this study was retrospective limited access to relevant clinical information, which may influence the interpretation of the results. Another limitation is the fact that sarcopenia was measured based on muscle mass, although the assessment of muscle function is recommended, and on the other hand the SMI value obtained for each patient may have been influenced by the estimation of heights used in some patients, due to lack of information in the clinical file. The lack of consensus on the diagnostic method for sarcopenia and on cut-off values is also a limitation. Even so, the studies found in the literature that analyzed the influence of sarcopenia in the EC used the same approach [10,26]. Finally, the literature on this topic is scarce, which made it difficult to analyze and compare the results.

Conclusion

Sarcopenia has been the target of numerous studies that seek to assess its impact on cancer disease. However, the influence of the presence of sarcopenia on disease free survival and overall survival remains to be elucidated. The fact that sarcopenia is a possible predictor of poor prognosis makes it an interesting factor to be researched and implemented in clinical practice, in the preoperative evaluation.

The presence of sarcopenia was not found to be a significant predictor of lower disease-free survival or lower overall survival in patients with esophageal cancer lymph node metastases.

In order to overcome the limitations found in the present study, it would be advantageous to carry out a study with a larger and more homogeneous sample in order to be able to analyze similar groups. It would also be essential to include functional assessment for a rigorous and more accurate diagnosis of sarcopenia. The scarcity of studies in patients with esophageal cancer lymph node metastases makes it essential to carry out further investigations in order to understand the true impact of loss of muscle mass and strength on the prognosis.

Conflict of Interest

The researchers declare that there is no conflict of interest in carrying out this study.

Bibliography

1. Gupta Bhawna and Narinder Kumar. "Worldwide incidence, mortality and time trends for cancer of the oesophagus". *European Journal of Cancer Prevention: The Official Journal of the European Cancer Prevention Organisation (ECP)* 26.2 (2017): 107-118.

2. Deng Han-Yu., *et al*. "Preoperative sarcopenia is a predictor of poor prognosis of esophageal cancer after esophagectomy: a comprehensive systematic review and meta-analysis". *Diseases of the Esophagus: Official Journal of the International Society for Diseases of the Esophagus* 32.3 (2019): doy115.

3. Global Burden of Disease Cancer Collaboration., *et al.* "The Global Burden of Cancer 2013". *JAMA Oncology* 1.4 (2015): 505-527.

4. Launoy Guy., *et al*. "Trends in net survival from esophageal cancer in six European Latin countries: results from the SUDCAN population-based study*". European Journal of Cancer Prevention: the Official Journal of the European Cancer Prevention Organisation (ECP) Trends in cancer net survival in six European Latin Countries: the SUDCAN study* 26 (2017): S24-S31.

5. Quint LE., *et al*. "Incidence and distribution of distant metastases from newly diagnosed esophageal carcinoma". *Cancer* 76.7 (1995): 1120-1125.

6. Ryan Aoife M., *et al*. "Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later". *The Proceedings of the Nutrition Society* 75.2 (2016): 199-211.

7. Abellan Van Kan G. "Epidemiology and consequences of sarcopenia". *The Journal of Nutrition, Health and Aging* 13.8 (2009): 708-712.

8. Cruz-Jentoft Alfonso J., *et al*. "Sarcopenia: revised European consensus on definition and diagnosis". *Age and Ageing* 48.4 (2019): 601.

9. Boshier PR., *et al*. "Assessment of body composition and sarcopenia in patients with esophageal cancer: a systematic review and meta-analysis". *Diseases of the Esophagus: Official Journal of the International Society for Diseases of the Esophagus* 31.8 (2018).

10. Prado Carla M M., *et al*. "Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study". *The Lancet* Oncology 9.7 (2008): 629-635.

11. Bray Freddie., *et al*. "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries". *CA: A Cancer Journal for Clinicians* 68.6 (2018): 394-424.

12. Ferlay Jacques., *et al*. "Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012". *International Journal of Cancer* 136.5 (2015): E359-386.

13. Ferlay Jacques., *et al*. "Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008". *International Journal of Cancer* 127.12 (2010): 2893-2917.

14. Plukker JThM and HL Van Westreenen. "Staging in Eoesophageal cancer". *Best Practice and Research Clinical Gastroenterology* 20.5 (2006): 877-891.

15. Rice Thomas W., *et al*. "Esophageal Cancer: Associations With (pN+) Lymph Node Metastases". *Annals of Surgery* 265.1 (2017): 122-129.

16. Vendrely Véronique., *et al*. "Prognostic factors in esophageal cancer treated with curative intent". *Digestive and Liver Disease: Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 50.10 (2018): 991-996.

17. Betancourt-Cuellar Sonia L., *et al*. "Esophageal Cancer: Tumor-Node-Metastasis Staging". *Radiologic Clinics of North America* 59.2 (2021): 219-229.

18. Short Matthew W., *et al*. "Esophageal Cancer". *American Family Physician* 95.1 (2017): 22-28.

19. Torre Lindsey A., *et al*. "Global cancer statistics, 2012". *CA: A Cancer Journal for Clinicians* 65.2 (2015): 87-108.

20. Siegal Steve R., *et al*. "Sarcopenia is not associated with morbidity, mortality, or recurrence after esophagectomy for cancer". *American Journal of Surgery* 215.5 (2018): 813-817.

21. Grotenhuis Brechtje A., *et al*. "Sarcopenia/Muscle Mass is not a Prognostic Factor for Short- and Long-Term Outcome After Esophagectomy for Cancer". *World Journal of Surgery* 40.11 (2016): 2698-2704.

22. Deng Han-Yu., *et al*. "Preoperative sarcopenia is a predictor of poor prognosis of esophageal cancer after esophagectomy: a comprehensive systematic review and meta-analysis". *Diseases of the Esophagus: Official Journal of the International Society for Diseases of the Esophagus* 32.3 (2019): doy115.

23. Oguma J., *et al*. "Prognostic significance of sarcopenia in patients undergoing esophagectomy for superficial esophageal squamous cell carcinoma". *Diseases of the Esophagus: Official Journal of the International Society for Diseases of the Esophagus* 32.7 (2019): doy104.

24. Harada K., *et al*. "Prognostic and clinical impact of sarcopenia in esophageal squamous cell carcinoma". *Diseases of the Esophagus: Official Journal of the International Society for Diseases of the Esophagus* 29.6 (2016): 627-633.

25. Işık A., *et al*. "Idiopathic Periportal Lymphadenopathy". *Gazi Medical Journal* (2016).

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