

Supracricoid Partial Laryngectomy in the Treatment of Laryngeal Cancer

Univariate and Multivariate Analysis of Prognostic Factors

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Objectives: To evaluate the oncological results of supracricoid partial laryngectomy as a treatment for selected glottic and supraglottic cancer in a large series of patients who had undergone uniform treatment over a 16-year period and to determine the different prognostic factors that may influence local control and survival.

Design: Retrospective clinical study.

Setting: Academic tertiary referral medical center.

Patients: The study population comprised 253 consecutive patients (234 men and 19 women) with glottic and supraglottic squamous cell carcinoma. The mean age was 58 years for men and 59.2 years for women.

Intervention: Supracricoid partial laryngectomy: 180 patients had undergone cricohyoidopexy and 73 had undergone cricohyoidoepiglottopexy.

Main Outcome Measures: Local control and overall survival. Potential prognostic factors for local control and survival were evaluated with univariate and multivariate models.

Results: The 3-, 5-, 10-, and 16-year overall survival rates in this group of 253 patients were 85.8%, 79.1%, 57.6%, and 57.6%, respectively. With regard to local control, univariate and multivariate analyses showed that a positive resection margin was the only important predictor of local control and that a dysplastic lesion at the margin of resection is just as aggressive as the presence of invasive carcinoma. When considering the prognostic factors influencing survival, univariate analysis showed that the tumor category, lymph node category, tumor stage, and recurrence all had a significant influence on the survival rate. Multivariate analysis showed that the most important predictor of survival was recurrence.

Conclusions: Supracricoid partial laryngectomy is a valid choice in the treatment of selected glottic and supraglottic cancer while maintaining laryngeal functions and achieving a high rate of local control. T category, N category, tumor stage, positive resection margins, and recurrence are the most important predictors of oncological outcome.

Arch Otolaryngol Head Neck Surg. 2005;131:620-625

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Financial Disclosure: None.

LARYNGEAL CARCINOMA IS THE second most common type of head and neck cancer after skin cancer and accounts for 3% of total cancer risk.¹ The optimal primary treatment for laryngeal cancer is still a matter of international debate.² The treatment proposed is often based on the extent of the disease, the clinician's experience and training, and geographic practice preferences.^{3,4} A prerequisite of fundamental importance in dealing with the dilemma of treatment selection in patients with laryngeal cancer is the identification of unfavorable prognostic determinants that can serve as guidelines in addressing the treatment to the individual patient.⁵ Although tumor stage has long been accepted as the best single determinant of local control and survival for patients with laryngeal cancer, the progn-

osis is complex and may depend on several other risk factors such as age, sex, histological grade, margins of surgical resection, and lymph node involvement.⁶ However, the importance of each of these factors has not been unequivocally demonstrated. Retrospective analysis using univariate and multivariate models, which analyze the pattern of association of various prognostic factors to identify the combination of variables that best predicts the local control and survival, will provide a more refined approach to the problem. In the literature, relatively few studies have addressed this issue by means of univariate and multivariate analysis.²⁻⁸ For this reason, the purpose of our retrospective study was to report the oncological outcome achieved in a series of 253 consecutive patients who had undergone supracricoid partial laryngectomy (SCPL) as uniform treat-

ment over a 16-year period and to determine, by means of univariate and multivariate models, a potential correlation between various prognostic factors and the oncological results. We believe that the identification of possible prognostic factors influencing oncological outcome may optimize the control of laryngeal cancer.

