

Transoral Laser Microsurgery of Supraglottic Cancer: A Survival Analysis

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Abstract

Introduction:

There needs to be more unanimity in the treatment approaches for supraglottic squamous cell carcinoma. This study evaluated the survival outcomes of patients who underwent transoral laser microsurgery for this type of cancer.

Materials and Methods:

This longitudinal study was conducted at a tertiary university hospital in Iran. Forty-one patients with supraglottic squamous cell carcinoma who underwent transoral laser microsurgery were included. The required data were extracted from medical records. Survival analysis using the Kaplan-Meier method was used to obtain the 5-year overall recurrence-free and laryngectomy-free survival rates.

Results:

This study included 40 males (97.6%) and one female (2.4%). The mean \pm standard deviation of patients' age was 55.17 ± 8.43 years. The 5-year overall recurrence-free survival rate in all patients was 68.0%. In contrast, 76.0% of the cases were laryngectomy-free after five years. Patients in the T1 and T3 categories had better overall and laryngectomy-free survival rates when stratifying by disease stage, respectively. The 3-year local control rates of tumor were 80.0%, 63.1%, and 82.3% for T1, T2, and T3, respectively. The larynx could be preserved in four patients (80.0%) with T1, 15 patients (57.8%) with T2, and 14 patients (82.3%) with T3.

Conclusion:

Our results suggest that transoral laser microsurgery may result in satisfactory recurrence-free survival and good oncologic outcomes. However, considering the indication of radiotherapy in some patients, the therapeutic effects of radiotherapy are part of the survival rate observed in this study.

Keywords: Carcinoma, Larynx, Microsurgery, Survival

Received date: 26 Oct 2023

Accepted date: 16 Sep 2024

*Please cite this article; Abdi Sofi S, Dabirmoghaddam P, Aghazadeh K, Karimi E, Naderyan Fe'li Sh. Transoral Laser Microsurgery of Supraglottic Cancer: A Survival Analysis. *Iran J Otorhinolaryngol*. 2024;36(6):647-654. Doi: 10.22038/ijorl.2024.75846.3543

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Introduction

Among all head and neck malignancies, laryngeal cancer constitutes about 20% of cases and ranks as the second most prevalent malignancy in the upper aerodigestive tract (1).

Among the various laryngeal subsites, primary supraglottic squamous cell carcinoma (SSC) is the second most prevalent form of laryngeal cancer (1). According to the national report on the cancer registry in Iran from 2003 to 2009, the age-standardized incidence rate of larynx cancer was 12.4 per 100,000 (2).

Moreover, in a study based on data from 10 years in Iran, it was observed that among all patients with laryngeal cancer, the supraglottic was the most common primary tumor location (3). Currently, there are several treatment modalities for SSC, including supraglottic laryngectomy, radiotherapy (RT), and transoral laser microsurgery (TLM) (4-6). Primary control, percentage of organ preservation, neck control, and survival rates can be considered parameters of successful treatment (5).

Supraglottic laryngectomy enables the preservation of a functioning larynx and eliminates the need for a permanent tracheotomy (7). In a recent systematic review and meta-analysis, the pooled incidence rates of bleeding and airway complications after transoral robotic supraglottic laryngectomy were 3.74% and 4.92%, respectively. These complications result in a mortality rate of 0.60% during the preoperative period (8).

Early or moderately advanced SSC may be effectively treated with supraglottic laryngectomy or RT (7,9). However, a systematic review and meta-analysis indicated that patients who underwent open organ preservation had better survival outcomes than those who underwent primary RT. So, 5-year disease-specific mortality was lower in the surgery group (odds ratio (OR)= 0.43, 95% confidence interval (CI): 0.31 to 0.60). 5-year overall mortality was also lower in the surgery group (OR= 0.40, 95% CI: 0.29 to 0.55) (10).

However, as experience increases, the benefits of TLM compared to other modalities are becoming increasingly evident. These advantages include organ and function preservation, reduced morbidity and mortality, and shorter hospitalization periods (5,11).

