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ESOPHAGOGASTRIC JUNCTION ADENOCARCINOMA: MULTIVARIATE ANALYSES OF SURGICAL MORBI-MORTALITY AND ADJUVANT THERAPY

Adenocarcinoma da transição esofagogástrica: análise multivariada da morbimortalidade cirúrgica e terapia adjuvante

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ABSTRACT - ***Background*** - In recent years the literature has recorded a progressive increase in the prevalence of adenocarcinoma of the esophagogastric junction. Several factors can interfere with the morbidity and mortality of surgical treatment. ***Aim*** - Non-randomized retrospective study of prognostic factors of operated patients by adenocarcinoma of esophagogastric junction, with or without post-operative chemotherapy and radiotherapy. ***Methods*** - Medical records were reviewed from patients treated at university hospital in the period of 1989 and 2009, to obtain data about pre and postoperative treatment. Cox's univariate and multivariate regression analysis of risk factors for prognostic of these patients were done with level of significance of 5 %. ***Results*** - Were reviewed 103 patients distributed as: 1) 78 (75.7%) patients without adjuvant therapy, and 2) 25 (24.3%) with it. All patients underwent surgical resection with curative intent. Cox's multivariate regression analysis of all patients showed that: lymphnode invasion N2 had greater risk of death in 5.9 times; broncopneumonia, in 11.4 times; tumoral recurrence during clinical following greater in 3.8 times. ***Conclusion*** - Tumoral recurrence, lymphnode metastasis and broncopneumonia in the postoperative period were factors of bad prognosis and contributed significantly to increase morbimortality and decrease global survival.

HEADINGS – Esophagogastric junction. Adenocarcinoma. Surgery. Chemotherapy. Radiotherapy.

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RESUMO - ***Racional*** - Nos últimos anos a literatura tem registrado aumento progressivo da prevalência do adenocarcinoma da transição esofagogástrica. Vários fatores podem interferir na morbimortalidade do tratamento cirúrgico. ***Objetivo*** - Estudo retrospectivo não-randomizado dos fatores prognósticos dos pacientes operados por adenocarcinoma da transição esofagogástrica, com ou sem quimio e radioterapia pós-operatórias. ***Métodos*** - Foram revistos os prontuários dos pacientes tratados em hospital universitário no período de 1989 a 2009, para obtenção de informações referente ao pré e pós-operatório. Análises de regressão univariada e multivariada de Cox dos fatores de risco para o prognóstico destes pacientes foram realizadas com nível de significância de 5 %. ***Resultados*** - Foram incluídos 103 pacientes assim distribuídos: 1) 78 (75,7%) não submetidos ao tratamento adjuvante, e 2) 25 (24,3%) submetidos a ele. Todos os pacientes foram operados com intenção curativa (esofagectomia e/ou gastrectomia). A análise multivariada de toda a casuística mostrou a influência dos seguintes fatores na sobrevida: invasão linfonodal, pacientes com N2 tiveram risco de óbito 3,4 vezes maior que os com N0; com N3, 5,9 vezes maior; com broncopneumonia, 11,4 vezes maior; com recidiva tumoral durante o seguimento clínico 3,8 vezes maior. ***Conclusão*** - A recidiva tumoral, metástase linfonodal e broncopneumonia no pós-operatório foram fatores de piora no prognóstico, contribuindo significativamente para elevar a morbimortalidade e diminuindo a sobrevida global.

DESCRITORES - Junção esofagogástrica. Adenocarcinoma. Cirurgia. Quimioterapia. Radioterapia.

INTRODUCTION

Esophageal cancer is the eighth most common tumor, with 481,000 new cases in 2008 (3.8% of all cancer cases), and the sixth most common tumor as a cause of death with 406,000 deaths worldwide (5.4% of total)[6]. In Brazil, the estimates from the National Cancer Institute for 2010 would be of 7,890 new cases in men and 2,740 in women, totaling 10,630 new cases annually, and being considered the eighth most frequent type of cancer among Brazilians[15].

Adenocarcinoma in the distal esophagus arises from the intestinal metaplasia of the epithelium (Barrett's), being secondary to chronic gastroesophageal reflux[26]. There is a strong link between its incidence and obesity (IMC > 30 kg/m2)[16]. This neoplasia develops in the dysplastic columnar epithelium, especially at the esophagogastric/cardia junction. It is also associated with white males[9]. The muco-epidermoid and the adenoid cystic are among the rare variants of adenocarcinomas[19].

