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Prognostic significance of surgical margins after transoral laser microsurgery for early-stage glottic squamous cell carcinoma

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ABSTRACT

Objectives: The impact of positive tumor margin status and other clinicopathological factors on prognosis in early stage glottic squamous cell carcinoma (SCC) treated with transoral laser microsurgery (TLM) remains unclear. This study examined overall survival (OS) rates of patients with positive tumor margin status compared to negative tumor margin status after TLM in clinical T1-2 glottic SCC.
Materials and Methods: The National Cancer Data Base (NCDB) was queried for patients who underwent resection of T1-2 glottic SCC by TLM. Patients were treated from 2004 to 2013. Overall survival was assessed with Kaplan-Meier curve analysis, and univariate and multivariate Cox proportional hazards analysis. Differences in clinicopathologic factors between positive and negative margin groups were compared using Pearson Chi-squared analysis.
Results: Of 747 patients meeting inclusion criteria, 598 (80.1%) had negative margins. Median follow-up time was 48.0 months. Unadjusted 5-year OS for positive margins (80.0%) was lower compared to that of negative tumor margins (82.9%), but this was not statistically significant ($P = 0.265$). This persisted after multivariate analysis ($P = 0.960$). When tumors were stratified by T stage (647 T1, 100 T2), unadjusted 5-year OS based on margin status remained statistically insignificant for both T1 ($P = 0.933$) and T2 tumors ($P = 0.350$).
Conclusion: Positive margins did not negatively impact overall survival among patients with TLM-treated early-stage glottic cancer. This finding might be useful clinically in deciding treatment modality for early stage glottic SCC.

Introduction

The estimated new cases and deaths of laryngeal squamous cell carcinoma (SCC) in 2019 is 12,410 and 3760 cases, respectively [1]. Current National Comprehensive Cancer Network (NCCN) guidelines support either surgery or radiotherapy as the standard of care for early stage glottic SCC [2]. In the case of positive tumor margins, NCCN guidelines recommend re-resection or adjuvant radiotherapy, although reports in the literature suggest that surveillance may be adequate [2–5]. A surgical option that has attained worldwide use since its inception in the 1970 s is transoral laser microsurgery (TLM) [6,7]. Among T1 glottic SSC, TLM and radiotherapy are equivalent with respect to voice and oncologic outcomes, with some evidence suggesting that TLM has superior laryngeal preservation rates [8,9]. There is a lack of comparative data on functional outcomes in T2 glottic SSC, although evidence suggests that TLM and radiotherapy have equivalent local control rates at 5 years in these cancers [10,11]. There is very limited randomized control trial (RCT) data comparing these two treatment modalities in glottic cancer. Aaltonen et al. conducted an RCT (n = 60) for T1N0 glottic SSC and found that voice quality after TLM tended to be breathier with a wider glottic gap compared to radiotherapy [12]. TLM can provide similar or superior outcomes to radiotherapy at a potentially lower cost [13]. Compared to open partial laryngectomy, TLM is associated with shorter hospitalization, lower morbidity, and superior functional outcomes [14].

While TLM has some functional outcome advantages, the limited visualization and exposure of certain lesions, particularly at the anterior commissure, can lead to treatment failure [15]. There is also some

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disagreement as to whether positive surgical margins translate to a worse prognosis in early glottic cancer [4,16–18]. Some studies consider positive margins as a factor contributing to poor prognosis [16,17], whereas others fail to show this negative impact [4,18], which may possibly be due to heterogeneity in patient selection. This complicates the post-operative management plan since the decision to treat positive margins for oncological control must be balanced with the need to preserve tissue for optimal vocal function [3]. The rate of recurrence with positive margins has been reported to range from 8% to 51% and may not serve as a reliable indicator of recurrence risk. [3,19–22]. Sigston et al. advocated for a watchful waiting approach after TLM since the glottis displays earlier symptoms than other subsites of the larynx, and concluded in favor of close monitoring [3]. With this strategy, they identified 15 instances out of 18 patients with positive margin status who had no recurrence and may have received unnecessary additional treatment if re-excision or adjuvant therapy were performed. A stronger understanding of the prognostic impact of positive surgical margins in early stage glottic SCC could facilitate more informed decisions regarding adjuvant therapy and may allow for decreased use of radiation therapy and incidence of its associated sequelae.