METHODS

We retrospectively reviewed 253 patients affected by squamous cell carcinoma of the larynx, who were treated with SCPL between January 1984 and December 2001 at the Department of Otorhinolaryngology of "La Sapienza" University, Rome, Italy. The group was composed of 234 (92.5%) men and 19 (7.5%) women, with a male-female ratio of 12.3:1. The mean age was 58 years for men and 59.2 years for women, ranging from 35 to 77 years. All of the patients had biopsy-proven squamous cell carcinoma. Of the 253 patients, 211 had glottic cancer and 42 had supraglottic cancer. The patients were staged according to the 1997 edition of the TNM classification established by the American Joint Committee on Cancer.⁹ The pathological TNM classification for cricohyoidopexy (CHP) and cricohyoidoepiglottopexy (CHEP) are illustrated in **Table 1**. Patient evaluation consisted of a complete clinical history and physical examination, with emphasis on head and neck evaluation, a complete blood cell count, liver function test, renal function test, and pulmonary function tests. All patients underwent chest radiography and computed tomography of the head and neck. We did not perform this procedure in patients with restrictive pulmonary functioning or poor general conditions. The type of SCPL chosen was based on tumor localization and extension. We performed 180 SCPLs with CHP and 73 with CHEP. The SCPL technique and indications have been previously reported.^{10,11} With reference to the lymph node treatment protocol, based on clinical evaluation of the neck, T site, and T stage, we performed only 2 unilateral functional neck dissections and 1 bilateral functional neck dissection in 73 CHEP cases. In 180 cases of CHP, we performed 96 unilateral functional neck dissections, 21 bilateral functional neck dissections, and 6 unilateral radical neck dissections. In all cases, a temporary tracheotomy was performed between the third and fourth tracheal rings. A nasogastric feeding tube was inserted in all patients during the course of the operation. In our institution, postoperative management of the tracheostomy and nasogastric feeding tube was standardized as follows:

- Swallowing rehabilitation with food of semisolid consistency and phoniatric exercises usually started 3 to 4 days after surgery.
- The nasogastric feeding tube was removed once the patient achieved proper swallowing with occasional aspiration.
- The tracheal cannula was removed if the patient had not developed a laryngeal stenosis and if a valid cough avoided occasional aspiration.

A postoperative histopathological examination of resection margins was always performed to verify the adequacy of resection. The status of resection margins was rated as follows:

- The presence of dysplasia or invasive carcinoma at the margins or less than 0.5 cm from the edge of the resection (close margin) was classified as positive surgical margins.
- Surgical margins free of dysplasia or invasive carcinoma at least 0.5 cm from the edge of the resection was classified as negative surgical margins.

Table 1. Pathological TNM Classification for CHP and CHEP

Pathological TNM Classification	CHP		CHEP Glottic (n = 73)	Total, % (N = 253)
	Glottic (n = 138)	Supraglottic (n = 42)		
T1 N0	6	2	19	10.7
T2 N0	68	22	48	54.5
T2 N1	4	2	0	2.4
T2 N2	2	1	0	1.2
T3 N0	45	7	5	22.5
T3 N1	2	3	1	2.4
T3 N2	1	0	0	0.4
T4 N0	7	3	0	4.0
T4 N1	1	0	0	0.4
T4 N2	2	2	0	1.6

Abbreviations: CHEP, cricohyoidoepiglottopexy; CHP, cricohyoidopexy

Postoperative radiotherapy (RT) was not systematically administered to our patients. The decision to use adjuvant RT was based on the presence of invasive carcinoma at the resection margin and on the presence of positive neck nodes with extracapsular spread of the disease. Thus, we reserved postoperative RT for 10 patients who had invasive carcinoma at the margins of resection. None of the patients with positive neck nodes had extracapsular spread of the disease. However, before the initiation of RT, the patient was informed of the disadvantages of RT on functional results. When distant metastases occurred, chemotherapy was administered.

