Applied Cancer Research 2007;27(4):175-181

Original Article

Survival Prognostic Factors in Esophagectomized Patients Due to Squamous Cell Carcinoma of the Esophagus

Felipe Jose Fernandez Coimbra,[1] Rubens Antonio Aissar Sallum,[1] Andre Luis Montagnini,[1] Ines Nobuo Nishimoto,[2]

1 Surgeon of the Department of Abdominal Surgery of A.C.Camargo Hospital

2 Statistician of the Center for Study and Research of A.C.Camargo Hospital

Abstract

Introduction: Among esophageal tumors, squamous cell carcinoma is the most common and with a poor outcome. Its prognostic factors are controversial and the long-term results dismal. It is essential, though, to have a detailed knowledge of the characteristics of this group of patients and its prognostic factors. **Objective:** To evaluate clinical, surgical and pathological parameters of patients with esophageal squamous cell carcinoma submitted to esophagectomy and identify prognostic factors of overall survival. Secondary Objectives: To evaluate surgery safety and mortality. **Methods:** A retrospective cohort study was done with 47 patients submitted to esophagectomy due to squamous cell esophageal cancer admitted in the Abdominal Surgery Department of A.C.Camargo Cancer Hospital, Sao Paulo. The period considered was October 1998 - December 2004. **Results:** Overall 2 and 5-year survival rates were 41.1% and 18.1%, respectively. There were statistically significant differences in 5-year overall survival probability for the treatment intention (p=0.0017), residual disease (R) (p=0.0111), lymphatic invasion (p=0.0180), T (p=0.0077), M (p=0.0166), clinical stage (p=0.0020). The independent prognostic factors were lymphatic invasion (HR=2.41) and pathologic "T" (HR=2.19). **Conclusions:** Surgical treatment of esophageal cancer is a safe procedure, with low hospital mortality (2.1 %). The most important factors associated to 5-year overall survival is treatment intention, residual disease (R), lymphatic invasion, and T M clinical stage. Independent prognostic factors are lymphatic invasion and pathologic "T".

Keywords: Prognosis. Esophagectomy, Esophageal Neoplasms. Carcinoma, Squamous Cell.

Introduction

Among tumors of the esophagus, spinocellular carcinoma (SCC) is the commonest,[1-3] having the highest incidence in the central region of Asia. In Brazil it is one of the ten most common and the sixth in mortality,[2] with a higher frequency in the South region.[2,4-6] This situation is changing, especially in Western countries, where there is a growing increase of adenocarcinomas, especially in North America and Western Europe.[7-9]

The main criteria for prognostic classification in esophageal SCC is TNM staging, which evaluates only tumor characteristics such as isolated criteria for staging and prognosis.[10] But many other factors have been identified. There is no consensus, however, about the independent factors, except for clinical staging.[9,11-19]

Surgical treatment followed by adjuvant therapy is the sequence of treatment adopted in most institutions. But the ideal surgical modality is a controversial question. Access

Corresponding Author:
Felipe Coimbra
Rua Professor Antônio Prudente, 211
01509-010 São Paulo, Brazil
E-mail felipej.f.c@uol.com.br

fields, the extension of resection and lymphadenectomy, as well as the variations of the usual technique are factors that can directly influence prognosis.[16-18,20-21] In world literature, 5-year survival in curative treatment varies from 5% to 30%.[22-26] In Brazil the literature is scarce and no other study detailed prognostic factors.

The decision of the adopted therapy is defined by the experience of the service, clinical conditions, tumor staging, location, expected complications and life expectancy of each patient. With these data, very often of an empirical character, treatment strategies are defined, but without considering concrete data as to the casuistry. Thus, it is essential to identify prognostic factors for this group, allowing a real knowledge of the disease in this specific casuistry, which directly interferes in the choice of treatment, aiming at better long-term survival rates.

