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Prognostic value of age, subglottic, and anterior commissure involvement for early glottic carcinoma treated with CO_2 laser transoral microsurgery: a retrospective, single-center cohort study of 261 patients

Filippo Carta[1] · Fabrizio Bandino[1] · Aurora Marta Olla[1] · Natalia Chuchueva[1,2] · Clara Gerosa[3] · Roberto Puxeddu[1]

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Abstract

Purpose CO_2 laser transoral microsurgery for glottic carcinoma, when indicated, has the well-established advantages of low morbidity and positive oncological outcomes. The present study aims to determine how patient age, and tumor site could negatively impact prognosis; other variables such as the status of the margins of resection, tobacco and alcohol intake, and the grade of differentiation of the tumors have been evaluated.

Methods This was a retrospective analysis on 261 patients with a glottic carcinoma who underwent CO_2 laser transoral microsurgery. The impact of different variables was calculated using univariate and multivariate analyses.

Results The study included 248 males and 13 females. The median follow-up period was 4.3 years. Five-year disease-specific survival, recurrence-free survival, local control with laser alone, overall laryngeal preservation, and overall survival rates were 99.4, 92.2, 93.8, 97.6, and 85.5%, respectively. Equivalent results were observed in young and elderly patients. Patients with positive margins after CO_2 laser transoral microsurgery showed a reduced local control with laser alone. T2 patients with true subglottic spreading and patients with anterior commissure involvement of grade 3 (Rucci's classification) experienced worse local control rates, despite free surgical margins confirmed by histology.

Conclusions CO_2 laser transoral microsurgery is an effective and reproducible single-stage modality therapy for young and elderly patients with glottic carcinoma. Superficial close margins can be managed by a careful wait-and-see policy, while positive margins should undergo surgical enlargement. In our experience, undifferentiated tumors, true subglottic extension, and anterior commissure involvement of grade 3 were associated with worse outcomes.

Keywords Glottic carcinoma · CO_2 laser · Endoscopy · Transoral microsurgery · Anterior commissure · Subglottic extension

Introduction

Laryngeal squamous cell carcinoma (LSCC) is a common malignancy, representing 30–50% of all neoplasms in the head and neck [1], with 157,000 new cases diagnosed worldwide in 2012 [1]. Treatment of LSCC is based on surgery and radiotherapy [2], but after the pioneering works of Strong and Steiner [3–5], the development of transoral microsurgery with the aid of a carbon dioxide (CO_2) laser led to an increased use of this minimally invasive and organ-preserving approach.

CO_2 laser transoral microsurgery (TOLMS) was initially used as a treatment for small lesions (Tis, T1a–b), achieving good oncological and functional results that encouraged

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✉ Filippo Carta
filippocarta@unica.it

1 Unit of Otorhinolaryngology, Department of Surgery, Azienda Ospedaliero-Universitaria di Cagliari, University of Cagliari, Cagliari, Italy

2 I. M. Sechenov First Moscow State Medical University, Moscow, Russia

3 Unit of Pathology, Department of Surgery, Azienda Ospedaliero-Universitaria di Cagliari, University of Cagliari, Cagliari, Italy

surgeons to endoscopically treat more advanced lesions (selected T2, T3, and even T4) and selected cases of recurrence after surgery or radiotherapy [6]. Currently, TOLMS is a well-standardized diagnostic and therapeutic procedure with a mean laser-disease control rate of 81.3% [7] and good functional results.

Adequate surgical experience in the management of the key points of the glottis (anterior commissure, subglottis, and paraglottic space) and complete removal of the tumor after precise preoperative work-up are universally accepted as the requirements to achieve optimal results [7–9].

Analyses of the functional results observed in our patients were submitted by the same surgeon for TOLMS as previously published [10].

The present study aims to determine how patient age, and tumor site could negatively impact prognosis; other variables such as the status of the margins of resection, tobacco and alcohol intake, and the grade of differentiation of the tumors have been evaluated.

Methods

This is a retrospective analysis of the clinical charts of a cohort of patients with glottic carcinoma submitted by the senior author for TOLMS from October 1993 to November 2005 and from December 2010 to January 2016 at the Department of Otorhinolaryngology of an Italian institution (ethic committee protocol number 216/2017).

Preoperative diagnostic assessment included videolaryngoscopy, and panendoscopy with 0°, 30°, and 70° rigid scopes. Beginning in 2013, videolaryngoscopy was coupled with narrow-band imaging (NBI), high-definition TV camera (Olympus Medical Systems Corporation, Tokyo, Japan), the IMAGE1 S System™ (Storz, Tuttlingen, Germany) and enhanced contact endoscopy (ECE) [11].

Computed tomography (CT) of the neck with contrast medium was used when clinical evaluation showed reduction of vocal cord mobility, subglottic extension or involvement of the anterior commissure, to rule out the invasion of the tumor into thyroid cartilage, pre-epiglottic and paraglottic spaces and to assess the neck status.

The exclusion criteria to submit the patients to TOLMS were carcinoma located in the anterior commissure with massive trans-commissural vertical spread, radiologic evidence of erosion of the inner cortex of the thyroid cartilage, significant involvement of the paraglottic space, vocal cord fixation, and inadequate laryngeal exposure using the Kleinsasser laser laryngoscope modified by Rudert with the Göttingen model suspension system (Storz, Tuttlingen, Germany). During the period of the study, 31 patients out of this case series underwent type II open partial horizontal laryngectomy (OPHL): 3 patients (3 males, mean age of 62.7 years, range of 49–70 years) for inadequate endoscopic exposure, 5 patients (5 males, mean age of 59.6 years, range of 58–63 years) for massive trans-commissural involvement of the anterior commissure, and 23 patients (22 males and 1 female, mean age of 60.9 years, range of 45–75 years) for unilateral arytenoid involvement.