The aims of this study were: (1) determine the potential impact of margin status on survival; (2) identify any clinicopathological factors associated with a positive margin status.

Methods

Data source

The NCDB is a hospital-based registry operated by the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Nearly 70% of all newly diagnosed cases of cancer in the United States are collected from more than 1500 Commission-accredited cancer programs. For laryngeal cancer in particular, 76.5% of all cases are captured by the NCDB [23]. Data are organized using nationally standardized coding definitions. The data used in this study is derived from a deidentified NCDB file. This NCDB analysis was performed with the approval of the institutional review board of St. Louis University School of Medicine, which waived the need for informed consent.

Study population

Patients treated from 2004 to 2013 were queried for squamous cell cancer at the glottis site using the International Classification of Disease for Oncology, 3rd Edition (ICD-0-3) (Table 1). Topography code C32.0 was used to identify glottic carcinoma. Histology codes 8070–8074, 8076, and 8078 were used to identify squamous cell carcinoma. Patients were excluded if they had multiple primary tumors, previous malignancy, distant metastases, did not have clinical T1 or T2 category primary tumors per American Joint Committee on Cancer (AJCC) staging guidelines, had unknown margin status, had received chemotherapy, or if they received radiation therapy before TLM. Patients who had passed away or were lost to follow-up in the 30-day post-operative period were also excluded in order to minimize type I error due to selection bias and possible perioperative complications.

Patient demographics and treatment variables

The treatment variables analyzed were definitive TLM treatment with or without post-operative radiotherapy from 2004 to 2013. TLM was defined by treatment codes 14, 24, and 25 (laser, laser ablation, laser excision). Patients were considered to have received radiotherapy if they received any radiation, regardless of the type or dose, after TLM.

Patient demographics analyzed included age at diagnosis, gender, race, Charlson-Deyo (CD) comorbidity scores, urban/rural setting, and median household income. Age at diagnosis was stratified into two groups: younger than 65 years and 65 years or older. Race was simplified to white, black, or other. The CD scores have 3 possible values: 0 corresponding to no comorbidity; 1 corresponding to cardiovascular disease, dementia, chronic obstructive pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, or diabetes; 2 corresponding to diabetes with chronic complications, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, or AIDS. Variables for urban/rural setting included metropolitan, urban, and rural, and were coded based on published files by the US Department of Agriculture Economic Research Service.

Healthcare systems factors that were analyzed included hospital facility type, insurance status, and institution case volume. Possible facility types were community cancer program, comprehensive community cancer program, and academic or research program including National Cancer Institute–designated comprehensive cancer centers, and integrated network cancer programs. Insurance status was stratified into private insurance, no insurance, Medicaid, Medicare, and other government insurance.

Tumor factors that were analyzed included histologic grade, margin status, and AJCC clinical T and N stages. Margin status was defined as negative if it was reported as "no residual tumor", and positive if it was reported as, "microscopic residual tumor", "macroscopic residual tumor", or "residual tumor, not otherwise specified". The clinical stage was categorized into T1 and T2 based on the AJCC guidelines at the year of diagnosis.

The primary endpoint was overall survival based on margin status from the date of diagnosis to the date that the patient died or was last contacted.

Table 1
Summary of filters applied to acquire the working cohort.

Cohort size	Filter
Cohort size	
105,593 (all laryngeal cancers)	None
51,849	Only glottic tumors
5010	Treated by TLM
4548	Conventional squamous cell histology
3003	Patients with cT1 or cT2 tumors with known nodal status
2156	Patients with known tumor grade
1620	Patients with primary tumors and no metastasis
982	Patients with known surgical margin status (300 of the patients who were filtered out had indeterminate margins)
861	Patients with known vital status at last contact
797	Patients who had follow-up for at least 30 days after surgery and did not die within that period
758	Patients who have not received chemotherapy
747 (final cohort)	Patients who either received no RT or had RT after TLM

NCDB, National Cancer Database; RT, radiotherapy; TLM, transoral laser microsurgery; cT1 or cT2, clinical stage 1 or 2.

