Resection margins and other prognostic factors regarding surgically treated glottic carcinomas

Alexander D. Karatzanis, Frank Waldfahrer, George Psychogios, Joachim Hornung, Johannes Zenk, George A. Velegrakis, Heinrich Iro

Angaben zur Veröffentlichung / Publication details:

Karatzanis, Alexander D., Frank Waldfahrer, George Psychogios, Joachim Hornung, Johannes Zenk, George A. Velegrakis, and Heinrich Iro. 2009. "Resection margins and other prognostic factors regarding surgically treated glottic carcinomas." *Journal of Surgical Oncology* 101 (2): 131–36. https://doi.org/10.1002/jso.21449.

Resection Margins and Other Prognostic Factors Regarding Surgically Treated Glottic Carcinomas

ALEXANDER D. KARATZANIS, MD, PhD,[1,2†] FRANK WALDFAHRER, MD, PhD,[1†] GEORGE PSYCHOGIOS, MD, PhD,[1‡] JOACHIM HORNUNG, MD, PhD,[1†] JOHANNES ZENK, MD, PhD,[1§] GEORGE A. VELEGRAKIS, MD, PhD,[2‖] AND HEINRICH IRO, MD, PhD[1*,‖]

[1]*Department of Otorhinolaryngology, Head and Neck Surgery, University of Erlangen-Nuremberg Medical School, Erlangen, Germany*
[2]*Department of Otorhinolaryngology, Head and Neck Surgery, University of Crete Medical School, Heraklion, Crete, Greece*

Background and Objectives: This study aims to assess the prognostic significance of free histopathologic margins in the surgical treatment of glottic cancer. Furthermore, it evaluates other prognostic factors regarding cases that receive surgical management for glottic lesions.
Methods: A retrospective case-series study was conducted at an academic tertiary referral center. The files of 1,314 cases that underwent primary surgical treatment for glottic cancer were studied. Various prognostic factors, including age, surgical procedure, T classification, N classification, histological grade, and status of margins were assessed in univariate and multivariate analyses. All variables were investigated for their association with local and regional disease control as well as disease specific and overall survival.
Results: Status of margins significantly affected disease specific survival and local control regardless of tumor stage in this series. All other variables assessed in the univariate analysis for their association with survival were also found to be significant. However, status of surgical margins and N classification were the only significant variables in multivariate analysis.
Conclusion: The prognostic value of negative surgical margins for the treatment of glottic cancer cannot be overestimated. Responsibility of the surgeon during primary surgical treatment of glottic carcinomas is emphasized.

INTRODUCTION

Laryngeal cancer represents one of the most common head and neck malignancies, accounting for approximately 1.2% of all new cancer cases in Western societies [1,2]. Laryngeal cancer mostly affects middle-aged men with a history of tobacco and alcohol use. The peak incidence of the disease is between ages of 50 and 60 years. Male to female ratio is currently 5:1 with an expected increase in the proportion of women affected by laryngeal cancer during years to come [1]. Due to the important physiologic functions of the larynx as well as the increased incidence of the disease, cancer of the larynx is associated with significant morbidity and mortality for the patient, in addition to increased financial costs for society [2,3].

More than half of laryngeal cancer cases involve the glottis [1]. Due to the sparse lymphatics of the glottis as well as the early symptom of persistent hoarseness associated with glottic carcinoma, most cases can be diagnosed at an early stage. Therefore, complete cure is usually a realistic goal, thus making treatment of glottic cancer an issue of great importance [4]. Multiple options are available for the management of glottic cancer today [3,4]. Certain features, such as tumor exact location, the presence of cartilage invasion, and patient and physician choice, influence the treatment decision [2,4]. During recent years a great focus towards improved functional outcome has been given by most physicians treating patients with glottic cancer [5]. Originally it was the advent of combined chemotherapy and radiation protocols that gave rise to the term organ preservation. Nevertheless, a wide array of organ preservation surgeries for glottic cancer also exists today. New technology and instrumentation have opened the way for endoscopic minimally invasive strategies, while a renewed interest has also been witnessed regarding open preservation surgeries [5].