Methods

We carried out a retrospective cohort study of forty seven patients of SCC of the esophagus treated consecutively with esophagectomy admitted by the Department of Abdominal Surgery of A.C.Camargo Hospital from October 1998 to December 2004. All patients were staged and evaluated by means of clinical examination, lab tests and specific image examinations (EED, EDA and bronchoscopy). For tumors of the esophagogastric junction and lower esophagus, tumors reaching the innermost third of the submucous membrane (SM1) or having high surgical risk (ASA III), transmediastinal esophagectomy with lymphadenectomy in abdominal and transmediastinal fields was indicated. Trans-thoracic access was chosen for thoracic tumors in patients of low surgical risk when it was expected to carry out lymphadenectomy in two or three fields and / or the existence of great thoracic masses. For tumors in cervical sites cervical access followed by abdominal access for reconstruction of feeding tube was chosen. All surgeries were carried out by the same surgical team. After resection all surgical samples were analyzed as regards pathological anatomy. Adjuvant therapy was carried out with radiotherapy for tumors larger than T2 or N1.

To describe variables, frequencies distribution, measures of central tendency and dispersion were used. The comparison among variables was carried out by qui-square frequency test and in 2x2 charts, Fisher Exact test was used. The 5% significance level was adopted. In survival analysis, Kaplan-Meier technique was used and the differences between survival curves were verified using log-rank test. Cox's regression model was used for estimating death relative risks, considering the interval of confidence of 95%. The stepwise (forward) technique was used for inclusion of variables in the multivariated model considering the level of signification of 10% for obtaining the independent prognostic factors.

Results

There was a predominance of males (80.8 %). The mean age was 59.9 years (median: 62 years, min.: 30 years, max.: 78 years). Dysfagia was the main symptom (95.7 %), followed by weight loss (55.3%), pain (23.4 %) and others (17%). The mean weight loss was 6.1Kg. Mean body mass index was 22.5 (14.3 to 28.8). The mean serum level was 4mg/100ml. The mean serum hemoglobin was 13.6g %. The Lymphocytes mean was 1601/mm3. Most patients had comorbidities (93.6 %). And 10 tumor had a cervical location while 28 were thoracic and 9 were located in the esophagogastric transition.

Treatment was curative in 41 patients (87.2%). Transdiaphragmatic resection was performed in 32 patients (68.1%), transthoracic in 15 patients (31.9%). Resection was considered R0 in 80.8 % of the sample. Only 15 patients (31.9%) needed blood transfusion. The mean surgery time was 412 minutes (240 to 690 minutes). Thirty four (72.3 %) patients had complications in the post-operative (25% pleural-pulmonary). Twenty one patients had adjuvant radiotherapy.

Degree of tumor differentiation was G1 and G2 in 91.1%, G3 and G4 in 8.9%. Lymphatic invasion was detected in 33 patients (70.2 %). The mean size of the tumor was 4.4 cm. Mean number of resected lymph nodes was 31.8. The mean of compromised lymph nodes was 3.8.

The distribution of patients according T stage was: T1 – six patients (12.7 %), T2 12 (25.5 %), T3 18 (38.3 %) and T4 11 patients (23.4 %). From the total of patients 20 (42.5%) were N0, 24 (51.1%) N1, and 3 were Nx (6.4%). Forty patients (85,1%) had no distant metastasis and 7 (14.95) were classified as M1. The disease of twenty patients were classified as EC I and II, and in 24 cases the disease was classified as EC III+IV.

The mean hospitalization time was 21 days (median of 15 days, range 7 to 14 days).

The most common recurrence was systemic in 19 cases (70.4%). Most of recurrences (87.1%; n=27) were diagnosed in the first two years after surgery. There was a death in intra-hospital treatment (2.1%). There was no follow up losses and mean follow up time was 20.4 months.

For the 5-year survival the number of lymphocytes (p=0.703), serum albumin dosage (p=0.0814), perineural invasion (p=0.0750), the number of resected lymph nodes (more or less than 27) (p=0.0908) presented rates with a tendency to be statistically significant. Table 1, Table 2, Figure 1.

