Surgical margins and prognosis in the treatment of laryngeal carcinoma with CO_2 laser

Original Article

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Abstract

Introduction: Surgical treatment of laryngeal cancer has evolved in recent decades to preserve organ function without compromising oncological safety. Transoral microsurgery with CO2 laser (TLM) has been widely adopted in the early stages of laryngeal cancer due to its effectiveness in tumor resection and organ preservation. However, the narrower safety margins compared to open techniques may increase the risk of local recurrence, highlighting the importance of close follow-up and identifying prognostic factors that influence local control and recurrence.

Objectives: The study aimed to identify prognostic factors associated with local control and recurrence in patients undergoing TLM for the treatment of laryngeal cancer.

Material and Methods: Patients with T1-T2 glottic carcinoma treated between 2013 and 2022 were included. Variables related to patient (age, gender, comorbidities, biomarkers), tumor (extent, staging, anterior commissure involvement) and treatment (surgical margins, need for adjuvant therapy) were assessed. Immediate local control (ILC) was defined by achieving negative margins after TLM. Complete local control (CL2) was defined as achieving local control with TLM as the only therapeutic intervention, regardless of the number of procedures performed, at least two years after the first procedure. Statistical analysis included univariate tests and binary logistic regression.

Results: 51 patients were analyzed (mean age 64.2 years), with CLi and CL2 rates of 52.9% and 82.4%, respectively, and an organ preservation rate of 94.1% at two years. CLi was significantly associated with early-stage tumors and without supra/subglottic involvement, with p-values of 0.005 and 0.033, respectively. Regarding CL2, it showed a significant association with lower platelet/lymphocyte ratio, absence of anterior commissure involvement, early-stage tumors and lower alcohol consumption, with p-values of 0.049, 0.039, <0.001 and 0.039, respectively. Binary logistic regression analysis confirmed these associations, highlighting that CLi was significantly associated with early-stage tumors (OR: 8.68; 95% CI: 1.35-101.41; p = 0.047), while CL2 was associated with

both early-stage tumors (OR: 57.24; 95% CI: 4.13-793.09; p = 0.003) and lower platelet/lymphocyte ratio (OR: 0.99; 95% CI: 0.99-0.999; p = 0.019).
Conclusions: TLM was shown to be effective and safe in the treatment of laryngeal cancer, with high rates of disease control and organ preservation. Factors such as tumour staging and platelet/lymphocyte ratio had a significant impact on outcomes. Careful assessment of these factors can optimize the treatment and follow-up of these patients.
Keywords: Transoral microsurgery using CO2 laser, Glottic carcinoma, Local control, Recurrence.

Introduction

In recent decades, surgical management of laryngeal carcinoma has progressed toward approaches that preserve organ function without compromising oncological safety. Transoral laser microsurgery (TLM), a minimally invasive technique, has been widely adopted in specialized centers for the treatment of early-stage laryngeal carcinoma due to its effectiveness in achieving complete tumor resection with clear margins[1]. However, acceptable safety margins in the larynx following TLM are narrower compared to those after open surgical techniques, potentially increasing the risk of local recurrence and compromising organ preservation[2]. This concern highlights the need for strict postoperative monitoring to enable early detection and timely management of recurrences[3].

Local disease control is the primary objective in the treatment of laryngeal carcinoma, as local recurrence is associated with poor outcomes, requires more aggressive interventions, and reduces the life expectancy and quality of life[3]. The identification of prognostic factors influencing local control and recurrence is essential for tailoring therapeutic strategies. This can help in optimizing the initial treatment and ensuring more targeted follow-up[4].

Although several studies have investigated factors such as demographic characteristics, preoperative biomarkers, tumor extent and staging, and treatment-related parameters, data specifically related to TLM remain limited. A better understanding of the factors affecting local control may improve clinical outcomes and reduce recurrence rates through more effective follow-up strategies[5].

Objectives

This study aimed to identify the prognostic factors associated with local control and recurrence in patients undergoing TLM for laryngeal carcinoma.