Adenocarcinomas of the esophagogastric junction are tumors that have their center within 5.0 cm proximal or distal from the cardia. From the endoscopic point of view, "endoscopic cardia" is the typical definition of the longitudinal folds of the gastric mucosa upper limit, rather than the Z line. This is a relevant reference point for the endoscopic classification[21]. Siewert et al.[20,22], described three different tumoral entities within the esophagogastric junction: a) type I esophagogastric adenocarcinoma: adenocarcinoma of the distal esophagus, which usually originates from an area of specialized intestinal metaplasia of the esophagus, that is, the Barrett's esophagus, and it may infiltrate the esophagogastric junction located distally; b) type II esophagogastric adenocarcinoma: true carcinoma of the cardia, which originates from the cardial epithelium or from short segments of intestinal metaplasia in the esophagogastric transition; c) type III esophagogastric adenocarcinoma: the subcardial gastric carcinoma, with the ability to infiltrate the proximal esophagogastric junction.

In recent years, has been recorded in literature a progressive increase in the prevalence of esophageal adenocarcinoma in the west[3,4]. The esophagectomy is the recommended treatment for esophageal adenocarcinoma[11]. However, patients diagnosed with esophageal cancer have a poor prognosis; with a five-year survival rate, ranging from 5 to 20% of the patients eligible for surgical treatment[28]. Therefore, recently other strategies such as adjuvant chemotherapy and radiotherapy have been tried in the esophageal adenocarcinomas[12,13,24,25].

This paper describes the main features and compare the survival rate of patients with esophageal adenocarcinoma operated at UNICAMP University Hospital, in the period from 1989 to 2009, evaluating the demographics, the characteristics of treated tumors, the post-operatively symptoms and complications, in order to identify the deterioration factors in the survival rate of these patients.

METHODS

A review of medical records, according to the Siewert classification of all patients diagnosed with esophageal adenocarcinoma, who had surgery with curative intent from 1989 to 2009, resulting in age, sex, race, tumor location, staging and survival rate[20]. The inclusion criteria were patients with Siewert types I, II or III esophageal adenocarcinomas[20,21,22] who underwent radical surgery The exclusion comprised of patients who underwent incomplete resection and the perioperative deaths. The Faculty of Medical Sciences - Ethics Committee - UNICAMP approved the study.

The study comprised of 103 patients, with or without postoperative chemoradiotherapy. Surgical procedures for tumoral resection consisted of: subtotal esophagectomy, total gastrectomy and total esophagogastrectomy, depending on the tumoral location. The alimentary transit reconstruction consisted of: a) esophagogastroplasty with isoperistaltic gastric tube, implemented via transmediastinal with cervical esophagogastric anastomosis[18]; b) Roux-en-Y esophagojejunal anastomosis; and c) cervical esophagocoloplasty.

The tumor staging was performed by analyzing the descriptive pathologic report of the tumors, while being updated to the latest TNM classification published[23].

The adjuvant treatment regimen used was proposed by MacDonald et al.[12], in 25 patients.

The sample's profile, including the study variables was described in frequency tables of categorical variables, in absolute values (n), in percentage (%), and descriptive statistics (with measures of position and dispersion - mean, standard deviation, minimum, maximum, median and quartiles values) from the continuous variables[2].

The analysis of association between two categorical variables was performed using the chi-square or the Fisher exact test (for expected values lower than 5). With the absence of the Normal distribution of variables; the Mann-Whitney (for two groups) and the Kruskal-Wallis (for three or more groups) tests were employed to compare the numerical variables.

The evaluation of the main factors related to survival rate used the Cox regression analysis; univariate and multiple models with the stepwise

criterion for variable selection. The length of survival comparison used the Kaplan-Meier method and the log-rank test[10,27]. The Cox multivariate analyses was performed with the whole group (103 patients); without adjuvant (78 patients) and with adjuvant (25 patients). The level of significance for statistical tests was of 5% ($p<0.05$); using the SAS for Windows (Statistical Analysis System), version 9.1.3 software.

RESULTS

Tables 1 and 2 show the distribution by color, sex, origin and age.