Table 1 - Statistically significant 5-years overall survival according to variables related to patient, treatmen, tumor characteristics and stating

Variable	Category	Overall Survival (%)		
		2 years	5 years	p- value
Overall survival		41.4	18.1	
Treatment intention	Curative	45.2	21.1	0.0325
	Palliative	16.7	0	
Residual disease	R0	47.6	22.2	0.0111
	R1+R2	13.2	0	
Lymphatic invasion	No	53.0	24.7	0.0017
	Yes	9.6	0	
T	T1/T2	64.4	35.8	0.0077
	T3/T4	26.4	7.7	
Metastasis	No	47.7	20.9	0.0166
	Yes	0	0	
Clinical staging	I/II	72.6	33.0	0.0020
	III/IV	17.8	8.9	

Table 2 - Prognostic factors

Variable	Category	Crude HR	Multivariate HR
Lymphatic invasion	No	1.0 (ref.)	1.0 (ref.)
	Yes	3.08 (1.5-6.4)	2.41 (1.1-5.1)
Pathological T	T1/T2	1.0 (ref.)	1.0 (ref.)
	T3/T4	2.6 (1.3-5.6)	2.19 (1.0-4.8)

HR: Death´s Hazard ratio according to Cox Regression Model

Discussion

Early detection followed by resection favors the best chance of cure for esophagus SCC. Long-term survival is in most cases dependant on tumor stage. In spite of the apparent improvement in the last decades, as noticed by Mirra et al.,[27] which showed an increase of

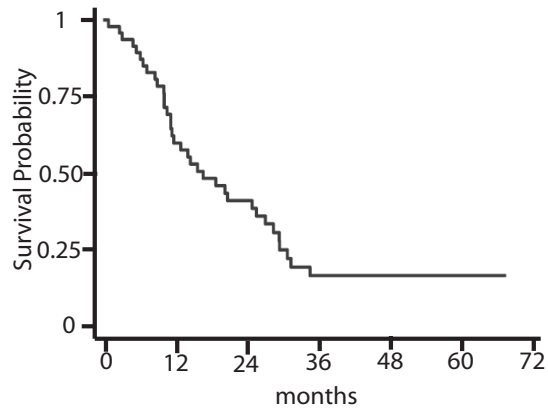

Figure 1 - Overall survival estimated by Kaplan-Meir method.

five-year survival from 3.7% to 9.0% along 40 years and also by other authors[28-29] the evolution of these patients is still precarious. In attempting to improve the results of surgical treatment, the pre- and post-operative adjuvance have been employed. However, some revisions showed only a little impact.[30-31]

Spinocellular carcinoma (SCC) of the esophagus is one of the malignant neoplasias of more complex treatment. The rate of global survival in five years is less than 30%, independently of the employed therapeutics.[17,22,25-27,32-33] Among treatment options, surgery is still the primary choice of reference.

Currently, the main classification criterion for tumor prognostic is TNM.[10] However, multiple predictive factors have been proposed as being still more important than TNM. In most studies, however, there is no consensus about independent factors in prediction, except for clinical staging.[11-19]

TNM classification, nevertheless, holds only regarding tumor characteristics. Thus, relevant information such as those about clinical conditions as well as factors linked to treatment are not considered in prognostic stratification. Both for cancer of the esophagus and for other neoplasias, the importance of those variables[9,15,18,29,34-36] have been demonstrated.

Independently of the advancements of therapeutics and the development of peri-operative cares, survival results for esophagus SCC remain dismaying. It is thus vital to know this group of patients, the identification of its prognostic factors for subsequently contribute to the choice of therapeutics and for better long-term survival

results.