The mean follow-up period was 4.3 years, ranging from 0.5 to 16 years. Follow-up was carried out for 247 patients (97.6%) for 10 years, for 2 patients for 12 years, for 2 patients for 14 years, and for 2 patients for 16 years. Follow-up end points included evidence of local recurrence, death from disease, and death from other causes. The overall survival time was defined as the interval between the date of surgery and either the date of the last consultation for censored observations or the date of death for uncensored observations. The disease-free interval was measured on the basis of the dates of surgery and diagnosis of first recurrence, except for patients who never presented recurrence, in which case the disease-free interval coincided with overall survival. Overall survival curves were developed using the Kaplan-Meier¹² method, and the difference in survival between groups was compared using the Mantel-Cox log-rank test.¹³

Various prognostic factors were investigated for their unadjusted association with recurrence and survival in univariate analysis using the χ^2 test. The covariates were also included in a multivariate analysis using the Cox regression model¹³ to estimate the hazard ratios of recurrence and death due to the combined effects of 2 or more prognostic factors. Statistical significance was set at the $\alpha = .05$ level. The prognostic factors analyzed were age, sex, status of resection margins, T stage, tumor stage, N stage, histological grade, postoperative treatment, and recurrence.

RESULTS

ONCOLOGICAL RESULTS

Overall Survival and Local Control

The Kaplan-Meier-estimated 3-, 5-, 10-, and 16-year overall survival rates in the group of 253 patients were 85.8%, 79.1%, 57.6%, and 57.6%, respectively (**Figure 1**).

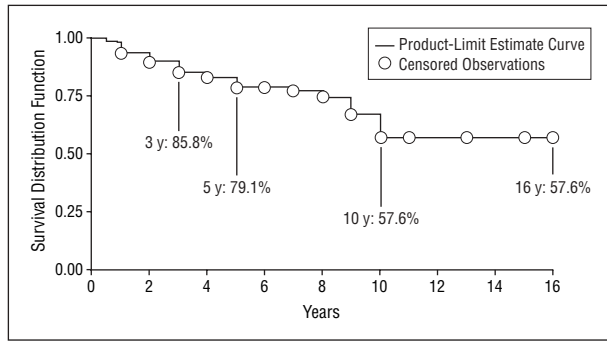


Figure 1. Kaplan-Meier analysis of overall survival in 253 patients treated with supracricoid partial laryngectomy.

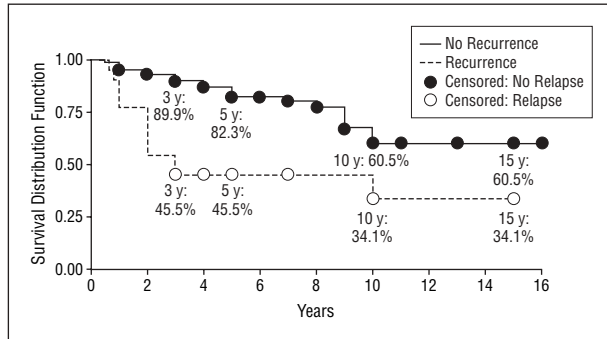


Figure 2. Kaplan-Meier analysis of overall survival in patients with and without recurrence (log-rank test, $P=.02$).

Twenty patients died of laryngeal carcinoma: 7 due to locoregional recurrence, 11 due to pulmonary metastases, and 2 due to bone metastases. Fifteen patients died of causes that were not related to laryngeal carcinoma: 7 due to secondary tumors, 2 due to intercurrent diseases, and 6 due to unknown causes.

There were 22 cases (8.7%) of locoregional recurrences: 19 cases at the primary site and 3 cases at neck lymph nodes. Details regarding the treatment of recurrence has been reported in a previous study.¹⁴ Surgery was performed on 18 patients. Total laryngectomy was the most common surgical procedure performed (9 cases). En bloc resection of overlying cervical skin was combined with total laryngectomy when the tumor spread to the soft tissues (4 cases). A near-total laryngectomy was reserved for only 2 patients. Radical neck dissections were performed on 3 patients with regional recurrence. Radiotherapy was administered as exclusive treatment in 2 patients and in combination with surgery or chemotherapy in 4 patients. Only 1 patient received chemotherapy alone.