TABLE 1 - Distribution by color, sex and origin of the total sample (n = 103). (MG=Minas Gerais; MS=Mato Grosso do Sul State; PR=Paraná State; SP=Sao Paulo State)

Race, Sex, Origin		Number of patients	
Race	White	93	90,29%
	Brown	7	6,8%
	Black	3	2,91%
Sex	Male	85	85,52%
	Female	18	17,48%
Origin State	MG	7	6,8%
	MS	1	0,97%
	PR	2	1,94%
	SP	93	90,29%

TABLE 2 - Distribution by age groups and the age descriptive data

Distribution by age groups		Number of patients	
Age (years)	30 – 39	6	5.83%
	40 – 49	18	17.48%
	50 – 59	32	31.07%
	60 – 69	36	34.95%
	≥ 70	11	10.68%
	Average	56.98	
	Standad deviation	10.28	
	Minimum	30.0	
	Median	58.0	
	Maximum	78.0	

It is observed prevalence of dysphagia, retroesternal pain followed by heartburn. Cigarette smoking and alcohol consumption was observed in 70.87% and 43.69%, respectively (Table 3).

TABLE 3 - The prevalence of symptoms, cigarette smoking and alcohol consumption

Prevalence of symptoms		Number of patients	
Dysphagia	Absent	30	29,13%
	Present	73	70,87%
Retrosternal pain	Absent	78	75,73%
	Present	25	24,27%
Heartburn	Absent	56	54,37%
	Present	47	45,63%
Gastrointestinal hemorrhage	Absent	89	86,41%
	Present	14	13,59%
Weight loss	Absent	34	33,01%
	Present	69	66,99%
Tabagism	Absent	30	29,13%
	Present	73	70,87%
Alcoholism	Absent	58	56,31%
	Present	45	43,69%

The tumor site in the classification of Siewert (7-9) was type I - 18.45% (n = 19), type II - 34.95% (n = 36) and type III - 46.60% (n = 48).

The techniques employed were esophagectomy surgical resection in transmediastinal 62.14% (n = 64), transthoracic esophagectomy in 1.94% (n = 2), in total gastrectomy in 32.04% (n = 33) and total esophagogastrectomy in 88% (n = 4).

Techniques for the reconstruction of alimentary tract were esophagogastroplasty in 63.11% (n = 65), Roux-en-Y esophagojejunal in 32.04% (n = 33) and esophagocoloplasty in 4.85% (n = 5).

The number of lymph nodes found in the resected surgical specimens were average of 19.41 (SD 14.65), zero minimum, maximum of 81 and median of 15.

During outpatient follow-up, tumor recurrence was recorded in 47.57% (n = 49) of patients.

The occurrence of postoperative complications and the number of late deaths during the follow-up are detailed in Table 4.

TABLE 4 - The prevalence of complications and late deaths

Postoperative complications / late deaths		Number of patients	
Anastomotic fistula	Absent	77	74,76%
	Present	26	25,24%
Stenosis of the anastomosis	Absent	66	64,08%
	Present	37	35,92%
Drainage of the thorax	Absent	58	56,31%
	Present	45	43,69%
Bronchopneumonia	Absent	92	89,32%
	Present	11	10,68%
Cardiologic (Arrhythmia)	Absent	102	99,03%
	Present	1	0,97%
Late deaths	Absent	67	65,05%
	Present	36	34,95%

The survival of patients was on average 31.98 months (standard deviation of 37.52) with minimum one month, maximum of 149 months and a median of 16 months.

Tables 5 and 6 present the results of the analysis of Cox regression models, relating the risk factors and patient survival. After univariate analysis, there was a multivariate stepwise criterion variable selection.

The analysis shows that factors that directly influence on survival: a) T3 and N3 b) stage III c) moderately differentiated tumor, d) tumor recurrence e) the presence of bronchopneumonia postoperatively f) performing esophagectomy by thoracotomy or total esophagogastrectomy.

However, after multivariate Cox regression showed that the most important factors influencing survival were: a) N2 and N3 b) bronchopneumonia postoperatively, and c) the presence of tumor recurrence during follow-up (Table 6).

Therefore, the final multivariate analysis shows the influence of the following factors on patient survival: N

TABLE 5 - Results from the Cox regression univariate for survival (ref.=reference for statistical analysis)

