

## ORIGINAL

## Staging and survival in esophageal cancer

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### ABSTRACT

**Background:** Esophageal cancer worldwide is the eighth and sixth most common cancer in terms of incidence and mortality, respectively. Early diagnosis and clinical staging of the tumor, followed by standard treatment and the surgeon's experience, are essential for better patient survival. **Objective:** The objective of this study was to evaluate the staging and survival of patients with esophageal cancer undergoing treatment in a low-volume hospital. **Patients and Methods:** A retrospective, hospital-based study was conducted to analyze survival, clinical staging and post-operative death rates. Survival analysis was performed using the Kaplan-Meier method and log-Rank test with 5% significant level. **Results:** Ninety-nine cases of squamous cell carcinoma of the esophagus were analyzed: 77 males (77.8%) and 22 females (22.2%). Most of the patients (68; 68.7%) were above 55 years of age. The standard treatment for esophageal cancer at the time of the study was surgical: esophagectomy with lymphadenectomy. Thirty-seven patients (37.4%) were submitted to surgical curative treatment and 62 (62.6%) to palliative care. For patients at initial stages of the disease, overall 1-year survival was 39%, with rates of 23% at 2 years and 17% in the third year. For advanced stages, survival ranged from 26.9% in the first year to 12.4% in the second year and 6.4% in the third year. **Conclusion:** Survival in patients with esophageal cancer was better in the initial stages in comparison with advanced stages.

**Keywords:** esophageal neoplasms, neoplasm staging, palliative care, surgery, survival.

### INTRODUCTION

Esophageal cancer is currently the eighth most common malignancy in the population worldwide and sixth in terms of mortality. Around 579,554 new cases of esophageal cancer and 489,123 deaths resulting from this type of cancer are predicted for 2015 in men and women worldwide<sup>1</sup>. Esophageal cancer is the third most common malignancy of the digestive tract, surpassed only by stomach and colorectal cancer<sup>2</sup>. In Latin America, low incidence and mortality rates are found in Mexico and Peru; however, rates in Brazil, Argentina, Chile, Uruguay and Puerto Rico are high<sup>3</sup>.

Esophageal cancer has a heterogeneous distribution throughout the world. It is considered a rare disease in industrialized and developed countries, with the exception

of Japan<sup>4</sup>. In countries where the incidence is high, such as China (73.2/100,000)<sup>5</sup> and Japan (20.5/100,000)<sup>6</sup>, cases are diagnosed starting from 30 years of age and the frequency increases with the patient's age. In Brazil, incidence rates range from 1-14/100,000, with higher rates in the south of the country (9-14/100,000), intermediate rates in the midwest and northeast (4-9/100,000) and lower rates in the north (1-2/100,000)<sup>7</sup>. As in the Asian countries, cases here also occur starting from 30 years of age<sup>5,6</sup>.

In Goiânia, incidence and mortality coefficients for esophageal cancer in 2003 were 8.4/100,000 and 6.4/100,000, respectively<sup>8</sup>.

The principal causative agents of esophageal cancer are alcohol, tobacco, fungal toxins, nutritional deficiencies, food, hot drinks, chemical carcinogens, occupational exposure and infectious agents. The most noteworthy of the infectious agents is the human papilloma virus (HPV), particularly HPV 16, 18 and 59 genotypes<sup>3</sup>.

Despite all the efforts made to control the incidence and mortality rates associated with this neoplasm through improvements in resources used for early diagnosis, advanced treatment techniques, awareness campaigns aimed at improving quality of life in populations, good nutritional habits, reduction in poverty levels, systematic anti-smoking campaigns and alcohol awareness campaigns, these rates are still expected to increase worldwide<sup>3-9</sup>.

The possibility of cure for the patient with esophageal cancer lies in early diagnosis and adequate preoperative staging followed by curative treatment. Radiotherapy

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and chemotherapy are modalities used in neoadjuvant and adjuvant treatment and in the case of unresectable lesions or even for dysphagia control in a palliative fashion<sup>10-13</sup>.

Currently, in Asia, the standard treatment for resectable esophageal cancer is chemotherapy followed by surgery. In the West, the treatment of choice is chemoradiotherapy and surgery, a combination that results in overall 5-year survival rates of up to 60%<sup>1,14</sup>. Previous to the advent of this multimodal treatment of esophageal cancer, overall survival ranged from 30-40%<sup>14</sup>.