All patients received ceftriaxone (1000 mg IV) the day of surgery or, as an alternative if allergic, ciprofloxacin (400 mg IV).

All patients underwent TOLMS under general anesthesia by orotracheal intubation with a Mallinckrodt tube (I.D. 5.0–7.0 mm; Athlone, Ireland). Sharplan 1030 and Acupulse carbon dioxide lasers with an Acuspot, Acublade 712 micromanipulator and Digital AcuBlade™ (Lumenis®, Israel) set on the superpulsed mode (2–10 Ws, 270-μm spot size) were used in the majority of the surgeries in the present series.

On the basis of the extension of the neoplasm, the endoscopic cordectomies were classified according to the European Laryngological Society (ELS) [12, 13]. Tumors involving the anterior commissure were classified according to Rucci et al. [14]: no involvement of the anterior commissure subsite (AC0); involvement of the anterior commissure subsite on only one side of the midline (AC1); involvement of the anterior commissure subsite that crosses the midline on only part of the longitudinal extension of this subsite (AC2); and involvement of the whole anterior commissure subsite on both sides across the midline (AC3).

Resections were always performed using an en bloc technique when the volume of the tumor allowed it, while larger tumors were removed using a piecemeal technique. Lesions involving the anterior commissure were resected together with the involved vocal cord, performing a subperichondrial dissection. Resections were performed in macroscopic free margins; if in doubt, histologic examination of the remaining margins using a frozen section was obtained intraoperatively. Specimens were sent for histology oriented by staining the superior edge with ink as to obtain the precise mapping of the lesions, and also after piecemeal removal. Elective neck dissection was never considered for cN0 patients.

After definitive histology, lesions were classified according to the 7th Edition of the Union for International Cancer Control–American Joint Committee on Cancer (UICC–AJCC) TNM-staging system [15].

When margins were histologically involved, surgical enlargement was generally planned, especially if the deep margin was involved. In some cases, a wait-and-see policy was adopted after patient counselling if the excision was believed to be radical.

After healing of the surgical wound, voice rehabilitation and regular follow-up were planned, according to the NCCN guidelines [16]: fibrolaryngoscopy coupled from 2013 with NBI every month during the first year, every 2 months during the second year and every 3–4 months until the fifth year in absence of any recurrence and/or second disease.

Patients included in the present study were followed up from the date of surgery until March 2017, when possible. The time-related study endpoints were overall survival (OS), disease-specific survival (DSS), recurrence-free survival (RFS), local control with laser alone (LCL) (including all patients who underwent one or repeated laser-surgical interventions, and patients with recurrent disease managed with repeated laser surgery), and overall laryngeal preservation rate (OLP). Statistical analyses were performed using GraphPad Prism software (GraphPad, San Diego, CA, USA). Survival probabilities over time were estimated using the Kaplan–Meier method. Univariate and multivariate analyses were performed using the Cox proportional hazards model. The log-rank (Mantel–Cox) test was applied to compare survival rates between different groups (pT category, grading category, alcohol and tobacco consumption, patients with or without anterior commissure involvement, patients with or without subglottic extension, status of surgical margins, patients older than 65 years and young patients). A p value < 0.05 was considered to be statistically significant.

The literature review was based on a MEDLINE search, using "glottic cancer", "transoral", "endoscopy", "elderly", "subglottic", "anterior commissure", and "CO_2 laser" as keywords.

Results

Patients and tumor characteristics, and the numbers and type of surgical cordectomies are detailed in Table 1.

Mean hospitalization time was 2.6 days. Only one immediate postoperative bleeding was observed, and it was managed using endoscopic cautery under general anesthesia. No feeding tube was inserted, and no tracheostomy was performed at the end of the procedure or in the postoperative period. Twenty-two patients (8.4%) experienced scar at the anterior commissure as a late complication, and among them, 5 patients required an endoscopic treatment of the web under general anesthesia.

The mean follow-up period was 5 years (median follow-up of 4.3 years), ranging from 2 months to 17 years. Six patients died within the first year after surgery due to other causes, 162 (62%) had a follow-up period longer than 3 years, 111 (42.5%) patients had a follow-up period longer than 5 years, and 29 (11.1%) patients had a follow-up period longer than 10 years.

Recurrences occurred in 17 out of the 261 patients (16 laryngeal relapses and 1 nodal recurrence). The recurrence rate was 6.5%, the mean recurrence time was 1.3 years, and the recurrence time ranged from 3 months to 3 years; 7 out of the 17 recurrences (41.2%) occurred within the first year, 6 out of 17 (35.3%) within the second year, and 4 out of 17 (23.5%) within the third year after surgery. Recurrent patients underwent TOLMS alone in 6 cases, TOLMS and radiotherapy in 1 case, radiotherapy alone in 1 case, type II OPHL in 1 case, type III OPHL in 1 case, type II OPHL and radiotherapy in 1 case, total laryngectomy (TL) in 3 cases, TL and radiotherapy in 1 case, and radical neck dissection and radiotherapy in 1 case; one patient refused to be treated and died of disease (Table 2). Patients of our series did not experience second relapse of disease.

In total, 9 patients (3.4%) were addressed for radiotherapy (total dose between 66 and 74 Gy): 4 patients after primary TOLMS for positive surgical margins, and 5 patients after recurrence (positive margins after endoscopic enlargement in 1 case, multifocal recurrent disease in 1 case, nodal metastasis in 1 case and neoplastic angioinvasion in 2 cases).