Statistical analysis

Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY). Pearson Chi-squared (χ^2) tests were used to assess associations between categorical variables and margin status with a significant level of $P < 0.05$. Overall survival (OS) was first examined using the Kaplan-Meier survival curves. Cox proportional hazards regression analysis included a univariate model to evaluate OS based on stage (T1 and T2) and margin status, and a multivariate model that has been adjusted for known clinical and nonclinical variables in the study (see below). The multivariate analysis estimated association between surgical margin status and any variables that were significant on univariate analysis. Variables assessed included age, sex, race, insurance, residence, median income quartile, CD comorbidity score, facility type, tumor site, grade, T stage, N stage, margin status, and adjuvant radiation therapy. These variables were chosen to identify the basic demographic, tumor, and treatment factors that could affect survival. The models yielded hazard ratios (HR) and 95% confidence intervals (CI).

To elucidate which patients received adjuvant versus salvage radiotherapy, a threshold of 180 days after primary TLM was set. Additionally, a sensitivity analysis was done to determine the effect of the 300 tumors with indeterminate margins which had originally been excluded from our cohort.

Results

Patient characteristics

A total of 747 patients (653 men and 94 women; median age 66.0 years (range, 21–90)) met inclusion criteria (Tables 1, 2). There were 300 other patients excluded due to indeterminate margins. The median follow-up time for the cohort was 48.0 (range, 1.2–133) months. The median follow-up time for those with negative margins and positive margins were 49.1 (range, 3.6–133) and 41.0 (range, 1.2–131) months, respectively. Most tumors were N0 (99.2%). Factors associated with positive surgical margins were tumor stage, tumor grade, receipt of adjuvant radiotherapy, and the facility type at which a patient was treated.

Overall survival

Unadjusted 2-year OS for positive and negative margin status was 90.7% and 94.6%, respectively. This difference was not statistically significant (HR, 1.78; 95% CI, 0.93–3.40; $P = 0.082$). Similarly, the unadjusted 5-year OS was 80.0% and 82.9% for positive and negative margins, respectively, which was also not statistically significant (HR, 1.30; 95% CI, 0.82–2.08; $P = 0.265$). Variables associated with worse 5-year OS under univariate analysis included: age over 65 years at diagnosis, CD score of 2 or greater, tumor grade of 3 or 4, T2 stage, positive node status, and radiation therapy (Table 3). Race, gender, insurance type and facility type were not associated with any survival difference. A sensitivity analysis was done to assess OS when the age cut-offs were set to 70 and 75 years. In both cases, older age was associated with decreased 5-year OS.

On multivariate analysis, most of the aforementioned variables in the univariate analysis remained significant with the exception of radiation therapy (HR, 1.19; 95% CI, 0.75–1.89; $P = 0.469$). Importantly, positive margin status was not associated with a worse 5-year OS (HR, 0.99; 95% CI: 0.60–1.63; $P = 0.960$).

Positive margin status was also not significantly associated with 5-year OS when assessing T1 tumors (Fig. 1a; HR, 0.97; 95% CI: 0.52–1.81; $P = 0.933$) and T2 tumors (Fig. 1b; HR, 1.44; 95% CI: 0.67–3.10; $P = 0.350$) separately.

In the negative margin group, 78 of the 80 patients who received radiotherapy did so within 180 days, with the remaining two being treated 207 and 721 days after TLM. In the positive margin group, all patients who received radiotherapy were treated within 180 days of TLM.

For the sensitivity analysis, two Kaplan-Meier survival analyses were done in which the indeterminate margin group was added to either the positive margin group (Fig. 2a; HR, 1.33; 95% CI: 0.97–1.83; $P = 0.078$) or to the negative margin group (Fig. 2b; HR, 1.17; 95% CI: 0.75–1.82; $P = 0.497$). In both cases, there was no significant change in overall survival with inclusion of indeterminate margins with either the positive- or negative-margin TLM patients.

Lastly, a survival analysis was done in which any patients who

Table 2
Patient characteristics based on surgical margin status.