Canis et al. recommended TLM for supraglottic laryngeal carcinoma, as they found

good oncologic and functional results in patients (5).

Moreover, Ambrosch et al. proposed that TLM can be considered an option for surgical preservation of the larynx in early and selected locally advanced supraglottic carcinomas. Consequently, a 5-year overall survival rate of 63% and a local control rate of 72% were recorded over the same period (4).

However, in a systematic review comparing TLM and RT for T2 glottic squamous cell carcinoma, weighted averages of local control at five years demonstrated similar results: 75.81% for RT versus 77.26% for TLM (12).

With this background, the treatment for supraglottic carcinoma remains controversial. This study aimed to evaluate recurrence-free and laryngectomy-free survival rates five years after TLM. In this regard, the overall 5-year recurrence-free and 5-year laryngectomy-free survival, local control, organ preservation rate, and stage-related survival were assessed.

Materials and Methods

Study design

This longitudinal study was conducted among 41 patients who underwent TLM for SSC at Amir A'lam Hospital, Tehran, Iran. Convenience sampling was performed. The required sample size was 43, obtained using the formula for estimating the population proportion, considering a random error of 5% and the expected 5-year recurrence-free survival rate of 80% from a previous study. Finally, 41 patients were included in the study. Exclusion criteria included other kinds of laryngeal malignancy, involvement of the glottis or base of the tongue or hypopharynx, and history of previous RT. The primary and secondary outcomes of interest were the time to recurrence after TLM and laryngectomy free after TLM, respectively.

Ethics approval

This study was approved by the Ethics Committee of Tehran University of Medical Sciences, which follows the ethics code of IR.TUMS.AMIRALAM.REC.1399.044. Patients gave informed verbal consent prior to the use of medical records. Patients' confidentiality was maintained, and data were presented in groups only.

Data collection

TLM was performed in all the patients between April 2013 and February 2016. All the patients underwent direct laryngoscopy and biopsy. Medical, surgical, and pathological records were reviewed to collect study data. The following data were extracted: date of surgery, date of recurrence, primary origin of the tumor, type of tumor, total laryngectomy or supracricoid partial laryngectomy status if performed, RT status, smoking status, opium consumption status, recurrence sites, and stages of cancer. Moreover, in March 2021, all patients were contacted by telephone to obtain information about whether they were alive and the presence of a tracheostomy.

The organ (larynx) preservation rate was defined as the percentage of patients not candidates for total laryngectomy.

Surgical technique

All surgical procedures were performed under general anesthesia using a transoral carbon dioxide laser approach (CO₂ laser). If necessary the patients were safely intubated with a small-bore laser with a double-cuff endotracheal tube. If possible, the lesions were resected using an en bloc technique. A light microscope (Zeiss, Germany) with a 400 mm focal lens and a CO₂ laser was used during the surgical procedure. The superpulse mode was used at 6-10 watts. During the surgical procedure, blood vessels with a diameter exceeding 0.5 to 1 mm were coagulated with bipolar forceps. A laser was used in cutting mode to obtain accurate histological data on the specimen. Performing frozen sections for intraoperative assessment of surgical margins is not commonly implemented. Specimens were sent to the pathology department for en bloc excisions after marking one designated edge. All surgical margins were evaluated in multiblock procedures, and a surgical margin containing over one millimeter of healthy tissue surrounding the tumor was considered negative. In the case of one mm or less for the distance between tumor and margin, it was considered as "close," and the presence of the tumor at one or more superficial and/or deep resection margins was classified as "positive."

Surgical procedures were classified according to the European Laryngological Society guidelines. Selective or modified radical neck

dissection was performed mostly one month after surgery, and adjuvant chemo/RT was performed in patients with perineural and vascular invasion, multiple positive lymph nodes, and/or extracapsular spread.

Based on definitive pathological reports, tumors were re-staged according to the eighth edition of the American Joint Committee on Cancer staging manual (13). A second endoscopic resection was performed concurrently with neck dissection in patients exhibiting positive margins.

