

Optimising oncologic outcomes in pT3 glottic cancers treated by transoral laser microsurgery: the impact of adjuvant treatment

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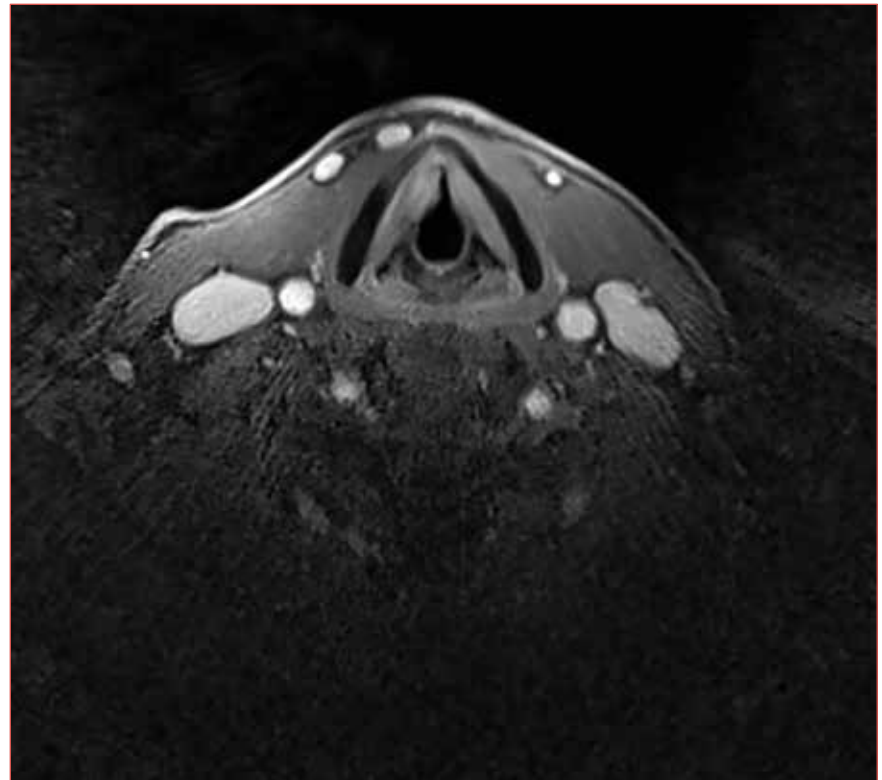
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Cover figure. cT3 glottic squamous cell carcinoma (SCC) with fixed vocal cord and normal arytenoid mobility centred in the mid-anterior third of the right true vocal fold, extending to the anterior commissure in the paramedian right region. Laterally, the tumour infiltrates the anterior paraglottic space (PGS) in its entirety, and is in focal contact with the perichondrium of the ipsilateral thyroid lamina. In the posterior third of the right true vocal cord, signal alterations consistent with perilesional oedema are predominant; within this context, the lesion does not appear to reach the vocal process of the arytenoid cartilage and ipsilateral posterior PGS. Postoperative histopathologic examination after transoral laser microsurgery confirmed the tumour to be a pT3 SCC without thyroid cartilage involvement, R0 margins, and no further adverse risk-factors. No adjuvant treatment was deemed necessary after multidisciplinary tumour board discussion.

Summary

Objective. The treatment strategy for cT3 glottic squamous cell carcinoma (SCC) is far from being standardised, and the role of adjuvant treatment(s) is not clearly defined. This study assessed the impact of adjuvant (chemo-)radiotherapy (CJRT) for patients with pT3 glottic SCC treated by transoral carbon dioxide laser microsurgery (CO₂ TOLMS) presenting adverse pathological features. **Methods.** A multicentric retrospective study was conducted at 3 referral hospitals, including patients with pT3 glottic SCC treated from January 2010 to October 2023. Demographic, clinical,

and histopathological data were collected, together with data on surgery, postoperative functional performance, adjuvant treatment(s) with (C)RT, and complications. Five- and 10-year overall (OS), disease-specific (DSS), disease-free (DFS), and total laryngectomy free survivals (TLFS) were estimated by Kaplan-Meier curves. Uni- and multivariate Cox proportional hazards regression models were used to determine independent risk factors for survivals.

