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Long-term Oncologic Outcomes of 1188 Tis-T2 Glottic Cancers Treated by Transoral Laser Microsurgery

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Abstract

Objective. To evaluate long-term disease-specific survival (DSS) and organ preservation (OP) rates in patients affected by Tis-T2 glottic squamous cell carcinoma (SCC) treated by carbon dioxide transoral laser microsurgery (CO_2 TOLMS).

Study Design. Single-center retrospective cohort study.

Setting. Tertiary academic hospital.

Methods. The study included patients treated by CO_2 TOLMS for Tis-T2 glottic SCC at the Department of Otorhinolaryngology–Head and Neck Surgery of the University of Brescia, Italy, from 1988 to 2018. The male:female ratio was 11.2:1, and the mean age was 64 years (range, 31-95). T categories were distributed as follows: 124 (10%) Tis, 646 (54%) T1a, 172 (15%) T1b, and 246 (21%) T2.

Results. Ten- and 20-year DSS rates were 97.6% and 96.3%, respectively, and 10- and 20-year OP rates were 94.7% and 93%. During the follow-up, 91% of patients were treated by CO_2 TOLMS alone, while the remaining needed adjunctive treatments. Assessing the impact of multiple sessions of CO_2 TOLMS, DSS showed no significant difference in terms of patients treated by 1, 2, or >2 procedures. Conversely, patients treated by >2 sessions of CO_2 TOLMS showed a significantly worse OP rate.

Conclusions. Our series validates CO_2 TOLMS as a long-term treatment strategy for early glottic SCC. Salvage CO_2 TOLMS provided optimal results in terms of DSS and OP in patients with recurrence after previous transoral surgery.

Keywords

transoral laser microsurgery, laryngeal cancer, glottic, early, long-term, oncologic outcomes

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Carbon dioxide transoral laser microsurgery (CO_2 TOLMS), as recently classified by Remacle and coworkers,[1] is an established treatment option for early-intermediate glottic squamous cell carcinoma (EIGSCC). However, its indications are highly variable and influenced mainly by institution- and country-based policies. Furthermore, decades after its introduction and implementation, high-quality data are still lacking confirming the value of CO_2 TOLMS as a therapeutic tool and its results in comparison with alternative options, such as radiotherapy (RT) and open partial horizontal laryngectomies (OPHLs),[2] especially in terms of long-term follow-up. The Cochrane Collaboration regularly updates a systematic review and meta-analysis aimed at assessing CO_2 TOLMS, RT, and partial laryngectomies for EIGSCC, including all prospective randomized trials on this topic.[3] However, the only study selected by the reviewers to date did not include patients treated by CO_2 TOLMS, and it was classified as being at high risk of bias.[4] For this reason, the comparison was limited to RT and partial laryngectomies.

However, high-quality data are essential to better assess surgical innovations and direct their development. The rationale is that if the opportunity for robust evaluation is not seized, widespread adoption of a given therapeutic tool may take place without adequate evidence. This is particularly true in settings where randomized clinical trials are not easily feasible due to technical constraints, ethical concerns, and patient preference. In this context, evidence should arise from high-quality nonrandomized prospective or retrospective studies specifically assessing each aspect of the technique. In particular, long-term outcomes represent one of the main measures to be considered.

The aim of our study was therefore to retrospectively evaluate long-term disease-specific survival (DSS) and organ

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preservation (OP) rates in a large homogeneous cohort of patients affected by Tis-T2 glottic squamous cell carcinoma treated by CO_2 TOLMS at a single academic institution.

Materials and Methods

This retrospective study included all patients treated by CO_2 TOLMS and not previously treated for Tis-T2 glottic squamous cell carcinoma at the Department of Otorhinolaryngology–Head and Neck Surgery of the University of Brescia, Italy, from January 1988 to December 2018. All patients were included since the early adoption of this technique at our hospital to better evaluate the impact of the related learning curve. Data were collected by staff members and senior residents through retrospective clinical charts review, reevaluation of recorded videoendoscopies and radiologic imaging, assessment of follow-up documentation, and phone interview. Clinical charts with insufficient information for accurate staging (n = 62) and/or lack of evaluation on postoperative outcomes (n = 82) were excluded from the study, which was mainly focused on long-term DSS and OP, thus estimating the impact of different salvage therapeutic approaches during the course of the disease.

