



Oncological and functional outcomes of transoral laser surgery for laryngeal carcinoma

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Received: 10 March 2018 / Accepted: 29 May 2018
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Abstract

Introduction Transoral laser microsurgery (TLM) has become the standard approach for treatment of early-stage laryngeal carcinoma in most institutions due to their good oncological and functional results with few local complications. The purpose of this study was to analyze the oncological and functional results of TLM in the treatment of laryngeal tumors at our Hospital.

Materials and methods Patients with laryngeal squamous cell carcinoma (LSCC) treated from 1998 to 2013 with TLM with curative intention, and with a minimum follow-up of 24 months, were reviewed.

Results 203 patients with LSCC were included. 195 patients were men (96%) and 8 women (4%), with a mean age of 63 years. The series includes 134 (66%) T1, 40 (20%) T2, and 29 (14%) T3-classified tumors. 116 tumors (57%) were in the glottis, 79 (39%) in the supraglottis and 8 (4%) in the anterior commissure. 16 patients (8%) received adjuvant radiotherapy. Initial local control was obtained in 75.5% of patients. The 5-year overall survival rate was 84% and the 5-year disease-specific survival was 90%. The presence of nodal metastasis ($p < 0.001$) and the involvement of the surgical margins ($p = 0.004$) were associated with a lower disease-specific survival in the multivariate analysis. All but three patients with local control of the disease reassumed oral diet, and none were tracheostomy-dependent. The 5-year laryngeal preservation rate was 85%.

Conclusions TLM is a minimally invasive treatment for early and moderately-advanced laryngeal carcinomas, with good oncologic and functional outcomes, and few complications as well.

Keywords Larynx · Cancer · Transoral · Laser · Prognosis

Introduction

The aim of surgery for early to moderately advanced laryngeal squamous cell carcinoma (LSCC) is to remove cancerous tissue and preserve the functions of the larynx, such as breathing, swallowing and speech, as much as possible. Until recently, open surgical conservative approaches and radiotherapy (RT) have competed as the standard treatment of early and moderately advanced laryngeal cancer. The advent of microsurgical endoscopic procedures using the CO₂ laser (transoral laser microsurgery, TLM) had resulted in an important advance in terms of more functional surgery,

with lower morbidity and a better quality of life for the patient [1]. TLM has become the standard surgical approach for early-stage tumors in most institutions. Similar rates of overall survival (OS), disease-specific survival (DSS) and loco-regional control have been found between open partial techniques and TLM [1, 2]. In addition, preservation of the osseocartilaginous frame in TLM could hypothetically result in better salvageability of local recurrences with extralaryngeal spread [3]. However, the role of TLM in moderately advanced carcinomas is still unclear.

TLM as treatment for T1–T2 LSCC has excellent outcomes [4–6], similar to that obtained with modern RT (such as intensity-modulated radiation therapy). Meta-analyses have shown that there were no significant differences between TLM and RT for local control and, for OS the analysis favoured TLM [7–9]. On the other hand, the results of TLM in patients with moderately advanced supraglottic carcinomas are better than the results with primary

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RT regarding not only local control and survival, but also respect to organ preservation [10]. However, further studies are necessary to compare functional and quality of life outcomes for each treatment modality. In addition, several studies showed that TLM is the most cost-effective treatment of glottis cancer [11, 12].

Considering the oncological, functional and economic factors, the TLM could be considered the method of choice for treatment for early to moderately advanced LSCC. The aim of our study was to evaluate the oncologic and functional outcomes of TLM for LSCC at our Department and to determine the influence of the clinic-pathologic factors in the prognosis of the patients.

Materials and methods

Patients

We reviewed the clinical records of the patients with LSCC, who were treated with TLM at the Hospital Universitario Central de Asturias, from 1998 to 2013. Written informed consent was obtained from each patient. Medical records were retrospectively reviewed, following institutional review board guidelines, and analyzed. All patients underwent CO₂ laser-assisted endoscopic surgery as primary treatment and the minimum follow-up of the patients included in the study was 24 months.