Results. One hundred and forty-one patients treated with CO₂ TOLMS for pT3 glottic SCC were included in the study. Twenty-six (18.4%) patients received adjuvant treatment(s): 19 (13.5%) received RT alone, and the remaining 7 (5%) received CRT. Five-year OS, DSS, DFS, and TLFS were 78.1%, 91.5%, 49.7%, and 64.8%, respectively. Age independently correlated with worse OS, DFS, and TLFS at both uni- and multivariate Cox analysis. Adjuvant therapy was an independent protective factor for recurrence or death (DFS) at univariate (hazard ratio [HR] 0.46, *p* = 0.03) and multivariate (HR 0.38, *p* = 0.01) Cox analysis.

Conclusions. This study suggests that adjuvant treatment with (C)RT has a positive impact on DFS for pT3 glottic SCC treated by CO₂ TOLMS. The similar OS, DSS, and TLFS observed in pT3 SCC treated by CO₂ TOLMS alone and a selected group of unfavourable lesions needing adjuvant (C)RT show that adding such a treatment on top of conservative surgery may ensure good oncologic outcomes even in a selected subgroup of more aggressive glottic pT3. Further prospective studies should be conducted to validate these findings and confirm the relevance of adjuvant treatment(s) in this setting.

Key words: larynx, cancer, T3, glottis, CO₂ laser, transoral microsurgery, adjuvant treatment, radiotherapy

Introduction

The treatment strategy for cT3 glottic squamous cell carcinoma (SCC) is far from being standardised, with multiple alternatives available within clinical guidelines¹⁻³. Selection of patients is key to achieve the best outcomes with the different treatment options (transoral carbon dioxide laser microsurgery [CO₂ TOLMS]⁴, open partial horizontal laryngectomies [OPHL], non-surgical organ preservation protocols, or total laryngectomy [TL]), but little is mentioned about how patients should be selected. Heterogeneous lesions can be included in the cT3 category: in fact, based on the 8th Edition of the TNM classification (8TNM)³, this category includes tumours infiltrating the inner cortex of the thyroid cartilage, as well as lesions invading the paraglottic space (PGS) and those causing vocal fold/arytenoid fixation. Most importantly, the 8TNM does not differentiate the site of neoplastic PGS involvement between an anterior versus posterior PGS, or the cause of vocal cord (and/or arytenoid) motility impairment, leaving apart the intrinsic subjectivity in evaluating such subtle clinical details⁵. These factors, however, have been demonstrated to be negative prognosticators for laryngeal SCC survival and organ preservation⁶⁻⁸. Given such a marked heterogeneity for cT3 glottic SCC, it is of paramount importance to correctly evaluate these patients, approaching the related therapeutic decision in a multidisciplinary tumour board based on features of the individual patient and tumour. CO₂ TOLMS has gained popularity in the last decades as a minimally invasive treatment technique that is also suitable for selected intermediate-stage cancers. Adequate patient selection, thorough preoperative assessment, and surgical skills are key in offering good oncological outcomes with this technique⁹. The main treatment-related limitation of CO₂ TOLMS is represented by the appropriate glottic exposure under rigid laryngoscopy. Tumour-related limitations for TOLMS in cT3 glottic lesions, on the other hand, are represented by thyroid cartilage invasion, extension to the

posterior PGS (with or without invasion of the posterior or lateral cricoarytenoid muscles), arytenoid fixation¹⁰, and significant supra- and/or subglottic extension⁹.

Despite comprehensive preoperative evaluation of the patient by flexible and rigid laryngoscopy plus radiological imaging (CT or MRI), local extension of the tumour may sometimes be underestimated. This occurs because the interface among thyroid cartilage (internal perichondrium) and tumour is not easily assessable, especially considering the perichondral reaction and inflammatory process that surrounds the lesion itself¹¹. On the other hand, evaluation of surgical margins after TOLMS also remains a significant challenge, preventing standardisation of this technique for T3 glottic tumours. Pathological assessment is often complicated by specimen shrinkage, thermal damage, and coarctation, which frequently lead to histological examinations that cannot confirm thorough oncologic radicality. Additionally, the reported high rates of positive or uncertain margins in this setting are likely overestimated, as shown by the substantial proportion of negative histological findings in subsequent “second look” procedures^{12,13}. Moreover, in some cases, further resection is either unfeasible (e.g., when involving deep cartilaginous margins) or poses substantial functional challenges for the patient.