Statistical analyses

In order to analyze data, SPSS software (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) was applied. The results were reported in frequency (proportion) and mean \pm standard deviation for describing qualitative and quantitative variables. A Chi-square or Fisher's exact test was used to compare the qualitative variables. An independent sample t-test was also applied to compare the quantitative variables. Kaplan-Meier analysis calculated 5-year survival rates, yielding overall and laryngectomy-free survival rates. A Log-rank test was also run to compare survival curves at different T-stages. In determining the local control rate, only local recurrences were considered events while patients were alive without local recurrence on follow-up time. The level of statistical significance was defined as p-values of less than 0.05.

Results

A total of 40 male (97.6%) and one female (2.4%) patient were included in this study. The mean and standard deviation of patients' age were 55.17 and 8.43 years, respectively. Eight (19.5%) and four (9.8%) patients underwent total laryngectomy and supracricoid laryngectomy after TLM, respectively. Sixteen patients (51.6%) received RT after TLM. Moreover, seven patients (17.1%) received total laryngectomy and RT. There had been tumor recurrences in 14 patients (34.1%).

The most recurrences occurred when the initial origin was in epiglottitis (64.3%), followed by the false vocal cord (57.1%), petiole (28.6%), pyriform sinus (14.3%), and epiglottis fold (14.3%). Table 1 depicts the clinical characteristics and prognostic factors of

recurrence among 41 cases of SSC. There was no statistically significant difference in the age and sex distribution of patients with and without recurrence ($p>0.05$). Similarly, no statistically significant difference was observed between pathologic features (i.e., lymph node

involvement and T-stage) ($p>0.05$). There was also no statistically significant difference regarding prognostic factors of recurrence (smoking and opium consumption) ($p>0.05$).

Table 1: Clinical Characteristics and recurrence prognostic factors among Supraglottic Squamous Cell Carcinoma cases

Variables	Recurrence		p-value
	Yes (n=14)	No (n=27)	
Gender			
Male	14 (100)	26 (96.3)	1.00*
Female	0	1 (3.7)	
Age (years)	52.57±8.49	56.52±8.24	0.16†
Lymph node involvement			
Yes	3 (21.4)	4 (15.4)	0.68*
No	11 (78.6)	22 (84.6)	
T-stage			
T1	1 (7.1)	4 (14.8)	0.65*
T2	8 (57.1)	11 (40.7)	
T3	5 (35.7)	12 (44.4)	
Smoking			
Yes	13 (92.9)	26 (96.3)	1.00*
No	1 (7.1)	1 (3.7)	
Opium consumption			
Yes	6 (42.9)	18 (66.7)	0.19‡
No	8 (57.1)	9 (33.3)	

Data expressed as frequency (proportion) or mean ± standard deviation *Fisher's Exact test †Independent sample t-test ‡ Chi-square test

The 3-year local control rates of tumor were 80.0%, 63.1%, and 82.3% for T1, T2, and T3, respectively. The larynx could be preserved in

four patients (80.0%) with T1, 15 patients (57.8%) with T2, and 14 patients (82.3%) with T3.

Table 2: Survival analysis for Supraglottic Squamous Cell Carcinoma cases

	Overall survival*			Laryngectomy-free survival**		
	Median (months)	Mean (months)	5-Year Survival Rate (%)	Median	Mean	5-Year Survival Rate (%)
All patients	96	73.76	68	84	76.22	76
T-stage						
T1 (n=5)	96	74.25	75	84	75.0	80
T2 (n=19)	96	65.18	61	84	74.50	74
T3 (n=17)	91	74.93	73	84	78.88	81

*Time to recurrence was considered, **time to laryngectomy-free was considered

Recurrence After TLM for Supraglottic Cancer

The results of the survival analysis are shown in Table 2. The overall survival (recurrence-free proportion) among all cases was 68.0% at five years. On the other hand, 76.0% of the cases were laryngectomy-free after five years. When stratifying by stage of the disease was done, patients with T1 and T3 categories had

better overall and laryngectomy-free survival rates, respectively. The Log-rank test found no statistically significant difference between the three stages in the overall and laryngectomy-free survival curves ($p=0.77$ and $p=0.95$, respectively). Corresponding Kaplan–Meier curves are shown in Fig 1 and 2.