Five patients developed a second laryngeal primary carcinoma more than 5 year after the first procedure: 4 of these 5 patients underwent TOLMS, while 1 patient refused to be treated with TL and died of LSCC progression. Twenty-two patients (8.4%) developed a second extra-laryngeal malignancy (9 lung, 2 colorectal, 2 stomach, 2 prostate, 1 lip, 1 esophagus, 1 tonsil, 1 tongue, 1 cornea, 1 pancreas, and 1 bladder).

Kaplan–Meier survival rates, Cox univariate and Cox multivariate analyses are reported in Tables 3, 4 and 5 and in Fig. 1.

Prognostic factors

Tobacco consumption

DSS, RFS, LCL, and OLP analysis did not show any tobacco consumption-related statistically significant differences.

Alcohol consumption

DSS, RFS, LCL, and OLP analysis did not show any alcohol intake-related statistically significant differences.

Positive margins

LCL was significantly lower in the ten patients with positive margins of resection after the first surgical procedure who could not undergo surgical enlargement (60%, $p < 0.001$), since 4 of them underwent adjuvant radiotherapy; RFS and OLP in these ten patients were 100%.

Anterior commissure involvement

Univariate analyses comparing patients without (156 out of 261 patients) and with anterior commissure involvement (105 out of 261 patients) did not show statistically

Table 1 Cohort of patients

Characteristics	No. of pts (%)
All	261 (mean age 64.6 years; range 29–90 years)
Male	248 (mean age 64.9 years; range 39–90 years)
Female	13 (mean age 58.6 years; range 29–84 years)
Male:female sex ratio	19:1
Tobacco consumption	226 (86.6%)
Daily alcohol consumption	198 (75.9%)
Preoperative biopsy	40 (15.3%)
Intraoperative biopsy	55 (21.1%)
Excisional biopsy	166 (63.6%)
Type of surgical cordectomies	21 type I cordectomy 62 type II cordectomy (in 9 cases extended to the anterior commissure) 64 type III cordectomy (in 13 cases extended to the anterior commissure) 18 type IV cordectomy 94 type V cordectomy - 48 a - 5 ab - 2 abc - 9 abcd - 8 ac - 6 acd - 6 ad - 5 b - 3 bc - 2 c 2 type VI cordectomy
Clinical N classification	261 cN0
Pathological T classification	24 pTis 150 pT1a 46 pT1b 41 pT2 (13 lesions presented a true subglottic spread)
Involvement of the anterior commissure	156 AC0 105 AC + (40.2% of the whole series, 68 T1 and 37 T2) - 31 AC1 (29.5%) - 65 AC2 (61.9%) - 9 AC3 (8.6%)
Grade of differentiation	175 well differentiated (67%) 47 moderately differentiated (18%) 11 poorly differentiated (4.2%) 28 undifferentiated (10.8%)
Margins of resection	251 (96.2%) free margins 212 (81.3%) margins more than 1 mm after definitive histology 6 (2.3%) margins more than 1 mm after intraoperative enlargement 10 (3.8%) close margins (less than 1 mm) - 9 patients underwent delayed endoscopic enlargement (histology of the enlargements was free of disease in all cases) - 1 patient underwent wait-and-see policy 23 (8.8%) negative margins after delayed endoscopic enlargement - Histology of the enlargements was free of disease in 10 patients - Histology of the enlargements showed dysplasia in 8 patients - Histology of the enlargements showed carcinoma invasive and/or carcinoma in situ in 5 patients[a] 10 (3.8%) positive margins 3 patients (1.1%) previously submitted for type IV and V resections extended to the perichondrium of the thyroid cartilage received radiotherapy (total dose 66–74 Gy) 1 patient (0.4%) underwent postoperative radiotherapy after TOLMS for multifocal in situ carcinoma with surgical margins positive for high dysplasia 6 patients (2.3%) were managed with a wait-and-see policy

AC0, no involvement of the anterior commissure. AC1, involvement of the anterior commissure on only one side of the midline. AC2, involvement of the anterior commissure that crosses the midline on only part of the longitudinal extension of this subsite. AC3, involvement of the whole anterior commissure on both sides across the midline

[a] Residual carcinoma was found in 2 patients with deep positive margins, and in 3 patients with superficial positive margins

Table 2 Recurrent patients

Patient/sex/age (years)	Type of cordectomy	pT	AC/SG/margins	Site of relapse/time of relapse (years)	Salvage treatment	Outcome/time of last follow-up visit (years)
DG/M/76.3	Va	1b	AC2/SG0/M0	Larynx/1.7	CO_2 laser transoral microsurgery + radiotherapy	DOC/2.5
FE/M/68.5	IV	1b	AC0/SG0/M0	Larynx/0.3	CO_2 laser transoral microsurgery	NED/7
MG/M/70.1	II	1a	AC0/SG0/M0	Larynx/0.6	Type II horizontal laryngectomy + radiotherapy	NED/5
VA/M/61.9	II	1a	AC0/SG0/M0	Larynx/2.4	CO_2 laser transoral microsurgery	DOC/11.1
RB/M/82.7	Vabc	2	AC2/SG0/M0[a]	Larynx/2.4	Refuse treatment	DOD/2.5
DE/M/72.8	II	1a	AC0/SG0/M0	Larynx/0.7	CO_2 laser transoral microsurgery	DOC/4.9
LS/M/76.6	Va	2	AC2/SG0/M0	Larynx/1.7	CO_2 laser transoral microsurgery	DOC/4.3
FG/M/64.1	Vacd	2	AC2/SG+/M0	Larynx/1.3	Type II horizontal laryngectomy	NED/11
MS/M/53.5	IV	1a	AC0/SG0/M0	Larynx/3	Total laryngectomy	NED/7.8
SC/M/61.4	III	1a	AC2/SG0/M0	Larynx/0.8	CO_2 laser transoral microsurgery	NED/2.5
CS/M/60.9	II	1a	AC0/SG0/M0	Larynx/1.8	CO_2 laser transoral microsurgery	NED/2.1
ZF/M/71.5	Vabcd	2	AC3/SG+/M0	Larynx/0.2	Total laryngectomy	DOC/0.5
PB/M/64.1	Vac	2	AC3/SG0/M0[a]	Larynx/1.2	Total laryngectomy	NED/2.9
RM/M/73.8	I	1a	AC0/SG0/M0	Larynx/1.2	Radiotherapy	NED/3
DS/F/62.8	Vabcd	2	AC2/SG+/M0	Larynx/0.5	Total laryngectomy + radiotherapy	NED/2.4
BM/M/51.7	Vb	1a	AC0/SG0/M0	Larynx/2.1	Type III horizontal laryngectomy	NED/2.2
SG/M/68.3	Vac	1b	AC1/SG0/M0	Neck node/0.9	Neck dissection + radiotherapy	NED/1.5