Another potential strategy to deal with the presence of uncertain margins is the implementation of adjuvant treatments (including [chemo]radiotherapy [(C)RT]) with the goal of laryngeal preservation¹⁴, although this is not exempt of adverse effects and complications. This is not the only indication for adjuvant therapy, as the National Comprehensive Cancer Network (NCCN) guidelines (version 4.2024) also recommend considering postoperative RT for patients with pT3 disease and adverse histopathological features¹. However, the indications for adjuvant therapy in this particular category of pT3 glottic SCC are not clearly defined, the possible oncological benefit of multimodal treatment is still unclear and, what is most relevant, could result in some functional impairment and/or potential sequelae for the patient. Moreover, one should no-

tice that recommendations for postoperative RT are primarily based on two landmark trials that demonstrated improved outcomes in patients with high-risk pathological features such as extranodal extension (ENE), positive (R1) or close (R close) margins, and advanced nodal disease^{15,16}. However, these studies predominantly involved tumours of the oral cavity, oropharynx, and hypopharynx where the prognostic impact of features like perineural (PNI) and lympho-vascular invasion (LVI) is well established. Laryngeal cancers were underrepresented – only 22% of cases in Bernier et al.¹⁵, with no subsite specification, and a mere 5% of glottic tumours in Cooper et al.¹⁶. This discrepancy highlights a limitation in applying these results uniformly across all head and neck subsites, particularly to glottic cancers, which may behave differently and warrant more tailored treatment considerations.

Therefore, this study assessed the impact of adjuvant treatment(s) by (C)RT in patients with pT3 glottic SCC treated by CO₂ TOLMS and presenting adverse pathological features.

Materials and methods

A multicentric retrospective study was conducted at the Departments of Otolaryngology – Head and Neck Surgery of Spedali Civili, University of Brescia (Italy), Hospital Clínic, Barcelona (Spain), and Ospedale Policlinico San Martino, Genoa (Italy) after approval by the appropriate Institutional Review Boards (NP4267). The study was carried out in accordance with the principles of the Helsinki Declaration.

Patients with glottic cancer who underwent CO₂ TOLMS with or without adjuvant (C)RT from January 2010 to October 2023 were reviewed and data collected. The inclusion criteria were: (1) biopsy-proven SCC; (2) originating from the glottic region; (3) staged as pT3 according to the 8TNM³. Exclusion criteria were: (1) patients with distant metastasis at the time of treatment; (2) (C)RT for previous head and neck tumours; (3) follow-up < 6 months; (4) history of re-resections by OPHL or TL to clear margins.

All patients underwent surgery with radical intent, by Type IV, V, or VI cordectomies according to the European Laryngological Society (ELS) classification^{17,18}. Elective or therapeutic neck dissection was performed concomitantly with CO₂ TOLMS according to the presence or suspicion of nodal metastasis at presentation. Routine prophylactic neck dissection (ND) was not indicated for cT3N0 tumours as per common policy among the 3 centres. All patients and their histological examinations were reviewed in multidisciplinary oncological head and neck boards and the indications to adjuvant treatment(s) discussed.

The variables collected included demographic data (age, gender, smoking, and alcohol consumption), previous CO₂ TOLMS, preoperative clinical TNM classification, vocal cord and arytenoid motility, details on surgical treatment, adjuvant treatment(s), anterior or posterior PGS invasion, surgical margins status, PNI and LVI, inner cortex thyroid cartilage involvement, areas of the larynx involved (such as anterior commissure, supraglottis, and subglottis), postoperative functional performance (dysphagia, ab ingestis pneumonia, and need for percutaneous gastrostomy or TL for functional reasons).

Based on preoperative imaging, tumours were classified as anterior or posterior to a plane tangential to the vocal process of the arytenoid and perpendicular to the ipsilateral thyroid lamina as described by Succo et al.^{6,19}. Clinically impaired arytenoid motility was also considered a sign of PGS posterior compartment involvement for patients without a preoperative CT scan available.