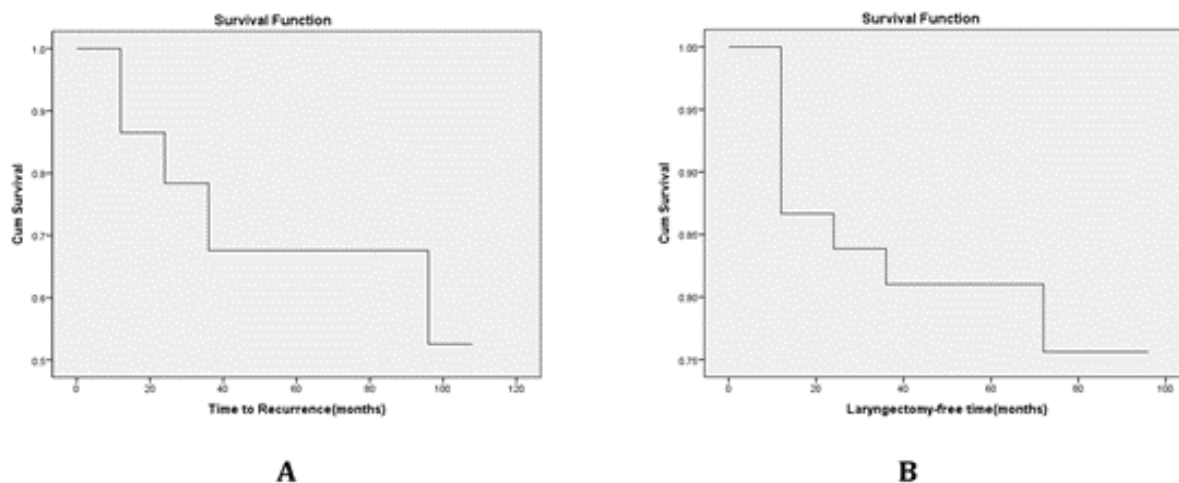


Fig 1: Overall (A) and laryngectomy-free (B) survival function of Supraglottic Squamous Cell Carcinoma cases.