There are several survival studies regarding esophageal cancer in high-volume hospitals, however, there is a lack of such studies in low-volume hospitals except for a lone study showing that survival in low-volume hospitals is lower than in high-volume ones due to several reasons, such as poor staff experience, inadequate staging of the patients and postoperative care<sup>10</sup>.

The aim of this study was to evaluate survival in relation to clinical staging in patients treated for squamous cell carcinoma of the esophagus in Araújo Jorge Hospital, a low-volume tertiary cancer hospital in the midwest region of Brazil.

## MATERIAL AND METHODS

This study is part of an international multicenter study organized by the International Agency for Research on Cancer (IARC) based in Lyon, France. The study was initiated in August 1998 and closed in June 2003.

### Study design

A hospital-based, retrospective study was conducted in which data referring to survival were taken from the charts of patients with esophageal cancer enrolled at the IARC Protocol Study and who were enrolled at Department of Digestive Tract Diseases at Araújo Jorge Hospital, Goiás Association for the Combat of Cancer (HAJ/ACCG), and who were receiving care at this institute between August 1998 and June 2003. All patients had histological confirmation of a squamous cell carcinoma of the esophagus.

The variables analyzed were: age at diagnosis, gender and clinical staging. Curative surgical treatment was done in initial staging and palliative care in advanced staging. The patient's vital status at 12, 24 and 36 months after treatment were also noted.

### Statistical analysis

The characteristics of the study population were described using absolute and relative frequencies, and associations were verified using the chi-square test.

In the survival analysis, passive and active surveys were made, the objective of the survival analysis being to evaluate the patient's vital status (alive/dead or lost to follow-up). Multiple techniques were used in the active survey to reduce the need to censor cases.

The use of multiple sources to obtain the follow-up data for the survival analysis is referred to as mixed or excluding follow-up and the results obtained are referred to as conservative<sup>15,16</sup>.

Survival analysis was performed using the SPSS® software program for Windows, version 18.0 to calculate survival using the Kaplan-Meier method for the gender, staging and treatment type, and the log-rank test with 5% significance level and CI of 95%.

### Ethical Aspects

This study was submitted to the Internal Review Board of the Teaching Hospital, Federal University of Goiás and approved under reference number 120/2011. In addition, it had been previously approved by the Internal Review Board of the Goiás Association for the Combat of Cancer (ACCG) as a subproject within a larger original study on June 30, 1998.

## RESULTS

Ninety-nine cases of squamous cell carcinoma of the esophagus were analyzed: 77 in men (77.8%) and 22 in women (22.2%). The majority of patients (68; 68.7%) were over 55 years of age. With respect to clinical staging, 46.4% were at initial stages of the disease, while 53 (53.5%) were at advanced stages. Of the patients with advanced stages of the disease, 38 (71.6%) were male and 15 (28.3%) female. Regarding vital status at the time of data analysis, 85 (85.8%) of the patients had died, 10 (10.1%) were still alive and 4 (4.0%) had been lost to follow-up. The recommended curative treatment for esophageal cancer at this time was esophagectomy with lymphadenectomy. Thirty-seven patients (37.4%) were submitted to radical treatment and 62 (62.6%) to palliative care (Table 1).

**Table 1.** Distribution of cases of esophageal cancer.

Variable	n	%
Gender		
Male	77	77.8
Female	22	22.2
Clinical stage		
I and II	46	46.4
III	27	27.2
IV	26	26.3
Treatment		
Surgical	37	37.4
Palliative	62	62.6
Vital Status		
Deceased	85	85.8
Alive	10	10.1
Lost to follow-up	4	4.0

Of the cases treated with curative surgery, five patients (13.5%) died postoperatively, i.e. in the 30 days following surgery, whereas of the patients who received palliative care, 15 (24.2%) died within 30 days. There was no statistically significant difference in this respect between the two groups ( $p = 0.325$ ; 95% CI: 1.30 [0.89-1.42]) (Table 2).

**Table 2.** Comparison of postoperative death and palliative care in cases of esophageal cancer.

Treatment	Death within 30 days*				<i>p</i> -value	95% CI
	Postoperative		Late			
	N	%	N	%		
Surgical	5	13.5	24	64.9		
Palliative	15	24.2	41	66.1	0.325	1.30 (0.89-1.42)

\* Excluding patients still alive and those lost to follow-up.