Whenever surgical management is selected for the treatment of cancer and no matter which type of surgery is used, the significance of achieving tumor-free surgical margins cannot be overstressed [6]. It has been widely accepted that complete excision of a tumor at the primary site is essential in order to ensure local control [7–9]. Therefore, the aim of any tumor surgery with therapeutic intent should be histologically confirmed disease-free margins [6]. Despite this common knowledge among surgeons, literature regarding the prognostic effects of positive margins for patients with laryngeal cancer is limited and inconsistent [10]. In this study, the prognostic significance of free margins in the surgical treatment of glottic cancer is assessed. In addition, other prognostic factors regarding patients undergoing surgical management for glottic lesions are evaluated.

METHODS

A retrospective study was conducted including patients newly diagnosed with glottic cancer between January 1970 and December

†Attending Otorhinolaryngologist.
‡ENT Resident.
§Professor.
‖Professor and Chairman.
*Correspondence to: Heinrich Iro, HNO Klinik, Kopf- und Halschirurgie, Universitatsklinikum Erlangen, Waldstr. 1, 91054 Erlangen, Germany. Fax: 09131-8536857. E-mail: heinrich.iro@uk-erlangen.de

2005, at an academic tertiary referral center (Department of Otorhinolaryngology, Head and Neck Surgery, University of Erlangen-Nuremberg Medical School, Erlangen, Germany). Relevant approval from the institutional review board of the hospital was obtained. The files of 1,532 cases in total were reviewed. Patients with insufficient data, systemic disease at the time of diagnosis, and histology other than squamous cell carcinoma, as well as patients admitted for primary radiotherapy were excluded from the study. Consequently, a total of 1,314 patients formed the final cohort of this study.

Follow-up end points included evidence of local and/or regional recurrence, and death from disease or other causes. Overall survival, representing the total mortality rate of patients, was calculated as the percentage of patients alive for more than 5 years divided by the total number of patients. Five-year disease specific survival, on the other hand, was defined as the percentage of patients alive for more than 5 years divided by the total number of patients who died of the tumor of interest. This rate included, therefore, only deaths specifically due to glottic cancer and excluded all other deaths in the patient group. Local and regional disease control, reflected the analysis of tumor recurrence in the primary site and the neck respectively, and were calculated from the date of surgery to the date of local or regional recurrence diagnosis respectively, or date of last follow-up. Local recurrence was defined as invasive carcinoma that developed after completion of initial treatment at the anatomic site of the primary tumor. Regional recurrence was defined as the presence of metastatic carcinoma in the lymph nodes of the neck developing after completion of initial treatment.

Various prognostic factors were investigated for their unadjusted association with local and regional disease control and disease specific survival in univariate analysis using the product-limit method of Kaplan–Meier and the long rank test. The covariates were also included in a multivariate analysis for their association with disease specific survival using Cox logistic regression method with backward selection. Variables such as age, surgical procedure, T classification, N classification, histological grade, and status of margins were all included in the univariate and multivariate analysis. The statistical software SPSS Version 16 (SPSS Inn., Chicago, IL) for Microsoft Windows was used for the analysis. A P value of less than 0.05 was considered statistically significant.

Tumors were staged according to the 2002 American Joint Committee on Cancer (AJCC) and the International Union against Cancer (UICC) classification [11]. Whenever necessary, TNM stage I and II tumors were grouped together and considered as early stage while III and IV were considered as advanced stage. All pathology reports were reviewed and surgical margins characterized by the presence of invasive carcinoma at the edge of resection on permanent section pathology were defined as positive. Accordingly, surgical margins not characterized by the presence of invasive carcinoma at the end of resection were defined as negative. Patients with positive margins at the end of surgical treatment were further evaluated for disease specific survival with regard to postoperative type of management. In all of these cases additional surgery had not been feasible for various reasons and their management included either radiotherapy, sometimes combined with chemotherapy, or close follow-up leaving further treatment for later if necessary. Decision regarding choice of management had been individualized for each patient. Factors considered in the selection of treatment for each case included patient wish, reliability of close clinical surveillance, presence of comorbidities, and the effect of adjuvant treatment on functional outcome.