Materials and Methods

This study included patients diagnosed with laryngeal carcinoma, staged as T1-T2 glottic tumors, who underwent surgical treatment between January 2013 and December 2022. Patient-related, tumor-related, and treatment-related variables were analyzed in a cohort that was followed up for at least two years at a single institution.

All procedures were performed under general anesthesia. Tumor resection was conducted using a superpulse mode laser (2–15 W), according to the surgeons' preferences.

Postoperative surgical margins were classified as positive, indeterminate, or negative. Positive margins demonstrated evident tumor infiltration. Margins were defined as indeterminate when the specimen was insufficient, when carbonization hindered proper evaluation, or when the tumor cells were found within < 2 mm of the margin. Negative margins showed no evidence of tumor infiltration, with tumor cells located ≥ 2 mm from the margin.

Surgical specimens were marked and oriented before being sent to the department of pathology. The need for adjuvant therapy (radiotherapy and/or chemotherapy) was assessed individually for each patient.

The primary outcomes assessed were:

- Immediate local control with TLM (iLC), defined as achieving negative margins after TLM, and two-year local control with TLM (2LC), defined as sustained disease control after TLM as the sole treatment modality, regardless of the number of procedures required. Local control was considered unsuccessful

in cases requiring adjuvant therapy due to persistent positive margins or conversion to radical surgery. However, in cases where adjuvant treatment was indicated because of poor prognostic or local disease factors (extracapsular extension, vascular invasion, or perineural invasion in the surgical specimen) despite negative surgical margins, disease control was considered to have been achieved.

Evaluated parameters:

- Patient-related variables included age, sex, excessive alcohol consumption (≥ 60 g/day), diabetes mellitus (DM), arterial hypertension (HTN), gastroesophageal reflux disease (GERD), and preoperative biomarkers (neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and absolute lymphocyte count.
- Tumor-related variables included tumor extent (supraglottic and/or subglottic), anterior commissure involvement, T stage, and pathologic tumor (pT) classification (early stages: pTis [in situ], pT1; intermediate stage: pT2).
- Treatment-related variables included the margin status (positive, indeterminate, or negative), need for adjuvant therapy, and organ preservation rate.

Preoperative medical records were analyzed for medical history of HTN, DM, and GERD. A patient was classified as having a medical condition when the diagnosis was mentioned in their medical records or when the patient was taking medications prior to the surgery. Patients were grouped according to the presence of continuous pharmacological treatment or mention of these conditions in the medical records.

Statistical analysis was performed using the SPSS® software, version 4.1.29 (IBM Corp., Armonk, NY, USA). Initially, descriptive statistics were used to characterize the sample, including means, standard deviations (SD), and proportions. Subsequently, univariate analysis was conducted to identify the associations among the variables. Categorical variables were analyzed using the chi-square or Fisher's exact test. Continuous variables were analyzed using the Student's t-test or Mann–Whitney test, depending on the data distribution.

Multivariate analysis was performed using binary logistic regression to identify the independent factors associated with immediate local control within a defined timeframe, considering positive, indeterminate, or negative margins. Results were reported as odds ratio (OR) with 95% confidence intervals (95% CI). A p-value < 0.05 was considered statistically significant.

Results

The study included 51 patients with laryngeal carcinoma who underwent curative treatment using TLM. The average patient age was 64.22 years (SD = 9.17). Sociodemographic data, tumor characteristics, and treatment details are shown in Table 1. The iLC and 2LC rates were 52.9% and 82.4%, respectively. The organ preservation rate after two years was 94.1%.