AC0, no involvement of the anterior commissure. AC1, involvement of the anterior commissure on only one side of the midline. AC2, involvement of the anterior commissure that crosses the midline on only part of the longitudinal extension of this subsite. AC3, involvement of the whole anterior commissure on both sides across the midline. SG0, no evidence of subglottic spread. SG +, intraoperative evidence of subglottic spread more than 1 cm below the glottic plane. M0, margins of resections not involved by the tumor after the first surgical procedure or delayed surgical enlargement. M +, patients with margins of resections involved by the tumor after one single or delayed surgical enlargement. NED, not evidence of disease. DOD, died of disease. DOC, death from other causes

[a] Patients with positive margins after the first surgical procedure who underwent endoscopic enlargement by CO_2 laser transoral microsurgery (no residual carcinoma was found)

significant differences in survival or local control rates. The multivariate analysis showed worse RFS, LCL, and OLP (74.1%, $p = 0.0446$; 71.1%, $p = 0.0187$; and 71.1%, $p < 0.0001$, respectively) in AC3 patients.

Subglottic extension

The Cox multivariate analysis showed that pT2 stage with a true subglottic spread was significantly associated with worse RFS, LCL, and OLP (74%, $p = 0.0098$; 67.3%, $p < 0.0001$; and 84.6%, $p < 0.0001$; respectively).

Grading

The Cox multivariate analysis showed that patients with undifferentiated tumors ($n = 28$) experienced worse LCL, and OLP (81.1%, $p = 0.0419$; 89.9%, $p = 0.0462$ respectively).

Elderly vs. young patients

One hundred and thirty-three patients were younger than 65 years, while 128 were elderly patients (46 patients were older than 75 years). DSS, RFS, LCL, and OLP analysis did not show any age-related statistically significant differences.

Discussion

LSCC is mainly a loco-regional disease, and its treatment is influenced by tumor characteristics, laryngeal anatomic boundaries, patient age and comorbidities, patient's voice expectations, medical facilities, and cost-effectiveness ratio of the procedures [8]. Radiotherapy is a time-consuming and expensive procedure and cannot be repeated in the case of recurrence or a second primary tumor in the region of irradiation [17]. OPHL is an effective conservative option but is associated with a well known and non-negligible perioperative morbidity [18]. It is currently well accepted in the

Table 3 Survival rates of the present series of patients

Population	Disease-specific survival 5 years	Recurrence-free survival 5 years	Local control with laser alone 5 years	Overall laryngeal preservation 5 years	Overall survival 5 years
All patients $n=261$	99.4% CI 96.1–99.9%	92.2% CI 87.7–95.1%	93.8% CI 90–96.6%	97.6% CI 94.2–99%	85.5% CI 79.4–90%
All Tis ($n=24$)	100% –	100% –	95.5% CI 71.9–99.3%	100% –	91% CI 68.5–97.7%
All T1 ($n=196$)	100% –	93.2% CI 88–96.2%	96.8% CI 92.3–98.7%	99.2% CI 94.2–99.9%	88.1% CI 81.1–92.6%
All T2 ($n=41$)	95.7% CI 72.9–99.4%	**81.5%** CI 62.5–91.5% $p=0.0266$	**79.5%** CI 60.7–90% $p<0.0001$	**88%** CI 70.1–95.5% $p=0.0005$	68.5% CI 46–83.2%
T2 SG0 ($n=28$)	94.7% CI 68.1–99.2%	85.6% CI 61.1–95.2%	85.6% CI 61.1–95.2%	90% CI 65.2–97.4%	65.5% CI 38.8–82.5%
T2 SG+ ($n=13$)	100% –	74% CI 38.2–91%	67.3% CI 34–86.5%	84.6% CI 51.2–95.9%	83.1% CI 47.2–95.5%
Age ≤65 years $n=133$	100% –	92.8% CI 86–96.3%	93.9% CI 87.6–97.1%	97.3% CI 91.6–99.1%	95.7% CI 88.6–98.4%
Age ≥ 65 years $n=128$	98.8% CI 91.8–99.8%	91.7% CI 84.5–95.6%	94.4% CI 87.8–97.5%	98% CI 91.9–99.5%	74.6% CI 63.8–82.6%
AC0 lesions ($n=156$)	100% –	93.9% CI 88.1–96.9%	96.2% CI 91–98.4%	99.1% CI 93.5–99.9%	89.5% CI 82–94%
AC + lesions ($n=105$)	98.4% CI 89.3–99.8%	89.7% CI 81–94.6%	91% CI 82.6–95.5%	95.3% CI 87.7–98.3%	78.6% CI 66.3–84.9%
M0 ($n=251$)	99.4% CI 98.8–100%	91.9% CI 90–93.8%	95.1% CI 93.6–96.6%	97.5% CI 96.4–98.6%	85% CI 84–87%
M + ($n=10$)	100% –	100% –	**60%** CI 44.5–61.5% $p<0.0001$	100% –	87.5% CI 75.8–99.2%

CI, confidence interval; values statistically significant in a univariate analysis are bold. SG0, no evidence of subglottic spread. SG+, intraoperative evidence of subglottic spread more than 1 cm below the glottic plane. AC0, no involvement of the anterior commissure. AC+, involvement of the anterior commissure. M0, margins of resections not involved by the tumor after the first surgical procedure or delayed surgical enlargement. M+, patients with margins of resections involved by the tumor after the first surgical procedure who did not undergo surgical enlargement

international guidelines that laser therapy plays the primary role in the treatment of early glottis cancer [19].