The Kaplan-Meier estimated 3-, 5-, 10-, and 15-year overall survival rates in the group of 22 patients with locoregional recurrence were 45.5%, 45.5%, 34.1%, and 34.1%, respectively (**Figure 2**). Overall survival at 3, 5, 10, and 15 years was significantly higher in patients without locoregional recurrence than in patients with local or regional failure (89.9% vs 45.5%, 82.3% vs 45.5%, 60.5% vs 34.1%, 60.5% vs 34.1%; log-rank test, $P=.02$) (Figure 2).

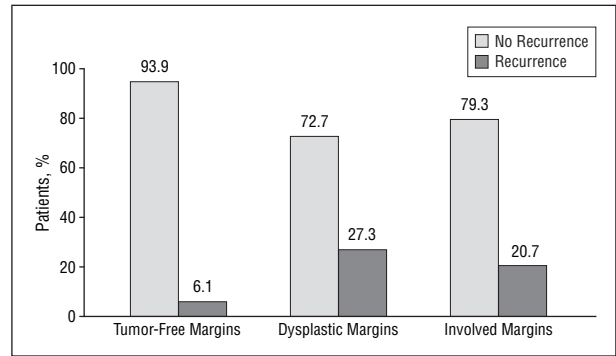


Figure 3. Univariate analysis: recurrence vs resection margins ($P=.002$)

Table 2. Multivariate Analysis of Factors Predicting Recurrence

Variable	Parameter Estimate	P Value (χ^2 Test)
Age	0.01	.71
Postoperative treatment	1.24	.13
N stage	-1.58	.10
T stage	0.36	.87
Tumor stage	-0.38	.86
Grading	0.28	.38
Status of resection margins	0.55	.06

Functional Results

With regard to functional results, 20 (7.9%) of 253 patients still had a tracheal cannula in place after 3 years. Seventy-one (97.2%) of 73 CHEP patients and 162 (90.0%) of 180 CHP patients were decannulated after 3 years. In the CHEP group, the nasogastric tube was removed after an average of 15 days (range, 9-90 days), and the tracheal cannula was removed after an average of 25 days (range, 15-90 days). In the CHP group, the nasogastric tube was removed after an average of 28 days (range, 15-90 days), and the tracheal cannula was removed after an average of 30 days (range, 20-90 days). Details of swallowing results and speech evaluation have been previously reported.^{10,11}

INFLUENCE OF PROGNOSTIC FACTOR ON ONCOLOGICAL RESULTS

We performed a univariate and multivariate statistical analysis of different possible prognostic factors in terms of local control and survival in our series of 253 consecutive patients treated with SCPL. Among the prognostic factors investigated in the univariate and multivariate analyses for their impact on local control, the presence of a positive resection margin was the only significant finding ($P=.002$ [**Figure 3**]; $P=.06$ [**Table 2**]). Of 253 patients who had undergone SCPL, 40 (15.8%) were identified as having positive surgical margins (11

dysplastic and 29 invasive carcinoma), whereas the remaining 213 (84.2%) had negative resection margins. Among the patients with positive resection margins, 20 were T2, 15 were T3, and 5 were T4. There is no statistical difference in the rate of positive margins between patients with early T stage and patients with advanced T stage (50% [T2] vs 12.5% [T4]; $P = .07$). Of the 40 patients with positive resection margins, 9 developed recurrence at the primary site, whereas of the 213 patients with negative resection margins, 10 developed recurrence at the primary site and 3 at the neck lymph nodes. The patients with positive resection margins had a significantly higher locoregional recurrence rate compared with the patients with negative resection margins (22.5% vs 6.1%; $P = .03$). Moreover, it appears that the presence of dysplasia or invasive carcinoma at the margin of resection had the same potential prognostic importance on locoregional recurrence (27.3% vs 20.7%; $P = .07$ [Figure 3]). None of the other factors tested in the univariate analysis showed a significant impact on local control (sex, $P = .58$; T stage, $P = .32$; N stage, $P = .66$; and tumor stage, $P = .60$). Also, in the multivariate analysis, the status of resection margins was the most significant factor related with local control, even when adjusting for the others ($P < .05$; Table 2). None of the other factors investigated (age, T stage, tumor stage, N stage, histological grade, and postoperative treatment) showed appreciable effects on local control (Table 2).