Data were recorded in a single database, regarding patient characteristics, endoscopic and imaging evaluation, tumor staging, type of surgery, recurrences, and follow-up. Redo CO_2 TOLMS for positive margins (R1) was considered part of the primary treatment since it was usually performed within 45 days from the index procedure.

All patients were preoperatively examined under local anesthesia with videolaryngostroboscopy (Kay Digital Strobe 9200; Kay Elemetrics Corporation) and transnasal flexible videoendoscopy (Olympus Medical System Corporation) with white light and narrow band imaging (implemented after June 2007). In selected patients (cT1b with anterior commissure involvement to T2), preoperative computed tomography or magnetic resonance was performed to exclude involvement of the laryngeal framework and/or visceral (paraglottic and preepiglottic) spaces. Magnetic resonance has been the primary imaging choice at our institution since 2005. The examination was performed following a specific protocol for laryngeal cancer, with fast sequences and surface coils directly applied to the neck.

Microlaryngoscopy was performed under general anesthesia and muscle paralysis. A laser-safe tube (Laser-Shield; Medtronic Xomed) with an internal diameter not wider than 6.0 mm was inserted. The widest laryngoscope able to guarantee satisfactory glottic exposure was chosen[5-7] and always suspended with the Boston University Suspension System (Pilling), which was employed to obtain a true suspension laryngoscopy, producing elevated vector forces on the laryngoscope.[8] Intraoperative rigid endoscopy by 0° and 70° telescopes (Karl Storz) with white light and narrow band imaging was accomplished during microlaryngoscopy to reassess and better delineate the superficial resection margins. Clinical Tis-T1a lesions underwent an excisional biopsy approach,[9,10] while larger cT1b-T2 were submitted to preoperative biopsy under local or general anesthesia. Transoral resections were performed by an en bloc technique (type I-IV cordectomies according to the European Laryngological Society classification)[11] or multibloc technique (type V or VI), depending on factors such as laryngeal exposure, tumor extension, site, and size. Surgical specimens were oriented at the end of the procedure by marking the superior edge with blue ink, thus allowing the dedicated head and neck surgical pathologist to easily identify the other superficial margins after appropriate definition of the type and side of cordectomy performed. In case of multibloc resections, a schematic drawing representing the 3-dimensional orientation of the inked surgical specimens was added to help its proper evaluation. Frozen sections were not routinely employed according to our institutional protocol. In extensive resections and in case of margins deemed insufficient at the intraoperative evaluation, extramargin resections were performed and the adjunctive specimens sent for definitive histopathology. Their negativity was thus considered indicative of an R0 resection.

The study was performed following the principles of the Declaration of Helsinki and was approved by the Research Review Board, Ethics Committee, of the ASST Spedali Civili of Brescia, Italy.

Statistical Analysis

Statistical analysis was carried out with Stata software version 13 (StataCorp). Overall survival, DSS, and OP rates were calculated with the Kaplan-Meier method, with events defined as death for every cause, death for laryngeal cancer, and total laryngectomy, respectively. For each survival estimate, the entry time was the date of conclusion of adjuvant treatment (if any) or date of surgery (for those not receiving further treatments). Event-free cases were censored at the last follow-up examination. Survival analysis was performed by univariate models based on log-rank test or Cox proportional hazard model, as appropriate. Hazard ratios were expressed as lifetime risks.

Results

A total of 1188 patients were included in the present retrospective analysis. The male:female ratio was 11.2:1, and the mean age was 64 years (range, 31-95). Patients were current or former smokers at the time of surgery in 92% of cases. Mean follow-up was 105 months (range, 1-350). Overall, 963 (81%) patients reached the 5-year time point. Furthermore, 440 (37%) had at least 10 years of follow-up and 71 (6%) at least 20.

Distribution of T categories was as follows: 124 (10%) Tis, 646 (54%) T1a, 172 (15%) T1b, and 246 (21%) T2. No patient had lymph nodes or distant metastases at presentation. Distribution of types of cordectomies according to the European Laryngological Society classification was type I in 83, type II in 381, type III in 247, type IV in 93, type V in 377, and type VI in 7. Resection of a second lesion on the contralateral vocal fold (ie, for treatment of multifocal Tis or T1b without anterior commissure involvement) was also performed in 92 patients.

