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ORIGINAL RESEARCH

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Management of positive resection margins following transoral laser microsurgery for glottic cancer

Usman Khan MD | Colin MacKay MSc | Matthew Rigby MD, FRCSC | Jonathan Trites MD, FRCSC | Martin Corsten MD, FRCSC | S. Mark Taylor MD, FRCSC

Division of Otolaryngology—Head and Neck Surgery, Department of Surgery, Dalhousie University, Halifax, Nova Scotia, Canada

Correspondence
Usman Khan, Division of Otolaryngology—Head and Neck Surgery, Department of Surgery, Dalhousie University, 5820 University Avenue, Room #3053, 3rd Floor Dickson Building, Halifax, NS B3H 2Y9, Canada.
Email: usman.khan@dal.ca

Abstract

Objectives: The current literature provides limited guidance on the management of positive margins (PMs) following transoral laser microsurgery (TLM) for glottic squamous cell carcinoma (SCC). Long-term data exploring the treatment of PMs with both initial observation and re-resection are limited. Our objective was to determine the optimal treatment for PM patients following TLM for glottic SCC.

Methods: Clinical information on glottic SCC patients with PMs following treatment with TLM was prospectively collected at our institution from 2007 to 2018. We use a laryngeal template during the initial TLM where the area of resection is outlined for future reference. Data were compared with univariate analysis and survival plots were generated using the Kaplan–Meier method.

Results: A total of 29 patients with PMs were treated with either re-resection (19 patients), close observation (6 patients), or adjuvant radiation alone (4 patients). Re-resection patients had SCC or severe dysplasia on initial margin pathology and 23% with early-stage disease had recurrence (T1–T2). Five (83%) patients who underwent close observation required re-resection based on clinical suspicion of recurrence (confirmed on final pathology), which was significantly different from the re-resection patients ($p < .05$). Close observation was therefore discontinued as a management of PMs. Four patients (21%) had no residual malignancy on re-resection specimens. Deep margins only accounted for 17% of all PMs. Disease-specific survival for all PM patients at 5 years was 82.4% (SE 9.6%, CI 53.4%–91.6%).

Conclusions: Our long-term experience with treating early-stage glottic SCC with TLM supports re-resection as an appropriate management for cases of PMs.

Level of Evidence: 4.

KEYWORDS
early glottic cancer, head and neck, laryngology

1 | INTRODUCTION

The treatment of glottic squamous cell carcinoma (SCC) centers on the principles of functional preservation and oncological control.[1]

This paper was presented at the 2021 Canadian Society of Otolaryngology—Head and Neck Surgery Annual Meeting.

Transoral laser microsurgery (TLM) has demonstrated excellent oncological outcomes and improved laryngeal function when compared to radiation alone for early-stage glottic SCC.[1] To achieve local oncological control, a complete excision with adequate margins is required. However, in cases of positive margins (PMs), the management of patients with glottic SCC remains controversial.[2–6]

There is currently no consensus on the management of glottic SCC patients with PMs as current clinical guidelines suggest re-resection or adjuvant radiotherapy.[2] Recent studies have advocated for close observation given that patients with PMs did not have different survival outcomes when compared to patients with negative margins.[2] Other studies have outlined low rates of disease recurrence with PMs or a risk of finding no residual tumor upon re-resection.[7–10] Across different institutions, several factors can contribute to different rates of PMs and re-resection outcomes, such as pathological criteria for determining residual disease, pathological artifact, retrospective identification of re-resection anatomical sites, adjuvant radiation and different methods of resection (piecemeal vs. en block).[2,11–13] While comparison of glottic SCC patients with positive versus negative resection margins (NMs) using national databases provides insights into patient survival, they do not capture variations in pathological evaluation of PMs or treatment protocols.

The goal of our study was to provide our long-term oncological outcomes with managing PMs using either re-resection or close observation following TLM for glottic SCC. We use a laryngeal template upon initial TLM alongside detailed operative reports to guide any future re-resections. We hypothesized that re-resection of PMs based on histopathology and retrospective identification of PM anatomical sites would optimize local oncological control.