Overall 1-year survival in the cases of esophageal cancer included in the present study was 32.7%, with survival rates being higher in the group of women compared to the men (36.4% versus 31.5%), higher in clinical stages I and II (39.1%; 95% CI: 0.72 [2.25-11.74]) compared to stages III and IV (26.9%; 95% CI: 0.06 [2.29-7.70]) ( $p = 0.85$ ), and higher in cases submitted to curative surgery (47.5%; 95% CI: 0.8 [6.12-9.20]) compared to those submitted to palliative care (23.7; 95% CI: 0.05 [4.55-6.81]) ( $p = 0.02$ ) (Table 3).

Overall 2-year survival was 16.4% for men and 22.7% for women and there was no statistically significant difference between these two groups in this respect ( $p = 0.72$ ; 95% CI: 0.06 [7.12-11.09] versus 95% CI: 0.04 [5.74-13.46]). For patients in whom the disease was at the initial stages (I and II), 2-year survival was 23.9% (95% CI: 0.06 [7.30-12.94]) compared to 12.4% (95% CI: 0.04 [6.26-10.69]) for those at advanced stages (III and IV) ( $p = 0.35$ ). Curative treatment resulted in an overall survival rate of 25.2% (95% CI: 8.45-14.43) compared to 12.4% for cases treated with palliative care (95% CI: 5.76-10.00) ( $p = 0.07$ ) (Table 4).

Overall 3-year survival was 11.0%, with a higher survival rate in women (a mean of 11.33 months) compared to men (a mean of 10.75 months) ( $p = 0.85$ ) (95% CI: 6.18-16.45 versus 95% CI: 8.05-13.45), respectively. In patients submitted to curative treatment, overall 3-year

survival rate was 19.60% compared to 6.30% for those treated with palliative care ( $p = 0.04$ ) (95% CI: 5.14-14.86 versus 2.34-5.65). No statistically significant difference was found in overall 3-year survival rates between the different clinical stages irrespective of gender ( $p = 0.063$ ). In stages I and II, overall survival was 23.9% with a standard error of 0.06 and 95% CI: 7.30-12.94 (Table 5, Figures 1, 2 and 3).

Hazard ratio (HR) with respect to death at 1, 2 and 3 years for patients at the initial stages of the disease was 1.5, 1.5 and 2.2, respectively, whereas for the advanced stages, HR was 1.7, 2.4 and 3.5. Comparing the forms of treatment (curative treatment vs. palliative care), the risk of death was 0.7 at 12 months, 1.7 at 24 months and 1.9 at 36 months in the case of curative surgery compared to 1.5 at 12 months, 1.6 at 24 months and 2.5 at 36 months for palliative care. These analyses show the increase in risk over time since diagnosis (Table 6). The patients submitted to palliative care are generally those patients with more advanced tumors and for this reason the risk of death was greater.

## DISCUSSION

The incidence of esophageal cancer varies greatly, even within a single country, as a function of exposure and the genetic susceptibility of individuals to different lifestyles<sup>17</sup>. Incidence rates in Brazil are heterogeneous and cases are generally diagnosed at advanced clinical stages when a curative treatment represents a challenge to the oncologist. Substantial progress has been made in the diagnosis and treatment options for esophageal cancer over the past 20-30 years. This includes the improvement and modernization of endoscopic techniques and the use of specific staining, imaging methods that permit more accurate clinical staging of this type of tumor and principally the implementation of the multimodal treatment approach. Multimodal management began with the work conducted by Roth et al. in 1988 and continues today with the use of neoadjuvant and adjuvant treatment with chemotherapy and/or radiochemotherapy followed by surgery with lymphadenectomy, sometimes with three-field dissection. All these advances have contributed towards a considerable improvement in the survival of patients with esophageal cancer<sup>13,18,19</sup>.