Among the nine patients (17.6%) who required adjuvant therapy, two achieved disease control with TLM alone; however, due to adverse prognostic factors identified in the surgical specimen, additional treatment was indicated. The remaining seven patients had positive surgical margins. All these data are detailed in Table 1. In the univariate analysis (tables 2 and 3), iLC was significantly associated with early-stage tumors (pTis/pT1, p = 0.005) and the absence of supraglottic and/or subglottic involvement (p = 0.033). Moreover, 2LC showed significant associations with a low PLR (p = 0.049), absence of supraglottic and/or subglottic involvement (p = 0.002), absence of anterior commissure involvement (p = 0.039), and early-stage tumor classification (p < 0.001). Notably, excessive alcohol consumption (≥ 60 g/day) significantly affected 2LC (p = 0.039). Multivariate logistic regression analysis (table 4) revealed a significant association between iLC and early-stage tumor classification (OR: 8.68; 95% CI: 1.35–101.41; p = 0.047); 2LC was also significantly associated with early-stage tumor classification (pTis/T1) (OR: 57.24; 95% CI: 4.13–793.09; p = 0.003) and showed an inverse correlation with PLR (OR: 0.99; 95% CI: 0.99–0.999; p = 0.019).

Table 1
Patient characteristics

Variable	No. of patients (%)
Sociodemographic characteristics	
Age	64,22 ± 9,17 (47-81)
Sex Male Female	 49 (96,1) 2 (3,9)
HTN	26 (51,0)
DM	12 (23,5)
GERD	19 (37,3)
Alcohol consumption < 60 g/day ≥ 60 g/day	 36 (70,6) 15 (29,4)
Biomarkers	
NLR	2,82 ± 1,99 (0,58-11,26)
PLR	124,16 ± 66,08 (46,73-326,25)
Absolute lymphocyte count	2,10 ± 0,87 (0,74-5,50)
Tumor characteristics	
Supraglottic and/or subglottic involvement	18 (35,3)
Anterior commissure involvement (y/n)	18 (35,3)
pT stage pTis pT1 pT2	 6 (11,8) 31 (60,8) 14 (27,5)
Stage Initial (pTis, pT1) Intermediate (pT2)	 37 (72,5) 14 (27,5)
Treatment	
Local control after the first TLM Negative margins Indeterminate margins Positive margins	 27 (52,9) 13 (25,5) 11 (21,6)
Adjuvant treatment CTRT RT	 2 (3,9) 7 (13,7)
Local disease control after 2 years	42 (82,4)
Organ preservation after 2 years	48 (94,1)

TLM, transoral laser microsurgery; DM, diabetes mellitus; HTN, arterial hypertension; GERD, gastroesophageal reflux disease; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RT, radiotherapy; CTRT, chemoradiotherapy.

Table 2
Univariate analysis of iLC and 2LC

Variable	iLC (%)	p	2LC (%)	p
Sex (m/f)	81.6 vs 50.0	.266	83.7 vs 50.5	.325
HTN (y/n)	76.0 vs 80.8	.679	88.0 vs 76.9	.253
DM (y/n)	66.7 vs 82.1	.227	83.3 vs 82.1	.646
GERD (y/n)	84.2 vs 75.0	.343	94.7 vs 75.0	.074
Alcohol consumption (< 60 g/day vs ≥ 60 g/day)	75.0 vs 86.7	.300	**88.9 vs 63.9**	**.039**
Supraglottic and/or subglottic involvement (y/n)	**61.1 vs 87.9**	**.033**	**61.1 vs 93.9**	**.006**
Anterior commissure involvement (y/n)	77.8 vs 78.8	**.599**	**66.7 vs 90.9**	**.039**
Staging (initial/intermediate)	**89.2 vs 50.0**	**.005**	**97.3 vs 42.9**	**<.001**

iLC, immediate local control with transoral laser microsurgery; 2LC, two-year local control with transoral laser microsurgery; DM, diabetes mellitus; HTN, arterial hypertension; GERD, gastroesophageal reflux disease;

Table 3
Univariate analysis of iLC and 2LC

Variable	iLC (r)	p	2LC (r)	p
Age	-.044	.759	-.221	.120
NLR	.335	.044	.080	.761
PLR	.079	.580	**-.314**	**.049**
Absolute lymphocyte count	-.042	.769	.145	.311

iLC, immediate local control with transoral laser microsurgery; 2LC, two-year local control with transoral laser microsurgery; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio

Table 4
Factors associated with iLC and 2LC in multivariate logistic regression analysis

	OR	CI	p
iLC			
Supraglottic and/or subglottic involvement	.939	.083-11.014	.960
Staging (initial*/intermediate)	8.684	1.354-101.412	**.047**
2LC			
Alcohol consumption (< 60 g/day vs ≥ 60 g/day*)	2.582	.250-27.011	.430
Supraglottic and/or subglottic involvement	.673	.123-15.011	.923
Anterior commissure involvement	5.211	.542-50.493	.154
Staging (initial*/intermediate)	57.23	4.131-793.084	**.003**
PLR	.991	.990-.999	**.019**

iLC, immediate local control with transoral laser microsurgery; 2LC, two-year local control with transoral laser microsurgery; PLR, platelet-to-lymphocyte ratio; OR, odds ratio; CI, confidence interval. The asterisk (*) indicates the reference category used in the logistic regression analysis

Discussion

The results of this study support the role of TLM as a safe and effective therapeutic strategy for laryngeal carcinoma. The high rates of organ preservation (94.1%) and overall disease control (82.4%) in this study are consistent with the findings in the existing literature supporting TLM as a minimally invasive alternative to more aggressive open surgery or isolated radiotherapy[6–8]. TLM offers surgical precision with reduced morbidity, enabling faster recovery and better preservation of laryngeal

function[9]. Among the tumor-related variables, anterior commissure involvement was associated with reduced 2LC in the univariate analysis (p = 0.039). This finding aligns with the results of previous studies highlighting the anatomical complexity of the anterior commissure and its negative influence on local tumor control[10–13]. While initial disease control may be achieved following TLM, anterior commissure involvement may be associated with reduced 2LC due to various factors[10–13].

1.The anterior commissure is a narrow and anatomically complex region, which poses significant surgical challenges, particularly in obtaining wide and clear resection margins. While iLC may be possible with the first TLM, the difficulty in achieving adequate free margins increases the risk of recurrence in the medium term.

2.Hidden submucosal spread - Tumors involving the anterior commissure are more prone to submucosal spread, which may not be fully visualized or resected during the initial surgery, leading to long-term recurrence.

3.Residual microscopic disease - Even when iLC appears satisfactory, microscopic residual disease may persist within the anterior commissure due to the limitations of complete excision, leading to an increased risk of long-term recurrence.

4.Decreased efficacy of multiple repeat interventions - With each additional TLM procedure, scarring and anatomical distortion can reduce the effectiveness, impair visualization, limit resection, and decrease the likelihood of achieving clear margins.

5.Biomechanical and vascular changes - Scars in the anterior commissure may alter local vascularization, weakening the immune response and favoring the proliferation of residual tumor cells.

Although iLC appears comparable (p = 0.599), anterior commissure involvement is an important parameter for long-term control due to the abovementioned cumulative factors. Smoking was excluded from the statistical analysis in this study due to the low prevalence in the sample (n = 3 with < 10 pack-years), which may have introduced sampling bias. However, it is a well-known risk factor for poor prognosis in laryngeal carcinoma due to its etiological role and established association with chronic inflammation and decreased effectiveness of conservative treatments[14,15].

Tumor extent was a key determinant of iLC and 2LC, with supraglottic and/or subglottic involvement significantly reducing both iLC (61.1% vs. 87.9%, p = 0.033) and 2LC (61.1% vs. 93.9%, p = 0.006). These findings are consistent with those of prior studies emphasizing the technical difficulty of obtaining adequate surgical margins in these regions due to their proximity to the paraglottic and pre-epiglottic spaces[16,17]. Moreover, subglottic spread often correlates with more advanced stages and increased surgical complexity, further contributing to poorer outcomes.