An adequate preoperative laryngeal evaluation is mandatory: analysis of the superficial extension of the lesions has been recently improved with bioendoscopy through the precise analysis of the neoangiogenesis [11, 20]. Vocal cord mobility is significant, because it is related to the tyro-arytenoid muscle or cricoarytenoid joint invasion and predicts the subsequent type of cordectomy or contraindication to laser treatment [21]. In our series of patients, fixation of the vocal cords for invasion of the cricoarytenoid joint, as preoperatively defined by laryngoscopy and CT examinations, was indeed an absolute contraindication for the endoscopic approach and even any OPHLs.

Laryngeal exposure is critical for a transoral approach [22]. In our department, a Göttingen model system associated with the largest laryngoscope according to a patient's anatomy is routinely used. Favorable vs. difficult/impossible laryngeal exposure can be predicted by the standardized preoperative laryngoscore [23]. In our experience, the use of the Benjamin laryngoscope (Holinger Benjamin Laryngoscope Adult Anterior Commissure, Storz, Germany) allows surgeons to overcome the majority of the difficult laryngeal exposures, and during the period of the study, only three patients underwent OPHL for inadequate laryngeal exposure.

An endoscopic approach allows a surgeon to tailor the resection on the basis of the extent of the tumor: treatment of T1 glottic cancer should be as conservative as possible in terms of tyro-arytenoid muscle resection, since muscle invasion is rare (5.5% according to our previous study performed on a series of 109 patients), and in many cases, type III and IV cordectomies can be regarded as excessive treatment [21]. In our experience, the posterior portion of the tyro-arytenoid muscle has been spared in type V cordectomies if not involved.

The controversy about voice results after laser endoscopic treatment vs. radiotherapy is still ongoing. A previous study performed by our group on voice outcomes after laser cordectomies reinforced by videolaryngostroboscopy as well as objective and perceptive evaluations, demonstrates that

Table 4 Univariate Cox analysis of prognostic covariates for recurrence-free survival, local control with laser alone, and overall laryngeal preservation

Variables	No. of pts	Recurrence-free survival			Local control with laser alone			Overall laryngeal preservation		
		5-year rate	HR[a]/unianalysis 95% CI	*p*	5-year rate	HR[a]/unianalysis 95% CI	*p*	5-year rate	HR[a]/Un analysis95% CI	*p*
Age										
≤65 years	133	92.8% (86–96.3%)	0.7786/0.3001–2.020	0.6069	93.9% (87.6–97.1%)	1.173/0.4094–3.362	0.7663	97.3% (91.6–99.1%)	1.680/0.3364–8.393	0.5272
Over 65 years	128	91.7% (84.5–95.6%)			94.4% (87.8–97.5%)			98% (91.9–99.5%)		
pT										
pT1	196	93.2% (88–96.2%)	0.2280/0.06171–0.8427	**0.0266**	96.8% (92.3–98.7%)	0.04042/0.008567–0.1907	**< 0.0001**	99.2% (94.2–99.9%)	0.02022/0.002217–0.1844	**0.0005**
pT2	41	**81.5% (62.5–91.5%)**			**79.5% (60.7–90%)**			**88% (70.1–95.5%)**		
Preoperative daily tobacco consumption										
Tobacco +	226	92.5% (90.6–94.5%)	0.3317/0.6947–1.4395	0.5646	93.7% (91.9–95.5%)	0.4453/0.5080–1.9683	0.5046	97.6% (96.4–98.8%)	0.09860/0.7115–1.4056	0.7535
Tobacco −	35	90.1% (85.5–95.9%)			97.1% (94.3–99.9%)			97.1% (94.3–99.9%)		
Preoperative daily alcohol consumption										
Alcohol +	198	91.1% (88.9–93.3%)	1.4275/0.4184–2.3901	0.2322	93.4% (91.4–95.4%)	0.04011/0.8779–1.1390	0.8413	97.4% (96.1–98.7%)	0.3870/0.5874–1.7024	0.5339
Alcohol −	63	95.9% (93–98.9%)			96.7% (94.4–99%)			98.4% (96.8–100%)		
M0	251	91.9% (90–93.8%)	2.843/0.2716–29.77	0.3832	95.1% (93.6–96.6%)	0.00018/261.7–115,303	**< 0.0001**	97.5% (96.4–98.6%)	2.849/0.05811–139.6	0.2779
M +	10	100% –			**60% (44.5–61.5%)**			100% –		
AC0	156	93.9% (88.1–96.9%)	1.884/0.7069–5.020	0.2054	96.2% (91–98.4%)	2.443/0.8160–7.312	0.1104	99.1% (93.5–99.9%)	4.600/0.8219–25.74	0.0824
AC +	105	89.7% (81–94.6%)			91% (82.6–95.5%)			95.3% (87.7–98.3%)		
T2 SG0	28	85.6% (61.1–95.2%)	3.396/0.5487–21.02	0.1886	85.6% (61.1–95.2%)	3.909/0.7585–20.15	0.1032	90% (65.2–97.4%)	3.014/0.3366–26.98	0.3239
T2 SG +	13	74% (38.2–91%)			67.3% (34–86.5%)			84.6% (51.2–95.9%)		