Characteristics	Negative margins (n = 598)		Positive margins (n = 149)		P values
	No.	%	No.	%	
Age					0.250
< 65	264	44.1	58	38.9	
≥65	334	55.9	91	61.1	
Sex					0.190
Male	518	86.6	135	90.6	
Female	80	13.4	14	9.4	
Race					0.553
White	516	86.3	133	89.3	
African American	57	9.5	10	6.7	
Other	25	4.2	6	4.0	
Insurance status					
Uninsured	13	2.2	3	2.0	
Private	267	44.6	53	35.6	
Medicaid	15	2.5	6	4.0	
Medicare	295	49.3	84	56.4	
Other government	3	0.5	2	1.3	
Not specified	5	0.8	1	0.7	
Median annual income quartile, $					0.680
< 30,000	62	10.4	17	11.4	
30,000–34,999	111	18.6	28	18.8	
35,000–45,999	176	29.4	41	27.5	
≥46,000	227	38.0	60	40.3	
Unknown	22	3.7	3	2.0	
Residence					0.573
Metropolitan	469	78.4	114	76.5	
Urban	93	15.6	25	16.8	
Rural	17	2.8	7	4.7	
Unknown	19	3.2	3	2.0	
Charlson-Deyo comorbidity score					0.889
0	484	80.9	119	79.9	
1	91	15.2	23	15.4	
≥2	23	3.8	7	4.7	
Facility type					**< 0.001**
Community cancer program	33	5.5	19	12.8	
Comprehensive community program	147	24.6	51	34.2	
Academic or research (includes NCI)	350	58.5	63	42.3	
Integrated Network Cancer Program	55	9.2	16	10.7	
Other or unknown program	13	2.2	0	0.0	
Tumor grade					**0.050**
1	193	32.3	41	27.5	
2	349	58.4	84	56.4	
3 or 4	56	9.4	24	16.1	
Tumor stage					**< 0.001**
T1	533	89.1	114	76.5	
T2	65	10.9	35	23.5	
Nodal stage					0.410
N0	594	99.3	147	98.7	
N1 or N2	4	0.7	2	1.3	
Radiation therapy received after TLM					**< 0.001**
No	518	86.6	79	53.0	
Yes	80	13.4	70	47.0	

TLM, transoral laser microsurgery; NCI, National Cancer Institute.

Table 3
Univariate and multivariate analysis of predictors of overall survival for all patients.

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* values	HR (95% CI)	*P* values
Surgical margin status				
Negative	1 [Reference]	NA	1 [Reference]	NA
Positive	1.303 (0.82–2.08)	0.265	0.987 (0.60–1.63)	0.960
Age				
< 65	1 [Reference]	NA	1 [Reference]	NA
≥65	2.509 (1.59–3.97)	< **0.001**	2.224 (1.39–3.55)	**0.001**
Charlson-Deyo comorbidity score				
0	1 [Reference]	NA	1 [Reference]	NA
1	1.318 (0.78–2.24)	0.308	1.054 (0.61–1.81)	0.849
≥2	6.201 (3.53–10.9)	< **0.001**	3.643 (1.97–6.74)	< **0.001**
Tumor grade				
1	1 [Reference]	NA	1 [Reference]	NA
2	1.506 (0.92–2.48)	0.107	1.384 (0.84–2.29)	0.204
3 or 4	2.990 (1.62–5.52)	< **0.001**	2.016 (1.06–3.85)	**0.033**
Tumor stage				
T1	1 [Reference]	NA	1 [Reference]	NA
T2	2.772 (1.78–4.31)	< **0.001**	2.354 (1.48–3.75)	< **0.001**
Nodal stage				
N0	1 [Reference]	NA	1 [Reference]	NA
N1 or N2	10.786 (3.94–29.6)	< **0.001**	5.222 (1.74–15.7)	**0.003**
Radiation therapy received after TLM				
No	1 [Reference]	NA	1 [Reference]	NA
Yes	1.577 (1.02–2.43)	**0.039**	1.187 (0.75–1.89)	0.469

CI, confidence interval; HR, hazard ratio.

received post-operative RT were excluded, which yielded a cohort of 597 patients (538 T1, 59 T2). Patients with positive margin status did not have a worse 5-year OS compared to those with negative margin status (Fig. 3; HR, 1.49; 95% CI: 0.80–2.77; $P = 0.208$).