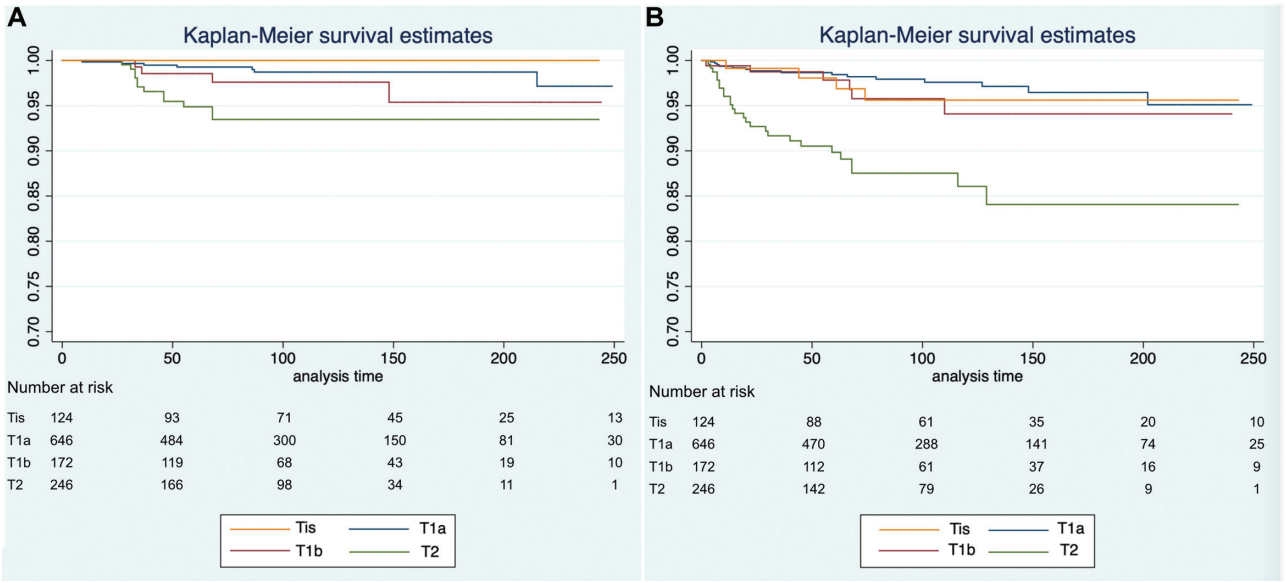

Figure 1. Kaplan-Meier curves showing (A) disease-specific survival and (B) organ preservation rates for different pT categories.

Table 1. DSS and OP Rates According to Disease Staging.

		DSS (95% CI), %		
	No. (%)	5 y	10 y	20 y
Carcinoma in situ	124 (10.4)	100 (—)	100 (—)	100 (—)
T1a	646 (14.5)	99.2 (98.1-99.7)	98.7 (97.1-99.4)	97.1 (91.3-99.1)
T1b	172 (20.7)	98.6 (94.3-99.6)	97.6 (92.7-99.2)	95.4 (86.5-98.5)
T2	246 (10.4)	94.9 (90.7-97.2)	93.5 (88.7-96.3)	93.5 (88.7-96.3)
	No. (%)	OP (95% CI), %		
Carcinoma in situ	124 (10.4)	98.1 (92.4-99.5)	95.6 (88.6-98.3)	95.6 (88.6-98.3)
T1a	646 (14.5)	98.4 (97-99.2)	97.6 (95.7-98.7)	95.1 (90.3-97.5)
T1b	172 (20.7)	97.8 (93.3-99.3)	94.1 (86.7-97.4)	94.1 (86.7-97.4)
T2	246 (10.4)	89.8 (84.8-93.3)	86.1 (79.4-90.7)	84.1 (76.1-89.6)

Abbreviations: DSS, disease-specific survival; OP, organ preservation.