In the present study, global survival in two and five years was respectively 41.4% and 18.1%. There are great variations in the results of the world literature. In a general way better results are observed in oriental studies. However, many variables must be considered, since the casuistry in the oriental centers is composed of a higher percentage of tumors in initial stages,[16,37-39] there is a mixture of SCC and adenocarcinoma[18,31,38-40] in analysis, there is difficulty for evaluating the impact of different adjuvant therapies and there are no prospective random studies showing the differences of results for the different types of surgeries in survival. In Brazil, global survival in five years varies from 3.7% to 27%, but prognostic factors are not normally approached.[3,29,41]

The independent prognostic factors in this study were lymphatic invasion (IL) (HR=2.41) and "T" (HR=2.19). The presence of IL represented a twice higher chance of death; also as pathological groups T3 and T4 present a twice higher risk of death than groups T1 and T2 in multivariated analysis. These results agree with the literature.[18,29,36,39-40,42]

In this casuistry factors referring to the tumor had higher prognostic importance, suggesting that the biological tumor aggressiveness is the most important element, independently of the type of surgical therapeutics or clinical conditions.

We see that the patients elected for surgical treatment correspond already to a group with better clinical conditions. This way, probably there is a preoperative "selection" that homogenizes the candidates for surgical therapeutics, showing that clinical factors are not very efficient in the determination of prognostics.[16,34,41,43] Several clinical aspects linked to the patient were studied, such as habits, age, comorbidities, nutritional factors, laboratorial factors and anesthetic risk. None of them had statistical significance in the analysis of survival.

Maybe one of the reasons for the low prognostic influence of the chosen therapeutics is the fact that all surgeries were carried out by the same surgical team, reducing the possibility of variations on procedure, complications and post-operative evolution. Another important element is the small number of cases for each type of surgery that allows no concluding results.

Among the treatment variables studied, the intention of treatment and the presence or not of residual disease influenced significantly five-year survival. In the literature these data are confirmed showing clear differences of 5-year survival in 20% to 35% for curative resections against less than 5% for palliative ones.[5,44] As for residual disease, we can think in the influence of tumor anatomopathological factors such as "T", degree of tumor differentiation, IL, among others.

Stein e Siewert[29] point as one of the causes for the improvement of the prediction in resected esophageal tumors the increase of R0 resections, and they also say that the implementation of neoadjuvant therapy is very important factor, that directly influences survival. Tachibana et al.[36] found as independent prognostic factors elements related both to the tumor and to the treatment (surgeon). The therapeutic factors were time of surgery more than seven hours and the quantity of transferred concentrates of red blood cells, if more or less than three unities.

In our study surgery time had no influence in survival, probably due to adequate anesthetic care and intensive therapy. Regarding blood transfusion, a third of patients received it and only one received three unities of concentrates of red blood cells. If we consider as higher risk the patients who received more than three unities of transfusion, as demonstrated by Tachibana et al.,[36] there are subsidies to credit to the low transfusion rate the absence of influence of this factor in prediction.

The choice of surgical access, transthoracic (TT) or transmediastinal (TM); the type of lymphadenectomy carried out, in one, two or three fields; the extension of surgery, with resection of other organs or not; and the type of anastomosis carried out, if manual or mechanical were not relevant factors for survival. Studies comparing TT and TM techniques show both to be equally effective.

Orringer et al.[45] studied 800 patients submitted to transmediastinal esophagectomy and reported 5-year survival of 23%, with mortality of 4% and lesser rates of respiratory complications, if compared with most studies with lymphadenectomy in three or two fields. Christein et al.[9] noticed, in 128 patients submitted to TM esophagectomy and 74 to TT a worse prediction in the second group and credit this result to a more frequent upper thoracic location and to a higher rate of blood transfusions.

The defenders of TT say that systematic radical lymphadenectomy offers the best chance of survival in the long term in sensitive cases, and an adequate staging reducing sub-staging of advanced tumors due to a better lymph node evaluation36. It is obvious, nevertheless, that the more extensive lymphadenectomy is more precisely the disease is staged reducing the effect of migration of staging.[16] In this analysis, there was no difference in survival in the different access or in the type of lymphadenectomy.

For cervical tumors, resection can affect the pharynx and the larynx. The access ways are the same

used for resection of tumors of other locations of the esophagus, but in these cases one should carry out cervical collar incision and regional lymphadenectomy must be jugular-carotidal, and not only recurrential.[46-48]

The elevated rates of post-operative complications in esophagectomies are known with immediate and long term consequences. Tachibana et al.[36] showed that in 287 patients submitted to esophagectomy in three fields by esophagic SCC postoperative morbidity was 80%. In this evaluation post-operative morbidity was high, as expected, being the commonest the respiratory ones, but without influencing survival.