Variable	Categories	P-value	H.R.*	IC 95% H.R.*
Group	Surgery (ref.)		1.00	---
	Adjuvant	0.106	1.76	0.89 – 3.47
Sex	Male (ref.)	---	1.00	---
	Female	0.220	1.61	0.75 – 3.42
Age	Continuous variable (years)	0.731	0.994	0.963 – 1.027
Race	White (ref.)	---	1.00	---
	Non-white	0.586	1.34	0.47 – 3.78
T	1+2 (ref.)	---	1.00	---
	3	0.015	4.41	1.34 – 14.52
N	0 (ref.)	---	1.00	---
	1	0.140	2.55	0.74 – 8.84
	2	0.051	2.62	0.99 – 6.91
	3	<0.001	6.09	2.45 – 15.12
Stage	I (ref.)	---	1.00	---
	II	0.168	4.36	0.54 – 35.49
	III	0.020	10.66	1.44 – 78.74
Degree	Well differentiated (ref.)	---	1.00	---
	Moderately differentiated	0.030	3.82	1.14 – 12.81
	Poorly differentiated	0.216	2.36	0.61 – 9.16
Number of lymph nodes	Continuous variable	0.856	0.998	0.974 – 1.022
Relapse	No (ref.)	---	1.00	---
	Yes	<0.001	3.47	1.66 – 7.26
Dysphagia	No (ref.)	---	1.00	---
	Yes	0.316	1.47	0.69 – 3.13
Retrosternal pain	No (ref.)	---	1.00	---
	Yes	0.340	0.65	0.27 – 1.57
Pyrosis	No (ref.)	---	1.00	---
	Yes	0.602	0.84	0.43 – 1.62
Gastrointestinal hemorrhage	No (ref.)	---	1.00	---
	Yes	0.272	1.64	0.68 – 3.98
Weight loss	No (ref.)	---	1.00	---
	Yes	0.334	1.43	0.69 – 2.98
Tabagism	No (ref.)	---	1.00	---
	Yes	0.184	0.63	0.32 – 1.25
Alcoholism	No (ref.)	---	1.00	---
	Yes	0.225	0.65	0.33 – 1.30
Fistula Complication	No (ref.)	---	1.00	---
	Yes	0.638	0.83	0.39 – 1.78
Stenosis Complication	No (ref.)	---	1.00	---
	Yes	0.534	1.23	0.64 – 2.37
Thorax Drainage Complication	No (ref.)	---	1.00	---
	Yes	0.052	1.95	0.99 – 3.82
Bronchopneumonia Complication	No (ref.)	---	1.00	---
	Yes	0.010	3.20	1.32 – 7.76
Surgical Technique	Total gastrectomy (ref.)	---	1.00	---
	Esophagectomy transmediastinal	0.424	1.38	0.62 – 3.07
	Others	0.043	5.14	1.06 – 25.00
Reconstruction of alimentary transit	Jejunum (ref.)	---	1.00	---
	Stomach	0.410	1.40	0.63 – 3.09
	Colon	0.183	2.88	0.61 – 13.60

* HR (Hazard Ratio) = hazard ratio for death, (n = 67 censures and n = 36 deaths).
IC 95% HR= 95% interval of confidence for the hazard ratio.

TABLE 6 - The multivariate Cox regression results for survival rate (ref.=reference for statistical analysis).

Selected variables	Categories	P-value	H.R.*	IC 95% H.R.*
1. N	0 (ref.)	---	1,00	---
	1	0,191	2,39	0,65 – 8,85
	2	0,019	3,38	1,22 – 9,36
	3	<0.001	5,94	2,14 – 16,45
2. Complication Bronchopneumonia	No (ref.)	---	1,00	---
	Yes	<0,001	11,38	3,90 – 33,24
3. Tumoral recurrence	No(ref.)	---	1,00	---
	Yes	0,002	3,83	1,62 – 9,06

*HR (Hazard Ratio) = hazard ratio for death; (n=67 censures and n=36 deaths).
IC 95% HR= 95% interval of confidence for the hazard ratio. Stepwise criterion for the variables selection.

(N2 have death risk 3.4 times greater than N0, N3 and has risk of death 5.9 times higher), bronchopneumonia postoperatively (11.4 times higher risk) and tumor recurrence during follow-up (3.8 times greater risk).

Comparing the groups without adjuvant (78 patients) and adjuvant (25 patients) the most important factors associated with worsening of survival in patients not undergoing adjuvant therapy were: lymph node invasion (p = 0.007 N1, N2 p = 0.006, N3 <0.001), pneumonia (p <0.001) and gastrointestinal bleeding (p = 0.030). In the patients undergoing adjuvant therapy was tumor recurrence (p = 0.008).