RESULTS

Of the 1,314 patients finally included in the study, 1,233 (93.8%) were men and 81 (6.2%) were women. Male to female ratio was 15:1. Mean age in the study group was 61 years, ranging between 15 and 97 years. Mean follow-up period was 67.9 months. According to the pathology reports, 1193 (90.7%) patients had negative surgical margins (R0) while 121 (9.3%) had positive margins (R+). Disease specific survival for the R0 group was significantly better compared to the R+ group (92.6% vs. 64.1%, $P < 0.001$), as shown in Table I and Figure 1. The R0 group included all patients with negative surgical margins regardless of the number of procedures that were necessary in order to achieve such margins. This was made possible due to the fact that patients who needed more than one operations—two in the vast majority—in order to achieve R0 status (235 cases) were found to have comparable survival rates with those where negative margins were achieved after a single procedure (944 cases, disease specific survival 92.8% vs. 91.3%, $P = 0.893$). It should be noted that in 12 cases re-resection margins were undetermined and these were excluded from this evaluation.

Local and regional control rates for the R0 group were 85.1% and 98.5% respectively. These rates were 60.3% and 94.6% respectively for the R+ group (Table I). Differences among the two groups for local control were statistically significant ($P < 0.001$). As previously shown with disease specific survival, among cases with R0 status local control was similarly not affected by the number of procedures necessary in order to achieve such status: in the 944 cases where a single operation had been sufficient local control was found to be 86.3%, while in the 235 cases where more than one—typically two—procedures had been necessary local control was 82.5% ($P = 0.772$).

Status of surgical margins significantly affected disease specific survival even when cases with early (95.7% for R0 vs. 79.4% for R+, $P < 0.001$) and advanced (76.4% for R0 vs. 29.4% for R+, $P < 0.001$) TNM stage tumors were separately evaluated, as shown in Figure 2. Among early stage cases with R0 status the number of procedures necessary again did not affect prognosis: 783 cases with free margins after one procedure and 198 cases where multiple operations were necessary showed comparable oncologic results (disease specific survival 95.7% vs. 91.8% $P = 296$, local control 94.6% vs. 92.8% $P = 0.621$).

Overall distribution of cases according to T classification of disease, with respective survival and disease control rates are presented in Table II. Furthermore, type of surgery and number of patients undergoing each procedure with respective survival and disease control rates are presented in Table III. In addition, this table shows the incidence of positive surgical margins with respect to type of surgery.

TABLE I. Five-Year Overall and Disease Specific Survival Rates, in Addition to Local and Regional Control Rates With Respect to Surgical Margin Status

Surgical margin status	Number of cases (%)	Overall survival (%)	Disease specific survival (%)	Local control (%)	Regional control (%)
R0	1,193 (90.7%)	71.5	92.6	85.1	98.5
R+	121 (9.3%)	43.2	64.1	60.3	94.6
P-value		$P < 0.001$	$P < 0.001$	$P < 0.001$	$P = 0.38$

R0, cases with negative surgical margins; R+, cases with positive surgical margins.