The variables included were: age, sex, histology and location of the tumors, tobacco and alcohol consumption, familiar and personal history of cancer, stage, histological grade, post-operative complications and the incidence of recurrence and second primary malignancy. Tumors were classified according the TNM classification of the International Union Against Cancer (7th Edition, 2010).

The surgical procedures were performed under general anaesthesia after oro-tracheal intubation with Sharplan 30C CO₂ Laser System and AcuPulse CO₂ Laser System. Endoscopic resection was performed using en-bloc or piecemeal techniques according to several variables, including size and localization of the tumor, as well as the laryngeal exposure. All the patients underwent a transoral laser CO₂ microsurgery with curative intent, following Steiner recommendations [13]. Extension of the resection was tailored according to the size and site of the tumor.

TLM was indicated in T1–T2 glottic tumors with adequate tumor exposure, irrespective of the age and comorbidities of the patient. The cordectomies were classified following the European Laryngological Society's classification [14] (Table 1). Type III cordectomy was the most frequent treatment. Two cases with involved surgical margins received adjuvant RT.

Table 1 Distribution of laser cordectomies following the classification of the European Laryngological Society [14]

Laser cordectomies	
Type I	12 (10%)
Type II	34 (27%)
Type III	38 (31%)
Type IV	11 (9%)
Type V	28 (23%)

Supraglottic laser laryngectomy was indicated in patients with T1–T2 and selected T3 (with limited preepiglottic space invasion) supraglottic tumors, with adequate exposure of the entire larynx evaluated in a previously diagnostic microlaryngoscopy. In addition, all patients had acceptable cardiopulmonary conditions, irrespective of age, and no major comorbidities (like neurological disease).

The indications for performing a selective neck dissection were absence of identifiable metastatic neck nodes or radiological findings of positive nodes without extracapsular spread. Ipsilateral neck dissections were carried out in patients with lateralized not crossing the midline tumors and no clinical disease in both sides of the neck. Neck dissections were staged in the first treated patients, but since year 2004 neck dissections are performed simultaneously with TLM in all cases.

Patients with supraglottic tumors with affected surgical margins, more than 2 positive nodes or extra-nodal extension in the pathological examination (16 patients) received postoperative RT within 3 months after the surgery.

Statistical analysis was performed with χ^2 tests with Yates' correction when appropriate. Survival curves were drawn up according to the Kaplan–Meier product limit estimate. For the estimation of disease-specific survival, the event analyzed was the death of a patient related to tumor progression; all other survival times were treated as censored. Differences between survival times were analyzed by the log-rank method. Cox proportional hazards models were utilized for multivariate analyses. The hazard ratios (HR) with 95% confidence interval (CI) and *P* values were reported. All tests were two-sided. Significance was defined at the $p \leq 0.05$ level for all comparisons.

Results

203 patients were included in the study. The characteristics of the patients and their tumors are shown in Table 2. 195 patients (96%) were men and 8 women (4%), with a mean age of 63 years (range 39–86 years). 180 patients were smokers (89%) and 142 had history of alcohol consumption (73%). The most common location of the tumor was the glottis (116 patients, 57%). In 79 patients (39%) the tumor was originated in the supraglottis and in 8 cases (4%) in the

Table 2 Characteristics of the patient population and their tumors

Variable	No. patients (%)
Mean age (range), years	63 (39–86)
Sex	
Male	195 (96)
Female	8 (4)
Alcohol consumption	
Unknown	18
Never	37 (20)
< 50 g/day	6 (3)
50–100 g/day	64 (35)
> 100 g/day	78 (42)
Tobacco consumption	
Unknown	16
Never	7 (4)
< 10 packs-year	3 (2)
10–40 packs-year	64 (34)
> 40 packs-year	113 (60)
Localization	
Glottis	116 (57)
Supraglottis	79 (39)
Anterior commissure	8 (4)
T classification	
T1	134 (66)
T2	40 (20)
T3	29 (14)
N classification	
N0	176 (87)
N1	9 (4)
N2a	2 (1)
N2b	7 (3.5)
N2c	7 (3.5)
N3	2 (1)
Disease stage	
I	131 (64)
II	28 (14)
III	27 (13)
IV	17 (8)
Histological grade	
Not available	25
Well differentiated	99 (56)
Moderately differentiated	52 (29)
Poorly differentiated	27 (15)
Residual disease	
Not available	8
No	180 (92)
Microscopically	15 (8)
Macroscopically	0 (0)

anterior commissure. The distribution of patients following the TNM classification is shown in Table 2. Most glottic tumors were T1 (90%). Nevertheless, supraglottic tumors were classified as T2–T3 in 70% of patients. Most tumors were well-differentiated carcinomas (55%).