2 | METHODS

Institutional research ethics board approval was obtained. Data were prospectively collected in a database for all patients who underwent TLM for glottic SCC at our institution from 2007 to 2018. All tumors were staged according to the American Joint Committee on Cancer (AJCC) edition at the time of diagnosis. Patients with positive resection margins on final pathology were separated into a distinct cohort from patients with NMs or undetermined resection margins. Positive resection margins were defined as evidence of SCC or severe dysplasia. Negative margins were defined as no SCC or dysplasia along the margins of the resection specimen. Patients were included regardless of their TNM staging as some tumors were upstaged during primary surgery. Patients who developed recurrent disease following an initial trial of close observation for PMs underwent re-resection at the site of the primary tumor. Re-resection TLM utilized a laryngeal template from the original surgery (Figure 1) and operative reports to identify anatomical areas for re-resection. Patients were excluded in cases of prior radiation treatment.

Data collected included patient age, gender, cigarette smoking history, alcohol intake history, date of diagnosis, date of recurrence, tumor stage, tumor type, lymphovascular invasion, perineural invasion, skeletal muscle invasion, nodal metastasis, margin locations, rere-section versus observation, radiation treatment, chemotherapy, stage of recurrence, total laryngectomy, length of follow-up, cause of death and date of death. Follow-up lengths were determined from the time of initial TLM surgery.

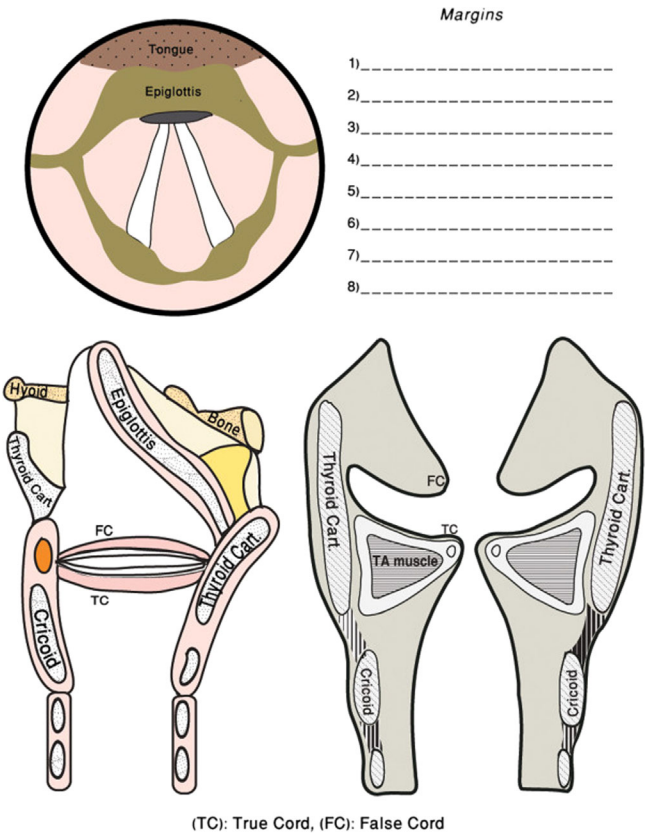

FIGURE 1 Laryngeal cancer template utilized on initial resection of glottic squamous cell carcinoma.[14]

2.1 | Statistical analysis

Univariate analysis was performed using Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables. Disease-specific survival and overall survival plots at 5 years were generated using the Kaplan–Meier method. Differences in survival were tested using log-rank comparisons. All statistical analysis was conducted on SPSS (IBM SPSS Statistics 25). A p-value of $<.05$ was considered significant for all tests.

3 | RESULTS

A total of 327 patients were treated with TLM for glottic SCC from 2007 to 2018. A total of 298 patients had NMs and 29 patients had PMs. Out of the 29 patients with PMs, 19 underwent re-resection,

6 underwent close observation (endoscopy every 3 months initially) and 4 underwent adjuvant radiation (no re-resection). Six patients with advanced disease that were upstaged on initial surgery or developed recurrence despite re-resection required further oncological treatment which included adjuvant radiation.