Surgical margins were defined as positive if tumour cells were clearly evident in the inked margin of the specimen, negative if resection was achieved within tumour-free margins > 1 mm, and uncertain if resection had close tumour-free margins (< 1 mm), or if it was not feasible to correctly evaluate the resection margins by the pathologist (in case of complex multi-bloc resection, marked thermal damage, or resection reaching cartilaginous structures). Due to the high rate of false positive margins in CO₂ TOLMS, a common policy shared by the 3 centres is to adopt a wait-and-see strategy for a single superficial positive margin, while proposing a transoral re-resection (if feasible) for multiple superficial and deep positive margins. Common indications for adjuvant (C)RT within the 3 multidisciplinary tumour boards were: pathological findings of clearly positive margins not amenable of re-excision, nodal category ≥ pN2a, and presence of PNI and/or LVI in the final histopathologic report.

Adjuvant RT was delivered by 3D conformal technique or by intensity-modulated RT (IMRT), and the dose ranged from 54 to 70 Gy on the tumour bed and neck nodes. Platinum-based chemotherapy was offered in combination with RT to all patients with ENE or R1 deep resection margins not amenable for re-excision, considering the patients' age and comorbidities.

Postoperative follow-up was conducted according to the ELS recommendations²⁰, including a flexible videolaryngoscopy every 2 months for the first 2 years, every 3-4 months for the third and fourth, every 6 months for the fifth, and once a year until the tenth. One MRI or CT scan every 6 months were performed in the first 2 years of follow-up. Additional clinical or radiological procedures were carried out according to the specific clinical presentation.

Statistical analysis

Categorical variables were summarised as counts and percentages. For continuous variables, a Shapiro-Wilk normality test was performed. If values were normally distributed, they were reported as mean \pm standard deviation (SD). For each patient, the time at risk was computed from the date of surgery to the date of the event of interest or the latest available clinical or radiological evaluation (censored observations). Overall survival (OS) was defined as the time from surgery to death; disease-free survival (DFS) as the time from surgery to disease recurrence (local, regional or distant) or death; disease-specific survival (DSS) as the time from surgery to death from disease; total laryngectomy free survival (TLFS) as the time from surgery to TL or death. These outcomes were estimated with the Kaplan-Meier method. Univariate survival analysis was performed using a Cox proportional hazards regression model to identify factors associated with survival. To determine independent risk factors for OS, DFS, and TLFS, variables that were significant in univariate analysis or those with clinical importance were introduced into a multivariate Cox proportional hazards regression model (forward and backward stepwise, $p < 0.05$ for entry, $p > 0.10$ for removal). Results were expressed in terms of hazard ratios (HR) and 95% confidence intervals (CI). A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using Stata/BE 17.0 (Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC, USA).

Results

One hundred and forty-one patients treated with CO₂ TOLMS for pT3 glottic SCC were included in the present study. Demographic and clinical data are shown in Table I. Considering high-risk features, information on PNI and LVI were available for only some of the specimens. PNI could be assessed in 86 tumours, being present in 19 of these, whereas LVI was assessed in 85 tumours and was positive in 20. Thyroid cartilage involvement could be assessed in 136 patients and inner cortex involvement was documented in 19 (14%). Margin status was reported as negative in 53 patients (37.9%), uncertain in 42 (30%), and positive in 45 (32.1%), with only one patient lacking this information. An elective or therapeutic neck dissection was performed in 13 patients (9.2%) when required, of which 8 had no evidence of regional metastasis at pathologic examination (pN0) and 4 were staged as pN1 and one as pN2a.

Following evaluation by the tumour board, a total of 26 patients (18.4%) received adjuvant treatment(s): 19 (13.5%) received RT alone and the remaining 7 (5%) received CRT. Twenty of these patients had R1 margins, and 4 uncertain

margins (2 with posterior PGS and subglottic involvement, and one with nodal metastasis). The remaining 2 had R0 margins with posterior PGS involvement and adverse histopathologic features (PNI, LVI, and/or inner perichondrium of thyroid cartilage involvement).

Regarding functional outcomes, none of the patients were tracheostomy-dependent or required a gastrostomy for enteral feeding at the last follow-up. Only one patient (0.7%) required functional TL but had not undergone adjuvant treatment.