With reference to impact on survival, among the variables tested in the univariate analysis, T stage ($P = .03$), N stage ($P = .03$), tumor stage ($P = .01$), and recurrence ($P < .001$) were all significant, with recurrence being the most significant ($P < .001$; **Figure 4**). Multivariate analysis revealed that recurrence was the only independent prognostic factor influencing survival, even when adjusting for the others ($P < .001$; **Table 3**).

COMMENT

Optimal primary treatment for laryngeal cancer is still a matter of international debate.² Surgical resection is the most frequently chosen treatment to cure this malignancy. Since the reports by Majer and Rieder¹⁵ and Piquet et al¹⁶ describing SCPL with CHEP or CHP for selected glottic and supraglottic carcinomas, numerous reports in the literature have documented good oncological and functional results that were achieved with these partial laryngeal resection techniques.^{10,11,17-19} The aim of this type of surgery is total removal of the tumor while preserving laryngeal function.^{17,18} In fact, this technique permits, through the conservation of a cricarytenoid unit, the creation of a neolarynx adequate for both swallowing and speaking without a permanent tracheostomy.

Analysis of data reported in the literature strongly suggests that SCPL reduces the indications for total laryngectomy in selected cases of advanced laryngeal carcinoma classified as T3 to T4 and results in higher local control and long-term laryngeal preservation rates compared with the conventional vertical partial laryngectomy and horizontal supraglottic laryngectomy per-

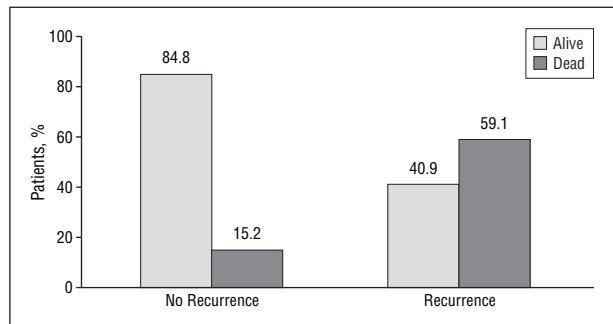


Figure 4. Univariate analysis: overall survival vs recurrence ($P < .001$)

Table 3. Multivariate Analysis of Factors Predicting Survival

Variable	Parameter Estimate	P Value (χ^2 Test)
Age	0.02	.24
Recurrence	1.36	<.001
N stage	-0.14	.74
T stage	-0.80	.15
Tumor stage	1.02	.08
Grading	0.28	.26
Status of resection margins	0.17	.40

formed in selected laryngeal carcinomas classified as T1b and T2.²⁰⁻²² Laccourreye et al²⁰ reported an excellent local control rate (98.2% at 5 years) in cases of T1 to T2 glottic carcinoma with extension to the anterior commissure treated with SCPL. Chevalier and Piquet,²¹ in a review of 61 patients with supraglottic squamous cell carcinoma classified as T1 to T4, reported a 97% local control rate after CHP. Recently, SCPL was also reported to be a possible modality of laryngeal preservation treatment in selected patients with local failure after laryngeal radiation therapy.²² Such data led Bridger²³ to assert that “in the near future any patient being evaluated for total laryngectomy should be considered for the less radical supracricoid partial laryngectomies.”