In the last years, improvements in surgery, anesthetic technique and intensive therapy have reduced morbidity rates and hospital mortality in patients submitted to esophagectomy, from levels superior to 20% to about 5% in the best centers.[17,18,20,29] In Brazil, the rate of post-operative mortality for this surgery varied from 2% to 55.3% in several technical employees.[3,20,27,49] In this experience hospital mortality was 2.1% (one case), resulting from mediastinitis due to anasthomotic fistula complications, similar to the best results of the literature.[18,29]

Neodjuvant treatment in patients with esophagus cancer was introduced more than 20 years ago, but[29] did not show improvements in global survival in most studies. However, more current investigations have demonstrated a tendency of improvement of the results in selected groups, without affecting operative morbimortality, probably due to improvements in (conformational) techniques, saving healthy tissues that were injured by older techniques.[9,24,29,45]

Stein e Siewert[29] report the growing use in the last two decades of neoadjuvant therapy with radiotherapy and chemotherapy. In Brazil, Tomasich et al.[40] compared the immediate effects in complications and hospital mortality in 132 patients submitted to esophagectomy, of whom 60 had neoadjuvance with chemotherapy or radiotherapy, and observed a number significantly higher of complications in patients having neoadjuvance, but without worsening of hospital morbidity.

Post-operative adjuvant treatment is also controversial.[4] In some patients adjuvant radiotherapy even worsen results regarding survival and only groups having mediastinal residual disease resected with palliative intention benefited.[5] Other prospective random studies showed a reduction of local recurrence and the incidence of tracheoesophagic fistulas after resection, without benefits for survival. Post-operative chemotherapy with several agents still did not prove its role in tumors of resected esophagi, besides not being well tolerated,[33] which makes it not to be carried out routinely except in inquiry protocols. The combination of post-operative radiotherapy and chemotherapy presented results that seem promising, but definitive prospective random studies are still necessary.[33]

In this study, adjuvance with radiotherapy was carried out in the cases of higher risk of recurrence. About half of the patients (44.7%) were submitted to radiotherapy alone and it was not a significant factor for survival. It was observed however a lesser number of local-regional recurrences.

If we compare the results with those of the literature, in which the most common type of recurrence is local-regional, we observe they were different from most studies,[36-37] since distant recurrence was more frequent (70.4%). This distribution is probably due to multiple factors, and among them maybe we may emphasize an oncologically adequate surgery, as well as the preventive effect of radiotherapy against local-regional recurrences.[44] Thus, these data corroborated the efficiency of surgical and complementary treatment employed, especially for the control of local-regional disease.

Based on the knowledge produced in this study, it was possible to observe the necessity of adjuvant therapy, pre- or post-operative, adapted to the control of distance disease in esophageal cancer, since the failure of surgery is obvious, even of the most radical ones, in the control of systemic recurrences.[9,36,50]

The factors related to the tumor were those of higher relevance in this casuistry. The analysis of the staging of these patients showed that most had tumors already advanced at diagnosis, with 61.7% T3 and T4, and 51.1% N1. These elements make a relevant fact stand out in the casuistry: late diagnosis. TNM classification was extremely efficient in the evaluation of the prediction in the studied patients. T3 and T4 groups were a factor of worse prognostic in the multivariated analysis[9,15,34,38] as already have shown several authors. Based on these findings, we may emphasize the importance of implementing strategies already adopted by some for a detailed preoperative diagnosis of T, with the routine use of endoscopic ultrasound scan.[29]

Lymph node compromising (N) was not statistically significant for survival in this study. Other parameters linked to lymph nodal disease were also evaluated, such as the number of compromised lymph nodes and lymph nodal ratio, and they did not show statistical significance. However, when the number of lymph nodes resected was analyzed, if less or more than 27, we observed better survival rates in the second group (4.6% versus 34.2%, p=0.0908). These findings corroborate the possibility of

micrometastatic disease and the therapeutic and staging value of radical lymphadenectomy, despite systemic limitations inherent to the surgical treatment.[16]

As expected, the presence of distant metastasis was a significant factor in survival in two (47.7% versus 0%) and five years (20.9%, p=0.0166). Other studied variables were not significant for survival in five years.