Complications related to treatment by CO₂ TOLMS were reported in 10 patients (8.9%): 8 presented a local bleeding (one requiring a temporary tracheostomy for airway protection) and 2 had cervical subcutaneous emphysema that was managed conservatively. Complications related to adjuvant (C)RT were reported in only one case developing laryngeal stenosis managed without tracheostomy.

Mean follow-up time was 63 ± 43.3 months. Five- and 10-year OS, DSS, DFS, and TLFS are reported in Table II. After a mean follow-up of 15.2 ± 13.5 months, 56 patients (39.7%) developed a recurrence. Of these, 12 presented with concomitant local and regional recurrences, 32 exclusive local recurrence, and 7 exclusive nodal relapse. Three patients (3.6%) developed local, nodal, and distant recurrence, and 2 developed local and distant recurrence.

Local recurrences were managed by CO₂ TOLMS in 14 patients (25.5%). Overall, 101 patients (71.6%) achieved adequate disease control with CO₂ TOLMS alone. However, 26 patients (18.4%) required salvage TL with neck dissection, 5 (3.5%) received an OPHL as salvage treatment, 3 (2.1%) underwent CRT, 2 (1.4%) RT alone, 3 (2.1%) selective neck dissection for exclusive nodal relapse, and 2 (1.4%) palliative and supportive care.

Results from uni- and multivariate Cox regression analysis for 5-year OS, DFS, and TLFS are shown in Table III. DSS was excluded from the analysis due to few numbers of events. No statistically significant differences were found between OS, DSS, and TLFS in pT3 treated by CO₂ TOLMS alone and those receiving adjuvant (C)RT. Age independently correlated with worse OS, DFS, and TLFS at uni- and multivariate Cox analysis. Kaplan-Meier survival estimates for OS, DSS, DFS, and TLFS are shown in Figures 1A-D. Adjuvant treatment(s) was an independent protector factor for recurrence of disease or death (DFS) at uni- (HR 0.46, p 0.03) and multivariate (HR 0.38, p 0.01) Cox analysis (Fig. 1C).

Discussion

To the best of our knowledge, this is the first study to assess the impact of adjuvant treatment with (C)RT on pT3 glottic

Table I. Demographics and tumour characteristics.

Age, mean \pm SD (years)	68.3 \pm 10.5	
Age > 65 years, n. (%)	92 (65.3)	
Males, n. (%)	124 (87.9)	
Smoker, n. (%)	125 (89.9)	
Regular alcohol consumption, n. (%)	53 (38.4)	
Impaired vocal cord/arytenoid motility at diagnosis, n. (%)	86 (61.4)	
cT	cT1, n. (%)	9 (6.4)
	cT2, n. (%)	35 (24.8)
	cT3, n. (%)	97 (68.8)
cN	cN0, n. (%)	130 (92.2)
	cN1, n. (%)	6 (4.3)
	cN2a, n. (%)	0 (0)
	cN2b, n. (%)	2 (1.4)
	cN2c, n. (%)	1 (0.7)
	cNx, n. (%)	2 (1.4)
Type of cordectomy	IV, n. (%)	22 (15.9)
	V, n. (%)	93 (67.4)
	VI, n. (%)	23 (16.7)
Neck dissection, n. (%)	13 (9.2)	
pN	pN0, n. (%)	8 (5.7)
	pN1, n. (%)	4 (2.8)
	pN2a, n. (%)	1 (0.7)
	pNx, n. (%)	128 (90.8)
Tumour grade	Well differentiated, n. (%)	6 (4.7)
	Moderately differentiated, n. (%)	93 (72.7)
	Poorly differentiated, n. (%)	29 (22.7)
Margin status	Negative, n. (%)	53 (37.9)
	Positive, n. (%)	45 (32.1)
	Uncertain, n. (%)	42 (30)
Thyroid cartilage involvement (inner cortex)	No, n. (%)	117 (86)
	Yes, n. (%)	19 (14)
Anterior commissure invasion	No, n. (%)	63 (47)
	Yes, n. (%)	71 (53)
Supraglottic invasion	No, n. (%)	85 (63.4)
	Yes, n. (%)	49 (36.6)
Subglottic invasion	No, n. (%)	97 (72.4)
	Yes, n. (%)	37 (27.6)
Anterior paraglottic space invasion	No, n. (%)	7 (5)
	Yes, n. (%)	134 (95)
Posterior paraglottic space invasion	No, n. (%)	104 (73.8)
	Yes, n. (%)	37 (26.2)
Adjuvant treatment	No, n. (%)	115 (81.6)
	RT, n. (%)	19 (13.5)
	CRT, n. (%)	7 (5)