**Table 3.** Overall 1-year survival for patients with esophageal cancer.

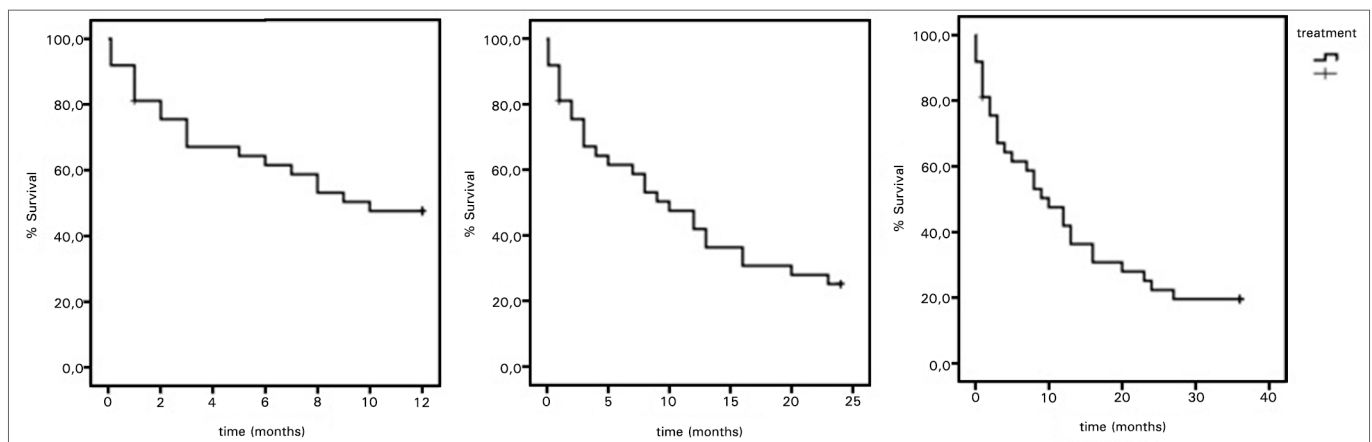
Factor	Mean (months)	Events (deaths)	Survival rate (%)	Standard error	<i>p</i> (log rank)	95% CI	
Gender	Male	6.38	51	31.5	0.05	0.9	3.56-8.44
	Female	6.56	14	36.4	0.10		0.6-11.36
Clinical stage	I and II	6.58	28	39.1	0.72	0.85	2.25-11.74
	III and IV	6.36	36	26.9	0.06		2.29-7.70
Treatment	Surgery	7.66	19	47.5	0.8	0.02	6.12-9.20
	Palliative	5.68	46	23.7	0.05		4.55-6.81

**Table 4.** Overall 2-year survival for patients with esophageal cancer.

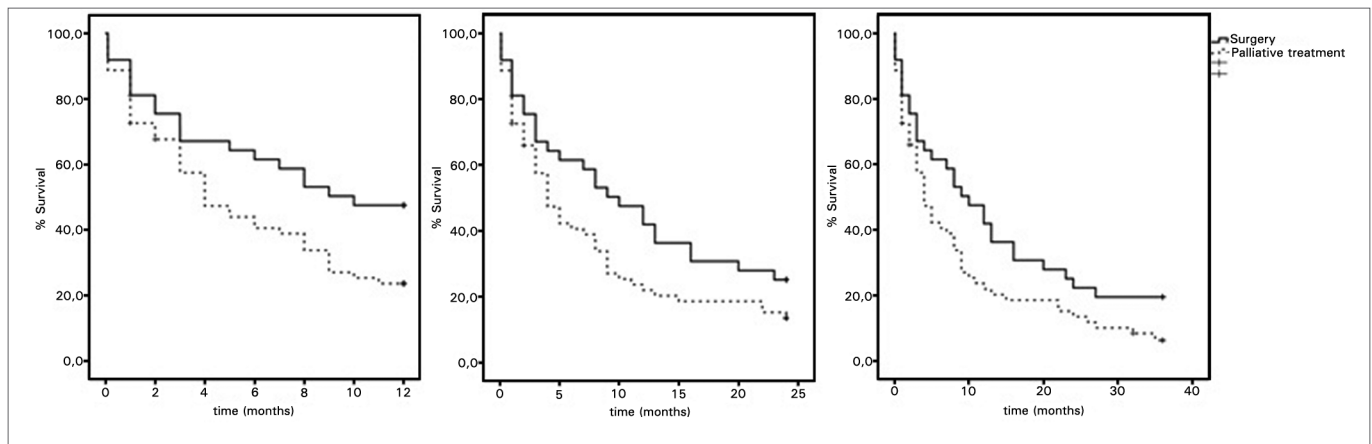
Factor		Mean (months)	Events (deaths)	Survival rate (%)	Standard error	p (log rank)	95% CI
Gender	Male	9.10	62	16.4	1.01	0.72	7.1-11.09
	Female	9.60	17	22.7	1.97		5.74-13.46
Clinical stage	I and II	10.12	35	23.9	0.06	0.35	7.30-12.94
	III and IV	8.48	43	12.4	0.04		6.26-10.69
Treatment	Surgery	11.44	27	25.2	1.52	0.07	8.45-14.43
	Palliative	7.88	52	13.5	1.08		5.76-10.00