IL was an independent prognostic factor and it confirms more recent data of the literature on the subject, showing to be a factor more important than N and M. Osugi et al.[16] evaluated 88 patients with SCC of the esophagus submitted to lymphadenectomy in three fields, and noticed what only IL correlated with the prediction in the multivariated analysis. They also showed that when there is IL, even in patients without lymph nodal metastasis (N0), an elevated risk of distant metastasis is present.

Thus, surgical treatment of esophageal SCC presents elevated rates of complications, but with low hospital mortality (2.1%). The factors of higher importance for 5-year global survival were intention of the treatment, R, IL, T, M and EC. The independent prognostic factors were IL and T.

To conclude, the deep knowledge of the casuistry and the study of its prognostic factors were shown to have extreme importance in the projection of future changes in the clinical and surgical procedures of the treatment of esophageal cancer, aiming at increasing long-term survival. We believe that with the growth of the casuistry it will be possible to have a higher number of prognostic factors and in a future analysis to investigate possible molecular prognostic markers in this select group of patients.

References

1. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide frequency of sixteen major cancers in 1990. Int J Cancer 1999;80:827-41.
2. Ministério da Saúde. Instituto Nacional de Câncer. Estimativas da incidência e mortalidade por câncer 2003. Rio de Janeiro: INCA; 2005.
3. Pinotti HW. A new approach to the thoracic esophagus by the abdominal transdiaphragmatic route. Langenbecks Arch Chir 1983;359:229-35.
4. Altorki N. Carcinoma of the esophagus. In: Bland KI, Daly JM, Karakousis CP, editors. Surgical oncology: contemporary principles e practice. Stamford: McGraw Hill; 2001. p.609-22.
5. Fok M, Wong J. Cancer of the esophagus. In: Zinner MJ, Schawartz SI, Ellis H editor. Maingot's abdominal operations. 10th ed. Stamford: Appleton e Lange; 1997. p.859-84.
6. Parkin SL, Whelan J, Teppo FL, Thomas DB. Cancer incidence in five continents, v.VIII. Lyon: IARC; 2005. (IARC Scientific Publication nº 155).
7. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF, Jr. Rising incidence of adenocarcinoma of the esophagus and cardia. JAMA 1991;265:1287-9.
8. Blot WJ, Mclaughlin JK. The changing epidemiology of esophageal cancer. Semin Oncol 1999;26(5 Suppl 15):2-8.
9. Christein JD, Hollinger EF, Millikan KW. Prognostic factors associated with resectable carcinoma of the esophagus. Am Surg 2002;68:258-62.
10. Sobin LH, Wittekind Ch. TNM. Classificação de tumores malignos. 6 ed. Trad. de Instituto Nacional de Câncer. Rio de Janeiro: INCA; 2004. Esôfago; p.64-8.
11. Bancewicz J, Osugi H. Oesophagus: epidemiology, investigation, and surgical management. In: McCulloch P, Kingsnorth A, editors. Management of gastrointestinal cancer. London: BMJ Publishing Group; 1996. p.97-123.