Tumor staging was another independent predictor of prognosis. Compared with pTis/pT1 tumors, pT2 lesions were associated with significantly worse immediate local control, with an OR of 8.68 (p = 0.047), consistent with the findings of previous studies that showed reduced effectiveness of TLM in more extensive lesions or those with greater involvement of laryngeal structures[18]. These advanced cases frequently require adjuvant radiotherapy or chemotherapy to achieve disease control.

Surgical margins remain one of the primary determinants of therapeutic success. Positive or indeterminate margins are commonly associated with poorer outcomes and a higher likelihood of requiring additional therapeutic interventions[9]. Although negative margins are ideal for minimizing the risk of recurrence, we found that in the absence of other poor prognostic indicators, indeterminate margins do not preclude disease control. This underscores the importance of proper orientation and marking of the surgical specimen for histopathological analysis, as well as the implementation of preoperative and intraoperative strategies to ensure optimal margin evaluation during TLM.

A key finding of this study was the relevance

of the PLR as a prognostic biomarker. Elevated PLR was significantly associated with poorer 2LC ($p = 0.009$). This inflammatory marker, calculated as the total number of platelets divided by the absolute number of lymphocytes, reflects the balance between platelet-mediated tumor-promoting mechanisms and lymphocyte-driven anti-tumor immunity. A high PLR may indicate a tumor microenvironment with increased chronic inflammatory activity and reduced immune response, favoring recurrence and disease progression. In this study, PLR was evaluated as a continuous variable, with increasing values correlating with reduced disease control. This finding suggests that PLR may serve not only as a diagnostic marker but also as an indicator for risk stratification and therapeutic planning in laryngeal carcinoma. Li et al. (2021)[19] demonstrated that PLR was an independent predictor of overall survival and progression-free survival in 147 patients with laryngeal squamous cell carcinoma. They proposed a PLR cutoff of 117.36, above which the prognosis worsens, supporting the relationship between systemic inflammation and tumor progression. Unlike the present study, Li et al.[19] found that the prognostic performance of PLR improved when it was analyzed in conjunction with other inflammatory indices, such as the NLR. This supports the integration of multiple inflammatory markers to improve prognostic accuracy, enhance risk stratification, and guide treatment decisions.

This study has some limitations. Its retrospective design and single-center setting may limit the generalizability of results. Additionally, Narrow Band Imaging (NBI) was not used during tumor resections. NBI is a valuable tool for detecting and delineating tumor margins, enhancing the identification of residual neoplasia, and detecting multifocal disease that may not be visible under conventional white light[20]. Not using NBI may have limited the accuracy of surgical margins and affected the results. Future studies with larger multicenter samples and systematic use of advanced technologies, such as NBI, are essential to validate these findings and further refine the prognostic models for TLM, particularly for surgical margin optimization.

The findings of this study highlight the importance of a multidimensional approach to laryngeal carcinoma, and that the identification of prognostic factors enables more effective and targeted treatment and follow-up. Furthermore, the use of biomarkers such as the PLR offers new possibilities for risk stratification and postoperative follow-up.

Future studies should investigate the potential of emerging technologies, including artificial intelligence systems for intraoperative margin analysis and advanced imaging techniques for surgical planning. These innovations may assist in overcoming the technical challenges associated with TLM, particularly in complex cases.

Conclusion

TLM was found to be an effective and safe approach for treating laryngeal carcinoma, demonstrating high rates of organ preservation and 2LC. Tumor extent and surgical margins significantly influence outcomes, highlighting the importance of a thorough prognostic evaluation. PLR emerged as a promising inflammatory marker, contributing to risk stratification and individualized treatment planning. Despite its limitations, this study supports the use of TLM as a therapeutic option and emphasizes the need for further research to optimize patient outcomes.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Data Confidentiality

The authors declare having followed the protocols used at their working center regarding patient data publication.

Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics

Committee and the 2013 Helsinki Declaration of The World Medical Association.

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Availability of scientific data

There are no datasets available, or publicity related to this work.

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