Discussion

This analysis compared survival outcomes between positive and negative margins in TLM-treated early stage glottic squamous cell carcinoma. We demonstrated that even after adjusting for relevant clinical and nonclinical variables, patients with positive margins following TLM-treated early glottic squamous cell carcinoma did not have significantly inferior survival rates compared with those with negative margins. To our knowledge, this is the largest analysis to compare survival outcomes based on margin status in TLM-treated T1 and T2 glottic squamous cell carcinoma. The results of our study might help in the clinical determination of treatment modality for these cases of glottic cancer.

There are several retrospective studies that have shown conflicting results regarding the significance of positive margins in early glottic cancer [3–5,16–18,21,24–30]. The heterogeneity of these studies may in part explain the conflicting results. Ansarin et al., excised specimens en bloc and reported that cases with positive margins had a lower disease-free survival and a higher rate of recurrence. However, en bloc resection can make it difficult to accurately determine tumor extent and depth, especially in larger tumors [18]. In contrast, piecemeal resection is able to better establish the depth of invasion without sacrificing oncologic control [7,30,31]. Also, cohorts with a greater proportion of T1b or T2 tumors have reduced survival rates and are also more likely to have positive margins [32]. Previous studies have shown 5-year OS rates for TLM-treated T1 and T2 glottic carcinoma to range from 71 to 95% [18,22,33,34] and 64.9–73% [18,22,35], respectively. Charbonnier et al. showed that their positive margin patients had decreased survival, with more than half of those patients demonstrating infiltration of the vocalis muscle [16]. Lee et al.'s cohort, whose positive margin patients were not shown to have worse survival, underwent strict case selection that excluded those with poor surgical exposure, suspicious thyroid cartilage, extralaryngeal extension per CT scan, and decreased vocal fold mobility which they suspected to be related to thyroid cartilage invasion [18]. Within our cohort, we found that 598 (80.1%) patients had negative surgical margins with the remainder having positive margins. This rate is comparable to the range found in the literature (9.3–39.8%) [5,16–18,21,28,30]. We examined the impact of surgical margins on 5-year OS in T1 and T2 tumors separately (Fig. 1), which did not demonstrate any significant difference in survival.

Additionally, there is still no consensus regarding post-operative treatment strategies for positive margins [34]. Current clinical guidelines suggest adjuvant radiotherapy or revision surgery [34]. Some authors propose systematic revision surgery in cases of positive margins in head and neck cancer [5,20,36–38], but residual tumors were found only in 17–58% of revisions, with 18% for the largest series (Jäckel et al.; 386 patients) [37]. Gallet et al. and Sigston et al. acknowledged that this may result in overtreatment of patients and recommended close monitoring in early glottic cancer with positive margins. It is possible that patients with positive surgical margins are more likely to be under strict follow-up and surveillance for recurrence, thereby equalizing their survival rate to that of patients with negative margins. Additionally, Jäckel et al. found that found that the negative prognostic value of positive or unclear margins was completely negated when laser revision surgery retrieved specimens histologically free of tumor tissue [37]. Patients with residual disease also benefited from revision surgery, although they had a significantly increased risk of locoregional failure [37]. Due to the low rate of residual cancer after second-look biopsy in early stage glottic cancer with positive margins, Michel et al. suggested that positive margins may not be a reliable indicator of survival. This is particularly true in small tumors which can be more difficult to analyze histological margin status due to their size and the thermal effects induced by the laser [4]. Our analysis demonstrated that those with positive margins were much more likely to receive RT versus those with negative margins (47.0% vs 13.4%; $P < 0.001$).

Although the NCDB does not track recurrence, positive margins have been shown to be an independent risk factor for local failure [5,24,30,37,39]. Recurrence rates range from 3.1% to 22.8% [3,19,21,22,36,40] in negative margins, while ranging from 8% to 51% in positive margin cases [3,19–22]. A recent study of Ansarin et al.'s cohort of 570 patients with cTis-cT3 glottic cancer found that 10.3% of the negative margin and 17.9% of the positive margin patients had recurrences [41]. These studies suggest that clear surgical margins do not necessarily predict absence of recurrence, and positive margins are not always associated with recurrence [5].