Surgical margins were microscopically involved in 15 of 195 cases (8%) with evaluable margins. Involvement of the surgical margins was more frequent in supraglottic tumors (17% of cases versus 2% in glottic and 0% in anterior commissure tumors; $p < 0.001$), and in tumors with higher T classification (1.5% in T1, 17% in T2 and 22% in T3 tumors; $p < 0.001$).

Forty-five patients (92%) underwent a neck dissection, which was performed simultaneously in 28 cases (62%) and staged in 17 (38%). A unilateral neck dissection was carried out in 2 patients (4%) and 43 (96%) underwent bilateral neck dissection. Except in 3 cases where type II modified radical neck dissection was performed, a selective neck dissection (levels II–IV) was done. From the 45 patients that received a neck dissection, 27 (60%) presented pathological neck metastasis (9 pN1, 16 pN2, and 2 pN3). Of the 4 patients who did not undergo a neck dissection, all of them had a cN0 neck. Three of them had a T1 tumor so they did not need to undergo neck treatment; and the remaining patient, with a cT3N0 tumor, had a poor performance status and the neck was treated with RT.

Patients had a median postoperative hospital stay of 3.5 days (range 1–95 days). The median postoperative stay in supraglottic tumors was 14 days (range 1–95 days), and in glottic and anterior commissure tumors was 2 days (range 1–25 days).

The major complications were bleeding (15 patients), respiratory infection (7 patients) and the need of tracheotomy (6 patients) There were no treatment-related deaths.

Oncologic results

Recurrent disease (including loco-regional recurrence and distant metastasis) developed in 60 patients (29%): 37 of them had a local recurrence (18%), 6 regional recurrence (3%), 8 loco-regional recurrence (4%), 5 loco-regional recurrence and distant metastasis (2.5%) and 4 distant metastases alone (2%). Forty-five patients (22%) developed a second primary tumor (20 cases in the lung, 6 cases in upper aerodigestive tract and 19 in other sites: prostate, colorectal, esophagus, urinary bladder, cutaneous, stomach) detected in a median of 35 months (14–60). Overall, local recurrence was observed in 50 patients (24.5%). Recurrences by site are shown in Table 3. The higher local relapse occurred in anterior commissure tumors (50%), followed by glottic (26%), and supraglottic tumors (19%) ($p = 0.16$). Local recurrence rate was increased in relation to the T classification, although the differences did not reach statistical significance

Table 3 Disease recurrence by tumor site

Site	Recurrence (%)				
	Local	Regional	Distant metastasis	Loco-regional	Loco-regional and distant metastasis
Glottis	22 (19)	1 (1)	0	4 (3.5)	4 (3.5)
Supraglottis	11 (14)	5 (6)	4 (5)	4 (5)	1 (1)
Anterior commissure	4 (50)	0	0	0	0

Table 4 Local recurrence in relation with clinic-pathological parameters

Parameter	No. cases	Local recurrence (%)	<i>P</i>
Tumor site			
Glottis	116	30 (26)	0.16
Supraglottis	79	16 (19)	
Anterior commissure	8	4 (50)	
T classification			
T1	134	28 (21)	0.21
T2	40	12 (30)	
T3	29	10 (34)	
Histological grade			
Well differentiated	99	27 (27)	0.82
Moderately differentiated	52	16 (31)	
Poorly differentiated	27	6 (22)	
Surgical margins			
Free	180		1
Involved	15	45 (25)	
Not available	8	4 (26)	

($p=0.21$, Table 4). The involvement of the surgical margins did not negatively influence the local recurrence rate ($p=1$, Table 4).