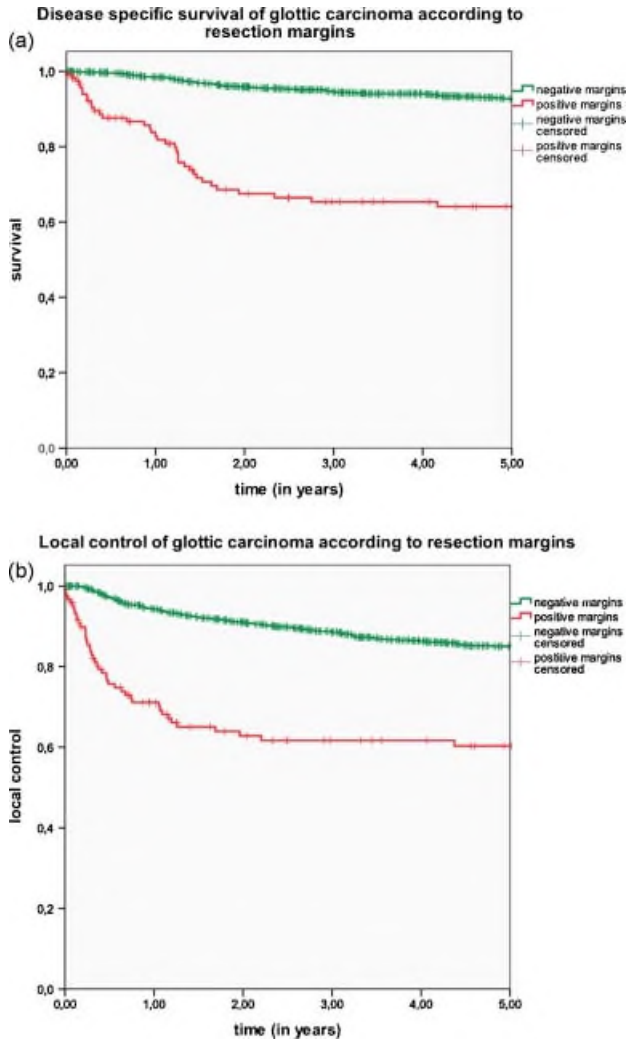

Fig. 1. Kaplan–Meier analysis of (**a**) disease specific survival (92,6% vs. 64.1%, $P < 0.001$) and (**b**) local control (85.1% vs. 60.3%, $P < 0.001$) for patients with negative (R0) and positive (R+) surgical margins. [Color figure can be viewed in the online issue, available at www.interscience.wiley.com.]

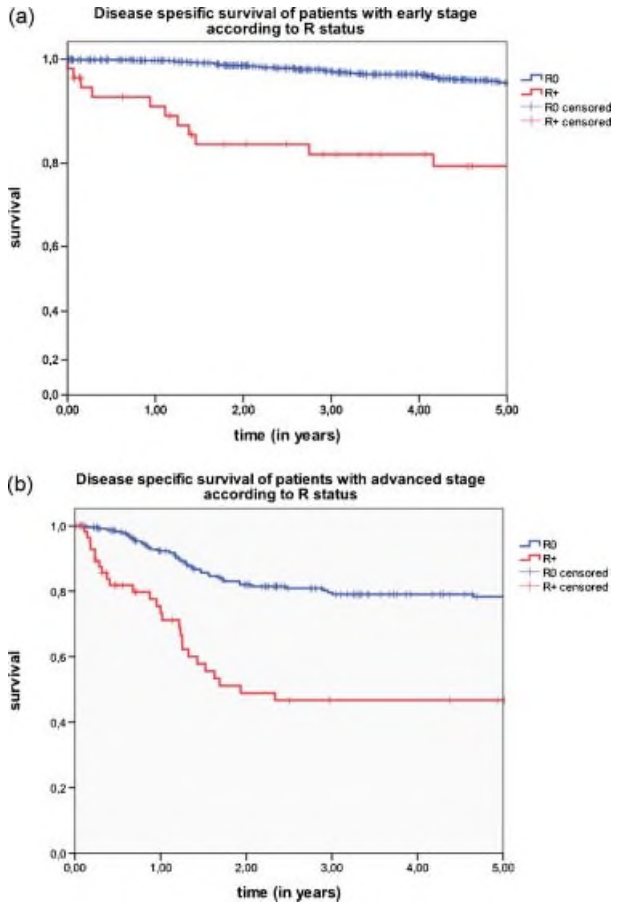

Fig. 2. Kaplan–Meier analysis of disease specific survival according to status of surgical margins for patients with (**a**) early (95.7% vs. 79.4%, $P < 0.001$), and (**b**) advanced, TNM stage (76.4% vs. 29.4%, $P < 0.001$). R0: cases with negative surgical margins. R+: cases with positive surgical margins. [Color figure can be viewed in the online issue, available at www.interscience.wiley.com.]

Distribution of patients with positive surgical margins according to postoperative type of management, with respective survival and disease control rates, are shown in Table IV. Disease specific survival was found to be significantly better for cases initially placed on follow-up (73.4% vs. 48.5%, $P = 0.036$). However, when cases with early and advanced stage tumors were separately evaluated a trend towards better disease survival was noted for follow-up cases compared to cases receiving radiotherapy, but statistical significance was not reached (Early stage: 84.6% vs. 84.1% respectively, $P = 0.27$. Advanced stage: 56.2% vs. 36.0% respectively, $P = 0.269$).

All remaining variables assessed in the univariate analysis for their association with disease specific survival, including age ($P < 0.001$), type of surgical procedure ($P < 0.001$), and histological grade ($P = 0.002$), were found to be significant. On the other hand, status of surgical margins and N classification were found to be the only significant variables in multivariate analysis. Age, T classification, type of surgical procedure and histological grade were not found to be significant. Multivariate analysis results are presented in Table V.