CI, confidence interval. M0, margins of resections not involved by the tumor after the first surgical procedure or delayed surgical enlargement. M +, patients with margins of resections involved by the tumor after the first surgical procedure who did not undergo surgical enlargement. AC0, no involvement of the anterior commissure subsite. AC +, involvement of the anterior commissure. SG0, no subglottic spread. SG +, subglottic spread more than 1 cm below the glottic plane

Statistical values are in bold ($p < 0.05$)

Table 5 Multivariate Cox analysis of prognostic covariates for recurrence-free survival, laryngeal preservation with laser alone, and overall laryngeal preservation

	No. of pts	Recurrence-free survival		Laryngeal preservation with laser alone		Overall laryngeal preservation	
		5-year rate	*p*	5-year rate	*p*	5-year rate	*p*
Grade of AC involvement							
AC0	156	93.9% (88.1–96.9%)	**0.0446**	96.2% (91–98.4%)	**0.0187**	99.1% (93.5–99.9%)	< **0.0001**
AC1	31	96.2% (75.7–99.5%)		96.5% (77.2–99.5%)		100%	
AC2	65	89.3% (77.5–95.1%)		91.2% (79.8–96.3%)		96.1% (84.7–99%)	
AC3	9	**74.1% (29–93%)**		**71.1% (23.3–92.3%)**		**71.1% (23.3–92.3%)**	
Grading							
G1	175	94.8% (93–96.6%)	0.2661	96.9% (95.5–98.3%)	**0.0419**	99.4% (98.8–100%)	**0.0462**
G2	47	87.3% (82–89.1%)		87.4% (82.1–92.7%)		92.9% (87.4–96.4%)	
G3	11	90.9% (82.2–99.6%)		100%		100%	
G4	28	80.6% (70–91.3%)		**81.1% (70.6–91.6%)**		**89.9% (80.5–99.5%)**	
T stage and subglottic extension							
T1	196	93.2% (88.1–96.2%)	**0.0098**	96.8% (92.3–98.7%)	< **0.0001**	99.2% (94.2–99.9%)	< **0.0001**
T2 SG0	28	85.6% (61.1–95.2%)		85.6% (61.1–95.2%)		90% (65.2–97.4%)	
T2 SG+	13	**74% (38.2–91%)**		**67.3% (34–86.5%)**		**84.6% (51.2–95.9%)**	

AC0, no involvement of the anterior commissure. AC1, involvement of the anterior commissure on only one side of the midline. AC2, involvement of the anterior commissure that crosses the midline on only part of the longitudinal extension of this subsite. AC3, involvement of the whole anterior commissure on both sides across the midline. G1, well differentiated. G2, moderately differentiated. G3, poorly differentiated. G4, undifferentiated. SG0, no subglottic spread. SG+, subglottic spread more than 1 cm below the glottic plane

Statistical values are in bold ($p < 0.05$)

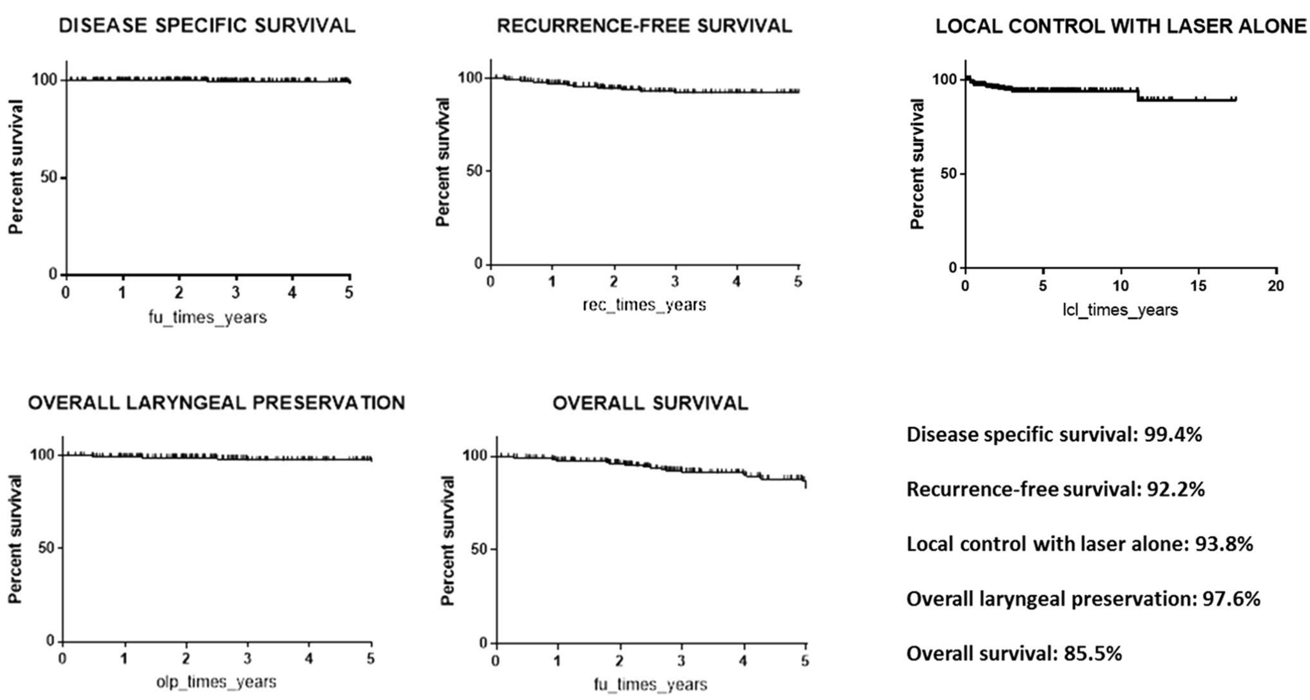

Fig. 1 Five-year survival curves

patients submitted to subepithelial (type I) and subligamentous (type II) cordectomies may have a voice quality that is as good as that of a control group of euphonic individuals, whereas after type III–VI cordectomies the voice outcomes are unpredictable and depends on the amount of scar after healing of the glottic plane [10].