Among the 37 cases that developed an isolated local recurrence, 14 cases were successfully salvaged with additional TLM, 4 with RT, and 19 cases required a total laryngectomy. Seven of these patients developed additional recurrences and died from the tumor. The 8 cases with loco-regional recurrence were salvaged with total laryngectomy and neck dissection in 6 cases and with radiotherapy in two cases. The disease recurred again in 5 cases who died from the tumor. Patients with distant metastasis received palliative treatment.

The 5-year DSS rate according to the Kaplan–Meier method for all 203 patients was 90%, and the 5-year OS was 84%. The 5-year DSS was 91% for stage I, 95% for stage II, 87% for stage III, and 59% for stage IV disease ($p<0.001$). The 5-year OS was 77% for stage I, 83% for stage II, 84% for stage III, and 33% for stage IV disease ($p<0.001$). DSS was significantly lower in patients that had nodal metastasis classified higher than N1 ($p<0.001$), in patients with T3 tumors

($p=0.035$) and in patients with affected margins ($p=0.01$) (Fig. 1). Location of the tumor was not associated with DSS ($p=0.82$). Patients with glottic tumors showed a better OS, although the differences did not reach statistical significance ($p=0.059$) (Fig. 2). Multivariate analysis (logistic regression) showed that the only parameters independently associated with a lower disease-specific survival were the presence of nodal metastasis $>N1$ (HR = 13.14; 95% CI 3.71–46.57; $p<0.001$) and involvement of surgical margins (HR = 6.23; 95% CI 1.79–21.66; $p=0.004$).

Functional results

A nasogastric feeding tube was needed in the postoperative period in 72 patients, all with supraglottic tumors. The remaining patients reassumed oral diet the day following surgery (all these patients had T1 classified tumors). The mean duration of nasogastric tube feeding was 10.8 ± 8.2 days (median 8 days). Nasogastric tube could be removed in all but 3 patients: 2 patients underwent total laryngectomy and another patient a laryngeal exclusion. 6 patients (3%) needed a temporal tracheotomy as consequence of dyspnea ($n=3$) or broncho aspiration ($n=3$). All tracheostomized patients due to dyspnea could be decannulated without problems.

The 5-year laryngectomy-free survival rate was 85% (84% in supraglottic tumors, 86% in glottic tumors, and 75% in anterior commissure tumors) (Fig. 3).

Discussion

Patients with LSCC classified T1 or T2, without nodal or distant metastases may be treated with TLM, open partial laryngectomy or RT. If we keep in mind that early tumors usually have good prognosis, the goals of the treatment are not only the cure, but also the larynx preservation with optimal voice quality, minimizing the complications and reducing costs. TLM in early LSCC has demonstrated to be an effective treatment, with 5-year recurrence-free survival rates that ranges from 80 to 94%, with preservation of the larynx in more than 90% of cases [1, 2, 4–6]. Recent systematic reviews and meta-analysis have shown the excellent results of TLM as definitive therapy for T1 and T2 in