Resection should ideally yield negative margins, but several factors are involved that can make this difficult to achieve: limiting tissue damage to preserve a functional larynx, considerable shrinkage of surgical margins due to TLM's laser cautery artifact which makes histologic analysis difficult, fragmentation of the operative specimens due to the fragility of the mucosa, and method of resection (en bloc vs piecemeal resection) [5]. The definition of margin status also varies among studies. A resection margin of 2 mm in glottic cancer is generally considered adequate [16], but resection artifacts and specimen shrinkage around this small margin can cause inaccurate assessments of the tumor edges [16,42]. The reported rate of indeterminate margins after TLM ranges from 17.2% to 33% [5,28,43], which is consistent with the NCDB's rate of 28.7% from this study. Our sensitivity analysis sought to determine if indeterminate margins may contribute to overall survival. However, inclusion of this sample (n = 300) did not change the OS for either margin category (Fig. 2). This suggests that excluding patients with indeterminate margins inFig. 1 is unlikely to be a source of bias for the role of margin status in overall survival.

Although our results suggest that positive margin status is not associated with worse survival, we were unable to identify how many of these tumors involved adjacent laryngeal structures due to limitations of the NCDB. It is possible that there is some selection bias in which

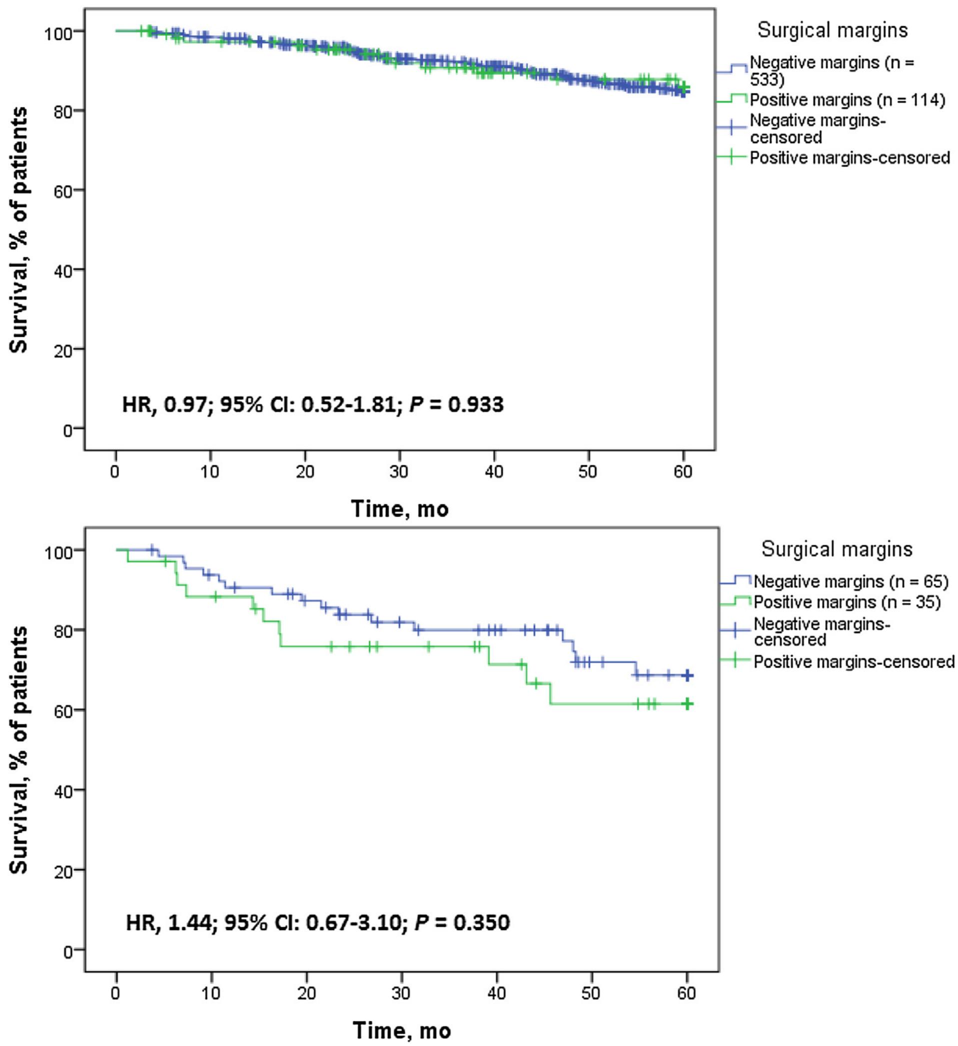

Fig. 1. Five-year unadjusted overall survival of early stage glottic squamous cell cancer based on surgical margin status; (a) only T1 cases, (b) only T2 cases.