SCC treated by CO₂ TOLMS. In this context, our preliminary results suggest that, if carefully selected, high-risk pT3 patients may benefit from adjuvant treatment(s) to reduce recurrence of disease, maintaining an OS, DSS, and TLFS that is comparable to more favourable pT3 lesions treated with CO₂ TOLMS alone.

It should be emphasised that, although the proportion of patients who underwent adjuvant treatment is not negligible (18.4%), it remains in line with, or even lower than, what has been reported in the literature for pT3 laryngeal cancers treated by open surgery²¹. Furthermore, it is important to note that selecting TOLMS as the primary treatment did not preclude the possibility of subsequent oncologic therapy, including TL or organ preservation protocols, when salvage treatments were required. Moreover, most received adjuvant therapy due to the presence of multiple histopathological risk factors that were not predictable preoperatively. This highlights the critical importance of accurate selection of cT3 cases that are suitable for TOLMS.

In our multicentric series, CO₂ TOLMS was a sound oncological treatment for selected pT3 glottic SCC, and the OS and DSS outcomes are comparable to the literature for this

other 5 adjuvant RT alone). Nineteen patients had 2 or more adverse pathological features suggesting adjuvant (C)RT. Retrospectively, it is difficult to ascertain whether decisions for adjuvant treatment(s) were taken exactly in the same way between the different multidisciplinary tumour boards, or why other patients with positive margins or other adverse pathological features did not receive such an indication (taking into account that some patients possibly declined it). The mean age of patients was, however, 66.5 ± 12.6 years, thus including a rather wide range of ages, potentially impacting the ensuing oncologic outcomes, as observed in our results.

NCCN treatment guidelines recommend adjuvant treatment(s) for patients with selected pT3 glottic SCC undergoing partial laryngectomy (endoscopic or open) showing adverse pathologic features such as ENE, positive and/or close margins, pN2-N3 nodal disease, PNI, LVI, and subglottic extension^{1,27-29}. Thus, adjuvant treatment is not recommended for patients with pT3N0-1 glottic SCC treated by TL (including ipsilateral or bilateral neck dissection) or T3N0 glottic SCC treated by partial laryngectomy in the absence of other adverse histopathological features mentioned above^{23,26}. Despite these recommendations, there is a wide variability in the number of patients treated by primary surgery who receive adjuvant treatment with (C) RT. Specifically, no studies investigating the role of adjuvant therapy in CO₂ TOLMS are available in the literature, but several have evaluated the impact of postoperative RT on patients with advanced-stage laryngeal cancer treated by other techniques. These studies mostly include tumours from different laryngeal subsites, open surgical approaches, and different treatment modalities. Overall, it was concluded that postoperative RT had no impact on survival for patients with pT3N0^{21,28} or pT3-T4 lesions²². However, many of these studies are constrained by imbalanced baseline characteristics between treatment groups, without appropriate statistical adjustments to account for these differences. Graboyes et al.²² analysed data from the National Cancer Data Base to evaluate the effect of postoperative RT on survival for surgically managed pT3-T4N0 laryngeal SCC with negative margins. The pT3N0 cohort comprised 674 patients (46.2% of the total study population), included tumours from different subsites of the larynx, and 42.3% (n = 285) were supraglottic tumours, while 34.4% (n = 232) were glottic lesions. The remaining patients had SCC of the subglottis, transglottic tumours, or laryngeal tumours not otherwise specified. Nearly 17% of the 674 patients (n = 113) with pT3N0 tumours underwent either open or endoscopic laryngeal preservation surgery, and 80% (n = 540) underwent TL. Approximately 24% of the

Table II. Overall (OS), disease-specific (DSS), disease-free (DFS), and total laryngectomy-free survival (TLFS) at 5 and 10 years.