12. Swisher SG, Holmes EC, Hunt KK, Gornbein JA, Zinner MJ, McFadden. Perioperative blood transfusion and decreased long-term survival in esophageal cancer. J Thorac Cardiovasc Surg 1996;11:2341-8.
13. Nishimaki T, Suzuki T, Suzuki S, Kuwabara S, Hatakeyama K. Outcomes of extended radical esophagectomy for thoracic esophageal cancer. J Am Coll Surg 1998;186:306-12.
14. Rice TW, Zuccaro G Jr, Adelstein DJ, Rybicki LA, Blackstone EH, Goldblum JR. Depth of tumor invasion is predictive of regional lymph node status for esophageal carcinoma. Ann Thorac Surg 1998;65:787-92.
15. Siewert RJ, Stein HJ, Feith M, Bruecher BL, Bartels H, Fink U. Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more then 1000 consecutive resections at a single institution in the Western world. Ann Surg 2001;234:360-9.
16. Osugi H, Takemura M, Takada N, Hirohashi K, Kinoshita H, Higashino M. Prognostic factors after oesophagectomy and extended lymphadenectomy for squamous oesophageal cancer. Br J Surg 2002;89:9009-13.
17. Cariati A, Casano A, Campagna A, Cariati E, Pescio G. Prognostic factors influencing morbity and mortality in esophageal carcinoma. Rev Hosp Clin Fac Med S Paulo 2002;57:201-4.
18. van Sandick JW, van Lanschot JB, ten Kate FJW, Tijssen JG, Obertop H. Indicators of prognosis after transhiatal esophageal resection without thoracotomy for cancer. J Am Coll Surg 2002;194:28-36.
19. Zafirellis K, Dolan K, Fountolakis A, Dexter SP, Martin IG, Sue-Ling HM. Multivariate analysis of clinical, operative and pathologic features of esophageal cancer: who needs adjuvant therapy? Dis Esophagus 2002;15:155-9.
20. Rangel M, Simões J, Cavalcanti D. Esofagectomia transdiafragmática por carcinoma epidermóide do esôfago: resultados imediatos. Rev Col Bras Cir 1994;21:17-20.
21. Blazeby JM, Conroy T, Hammerlid E, Fayers P, Sezer O, Koller M, et al. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. Eur J Cancer 2003;39:1384-94.
22. Lerut T, De Leyn P, Coosemans W, Van Raemdonck D, Scheys I, LeSaffre E. Surgical strategies in esophageal carcinoma with emphasis on radical lymphadenectomy. Ann Surg 1992;216:583-90.
23. Bosset JF, Gignoux M, Triboulet JP, Tiret E, Mantion G, Elias D, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous cell cancer of the esophagus. N Engl J Med 1997;337:161-7.
24. Ancona E, Ruol A, Snati S, Merigliano S, Sileni VC, Koussis H, et al. Only pathologic complete response to neoadjuvant chemotherapy improves significant the long term survival of patients with resectable esophageal squamous cell carcinoma. Cancer 2001;91:2165-74.
25. De Vita F, Di Martino N, Orditura M, Cosenza A, Galizia G, Del Genio A, et al. Preoperative chemotherapy for squamous cell carcinoma and adenocarcinoma of the esophagus. Chest 2002;122:1302-8.
26. Ishibashi Y, Hanyu N, Nakada K, Suzuki Y, Yamamoto T, Takahashi T, et al. Endothelin protein expression as a significant prognostic factor in oesophageal squamous cell carcinoma. Eur J Cancer