The 5-year DSS, RFS, LCL, OLP, and OS of the present series of patients were 99.4, 92.2, 93.8, 97.6, and 85.5%, respectively, and these values are comparable to those reported in the literature [7, 24–26]. Different prognostic factors may decrease the efficacy of TOLMS, such as positive surgical margins, involvement of anatomic regions at risk to be uncontrolled by TOLMS (i.e., the anterior commissure, paraglottic space, and subglottis), and patient age, and these factors must be carefully considered during the endoscopic management of patients with glottic carcinoma.

Although tobacco consumption was strongly related to the incidence of LSCC (86.6% of our patients reported a daily consumption of tobacco), daily alcohol and/or tobacco intake was not related to statistically significant different outcomes.

Positive margins are generally associated with an increased risk of recurrence [27]; therefore, the goal of all the procedures is the complete removal of the tumor at the first attempt by obtaining clear margins in healthy tissue. At the glottic level, most authors consider 1–2 mm as an adequate margin, although some authors have suggested that margins less than 0.5 mm may be sufficient in Tis–T1 carcinoma, as the ligament still forms a barrier to the spreading tumor in early lesions [26]. When margins are considered inadequate, the wait-and-see approach with close monitoring or second-look procedures are reported in the literature [26].

In the present series, 251 procedures (96.2%) showed free margins after the resection: 218 patients (83.6%) were with surgical margins more than 1 mm after primary surgery, 10 patients (3.8%) showed surgical margins less than 1 mm and underwent a second TOLMS in 9 cases, while 1 patient refused any further treatment; histology did not show residual tumor in all cases, and there were no recurrences in all these 10 patients; such over-treatment in 9 patients, could be avoided by adopting a strict wait-and-see policy also with close margins; twenty-three patients (8.8%) with positive margins after primary surgery underwent a second TOLMS with an enlargement of the surgical area at the involved margin/s at least 2 weeks after the first surgery (histology confirmed that all the surgical margins of these 23 enlargements were performed in healthy tissue). Histology after a second TOLMS performed for positive margins ($n = 23$) showed a residual tumor in 5 cases only (21.7%). According to Fiz et al. [28], our patients with deep positive margins ($n = 9$) presented a higher, although not statistically significantly, rate of residual carcinoma (22.2 vs. 12.5%; $p = 0.4813$).

Ten patients (3.8%) with positive margins after primary surgery did not undergo surgical revision: 4 cases underwent postoperative radiotherapy (3 had a positive deep margin not amenable to enlargement, and 1 exhibited multifocality; there was no evidence of disease in these 4 patients after 1, 4, 5, and 12 years of follow-up, respectively), and 6 patients were managed with close follow-up since the surgeon's intraoperative evaluation was of a macroscopical radicality (no recurrences were noted after 11, 6, 2, 3, 11, and 2 years of follow-up, respectively, in these 6 patients).

In the present series, patients with positive margins who did not undergo surgical enlargement did not experience any recurrence but, according to the univariate Cox analysis, they experienced reduced 5-year LCL (60 vs. 95.1% in patients with negative margins, $p < 0.001$), since 4 patients underwent radiotherapy. When margins of resection are involved by the tumor at histology, a second TOLMS should be recommended when possible [29], but the close margin does not represent in our experience an absolute indication for revision laser surgery and in some instances, also for superficial involved margins at histology, the subjective evaluation of experienced surgeons could avoid unnecessary second procedures.

The anterior commissure region has been identified in several studies as a laryngeal subsite at risk for local treatment failures [9, 14, 30–32], especially when the vertical plane of the anterior commissure is involved. In these cases, there is the need for a complete and proper endoscopic exposure of the anterior commissure, but in some instances, it can be difficult for the narrow-angle and V-shaped configuration of the thyroid cartilage; as a consequence, a complete set of laryngoscopes is mandatory, and for difficult exposures, smaller laryngoscopes of different shapes associated with a good external counter-pressure [33] allow the management of the anterior commissure in almost all cases. Tumors with pure horizontal spread in the anterior commissure are still a good indication for transoral approach, while when tumors located in the anterior commissure are part of a trans-commissural tumor, an OPHL can be considered since the insertion to the cartilage by the Broyles' ligament formed by the union of the thyroepiglottic ligament and the attachment of the vocal ligaments, is a weak point, where LSCC can penetrates the cartilage transforming a T1 tumor into a T4 [26]. In our series, the anterior commissure was always treated by a wide subperichondrial resection, by dissecting the inner aspect of the cartilage that attaches to Broyles' ligament and removing the dense fibroelastic tissue of this area. In our series of patients, an AC1 and AC2 involvement did not show a statistically significant impact on patient prognosis, but the nine AC3 patients experienced lower 5-year RFS (74.1%, $p = 0.0446$) and required a TL in 2 cases due to the microscopic neoplastic spread in the pre-epiglottic space, which is impossible to treat with a conservative procedure. According with Hoffmann et al. [24], recurrence after laser cordectomy for early glottic tumors that were initially classified as Tis or T1a involving the anterior commissure should be controlled by repeated laser procedures.