most tumors in our cohort had not spread to nearby or functionally critical structures or were in a favorable anatomical position, and that our findings are only pertinent in that subset of patients. There are several factors outlined in a review by Peretti et al. that can impact the effectiveness of TLM [44]. Tumors with anterior commissure involvement in the horizontal plane provide for a good indication for TLM, whereas those growing in the cranio-caudal direction are much more difficult to visualize and resect completely. Involvement of the crico-arytenoid joint can also be considered a contraindication to TLM since the adjacent nerves and vasculature represent possible pathways for tumor spread.

Importantly, the lack of recurrence data in the NCDB prevents this study from determining how many patients treated with either primary TLM or radiotherapy required salvage laryngectomy. It is unclear if patients with positive surgical margins had a higher rate of salvage laryngectomy, however treatment failure after definitive radiotherapy also primarily entails total laryngectomy. Thus, this NCDB study still demonstrates that among patients who only received TLM, those with positive margins did not necessarily have decreased survival in the absence of salvage surgery.

In this study of early stage glottic tumors, positive and negative margin status groups differed mainly in tumor and system factors. Not surprisingly, positive margin status was more likely to be associated with T2 and high-grade tumors. Per the 2019 NCCN guidelines, adjuvant radiation therapy is a recommended option for adverse tumor features, which would explain its higher utilization in positive margins.

The NCDB offers several benefits over other population-based databases, including a larger sample size, broader inclusion of ages, and better representation of TLM. Limitations of the NCDB include its retrospective nature, potential errors in data abstraction, and lack of adequate data involving depth of invasion, recurrence, tumor size, comorbidities, functional status, and extension to the anterior commissure and other structures. Dose-dependent risk factors such as smoking, and alcohol use were not available. Additionally, survival outcomes were limited to overall survival, because the NCDB does not provide disease-specific survival.

Conclusion

The role of margin status as a prognostic factor in TLM-treated early glottic squamous cell carcinoma has historically been subject to debate. The association of positive margins and survival has been reported with mixed results. This national cohort study shows that positive margin status in the setting of early stage glottic squamous cell carcinoma treated with TLM is not associated with lower overall survival rate. With appropriate patient selection in early stage glottic tumors, TLM and close follow-up may be beneficial for management without affecting overall survival.