DISCUSSION

The literature has shown a gradual increase in the frequency of esophageal adenocarcinoma, not only in the west[2,8,17] but also in some Eastern countries[10,27]. Devessa et al.[4], reported that among U.S. males, since 1976, have occurred an annual increase of 8-10% in the incidence of esophageal and gastric cardia adenocarcinoma, a higher growth rate compared to other types of tumors. Blot et al.[2] confirmed the previous data, adding that, in contrast to the increase in adenocarcinoma of the esophagus and cardia, there is a stability trend in the incidence of epidermoidal carcinoma during the same period and a slight decline in the incidence of the stomach distal. However, the increased incidence of this type of tumor was not accompanied by a significant improvement of its prognosis, and esophageal cancer is considered a poor prognosis disease[28].

Pera et al.[17], in the U.S.A., reported an increase of five to six times the incidence of esophageal adenocarcinoma from 1971 to 1974, comparing the results from 1935-1971 to 1974-1981.

In Japan, Kusano et al.[10] in a review of 6,953 patients with advanced gastric adenocarcinoma operated at Tokyo's National Cancer Center Hospital, during the period of 1962 to 2005, including 520 patients with adenocarcinoma of the esophagogastric junction. They observed a 2.3% incidence of esophagogastric junction adenocarcinoma during the 1962-1965 period, and a 10% increase during the 2001-2005 period. The authors also noticed an increase to the proportion of Siewert type II tumors from 28.5% (1962-1965) to 57.3% (2001-2005), while the Siewert type I tumors remained around to 1.0 %.

However, the increased incidence of this tumor was not accompanied by a significant improvement of its prognosis, and esophageal cancer is still considered a poor prognosis disease[28].

The immediate postoperative complications reported in the review of 300 total gastrectomies performed at the same University Hospital[1] were: incision infection (7.3%), fistula of the esophagojejunal anastomosis (6%), abdominal abscess (3%), pancreatic fistula (2.6%) and

duodenal fistula (2.3%), respectively. This total, 40 total gastrectomies (13.3%) were because of cardia adenocarcinoma. Grotenhuis et al.[7], in 2010, while reviewing several studies with patients who underwent esophagectomy, highlighted the age, the cardio-pulmonary conditions and the nutritional status as being risk factors during the preoperative stage.

Gagliardi et al.[5], in 2004, evaluated the variables that can influence the immediate postoperative complications, and the hospital mortality of patients with esophageal cancer, who underwent radical surgical treatment and palliative. They also analysed retrospective data from 60 patients, mostly with histologic epidermoidal carcinoma. The authors found that, the pleuropulmonary complications, the sepsis, the cervical anastomotic dehiscence, the mediastinitis, and the death, significantly correlated with the palliative surgery, the mediastinitis, and the tumor localized in the upper thoracic and the sepsis. These variables interdependence allows for the statement, that in patients with esophageal cancer undergoing palliative surgery who developed the pleuropulmonary complications were 13.8 times more frequent.

Morita et al.[14], in 2011, reviewed the factors associated with hospital mortality rates of 1,106 patients, who underwent esophagectomy for esophageal cancer in the period from 1969 to 2009. The multivariate analysis revealed that both the esophagectomy before 1979, as well as the patients' age (odds ratio 1.070 for each one year age increase), and the incomplete resection (odds ratio 2.265) were unrelated factors associated with the hospital mortality rate. At the beginning of the casuistic, the most common causes of hospital deaths were pulmonary complications, however, the tumoral recurrence recently became the most common cause.

The univariate analysis with the Cox regression performed in this casuistic, records factors associated with significant worsening of the survival rate. Among these factors, are highlighted, the data inherent to the tumor; such as the stage T3, the stage N3, the staging III, the moderately differentiated degree, which confirms that the larger tumors, more advanced and less differentiated have the worst prognoses.

In addition, two clinical conditions were associated with poor prognosis in both univariate and multivariate analyzes, respectively, the presence of bronchopneumonia in the postoperative and the tumoral recurrence. The occurrence of bronchopneumonia may be associated with these patients' poor general health and nutrition, compared to patients without this kind of complication.

The transthoracic esophagectomy and total esophagogastrectomy were associated with poor prognosis in the univariate analysis, however, they went unconfirmed in the multivariate analysis. They are major surgeries that had an expectation of increased surgical morbidity and mortality.

CONCLUSION

In conclusion, the presence of tumoral recurrence and lymph node invasion (stages N2 and N3) are factors in the worsening survival prognosis. Conversely, the extent of the neoplastic disease at diagnosis is an important intrinsic factor, reflecting the disseminated disease in which surgery is the last therapeutic resource. Furthermore, the poor prognosis factors emphasize the need for the development of new therapeutic strategies for an advanced systemic disease.

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