The majority of patients were male (93%) and the average age was 65 years old (Table 1). There was a prevalence of cigarette smoking (90%) and alcohol consumption (72%) in our patient cohort. A total of 22 patients had early-stage SCC (T1–T2), while 7 patients were upstaged to T3 upon initial surgery based on intraoperative findings. Aggressive pathological features such as lymphovascular invasion, perineural spread, and muscle invasion were more common in upstaged tumors. Positive deep margins accounted for only 17% of cases, while margins from other sites were more common (83%) (Table 2). A total of three patients (10%) had more than one PM. PMs were pathologically described as invasive SCC (83%), focal SCC (7%), severe dysplasia (7%), or a combination of carcinoma in situ (CIS) and focal SCC (3%). A total of six patients (21%) had multiple recurrences. A total of 10 patients (34%) underwent adjuvant radiation treatment during their treatment course. A total of 4 out of 19 (21%) patients had no residual tumor or dysplasia on re-resection specimens. In some of these cases, the pathology report mentioned cautery artifact or hyperplasia in the specimen. The remaining patients had dysplasia or residual SCC in the re-resection specimen.

Glottic SCC patients with PMs who underwent re-resection ($n = 19$) or observation ($n = 6$) were compared (Table 3), revealing a disease recurrence of nine patients (47%) for re-resection cases compared to five patients (83%) in the close observation group. However, six out of these nine patients were upstaged to T3 disease in the re-resection cohort during surgery and were therefore analyzed separately. A disease recurrence was observed in three patients (23%) with early-stage glottic SCC (T1–T2) ($p < .05$).

Disease-specific survival for all glottic SCC patients with PMs at 5 years was 82.4% (SE = 9.6%, 95% CI = 53.4%–91.6%) (Figure 2). Median DSS could not be calculated as less than half the cohort died of disease. Overall survival at 5 years was 70.0% SE = 8.0%, 95% CI = 68.1%–99.7%). Median OS was greater than 5 years (100 months).

4 | DISCUSSION

Our long-term analysis of glottic SCC patients with PMs following TLM supports the utility of re-resection as the recurrence rates were relatively low in early-stage glottic SCC (T1–T2) when compared to close observation alone. Our approach to identifying the area of re-resection uses descriptions of margin locations in the original operative report and visual depiction on the standardized laryngeal template (Figure 1).

The pathological detection of PMs has been an area of debate in the literature, as it can be influenced by laser artifact and tumor shrinkage.[11,12,15] As such, pathological determination of PMs can differ between studies, particularly in regard to the degree of dysplasia. Our group previously conducted a randomized controlled blinded study which confirmed an increasing degree of artifact with CO_2 laser, however, there was no significant difference in interpretability.[14] In the present study, specific descriptions on final pathology were used

TABLE 1 Patient demographics and initial tumor characteristics of glottic squamous cell carcinoma patients treated with transoral laser microsurgery who were determined to have positive margins.

Variable	*n* (%)
Gender	27 M:2 F (93:7)
Age	65
Smoking (>10 pack year history)	26 (90)
Alcohol (>7 drinks per week)	21 (72)
Stage	
T1	10 (35)
T2	12 (41)
T3[a]	7 (24)
Type	
Invasive SCC	28 (97)
Papillary SCC	1 (3)
Lymphovascular invasion	4 (14)
Perineural invasion	6 (21)
Muscle invasion	5 (17)

Abbreviation: SCC, squamous cell carcinoma.
[a]Upstaged at the time of surgery.

TABLE 2 Treatment course and margin characteristics of glottic squamous cell carcinoma patients treated with transoral laser microsurgery who were determined to have positive margins.

Variable	*n* (%)
Margin positive	
Deep	5 (17)
Other	24 (83)
>1 Margins positive	3 (10)
Multiple recurrences	6 (21)
Re-resection	19 (66)
Initial observation	6 (21)
Reresection after observation	5 (17)
Adjuvant radiation	10 (34)
Total laryngectomy	5 (17)
Margin type	
SCC	24 (83)
Small focus of SCC	2 (7)
Severe dysplasia	2 (7)
CIS/SCC focus	1 (3)

Abbreviation: SCC, squamous cell carcinoma.