TABLE II. Overall Distribution of Cases According to Local Stage (T Classification) of Disease, With Respective Survival and Local Control Rates

T classification	Number of patients (%)	Disease specific survival (%)	Overall survival (%)	Local control (%)
pTis	111 (8.4)	98.9	80.3	87.3
pT1	554 (42.2)	96.5	81.0	86.9
pT2	398 (30.2)	90.8	66.2	82.7
pT3	122 (9.2)	78.7	44.1	78.3
pT4	120 (9.1)	59.5	39.1	64.5
Non-specified	9 (0.6)	88.9	51.9	72.9

TABLE III. Types of Different Surgical Procedures With Respective Survival and Disease Control Rates, as well as Incidence of Positive Surgical Margins

Surgical technique	Number of patients	Overall survival (%)	Disease specific survival (%)	Local control (%)	Incidence of positive resection margins (%)
Transoral laser surgery	662	73.5	93.4	83.1	9.3
Open chordectomy	51	87.4	100	88.5	0
Vertical hemilaryngectomy	329	68.7	89.3	80.9	6.7
Supracricoid laryngectomy	23	68.3	68.3	65.5	43.4
Total laryngectomy	188	44.4	73.2	79.3	12.7
Others	61	81.2	96.6	92.0	6.5

DISCUSSION

Billroth is credited for performing the first total laryngectomy for cancer in 1873 [12]. Over time not only has the procedure of total laryngectomy been modified, but also less radical operations aiming on voice and swallowing preservation have emerged [13]. Today, surgical management of glottic cancer is characterized by marked diversity, while its role and indications with regard to other available treatment modalities, such as radiotherapy, remain a subject of continuous controversy [13,14]. Consequently, there is considerable debate on treatment of glottic cancer with regard to local control, laryngeal preservation rates, survival, functional outcome, and salvage options for treatment failures [4,15]. Nevertheless, in many countries today surgical resection remains the most frequently chosen treatment for the management of laryngeal cancer [16].

Surgical treatment of glottic cancer includes external total or partial surgery and more recently transoral laser surgery [14]. Transoral laser surgery is an established mode of treatment for early and moderately advanced glottic carcinomas [4,5,17]. This approach allows early stage tumors to be totally removed with minimal functional cost for the vocal cords [14]. In addition, laser surgery may offer favorable outcomes in selected cases of advanced or recurrent glottic cancer, with relatively low morbidity and mortality [18]. In our series, the largest amount of patients with glottic cancer were treated by transoral laser microresection (662 subjects, 50.38%). Cordectomy performed through a laryngofissure, although popular in the past, is now infrequently utilized for the management of early carcinoma of the true vocal cord. Although this is a very effective procedure with regard to tumor control, voice quality is significantly inferior compared with other available treatment modalities [3,4,19]. Only 51 (3.8%) patients were managed by open cordectomy in our series. Other forms of laryngeal conservation surgery, including vertical hemilaryngectomy, have been used in order to control more advanced glottic carcinoma while preserving laryngeal function to some extent [19,20]. Vertical hemilaryngectomy was performed on 329 (25.1%) patients in our series. Finally, total laryngectomy, which is traditionally the standard against which all other forms of treatment must be measured [19], was performed on 188 (14.3%) patients. Considering the fact that laser microsurgery has been introduced in clinical practise much later compared to all other surgical techniques, it becomes obvious from these results that today the vast majority of surgically treated glottic carcinomas undergo laser microresection.

No significant differences in survival rates among patients undergoing different surgical procedures were noted in our series, with the exception of total laryngectomy which was related with significantly low overall survival (Table III). Nevertheless, such a finding should not be viewed independently, but only in relation to the tumor stage which greatly affects the decision to perform a specific operation. Consequently, more advanced carcinomas would necessitate the performance of more radical procedures and would, at the same time, be associated with poorer prognosis. Other factors, such as age should also be taken into account, since total laryngectomy cases in our series had a higher mean age, therefore explaining a lower overall survival when, at the same time, disease specific survival remained comparable with other procedures.