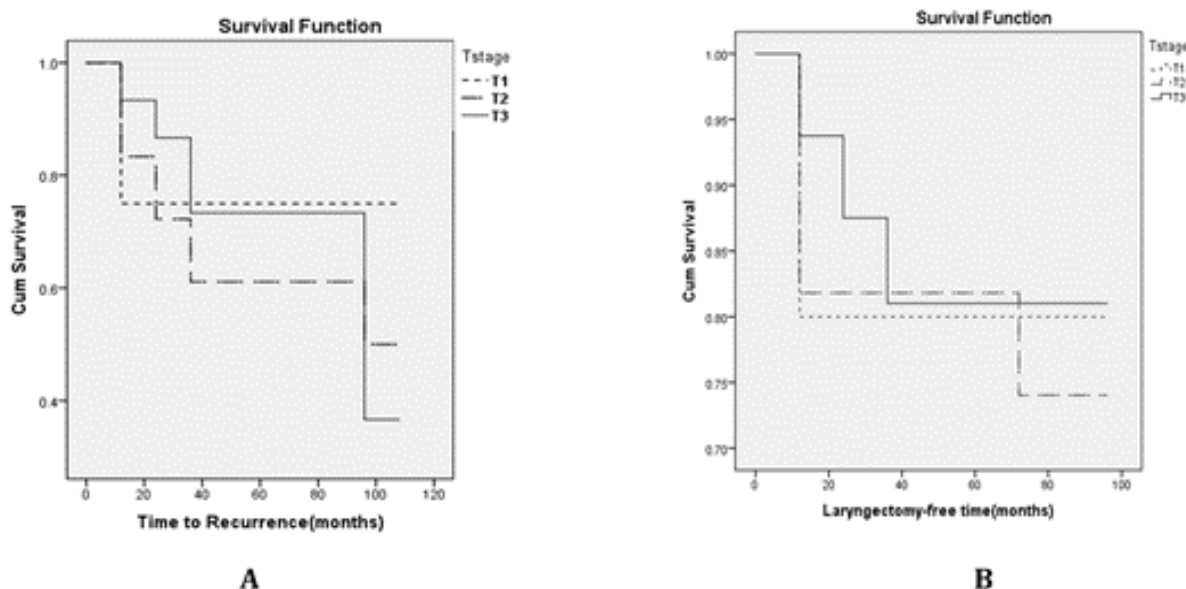


Fig 2: Overall (A) and laryngectomy-free (B) survival function of Supraglottic Squamous Cell Carcinoma cases by T-stage.

Discussion

This study investigated the oncological outcomes of supraglottic carcinoma after TLM. Notably, a significant proportion of our study population was classified as stage II (46.3%) and stage III (41.5%) tumors. The findings showed that 68% of patients with SSC were recurrence-free after TLM. In addition, 76.0%

of SSC cases were laryngectomy-free after five years.

Although SSC leads to various outcomes, it is generally worse than its glottic counterpart, with 5-year overall survival ranging from 47% to 56% for stage III disease and 29% to 45% for stage IV disease (1). Currently, different treatments are available for supraglottic

carcinomas. Open-neck supraglottic laryngectomy, transoral robotic surgery, RT, and TLM are treatment modalities for SSC (4, 6,14). The findings of a meta-analysis conducted by Patel et al. in 2018 suggested that primary surgery may result in lower disease-specific and overall mortality rates than primary RT (10). Findings of a study conducted by Sykes et al. indicated that RT in patients with node-negative supraglottic carcinoma of the larynx can achieve a crude 5-year survival rate of 50% and a 5-year survival rate of 70% after adjusted for intercurrent deaths (15). In recent years, glottis-preserving TLM has become important in the surgical treatment of supraglottic carcinoma because of the division and removal of tumors in several pieces (14).

TLM also has several additional benefits compared with conventional supraglottic laryngectomy. These include preserving more healthy tissues attributed to the spatial cutting properties of the CO₂ laser in the distinction between healthy tissue and a tumor, no need for tracheostomy in most cases, better recovery of swallowing function, lower frequency of aspiration or pneumonia, and shorter duration of both surgery and hospitalization (11,14).

However, the hemostatic effect of the laser seals tissues, such as lymphatic microvessels, without a higher risk of tumor spread than an open approach (14). Furthermore, the unique cutting characteristics of the CO₂ laser enable the distinction between healthy tissue and tumors during surgery, as it allows for precise incisions through the tumor. This capability facilitates the preservation of more healthy and functionally important structures.

Fatih Gökmen et al. observed that supraglottic larynx cancer patients who underwent TLM had good functional outcomes; however, there was no significant difference in oncological outcomes with those who underwent open partial laryngectomy (16). Canis and associates recommend primary TLM in combination, either alone or in conjunction with neck dissection and (chemo)radiotherapy for patients with supraglottic carcinoma (14) as their study showed a 5-year recurrence-free survival rate of 80.5% for stage 1+2 and 64.9% for stage 3+4 (14). In addition, in a study conducted in Iran by Khadivi et al., 27.3% of patients undergoing TLM developed laryngeal cancer recurrence over 36 months (17). Compared with Canis et

al., our findings are relatively similar. Thus, we observed a 5-year recurrence-free survival rate of 75%, 61%, and 73% for the T1, T2, and T3 stages, respectively. Indeed, in both our study and the Canis study, more than half of the patients had no recurrence after five years. This consistency may be due to the similarity in the disease stage and outcome measures between studies. Our finding also agrees with the study by Khadivi et al., which indicates the similarity between the characteristics of the patients in the two studies.