As previously reported by other authors [25], undifferentited tumors show worse outcomes compared to well-differentiated tumors (Table 5), but we belive that there are still not enough evidences to modify the treatment strategy according to histologic grade in patients with early LSCC.

The posterior portion of the paraglottic space is in close proximity to the cricoarytenoid joint, and lesions extending to this area can be uncontrolled with TOLMS [34, 35]. To differentiate the mass effect of the lesion on the vocal cord from the cricoarytenoid fixation for muscle invasion during the preoperative evaluation of the arytenoid mobility, substantial experience is required, and CT scan or magnetic resonance imaging can be helpful to rule out the posterior spread of the tumor. Lesions invading the paraglottic space should be correctly classified as T3 and treated very carefully with TOLMS. The results of endoscopic management of advanced (T2 and T3) lesions of the glottis reported in literature [7, 36–38] show that TOLMS approach in T3 patients offers a 5-year regional control of 79.6%, local control with laser alone of 71.6%, and a laryngeal preservation rate of 51–72.7% [7, 37, 39]. These results appear suboptimal compared to those of OPHLs, characterized by local control rates of 94% regardless of the T stage of the cancer [40], suggesting that best treatment in advanced lesions is yet to be standardized. In our series, patients with vocal cord fixation were not treated with TOLMS and were addressed for open-neck procedures, chemo-radiotherapy or TL.

A primary subglottic carcinoma is rare, and lesions of this area are generally related to caudal spreading below the free margin of the true vocal cord [41]. In the present series, 13 lesions showed a true subglottic invasion confirmed by histology; among them, 1 patient was addressed for radiotherapy for a deep positive margin of resection, and 3 patients (23.1%) experienced a recurrence and underwent type II OPHL in 1 case and TL in 2 cases. According to the multivariate Cox analysis, RFS, LCL, and OLP were statistically worse in T2 patients with a true subglottic spread despite free surgical margins confirmed by histology (74, 67.3, and 84.6%, respectively, vs. 85.6, 85.6, and 90%, respectively, observed in T2 without subglottic extension, and 93.2, 96.8, and 99.2%, respectively, observed in T1). In these patients, TL and/or radiotherapy allowed effective local control after relapse of the disease (DSS of 100%); as a consequence, T2 lesions with subglottic extension of more than 1 cm should be considered as moderately advanced, and in our opinion, adjuvant therapy could be considered.

OPHL is generally considered to be too risky in elderly patients with a glottic carcinoma due to low compliance of rehabilitation [42], while TOLMS avoids the tracheotomy and has a minimal negative impact or no negative impact on swallowing, allowing an early rehabilitation. Our analyses confirmed the absence of formal age-related contraindications to TOLMS.

Occult metastases are rare (1.2% in the literature [25] and 0.4% in our series), so elective lymphadenectomy is not justified for early or intermediate glottic cancer treated with TOLMS.

The role of adjuvant radiotherapy in cases of early or intermediate glottic cancer is still unclear and does not seem to have a positive impact on local relapse [25]. In our series, adjuvant radiotherapy was considered necessary in 4 out of the 261 patients (1.5%) and was associated with a good control of the disease (no recurrence after 12, 5, 4, and 1 years of follow-up, respectively, in the 4 patients), but we cannot state any definitive conclusion.

All the recurrences were observed within 3 years from surgery; after 3 years, we did not encounter any recurrence. This observation indicates that a strict follow-up must be applied during the first 3 years, possibly including a biologic endoscopy and eventually magnetic resonance imaging, as already demonstrated by Ravanelli et al. [43]. In the case of recurrent disease after TOLMS, further TOLMS, OPHLs, radiotherapy or TL are still available. The percentage of recurrent patients from the series that Lucioni treated with TL or type III OPHL (24.2%) [44] is comparable to our percentage (29.4%); five additional patients from their series experienced a definitive TL for a second relapse (no second recurrence has been observed in our patients who were treated with an open salvage surgery), with a definitive TL rate of 17.7% (23.5% in our series). As a consequence, TL is still recommended as a rescue therapy for recurrent LSCC, and type II/III OPHL can be considered as a valid organ-sparing rescue alternative in selected cases. In our series, radiotherapy was considered necessary with curative intent in 1 out of 17 recurrent patients (5.9%) with multifocal recurrence, and adjuvant in 4 out of 17 cases (23.5%) and was associated with a good control of the disease (no second recurrence after 2.5, 5, 3, 2.4, and 1.5 years of follow-up, respectively, in these 5 patients), but we cannot state any definitive conclusion.

A second primary tumor was experienced by 22 patients (8.4%) during the first 5 years of follow-up. Rennemo et al. [45] reported an incidence of second primary malignancy of 17% in 2063 patients treated for head and neck cancer (24% to the lung). Since laryngeal and lung tumors are strongly correlated with smoking habits, even patients treated for early glottic cancer should be followed up with at least chest imaging in addition to the loco-regional follow-up.

Conclusions

This study confirms that TOLMS is an effective and reproducible single-stage modality therapy for young and elderly patients with Tis, T1 and selected cases of T2 glottic carcinoma, with a high rate of laryngeal preservation.

Statistically negative prognostic factors after TOLMS in this case series were undifferentiated tumors, AC3 and subglottic involvement for which close follow-up or adjuvant therapy should be carefully considered.

Superficial close margins can be managed by a careful wait-and-see policy, while patients with positive margins should undergo surgical enlargement whenever possible, and adjuvant therapy should be considered when the deep involved margin cannot be revised like after type IV cordectomy, or multifocal disease.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Ethical approval The research did not involve any animal models; the research involved human participants in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards; and informed consent was obtained from all individual participants included in the study.

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