TABLE 3 Comparison of recurrence rates of glottic squamous cell carcinoma patients with positive margins following transoral laser microsurgery who were treated with re-resection or close observation.

	Re-resection ($n = 19$)	Observation ($n = 6$)	Univariate analysis
Recurrence	9 (47%)	5 (83%)	
T1	5	4	
T2	8	2	
T3	6		
Recurrence for early stage (T1–T2)	3 (23%)	5 (83%)	$p < .05$

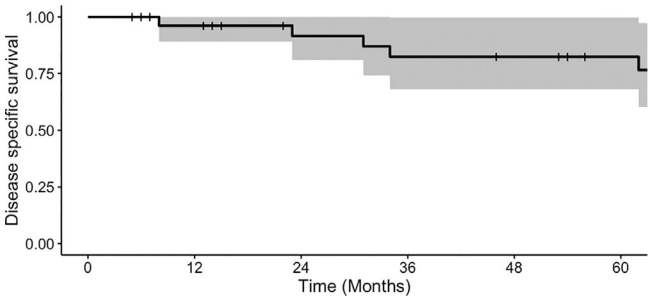

FIGURE 2 Disease-specific survival of all glottic squamous cell carcinoma patients treated with transoral laser microsurgery who were determined to have positive resection margins.

to determine a "positive" resection margin, such as regions of SCC, focal SCC, or severe dysplasia.

The current literature has conflicting results regarding re-resection versus observation for PMs in glottic SCC, primarily due to low rates of recurrence with PMs and the risk of detecting no residual disease after re-resection.[10,12,16,17] There is a wide range of residual tumor detection rates after re-resection that have been reported in the literature, suggesting a variety of tumor selection, detection, and treatment approaches. For instance, some studies have studied close observation after laser cordectomy for T1 tumors alone.[9,18] These patient groups are likely to have lower rates of recurrence considering the inclusion of early-stage tumors only. Descriptions of how surgeons determine the anatomical area of re-resection are frequently not available and can also be a contributor to detection of no residual disease.[10] The inclusion of methods used to detect anatomical areas of re-resection would advance the comparison of re-resection outcomes between different centers. Our study used a standardized laryngeal template and detailed operative reports to help guide the identification of the highest-risk areas requiring re-resection to maximize margin control. Close observation entailed endoscopy at 3 months in an outpatient clinic setting. PMs can also be partially consequent from encountering larger tumors than expected during endoscopic resection as shown in our experience. The majority of our cases demonstrated dysplasia or SCC on the re-resection specimen compared to 17%–58% in the literature, although many studies only included T1 tumors.[2,9,18]

Jumaily et al. have provided excellent insights into the lack of survival difference between patients with PMs and NMs.[2] Multicenter databases do not capture the heterogeneity of management protocols across different centers or monitor disease recurrence as acknowledged by the researchers.[2] For instance, close observation can range from frequent (6–12 weeks) endoscopy in outpatient clinics or a systematic second look by direct laryngoscopy under general anesthesia regardless of marginal status.[12] Similarly, methods of re-resection vary across centers (piecemeal vs. en block).[19,20] The selection of tumors that are amenable for TLM can also differ across centers.[21] Therefore, management of PMs should also be interpreted in the context of institutional protocols used for detecting and treating anatomical sites that are suspicious for residual disease, as well as original tumor pathology.

This study does have limitations. The small sample size of observation patients is a limitation, although observation was discontinued due to high rates of disease recurrence. Functional and quality-of-life data, such as Voice Handicap Index scores, were not available for all patients after re-resection. The selection of patients for observation was not randomized, but rather a combination of patient factors was considered during tumor boards, such as the ability to attend frequent close observation appointments, tumor stage, pathology, and overall patient preference.

5 | CONCLUSIONS

Re-resection following the detection of PMs for early-stage glottic SCC patients treated with TLM is associated with lower rates of recurrence when compared to close observation in our patient cohort. Our oncological strategy centers on determining PM status with histopathological evidence of SCC or dysplasia and utilization of a laryngeal template in conjunction with operative reports to guide anatomical re-resection.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Usman Khan https://orcid.org/0000-0003-3627-8277

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