For the entire cohort, 10- and 20-year overall survival rates were 76.4% and 42.8%, respectively. The 10- and 20-year DSS rates were 97.6% and 96.3%. The 10- and 20-year OP rates were 94.7% and 93%. For DSS, T categories adequately stratified long-term survival, with an incremental risk of death going from Tis to T2 tumors. In particular, 10- and 20-year survival rates were both 100% for Tis, 99% and 97% for T1a, 98% and 95% for T1b, and both 93% for T2 (**Figure 1A**, **Table 1**).

For OP rates, it was possible to observe a bimodal distribution, with optimal results in Tis, T1a, and T1b and significantly worse laryngeal preservation for T2 tumors (P = .009). Specifically, 10- and 20-year OP rates were both 96% for Tis, 98% and 95% for T1a, both 94% for T1b, and 86% and 84% for T2 (**Figure 1B**, **Table 1**).

During the study time frame, 91% of patients were treated by CO_2 TOLMS alone, while the remaining needed adjunctive treatments (RT, chemotherapy, chemoradiotherapy, OPHL, or total laryngectomy) for disease control—specifically, 12% of Tis, 5% of T1a, 11% of T1b, and 20% of T2 ($P <$ .001). Total laryngectomy was performed in 3% of Tis, 2% of T1a, 5% of T1b, and 10% of T2 ($P <$ .001).

In terms of the date of surgery (first 5 years [1988-1992] vs last 25 [1993-2018]), no significant difference in DSS and OP rates was observed between the groups, thus confirming the negligible impact of the learning curve on survival of EIGSCC. The same was true when the first 15 years (1988-2002, in which only 1 surgeon [G.P.] was in charge of CO_2 TOLMS at our department) were compared with the last 15 (2003-2018, in which 3 other surgeons [C.P., F.D.B., and A.P.] started working in this field).

For the impact of multiple sessions of CO_2 TOLMS, DSS showed no significant difference among patients sequentially treated by 1, 2, or >2 procedures (**Figure 2A**, **Table 2**).

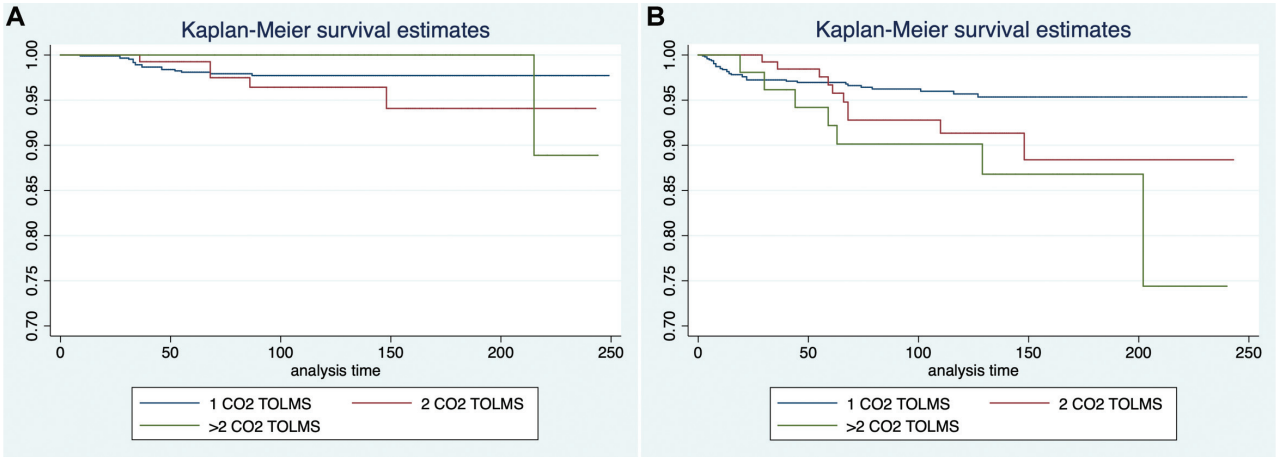

Figure 2. Kaplan-Meier curves showing (a) disease-specific survival and (b) organ preservation rates according to the number of CO_2 TOLMS procedures. CO_2 TOLMS, carbon dioxide transoral laser microsurgery.

Table 2. DSS and OP Rates According to the Number of CO_2 TOLMS Procedures.