2003;39:1409-15.
27. Mirra AP, Justo FA, Miziara JE, Schneider CA, Trippe N. Historical evolution of the treatment of esophageal cancer at the Hospital A.C. Camargo, São Paulo, Brazil. Rev Assoc Med Bras 1995;41:277-83.
28. Law S, Kwong DL, Kwok KF, Wong KH, Chu KM, Sham JS, et al. Improvement in treatment results and long-term survival of patients with esophageal cancer: impact of chemoradiation and change in treatment strategy. Ann Surg 2003;328:339-47.
29. Stein HJ, Siewert JR. Improved prognosis of resected esophageal cancer. World J Surg 2004; 28:520-5.
30. Lehnert T. Multimodal therapy for squamous carcinoma of the oesophagus. Br J Surg 1999;86:727-39.
31. Geh JI, Crellin AM, Glynne-Jones R. Preoperative chemoradiotherapy in oesophageal cancer. Br J Surg 2001;88:338-56.
32. Bosset JF, Lorchel F, Mantion G. Neoadjuvant treatment of early stage squamous cell carcinoma of the esophagus. Dis Esophagus. 2002;15:117-20.
33. Parikh AA, VaporciYan AA, Swisher SG. Esophageal carcinoma. In: Feig BW, Berger BW, Fuhrman GM, editors. The MD Anderson surgical oncology handbook. Philadelphia: Lippincott Williams & Wilkins; 2003. p.145-57.
34. Igaki H, Kato H, Tachimori Y, Sato H, Daiko H, Nakanishi Y. Prognostic evaluation for squamous cell carcinomas of the lower thoracic esophagus treated with three-field lymph node dissection. Eur J Card Thorac Surg 2001;19:887-93.
35. [Anonymus] Prognostic significance of CyclinD1 and E-Cadherin in patients with esophageal squamous cell carcinoma: multiinstitutional retrospective analysis. Research Committee on Malignancy of Esophageal Cancer, Japanese Society for Esophageal Diseases. J Am Coll Surg 2001;192:708-18.
36. Tachibana M, Kinugasa S, Yoshimura H, Shibakita M, Tonomoto Y, Dhar DK, et al. Clinical outcomes of extended esophagectomy with three-field lymph node dissection for esophageal squamous cell carcinoma. Am J Surg 2005;189:98-109.
37. Shimada H, Kitabayashi H, Nabeya Y, Okazumi S, Matsubara H, Funami Y, et al. Treatment response and prognosis of patients after recurrence of esophageal cancer. Surgery 2003;133:24-31.
38. Swanson SJ, Batirel HF, Bueno R, Okazumi S, Matsubara H, Funami Y, et al. Transthoracic esophagectomy with radical mediastinal and abdominal lymph node dissection and cervical esophagogastrostomy for esophageal carcinoma. Ann Thorac Surg 2001;72:1918-24.
39. Ellis FH, Jr. Standard resection for cancer of the esophagus and cardia. Surg Oncol Clin North Am 1999;8:279-94.
40. Tomasich FD, Valladares GC, Demarchi VC, Gagliardi D. Influence of neoadjuvant treatment on morbidity-mortality of esophagectomies. Rev Assoc Med Bras 2003;49:300-5.
41. Zilberstein B, Cecconello I, Nasi A, Domene CE, Pinotti HW. Transdiaphragmatic resection of esophageal câncer. ABCD Arq Bras Cir Dig 1993;8:3-9.
42. Rizk NP, Bach PB, Schrag D, Bains MS, Turnbull AD, Karpeh M, et al. The impact of complications on outcomes after resection for esophageal and gastroesophageal junction carcinoma. J Am Coll Surg 2004;198:42-50.
43. Fang W, Igaki H, Tachimori Y, Sato H, Daiko H, Kato H. Three field lymph node dissection for esophageal cancer in elderly patients over 70 years of age. Ann Thorac Surg 2001;72:867-71.
44. Collard JM, Otte JB, Fiasse R. Five-year survival after resection of the oesophagus for cancer. Br J Surg 1992;79(Suppl):S94-5.
45. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy: clinical experience and refinements. Ann Surg 1999;230:392-403.
46. Coimbra FJF, Sallum RA. Tumores do esôfago cervical, in Kowalski LP. Afecções cirúrgicas do pescoço. Rev Col Bras Cir 2005;II:411-20.
47. McKeown KC. The surgical treatment of the carcinoma of the oesophagus: a review of the result in 478 cases. J T Coll Surg Edinb 1985;2:497-504.
48. Sallum RA, Coimbra FJ, Herman P, Montagnini AL, Machado MA. Modified pharyngogastrostomy by a stapler technique. Eur J Surg Oncol 2006;32:540-3.
49. Coral RP, Velho AV. Drenagem pleural: um tempo importante da esofagectomia transdiagrafmatica por cancer de esofago? Rev Col Bras Cir 1990; 17:129-32.
50. Pinotti HW, Cecconello I, De Oliveira MA. Transhiatal esophagectomy for esophageal cancer. Semin Surg Oncol 1997; 13:253-8.