When evaluating a patient with laryngeal carcinoma, a thorough diagnostic work-up is essential in order first to decide if surgery is indicated and then which procedure can lead to maximum tumor control and functional outcome. Nevertheless, despite detailed preoperative diagnostic assessment, complete surgical resection of the primary tumor is not always feasible. Tumor size and specific anatomic location are two main reasons for this potential discrepancy [8,21,22]. The histologically confirmed presence of tumor at the resection margin of a surgical specimen is described in the literature as a positive tumor margin [8,11]. On the other hand, the significance of the presence of invasive carcinoma near the border of resection remains an issue under debate [11]. Size of an oncologically safe resection margin seems to depend on the anatomic site [10]. With regard to the

TABLE IV. Distribution of Cases With Positive Surgical Margins (R+) According to Postoperative Management, With Respective Survival Rates

Type of management	Number of patients	Overall survival (%)	Disease specific survival
Total follow-up	74 (61.2%)	54.4	73.4%
Total RT	47 (38.8%)	27.2	48.5% ($P = 0.036$)
Early stage follow-up	44	48.5	84.6%
Early stage RT	18	66.5	81.1% ($P = 0.27$)
Advanced stage follow-up	30	45.1	56.2%
Advanced stage RT	29	17.1	36.0% ($P = 0.269$)

Total follow-up, total number of cases that were placed on close follow-up leaving further treatment for later if necessary; Total RT, total number of cases that received postoperative radiotherapy, alone or combined with chemotherapy; Early stage follow-up, TNM stage I and II cases that were placed on follow-up; Early stage RT, TNM stage I and II cases that received postoperative radiotherapy, alone or combined with chemotherapy; Advanced stage follow-up, TNM stage III and IV cases that were placed on follow-up; Advanced stage RT, TNM stage III and IV cases that received postoperative radiotherapy, alone or combined with chemotherapy.

TABLE V. Multivariate Analysis of Variables Predicting Overall Survival

R-status	$P < 0.001$, OR = 1.013, 95% CI: 1.009–1.017
N-stage	$P < 0.001$, OR = 1.010, 95% CI: 1.006–1.014
Histological grade	$P = 0.075$, OR = 0.952, 95% CI: 0.902–1.005
T-stage	$P = 0.263$, OR = 1.004, 95% CI: 1.002–1.006
Type of surgical procedure	$P = 0.603$, OR = 1.002, 95% CI: 0.995–1.009
Age	$P = 0.743$, OR = 1.001, 95% CI: 0.983–1.019

OR, odds ratio; CI, 95% confidence interval.

head and neck region, oral cavity and pharyngeal tumors have shown an increased propensity for submucosal spread warranting perhaps a wide resection margin [23]. On the other hand, due perhaps to the lack of lymphatic drainage in the glottic region, surgical achievement of wide margins seems to be of minor importance in this area as these have not been associated with better local control [10,23]. In addition, such margins could obviously have a negative effect on functional outcomes when organ preservation surgery is performed. Consequently, in the present study, all pathology reports were reviewed and resection margins were considered as positive in cases where invasive carcinoma was present at the border of resection on permanent pathology sections. The incidence of positive resection margins in the head and neck area varies from 3% to 60% [24]. Such a significant variation could be the result of a different interpretation of tumor free margins, as well as a high percentage of locally advanced carcinomas in certain reports [10]. Nevertheless, an incidence of approximately 10% should be realistically expected in most series [10,24]. This is in agreement with the results in our study where the overall incidence of positive resection margins was 10.2%.

No significant differences were noted in our series regarding the incidence of positive resection margins among different types of surgical procedures. The only exception was supracricoid partial laryngectomy where a surprisingly high rate of positive surgical margins was found. Although a lower incidence of positive margins should be expected with more radical procedures, these procedures are more often advocated with more advanced disease, thus making the interpretation of results rather difficult. Nevertheless, it should be emphasized that the application of laser for the treatment of laryngeal cancer generally offers significant advantages with regard to margin control, as it allows for easy, repeated and direct access to the tumor site [4,6,18]. On the other hand, laser surgery may pose increased difficulties in order for pathologists to reliably assess the status of tumor resection margins [4,6,14]. Reasons for this discrepancy are related to the nature of CO_2 laser itself and include tissue contraction and evaporation, heat artifacts, or even small size of samples [6]. Such difficulties often result in surgical margins falsely assessed as positive or undetermined on permanent histology [6,14]. However, an acceptable incidence (9.3%) of positive margins for laser surgery was noted in our series.