**Table 5.** Overall 3-year survival for patients with esophageal cancer.

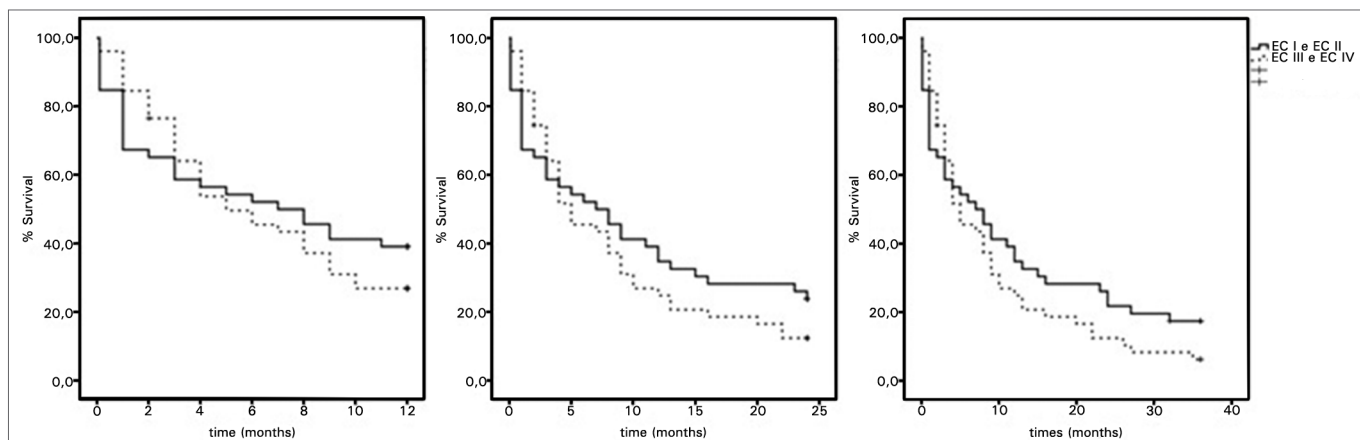
Factor		Mean (months)	Events (Deaths)	Survival rate (%)	Standard error	p (log rank)	95% CI
Gender	Male	10.75	66	10.8	1.37	0.85	8.05-13.45
	Female	11.33	19	13.6	2.62		6.18-16.48
Clinical stage	I and II	12.45	38	17.4	0.05	0.27	8.60-16.30
	III and IV	9.55	46	6.2	0.03		6.66-12.44
Treatment	Surgery	13.87	29	19.6	2.48	0.04	5.14-14.86
	Palliative	9.09	56	6.3	0.84		2.34-5.65



**Figure 1.** 1-, 2- and 3-year survival of patients with esophageal cancer treated with curative surgery.



**Figure 2.** 1-, 2- and 3-year survival in patients with esophageal cancer according to type of treatment.



**Figure 3.** 1-, 2- and 3-year survival in patients with esophageal cancer according to clinical stage.

**Table 6.** Analysis of hazard ratio at 1, 2 and 3 years for patients with esophageal cancer according to the type of treatment and clinical stage of the disease.

Variable	Survival Rate (%)		HR	p-value
	Men	Women		
<b>Curative treatment</b>				
1-year survival	48.4	45.5	0.7	0.74
2-year survival	20.1	36.4	1.7	0.89
3-year survival	16.1	27.3	1.9	0.91
<b>Palliative care</b>				
1-year survival	22.8	27.3	1.5	0.89
2-year survival	14.5	9.1	1.6	0.78
3-year survival	7.8	0	2.5	0.73
<b>Clinical stages I and II</b>				
1-year survival	42.1	0.25	1.5	0.39
2-year survival	23.7	25	1.5	0.53
3-year survival	18.4	12.5	2.2	0.46
<b>Clinical stages III and IV</b>				
1-year survival	19.9	46.2	1.7	0.27
2-year survival	8.5	23.1	2.4	0.33
3-year survival	2.8	15.4	3.5	0.32

HR: Hazard Ratio.