This technique was introduced in our department in 1984 and has since been performed on 253 consecutive patients with selected glottic and supraglottic carcinomas as an alternative for vertical partial laryngectomy and total laryngectomy, with good oncological and functional results. The Kaplan-Meier estimated 3-, 5-, 10-, and 16-year overall survival rates in the group of 253 patients were 85.8%, 79.1%, 57.6%, and 57.6%, respectively (Figure 1). We believe that a scrupulous application of the indication is the key to oncological success. The indication and contraindication of this surgical procedure have been extensively illustrated in previous reports.^{10,11} Postoperative RT was not systematically administered to our patients to avoid the collateral effects of this procedure on functional outcomes. Radiotherapy was performed only when invasive carcinoma was present at resection margins or when extracapsular spread was present in positive neck nodes. Thus, we reserved postoperative RT for 10 patients who had invasive carcinoma at resection margins. Before administering RT,

the patients were informed that RT could compromise the recovery of good voice quality and cause a delay in the closure of the tracheostomy. In patients requiring postoperative RT on the neck because of extracapsular spread, the larynx was protected to avoid complications such as laryngeal radionecrosis, laryngeal and esophageal stenosis, and skin necrosis.

In accordance with Kowalski et al,⁶ we believe that the oncological results for laryngeal cancer vary not only because of patient selection criteria and quality of medical care but also as a function of many other tumor and patient factors. Several demographic, clinical, pathological, and therapeutic characteristics have been reported to be prognostic for local control rate and overall survival of patients with laryngeal carcinoma. Although tumor stage has long been clinically accepted as the best single determinant of survival for patients with laryngeal cancer, prognosis is complex and may depend on several other risk factors such as age, sex, histological grade, margins of surgical resection, and lymph node involvement. Most of the studies of prognostic factors have been achieved by univariate analysis.³⁻⁸ Many prognostic factors are interrelated and their independent predictive effects on recurrence and survival cannot be readily demonstrated by the univariate analysis. Adequate investigation of the statistical association between prognostic factors and recurrence or survival time requires the use of regression models that allow accommodation of the effects of multiple covariables. In the present study, the knowledge concerning the relative importance of each risk factor analyzed for its association with recurrence and survival has been derived from studies based on univariate and multivariate analyses using Cox regression models. There have been few investigations in which the prognostic determinants for laryngeal carcinoma have been evaluated by univariate and multivariate methods.²⁻⁷ In particular, the paucity of studies based on uniformly treated patients with laryngeal cancer prompted us to conduct the present investigation. We thus carried out a univariate and multivariate statistical analysis of different possible prognostic factors in terms of survival and local control in a series of 253 patients uniformly treated with SCPL over a 16-year period.

With regard to local control, among the factors analyzed using the univariate model, the presence of positive surgical margins was the most important determinant for recurrence ($P=.002$; Figure 3) whereas sex ($P=.58$), T stage ($P=.32$), N stage ($P=.66$) and tumor stage ($P=.60$) were not significant. Also in the multivariate analysis, the presence of positive resection margins was the only significant factor, with respect to the P values of the other factors investigated, related with recurrence, even when adjusting for the others ($P=.06$; Table 2). None of the other factors investigated with multivariate analysis showed an independent effect on recurrence (Table 2). The risk of recurrence among the patients with positive margins after resection of the primary tumor was higher than in patients with negative margins (22.5% vs 6.1%; $P=.03$). Moreover, the presence of dysplastic lesions or invasive carcinoma at the resection margins had the same potential prognostic importance on the recurrence rate (27.3% vs 20.7%; $P=.07$; Figure 3). In fact, as

previously reported,²⁴ the presence of dysplastic lesions or invasive carcinoma at the margins of resection did not result in a significantly different proportion of recurrence, but rather in a different timing of recurrence. The patients with an invasive tumor at the margin developed local recurrence in a shorter period compared with those with dysplastic lesions. We think that the development of local recurrence in a shorter period depends on the biological characteristics of the tumor because dysplastic lesions and invasive carcinoma are 2 aspects of the same disease at different times. The prognostic importance of the involvement of surgical margins has been recorded in the literature.²⁴

Postoperative irradiation has been reported to improve survival among patients with positive surgical margins.²⁵ However, this has not been confirmed in our experience.²⁴ Postoperative treatment did not show a significant effect on recurrence (Table 2). Our finding of a strong influence of surgical margins on recurrence highlights the importance of the systematic study of surgical margins using frozen sections and that additional resection of laryngeal mucosa has to be performed whenever necessary to obtain free margins of resection. If the tumor extension did not remain within the limits of a partial resection, a total laryngectomy could be necessary.