		DSS (95% CI), %		
CO_2 TOLMS	No. (%)	5 y	10 y	20 y
1	988 (83.2)	98.1 (96.9-98.9)	97.7 (96.3-98.6)	97.7 (96.3-98.6)
2	147 (12.4)	99.2 (94.8-99.9)	96.4 (90.7-98.7)	94.1 (84.9-97.8)
>2	53 (4.4)	100 (—)	100 (—)	88.9 (43.3-98.3)
	No. (%)		OP (95% CI), %	
1	988 (83.2)	97 (95.6-97.9)	95.7 (93.9-97)	95.3 (93.4-96.8)
2	147 (12.4)	96.7 (91.4-98.8)	91.3 (83.8-95.5)	88.4 (77.7-94.2)
>2	53 (4.4)	92.2 (80.5-97)	90.1 (77.9-95.8)	74.4 (41.2-90.6)

Abbreviations: CO_2 TOLMS, carbon dioxide transoral laser microsurgery; DSS, disease-specific survival; OP, organ preservation.

Conversely, patients treated by >2 sessions of CO_2 TOLMS showed a significantly worse OP rate (P = .008) with a hazard ratio of 3 (**Figure 2B**).

Regarding the influence of the type of treatment in patients developing recurrence after transoral surgery, it was possible to observe an opposite trend between DSS and OP. In fact, patients salvaged by (chemo)radiotherapy had a significantly lower DSS (P = .008; hazard ratio, 6.6) when compared with OPHL and repeat CO_2 TOLMS (**Figure 3B**), while OPHL led to a lower chance of final OP (P = .047; hazard ratio, 3.5) when compared with (chemo)radiotherapy and redo CO_2 TOLMS (**Figure 3B**). In both cases, patients amenable to salvage CO_2 TOLMS had optimal results in terms of DSS and OP rates.

Discussion

Our series provides an oncologic long-term validation of CO_2 TOLMS as an ideal treatment strategy for EIGSCC. While long-term overall survival did not prove to be strictly correlated with such a procedure, since it was mainly influenced by patients' advanced age, DSS and OP were well over 90% at 10 and 20 years of follow-up, with the exception of OP in T2 glottic squamous cell carcinoma. The minimally invasive transoral approach herein considered, in fact, proved to be a repeatable procedure, maintaining optimal DSS even after multiple interventions. In line with such an assumption, OP was significantly reduced only in patients needing >2 transoral operations. In patients needing salvage treatment after CO_2 TOLMS, a revision transoral resection provided optimal results in terms of DSS and OP. Conversely, patients needing different laryngeal preservation treatments as salvage experienced significantly lower OP (OPHL) and DSS ([chemo]radiotherapy).

To the best of our knowledge, this is the largest series assessing long-term outcomes of CO_2 TOLMS for EIGSCC to date. Study endpoints were selected to provide accurate information on the disease course in relation to the characteristics of EIGSCC while minimizing the risk of bias. In fact, local relapse represents the main mode of failure, and multiple transoral resections may successfully achieve long-term local control without compromising survival. In this view, DSS provided an overall measure of the disease course