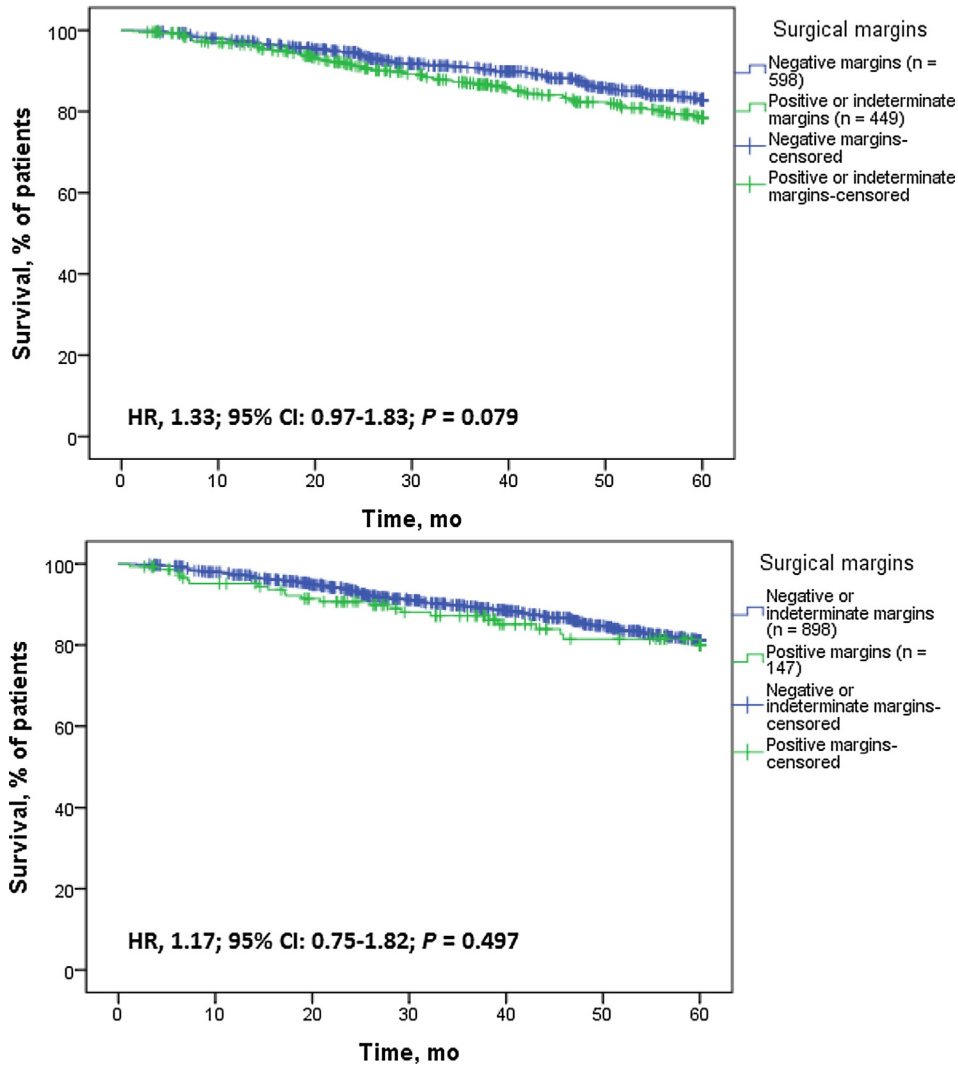

Fig. 2. Five-year unadjusted overall survival of all early stage glottic squamous cell cancer based on surgical margin status in which all the indeterminate margin cases were added to either: (a) positive margin group or (b) negative margin group.

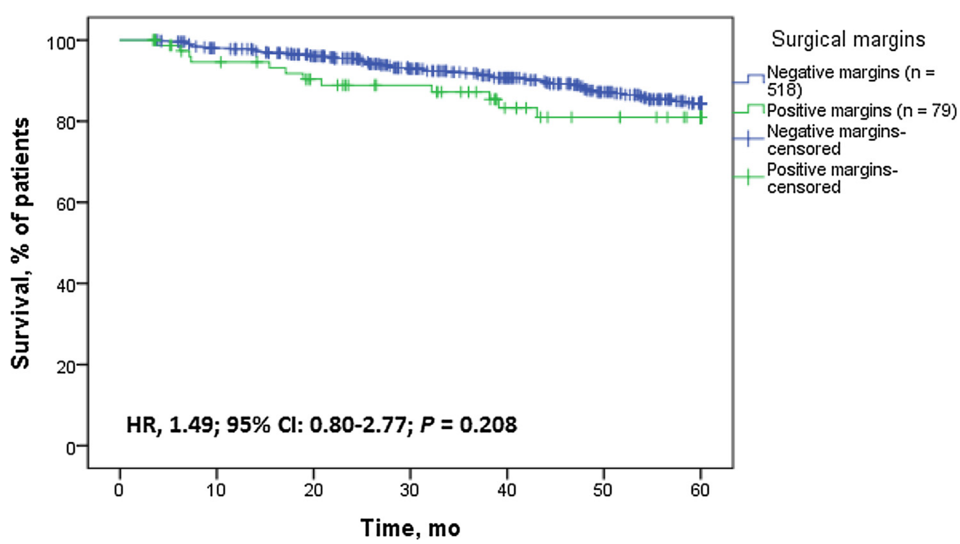

Fig. 3. Five-year unadjusted overall survival of early stage glottic squamous cell cancer excluding those receiving post-operative radiotherapy based on surgical margin status.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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