It has been previously established that patients with head and neck cancer exhibiting positive resection margins have significantly higher rates of local or regional recurrence and even show decreased survival [6–8]. However, knowledge regarding specifically the prognostic effect of positive margins in patients with laryngeal cancer is not very extensive [10,25]. This report focuses on the prognostic significance of surgical margins for glottic carcinoma cases in particular. In our series, local disease control rate was 85.1% for patients with negative surgical margins and 60.3% for patients with positive margins. Difference between the two groups was found to be significant ($P < 0.001$). Although surgical margin status strongly affected local control in our series, regional control showed no significant differences between cases with negative and positive surgical margins (Table I). This comes in agreement with the common knowledge among surgeons that an oncologic procedure with safe surgical margins represents the best chance in order to achieve local control of the disease [7–9].

Disease specific survival was also found to be significantly better for patients with negative surgical margins compared to patients with positive margins (Fig. 1). Impact of surgical margin status on survival remained significant even when cases with early (I and II) and advanced (II and IV) stage of disease were separately evaluated (Fig. 2). This was done in order to eliminate the potential additional effect of disease stage on prognosis. Results showed that status of surgical margins significantly affects oncologic outcome regardless of accompanying disease stage. On the other hand, positive resection margins were found to be more often associated with advanced T classification carcinomas. This result was statistically significant suggesting that, as would be expected according to common sense, an increased incidence of positive resection margins should be anticipated when treating locally advanced carcinomas.

It should be noted that the R0 group in our series included all cases with negative surgical margins, regardless of the number of procedures necessary in order to achieve such margins. As previously mentioned, this was made possible due to the fact that cases with R0 status after one or more than one surgical procedures were found to have comparable oncologic results. By combining these cases together, larger groups were made available for statistical evaluation. In addition, this finding revealed an increased significance of repeated surgery in cases where residual disease is found on the resection borders of permanent histology sections, since it is not the number of surgical procedures but the final histologic status that actually affects prognosis.

Postoperative management of patients with positive surgical margins is a controversial issue [6,10]. Revision surgery has been shown to be a valid option for such cases [7]. Moreover, it has been suggested that postoperative radiotherapy may protect patients from local recurrence whenever surgical margins are compromised and additional surgery is not feasible [6,10]. Conversely, it has also been stated that close follow-up, leaving further treatment for later if necessary, might represent the best management option for these cases arguing that radiation therapy may compromise functional recovery and also prevent early detection of recurrences [10]. Subjects with compromised resection margins at the end of surgical treatment in this series were either treated by postoperative radiotherapy, sometimes combined with chemotherapy, or received no adjuvant treatment and were placed on close follow-up, leaving further management for later if necessary (Table IV). It should be noted that all cases in this group had either refused to undergo further surgery or had been considered poor surgical revision candidates due to other factors such as general health status. Interestingly, cases that were initially placed on follow-up showed significantly better disease specific survival rates compared with cases that underwent radiotherapy. When early and advanced disease stage cases were separately evaluated, however, survival rates were found to be comparable (Table IV). Nevertheless, these results suggest that close follow-up, leaving further treatment for later if necessary, is a valid option for cases with positive surgical margins, at least when further surgery is not an option. Radiotherapy, on the other hand, does not seem to offer increased survival rates for this specific group of patients.

Among the other variables that were assessed for their association with survival, including age, type of surgical procedure, histologic grade, T classification, and N classification, all were found to be significant on univariate analysis. On multivariate analysis, only N classification and status of surgical margins were found to be significant variables in this study (Table V). Statistical significance of N classification emphasizes the need for timely diagnosis and management of glottic cancer, since regional disease is quite uncommon during early local stages. On the other hand, age, type of surgical procedure, histological grade, and, interestingly, T classification, were not found to be significant on multivariate analysis.

CONCLUSION

Surgical management generally offers satisfactory oncologic results in glottic cancer as long as free histopathologic margins can be achieved. The surgeon's responsibility during primary treatment of glottic lesions is therefore emphasized.