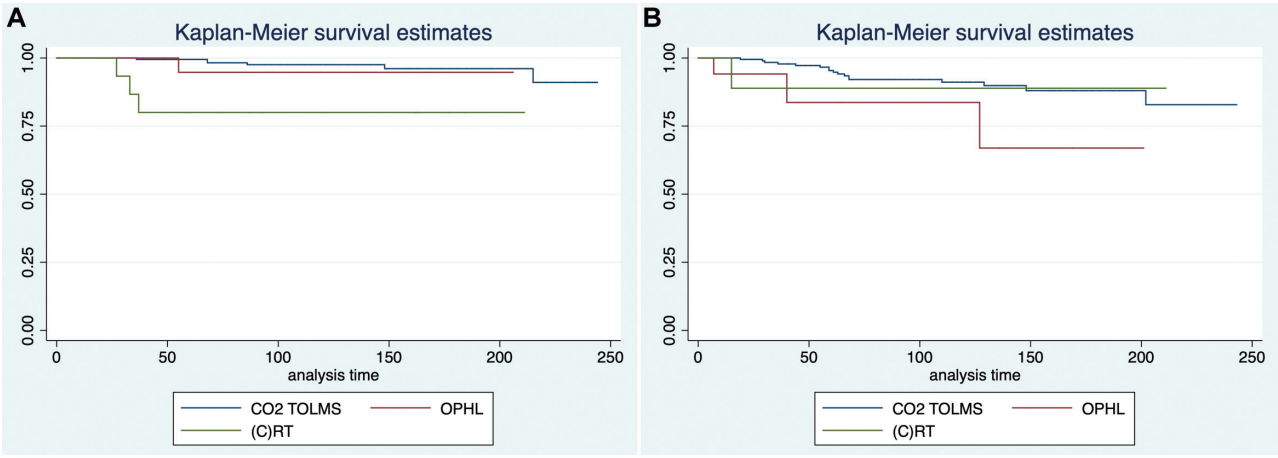

Figure 3. Kaplan-Meier curves showing (A) disease-specific survival and (B) organ preservation rates in patients with recurrence according to the type of salvage surgical procedure. CO_2 TOLMS, carbon dioxide transoral laser microsurgery; (C)RT, (chemo)radiotherapy; OPHL, open partial horizontal laryngectomy.

and the probability of long-term control obtained by CO_2 TOLMS with eventual adjunctive procedures. This allowed us to take into account the chance of disease control by a single surgical procedure, that of salvage after single or multiple recurrences, and the impact of combined treatment strategies. However, it is essential to consider that multiple local procedures may lead to progressive functional impairment and a higher risk of recurrence involving the laryngeal framework, ultimately influencing OP. Therefore, this endpoint should be considered an accurate indicator of the chance of conservative disease management.

Reports assessing oncologic outcomes of CO_2 TOLMS in EIGSCC are progressively increasing in the literature, as described in a recent article by Mendelsohn et al.[12] This has been favored by the first descriptions of the oncologic validity of this procedure by Steiner and coworkers,[13] as well as by the introduction of the European Laryngological Society classification of CO_2 TOLMS cordectomies.[11] In fact, the dissemination of such a well-defined classification scheme optimized, in the last 20 years, the chance to collect and compare outcomes in a standardized manner. Thanks to the numerous series now present in the international literature, CO_2 TOLMS is currently considered a valid treatment option for laryngeal cancer even in the absence of high-quality randomized clinical trials comparing it with alternatives (ie, RT and OPHL). In particular, several systematic reviews and meta-analyses have confirmed its noninferiority as compared with RT for EIGSCC, in terms of oncologic and functional outcomes,[14-20] with a trend toward better results in CO_2 TOLMS. However, because of the relatively recent widespread use of CO_2 TOLMS, there is a paucity of information on long-term oncologic and OP results.

A typical concern in consideration of the minimally invasive nature of this type of surgery, aimed at preserving the majority of laryngeal mucosa, is the potential risk of tobacco-related field cancerization. Notwithstanding, CO_2 TOLMS is a repeatable procedure, and subsequent interventions may successfully manage local recurrences and second tumors. As confirmation of this evidence, our results showed stable DSS and OP rates even decades after primary treatment, thus demonstrating that the diffuse oncogenic effect of smoking does not impair survival and laryngeal preservation when a minimally invasive option has been chosen. In particular, even adjunctive CO_2 TOLMS for relapse/second tumor did not significantly impair DSS. However, patients needing >2 procedures represented a high-risk subgroup with significantly lower OP, potentially reflecting a higher local aggressiveness of the primary tumor and/or a more pronounced tendency toward dysplastic/neoplastic transformation of the residual laryngeal mucosa.

These results confirm the importance of treating EIGSCC with a single-treatment modality,[21] avoiding RT in case of persistence, recurrence, or second tumor still amenable to CO_2 TOLMS.[22] In this view, CO_2 TOLMS should be regarded as a repeatable procedure, and patients should be carefully monitored according to dedicated protocols, including seriate biologic endoscopic and radiologic examinations,[23-25] to avoid late diagnosis of recurrence/metachronous tumor in the presence of laryngeal framework involvement.[26] Our data confirm that CO_2 TOLMS, with adequate indications and patient selection, provides optimal oncologic results as a salvage procedure after previous transoral laser surgery, as already demonstrated by our group in the clinical setting of failure after RT.[27,28] In recurrent cases not manageable by CO_2 TOLMS, it should be considered that OPHL, although associated with lower OP, resulted in a better DSS than RT. However, it is essential to take into account the potential bias of patient selection, since patients with heavier comorbidities may be more frequently directed to RT.