With reference to survival, among the factors investigated in this study with univariate analysis, T stage, N stage, tumor stage, and recurrence were found to be the most important determinants of survival. In univariate analysis these factors were all significant, with recurrence being the most significant ($P<.001$; Figure 4). It is generally agreed in the literature that local extension of the primary tumor (T stage) is directly associated with prognosis. Also in our series, the univariate analysis showed that the patients with laryngeal cancer staged as T4 had a higher risk of death compared with those with less extended lesions ($P=.03$). Cervical lymph node metastasis is well known to be a prognostic negative factor with regard to survival for most head and neck tumors. A general tendency of poorer prognosis has been reported in the literature as a consequence of a higher number of larger or ruptured metastatic nodes. Considering the lymph node status, we demonstrated with univariate analysis that the size and the number of positive nodes (N stage) were associated with a poorer prognosis ($P=.03$). The most important determinant of survival in this group of variables was recurrence, which in our series was strongly associated with poor survival (Figure 4). This finding was confirmed in the multivariate analysis, which was carried out for age, type of surgery, histological grade, postoperative treatment, T stage, N stage, tumor stage, and recurrence, as well as the status of the resection margin. The only independent predictor factor for overall survival was recurrence, even when adjusting for the other factors ($P<.001$; Table 3). In fact, although salvage surgery can be performed, if the cancer recurs, the short-term prognosis is extremely poor.

From these data it was found that although a positive resection margin is the only predictor for recurrence and recurrence is the most important factor influencing survival, the resection margins do not have an independent

prognostic value in survival even when adjusting for the other factors. We believe that it depends on the strong individual association that T stage and N stage have in predicting death. Moreover, we were not able to demonstrate a significant correlation between a positive resection margin and advanced T stage. However, the influence of surgical margins on recurrence, demonstrated in multivariate analysis, highlights the role this factor plays in optimizing therapeutic strategies. In fact, when a positive margin is present, additional resection of laryngeal mucosa should be performed to obtain free margins of resection, and when tumor extension does not remain within the limits of a partial resection, a total laryngectomy may be necessary.

CONCLUSIONS

Supracricoid partial laryngectomy is widely accepted as treatment for selected laryngeal carcinomas classified as T1b and T2 and for selected cases of advanced laryngeal carcinoma classified as T3 to T4.²⁰⁻²² The correct application of oncological indications allow CHEP to be a valid alternative to partial laryngeal surgery and CHP to be a possible alternative for total laryngectomy with the creation of an adequate neolarynx from a functional point of view for both swallowing and speaking. Our experience, based on a large series of patients treated with a uniform surgical technique over a 16-year period, shows that oncological success depends on the respect of the indications for SCPL, as well as on the careful selection of patients. In fact, although salvage surgery can be performed, when recurrence occurs the short-term prognosis is extremely poor. We believe that the treatment results for laryngeal cancer vary not only according to patient selection criteria and quality of medical care but also to a function of several prognostic factors. The identification of unfavorable prognostic factors on local control and survival in patients with laryngeal cancer may improve the treatment strategies and follow-up planning. Even though the results are, for the most part, comparable to those reported in literature, the peculiarity of our study lies in the homogeneity of treatment performed in a large series of patients with laryngeal cancer with a long-term follow-up of up to 16 years.

Submitted for Publication: September 3, 2004; accepted March 22, 2005.

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Previous Presentation: This study was presented at the Sixth International Conference on Head and Neck Cancer; August 8, 2004; Washington, DC.

Acknowledgment: We thank Maria Grazia Saladino for help in the manuscript preparation.

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