Surgical resection is the treatment of choice for initial stage esophageal cancer. Nevertheless, only 40-50% of patients are eligible for this treatment. In the present study, the disease was in its initial stages in only 26.7% of patients (46 cases) and this finding is in agreement with reports from a series of studies conducted in Asia<sup>14-16</sup>.

Neoadjuvant therapy, first described by Roth et al.<sup>19</sup> at the end of the 1980s, is a relatively new form of curative treatment for esophageal cancer. For a long time it was restricted to only a few service providers because of the major complications resulting from the treatment; however, it has come to be more widely adopted in the past decade and has been received with greater enthusiasm.

Nevertheless, if partial or complete response of the lesion is not achieved with this form of treatment, the patient may miss out on the possibility of being submitted to curative surgical treatment<sup>13</sup>. Five-year survival rates for esophageal cancer were between 30% and 50%<sup>13</sup>. With the multimodal form of therapy adopted over the past two decades, this survival has increased to around 60% at five years<sup>13,18</sup>.

In the patients in this study who were submitted to surgical treatment, postoperative death occurred in 13.5% of cases. This finding is in agreement with data published by the Harvard School of Public Health in a study on the surgical treatment of esophageal cancer in which the postoperative mortality rate was 12.5% in US hospitals that were considered to have a low volume of surgery. For the purpose of that analysis, hospitals were considered to be low volume if they performed fewer than 13 esophagectomies annually<sup>10</sup>. On the other hand, in high-volume hospitals, postoperative mortality was around 5%<sup>19-21</sup>, as reported in a study conducted in China by Yang et al.<sup>21</sup> in which these investigators reported a postoperative mortality rate of 5.9% in patients over 70 years of age submitted to curative surgical treatment of esophageal cancer in a high-volume hospital.

In the present study, loss to follow-up at the end of evaluation was limited to four patients, representing 4% of the total sample.

Overall 2- and 3-year survival rates were 25.2% and 19.6%, respectively, poorer than those reported in the literature during the same period in low-volume hospitals. These poor percentages are principally due to the fact that multimodal treatment for esophageal cancer, which consists predominantly of chemotherapy or neoadjuvant or adjuvant chemoradiotherapy, was not used. When this study was conducted, multimodal treatment was not yet part of the protocols implemented in this institute.

At the beginning of this millennium, multimodal management was implemented as part of the treatment of esophageal cancer in Japan, Korea, China and in the United States, a practice that rapidly led to an improvement in 2- and 5-year survival rates in patients submitted



to staging and selected for neoadjuvant treatment with chemotherapy or radiochemotherapy compared to those submitted to surgery alone<sup>13,21-23</sup>.

In this study, curative surgery at clinical stages I and II (initial stages) resulted in overall 2- and 3-year survival rates of 23.9% and 17.4%, respectively. In patients with clinical staging III and IV (advanced stages), overall 2- and 3-year survival was 12.4% and 6.2%. This study is restricted to patients who were classified as stage III preoperatively but who progressed to stage IVa following surgery when lymph node involvement was detected.

The results of this study show no statistically significant difference in overall 2- and 3-year survival between patients at initial stages of the disease and those at advanced stages.

Studies conducted by Yu et al.<sup>17</sup> showed that surgical treatment alone led to high recurrence rates (37-40%) in three years, reflected in a reduction in the survival rate of these patients<sup>19,24</sup>.

In 2000, the University of New York<sup>25,26</sup> published the results of the treatment of esophageal cancer in the United States and the survival rates in the patients. Around 800 hospitals with low and high volumes of surgery were included in that study, which involved more than 3,000 patients. Survival in the first year of this malignancy ranged from 70% at stage I to 18% at stage IV. In the current study, patient survival ranged from 39% to 17%, lower than the rates found in the literature.

Esophageal cancer is rare in this institute and our experience is minor compared to that accumulated with other solid tumors; nevertheless, postoperative mortality was similar to that reported by large centers. A limitation of this study was that it failed to evaluate relevant data that could have interfered with survival such as body mass index, comorbidities and risk factors such as smoking and alcohol consumption.

In conclusion, these findings show that being at an initial clinical stage is a factor predictive of better survival in patients with esophageal cancer. Survival was better in female patients, despite the fact that the majority of women were at advanced stages (13 vs. 8) compared to around 50% of the men in the study (38 vs. 39). The factors that led to better survival in the women in the study merit further investigation.

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