While other authors validated the efficacy of CO_2 TOLMS in large monoinstitutional series,[29-34] our long-term data provide confirmation of the absence of a significant outcome difference, at least concerning EIGSCC, related to the surgeons' learning curve. Moreover, in terms of long-term functional outcomes, a recent analysis by Ma et al[35] reported better results with CO_2 TOLMS than with RT. This may be

related to the progressive tissue fibrosis that continues even years after primary irradiation, while vocal outcomes after CO_2 TOLMS tend to stabilize after 6 months.[36] Moreover, repercussions on quality of life seem to be limited to the 3-month time point,[37] since various phenomena of coping, adaptation, and rehabilitation may play a role in improving vocal performance with time. Finally, long-term general quality of life seems to be adequately maintained in patients treated by CO_2 TOLMS, as demonstrated by Valls-Mateus et al,[38] similar to what is seen in immediate posttreatment outcomes.[39]

These results may help to better guide the treatment for EIGSCC at the level of a multidisciplinary tumor board, choosing between CO_2 TOLMS and RT on the basis of personalized evidence-based criteria and not standardized policies. In particular, while not directly related to treatment outcomes, patient preference should be carefully considered in the long-term management of the disease. In this regard, CO_2 TOLMS is frequently reported as the patients' treatment of choice[40-42]: this is of particular interest in consideration of its favorable cost-effectiveness ratio as compared with RT.[43]

The UK NICE guidelines (National Institute for Health and Care Excellence) advise transoral surgery for all T1a tumors, whereas CO_2 TOLMS and RT are both suggested for T1b to T2 lesions.[44] Similarly, according to the Dutch guidelines for treatment of laryngeal squamous cell carcinoma, CO_2 TOLMS is the treatment of choice for superficial T1a midcord lesions, while for more extended T1 and T2 tumors, RT is still the most advocated treatment.[45] Therefore, RT remains the most frequently applied treatment for EIGSCC in Northern Europe and United States, as demonstrated by a Surveillance, Epidemiology and End Results–based population study[46] on 5333 patients treated by RT versus 1913 treated by surgery alone. In light of the long-term results that we present here, a similar validation of patients treated by RT is warranted to adequately compare its validity and fine-tune treatment indications for those affected by EIGSCC.

Concerning study limitations, this is a retrospective cohort that focused only on DSS and OP. Consequently, a number of confounding factors may have played a role in the choice of treatment and its oncologic results. However, these limitations are partially mitigated by the large number of patients, the selection of a specific subgroup of laryngeal cancer (ie, EIGSCC), and the precise definition of straightforward endpoints to be investigated.

Conclusions

Our series provides long-term insight of CO_2 TOLMS as a treatment strategy for EIGSCC. In particular, DSS was not significantly reduced even after multiple procedures. A decline in the OP rate was observed only in patients needing >2 CO_2 TOLMS procedures. Finally, revision CO_2 TOLMS provided optimal results in terms of DSS and OP even in patients with recurrence after prior transoral surgery.

Author Contributions

Cesare Piazza, study design, drafting of the manuscript, revision of the manuscript, final approval, final agreement; **Alberto Paderno**, study design, drafting of the manuscript, revision of the manuscript, final approval, final agreement; **Francesca Del Bon**, study design, drafting of the manuscript, final approval, final agreement; **Davide Lancini**, study design, drafting of the manuscript, final approval, final agreement; **Milena Fior**, study design, drafting of the manuscript, final approval, final agreement; **Giulia Berretti**, study design, drafting of the manuscript, final approval, final agreement; **Paolo Bosio**, study design, drafting of the manuscript, final approval, final agreement; **Alberto Deganello**, study design, drafting of the manuscript, final approval, final agreement; **Giorgio Peretti**, study design, drafting of the manuscript, revision of the manuscript, final approval, final agreement.

Disclosures

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