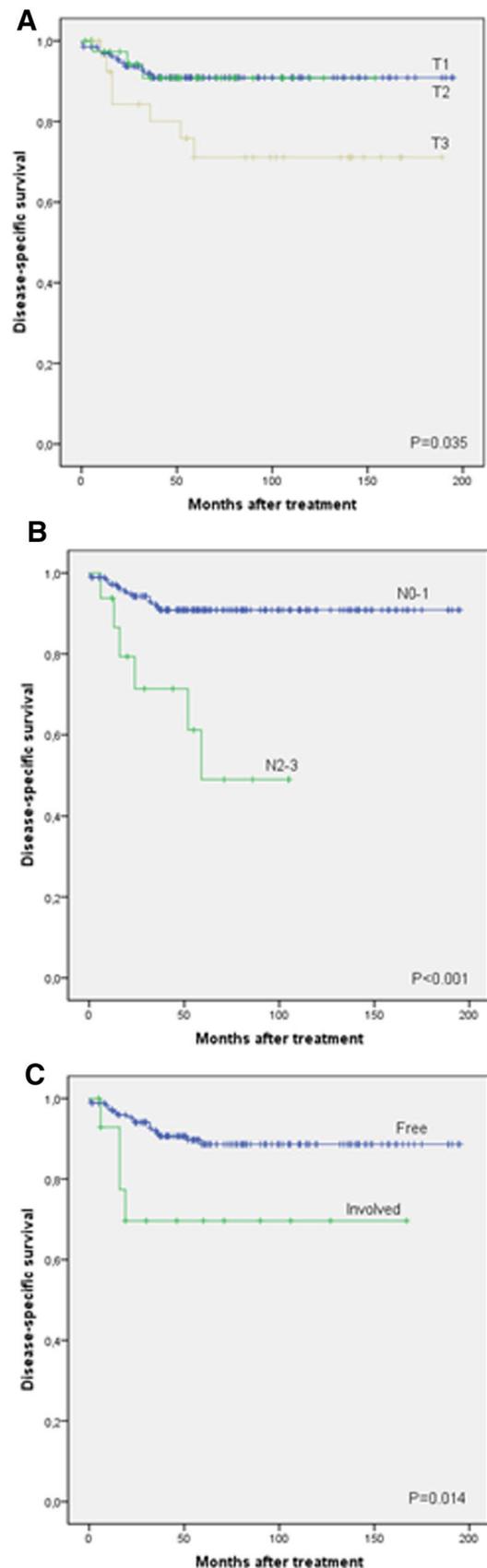
Fig. 1 Kaplan–Meier curves of disease-specific survival depending on T-classification (a), N-classification (b), and surgical margins (c)

LSCC, with local control rates better than with RT, both in glottic [7–9] and supraglottic tumors [10]. Likewise, we had a 75% 5-year local recurrence-free survival rate and 85% of patients preserved their larynx. Our slightly lower control rates could be explained by the inclusion of T3 supraglottic tumors. Endoscopic procedures should be limited to tumors completely exposable during microlaryngoscopy. In this way, they are usually indicated in T1–T2 tumors, but it could also be used in selected T3 carcinomas (in our series, supraglottic tumors with limited preepiglottic space invasion). With careful selection of the patients, transoral supraglottic laryngectomy in T3 carcinomas was considered a treatment option with either oncologic and larynx preservation results similar to those obtained with chemoradiation [1].

In addition to the effectiveness in disease control, TLM is interesting as first treatment because it leaves all treatment options open in patients with local recurrence or a second primary tumor in the head and neck region. In our series, half of the cases with local recurrence could be successfully salvaged with additional TLM or RT, with preservation of the laryngeal function.

Regarding prognostic factors, involvement of anterior commissure has been reported to affect local tumor control and organ preservation [15, 16]. This area has an increased risk of tumor spread into the thyroid cartilage due to the attachment of the vocal fold at a point where the laryngeal perichondrium is interrupted. This worse prognosis is also observed in our series, with a 50% local recurrence rate and a lower laryngeal preservation rate (75%) than cases without anterior commissure involvement. However, in other studies although glottic carcinomas with anterior commissure involvement treated with TLM are more likely to have either positive or uncertain resection margins, the management with this procedure is not associated with reduced local control or laryngeal preservation [17]. It should be considered that in this last study many patients received complementary RT.

Negative margins are essential in limiting local recurrence. Blanch et al. [18] analyzed the relevance of margins in transoral laser microsurgery among 357 patients treated for cancer. This group found that tumor involvement of the surgical margin was associated with higher rates of local relapse, distant metastasis and the necessity of salvage surgery, together with a lower specific actuarial survival rate. However, we did not find a higher rate of local recurrences in the cases with affected surgical margins. This could be attributable to the administration of postoperative radiotherapy in these cases. In contrast, surgical margins involvement was associated with a lower DSS. This discrepancy between local control and DSS could be explained by the association