Likewise, there was a relatively consistent finding regarding the 5-year laryngectomy-free survival rate in our study with a previous study conducted by Kujath et al. (18). The 5-year laryngectomy-free survival rate was 87% after TLM in patients with glottic carcinoma in the Kujath et al. study, and we found that 76% of our sample was laryngectomy-free after five years.

Regarding the local control rate, Canis et al. achieved a 5-year local control rate of 85% for patients classified as pT1/pT2, 82 % for those with pT3, and 76 % for pT4 among patients diagnosed with SSC (14). Moreover, the 2-year estimates for local control were 97% among SSC cases in a study conducted by Grant et al. (11). In addition, the 5-year local control rates and 5-year ultimate local control rate among patients with SSC were 72 and 92%, respectively in a study performed by Ambrosch et al. (4). However, the 3-year local control rates in our study were 80%, 63.1%, and 82.3% for T1, T2, and T3 respectively. It seems more logical to compare our findings with those of Grant et al. because of the proximity in the local control period. Accordingly, better outcomes observed in their study can be attributed to the fact that 42% of the patients had pT3/4 tumors, while in our study, most patients exhibited advanced disease, with 12.2% in T1, 64.3% in T2, and 41.5% in T3.

The application of TLM to preserve the larynx in locally advanced supraglottic carcinomas remains a subject of ongoing debate (4).

However, a recently published systematic review and meta-analysis of key oncological outcomes confirmed that TLM is a valid surgical option for larynx preservation in advanced T3–T4 laryngeal cancer (19). Canis et al. found that organ preservation occurred in 100%, 96%, 93%, and 84% of patients at pT1,

pT2, pT3, and pT4, respectively. Overall, the results for larynx preservation were 93% (14). Furthermore, Ambrosch et al. observed that the larynx could be preserved in 89% of patients under TLM. Additionally, preservation of the larynx has been achieved in 91% of patients with pT1, 97% of those with pT2 tumors, 89% of patients with pT3 tumors, and 69% of patients presenting with pT4a primary tumors (4). In the study of Khadivi et al., the larynx was preserved in 98.5% of patients undergoing TLM (17). In comparison, in our study, it was observed that the larynx was preserved in four patients (80.0%) with T1, 15 patients (57.8%) with T2, and 14 patients (82.3%) with T3.

A multicenter case-control study conducted in Central Europe revealed notable dose-response trends concerning the frequency and duration of tobacco use for supraglottic cancers (20). Consequently, individuals who smoked currently exhibited an increased risk of SSC (OR=3.23, 95% CI of 1.72 to 6.42). The use of opioids was also found to be associated with an increased risk of head and neck cancers in a case-control study conducted in Kerman, Iran (Adjusted OR= 8.13, 95% CI: 4.08 to 16.2) (21). In our study, there was no statistically significant relationship between smoking, opium consumption, and SSC recurrence (P-value>0.05). The observed insignificance may be due to the limited sample size.

Our study provides evidence on the application of TLM in patients with SSC. However, some limitations should be considered when using these results. First, a limited number of patients were included because this was a single-center study. Moreover, considering the indication for radiotherapy after TLM in some patients, a part of the survival rate observed in this study could be affected by the therapeutic effects of radiotherapy. Due to the limitation of the sample size in this study, it was not possible to carry out a stratified analysis. Therefore, it is suggested that in future studies, using a larger sample size, the survival rates of patients who underwent TLM and those who underwent TLM plus radiotherapy should be investigated separately.

Conclusion

Despite many studies on the results of different treatment modalities, any discussion

on oncologic outcomes may be challenging. The complexity is due to the different stages of the disease, outcome measures, use of different statistics, and investigation of the different laryngeal sites of origin. However, according to the present study, TLM can be considered a method with good oncologic outcomes for supraglottic carcinomas. Our findings showed that laryngectomy can be avoided with TLM in most cases. Nevertheless, it is necessary to conduct more comprehensive studies by including a comparison group and larger sample size to draw more definite conclusions about the use of TLM compared to other treatments.

Acknowledgments

The authors are grateful to the staff of the Department of otorhinolaryngology at Amir A'lam Hospital for their help with data collection.

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