REFERENCES

1. Chu EA, Kim YJ: Laryngeal cancer: Diagnosis and preoperative work-up. Otolaryngol Clin N Am 2008;41:673–695.
2. Davis GE, Schwartz SR, Veenstra DL, et al.: Cost comparison of surgery vs organ preservation for laryngeal cancer. Arch Otolaryngol Head Neck Surg 2005;131:21–26.
3. Starmer HM, Tippet DC, Webster KT: Effects of laryngeal cancer on voice and swallowing. Otolaryngol Clin N Am 2008;41:793–818.
4. Agrawal N, Ha PK: Management of early-stage laryngeal cancer. Otolaryngol Clin N Am 2008;41:757–769.
5. Tufano RP, Stafford EM: Organ preservation surgery for laryngeal cancer. Otolaryngol Clin N Am 2008;41:741–755.
6. Jackel M, Ambrosch P, Martin A, et al.: Impact for re-resection for inadequate margins on the prognosis of upper aerodigestive tract cancer treated by laser microsurgery. Laryngoscope 2007; 117:350–356.
7. Batsakis JG: Surgical margins in squamous cell carcinomas. Ann Otol Rhinol Laryngol 1988;97:213–214.
8. Iro H, Waldfahrer F, Altendorf-Hofmann A, et al.: Transoral laser surgery of supraglottic cancer. Arch Otolaryngol Head Neck Surg 1998;124:1245–1250.
9. Pfreudner L, Willner J, Marx A, et al.: The influence of the radicality of resection and dose of postoperative radiation therapy on local control and survival in carcinomas of the upper aerodigestive tract. Int J Radiat Oncol Biol Phys 2000;47: 1287–1297.
10. Gallo A, Manciocco V, Tropiano ML, et al.: Prognostic value of resection margins in supracricoid laryngectomy. Laryngoscope 2004;114:616–621.
11. American Joint Committee on Cancer (AJCC). Manual for staging of cancer. 6th edition. New York, NY: Springer-Verlag; 2002. pp. 47–57.
12. Weir NF: Theodore Billroth: The first laryngectomy for cancer. J Laryngol Otol 1973;87:1161–1169.
13. Agrawal N, Goldenberg D: Primary and salvage total laryngectomy. Otolaryngol Clin N Am 2008;41:771–780.
14. Sigston E, de Mones E, Babin E, et al.: Early stage glottic cancer. Oncological results and margins in laser cordectomy. Arch Otolaryngol Head Neck Surg 2006;132:147–152.
15. Hoffman HAT, Porter K, Karnell LH, et al.: Laryngeal cancer in the United States: Changes in demographics, patterns of care, and survival. Laryngoscope 2006;116:1–13.
16. Yilmaz T, Turan E, Gürsel B, et al.: Positive surgical margins in cancer of the larynx. Eur Arch Otorhinolaryngol 2001;258:188–191.
17. Steiner W: Experience in endoscopic surgery of malignant tumors of the upper aerodigestive tract. Adv Otorhinolaryngol 1988; 39:135–144.
18. Grant DG, Salassa JR, Hinni ML, et al.: Transoral laser microsurgery for recurrent laryngeal and pharyngeal cancer. Otolaryngol Head Neck Surg 2008;138:613.
19. Eibling DE: Surgery of glottic carcinoma. In: Myers EN, editor. Operative otolaryngology, head and neck surgery. Philadelphia, PA: Saunders WB; 1997. pp. 416–443.
20. Spector JG, Sessions DG, Lennox J, et al.: Management of T3N1 glottic carcinoma: Therapeutic outcomes. Laryngoscope 2006; 116:106–110.
21. Chone CT, Yonehara E, Martins JEF, et al.: Importance of anterior commissure in recurrence of early glottic cancer after laser endoscopic resection. Arch Otolaryngol Head Neck Surg 2007; 133:882–887.
22. Roh JL, Kim DH, Park CI: The utility of second-look operation after laser microresection of glottic carcinoma involving the anterior commissure. Laryngoscope 2008;118:1400–1404.
23. Lee JG: Detection of residual carcinoma of the oral cavity, oropharynx, hypopharynx and larynx: A study of surgical margins. Trans Am Acad Opthalmol Otolaryngol 1974;78:49–53.
24. Jacobs JR, Ahmad K, Casiano R, et al.: Implications of positive surgical margins. Laryngoscope 1993;103:64–68.
25. Thabet MH, Talaat M, Rizk AM: Pitfalls in the surgical management of cancer of the larynx and hypopharynx. Otolaryngol Head Neck Surg 2000;123:482–487.