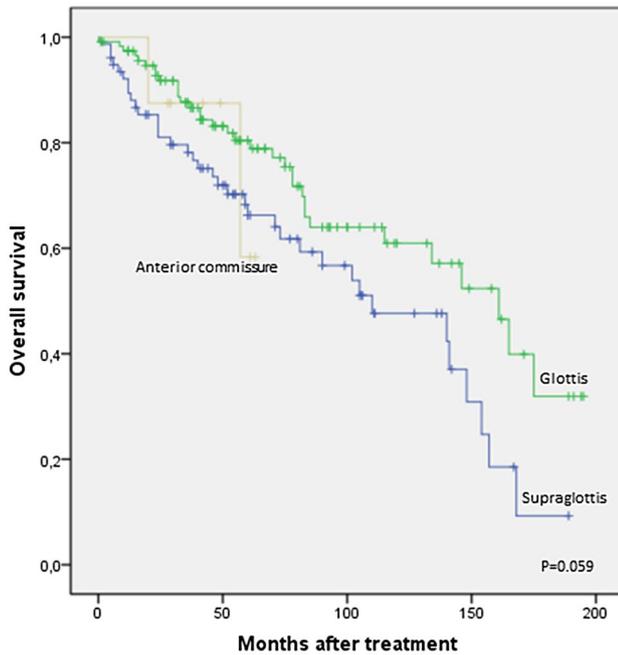


Fig. 2 Kaplan–Meier curves of overall survival according to tumor localization

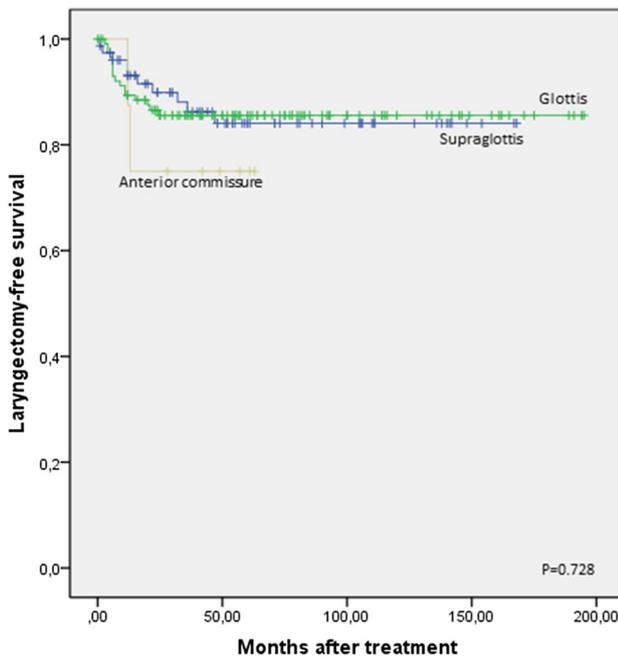


Fig. 3 Kaplan–Meier curves of laryngectomy-free survival according to tumor localization

of surgical margins involvement with poor prognosis factors such as T3 tumors.

As could be expected, the parameter with the higher influence in DSS was the N classification, with N2–N3 cases showing the worse prognosis. T classification was also

associated with local control of the disease, with an increase in local recurrence rates as T classification increases. However, the DSS was only significantly worse in the T3 classified cases. This could be due to a higher rate of successful salvage treatment in T2 cases, and a higher rate of nodal metastasis in T3 cases.

Regarding the complications of TLM for LSCC, it could be considered a safe procedure, as no treatment-related deaths were observed in our study, as in most other [2, 19, 20]. The most frequent complications were postoperative bleeding (7% of patients) and aspiration pneumonia (3% of patients), that are the complications also more frequently described for this procedure [19, 20]. Cases of aspiration pneumonia occurred only in supraglottic tumors. These patients were usually older patients, and patients with poor preoperative pulmonary function. Three of these patients were unable to reassume an oral diet and required a total laryngectomy or a laryngeal exclusion. As previously mentioned, the laryngeal preservation rate (patients with a functioning larynx) in our series was 85%, that compares well to other series including T2–T3 tumors, that report laryngeal preservation rates between 80 and 90% [4, 6, 21–23]. It should be borne in mind when assessing these results that only a small proportion (9%) of patients in our series received postoperative RT.

In conclusion, TLM offers an effective treatment option in terms of oncologic control and function preservation in early and moderately advanced stages of LSCC, with minimal complications. The most relevant prognostic factors were the T and N classifications, and the involvement of the surgical margins.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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