	5-year survival % (95% CI)	10-year survival % (95% CI)
OS	78.1 (69.3-84.6)	56.4 (42.9-67.9)
DSS	91.5 (84.6-95.3)	87.6 (78.1-93.1)
DFS	49.7 (40.7-58.1)	31.7 (21.6-42.2)
TLFS	64.8 (55.5-72.6)	42.7 (30.2-54.6)

category of tumours²²⁻²⁴. Nevertheless, in this series 5-year DFS was substantially lower (49.7%, CI 95%: 40.7-58.1%), an outcome that can be explained by the definition of DFS in our study, which included deaths as events and not as censored observations. Moreover, some local recurrences could be successfully managed by a further CO₂ TOLMS. Most of the patients in our study received adjuvant treatment with (C)RT if R1 margins were obtained after a first transoral procedure with curative intent. In particular, among 26 patients receiving adjuvant treatment(s), this was the only adverse pathological feature in 6 (one received CRT, whereas the

patients with pT3N0 disease (n = 159) received postoperative RT. In their analysis, the unadjusted 5-year OS rate for pT3N0 laryngeal SCC was 66.2% (70% in patients with adjuvant RT and 64.7% in those without adjuvant RT; p = 0.259). Age ≥ 65 years, increasing number of comorbidities, Medicare insurance, glottic tumour location, removal of < 18 lymph nodes during neck dissection, and performance of TL were associated with decreased OS in univariate analysis. In multivariable Cox regression analysis, the addition of postoperative RT was still not associated with improved survival (adjusted HR 0.88, 95% CI 0.64-1.21). On the contrary, improved OS was observed in patients with pT4aN0 who received postoperative RT. The authors concluded that patients with pT3N0 laryngeal SCC could potentially be treated with single-modality therapy. However, the study did not evaluate disease recurrence and DSS.

Similar studies focusing on T3N0 glottic tumours²⁹, T3-4aN0-1²⁴, and T3-4N0 laryngeal SCC²⁸ have been reported in the literature independently from the treatment used. In no study were there statistically significant differences between patients treated with adjuvant RT and those who received surgery alone.

Conversely, our results are in line with a recent large-scale, population-based analysis using the SEER database by Cooper et al.²¹, which demonstrated that adjuvant RT following primary surgery significantly improved both DSS and OS in patients with pT3 laryngeal SCC. Importantly, this benefit was evident even among node-negative patients and remained significant after adjustment for demographic and clinical variables, including nodal dissection. These findings reinforce the relevance of adjuvant RT in improving oncologic outcomes for high-risk patients, particularly those with unfavourable histopathologic features and fur-

ther supports the rationale for a multimodal approach in selected pT3 SCC treated with CO₂ TOLMS.

Our findings are further supported by the results of a meta-analysis by Li et al.³⁰, which demonstrated that adjuvant RT significantly improved OS, DFS, and local control rates compared to surgery alone, with consistent findings across multiple cohorts and minimal heterogeneity. Notably, the survival benefit of adjuvant RT was evident even in the absence of traditional high-risk pathological features. These results provide additional evidence that supports the use of adjuvant treatment in selected high-risk pT3 cases, reinforcing the role of a multimodal therapeutic approach after TOLMS.

Two studies compared the survival outcomes of patients with T3 glottic cancer treated with surgery- or RT-based approaches. The study by Ko et al.³¹ included 2,622 patients with T3N0M0 glottic SCC, and the surgical and RT groups exhibited similar 5-year adjusted OS rates (53% and 54%, respectively). Surgical approaches included hemilaryngectomy (excluding supraglottic horizontal laryngectomy or OPHL type I according to the ELS classification³², TL, and pharyngolaryngectomy). In the study by Al-Gilani et al.³³, OS showed a statistically significant and clinically meaningful improvement in patients with T3 glottic SCC who underwent surgery compared with non-surgical treatments. The 5-year OS for non-surgical management, surgery alone, and surgery plus adjuvant treatment were 36% (95% CI, 30-42%), 41% (95% CI, 30-53%), and 41% (95% CI, 32-51%), respectively. Although CO₂ TOLMS has been considered a safe procedure with a low rate of complications and associated with earlier functional recovery, is not exempt from potential peri- and postoperative complications³⁴, which depend on tumour extension, localisation, surgical experience, and presence of comorbidities such as diabetes mellitus³⁵. Postoperative bleeding has been reported as the most com-

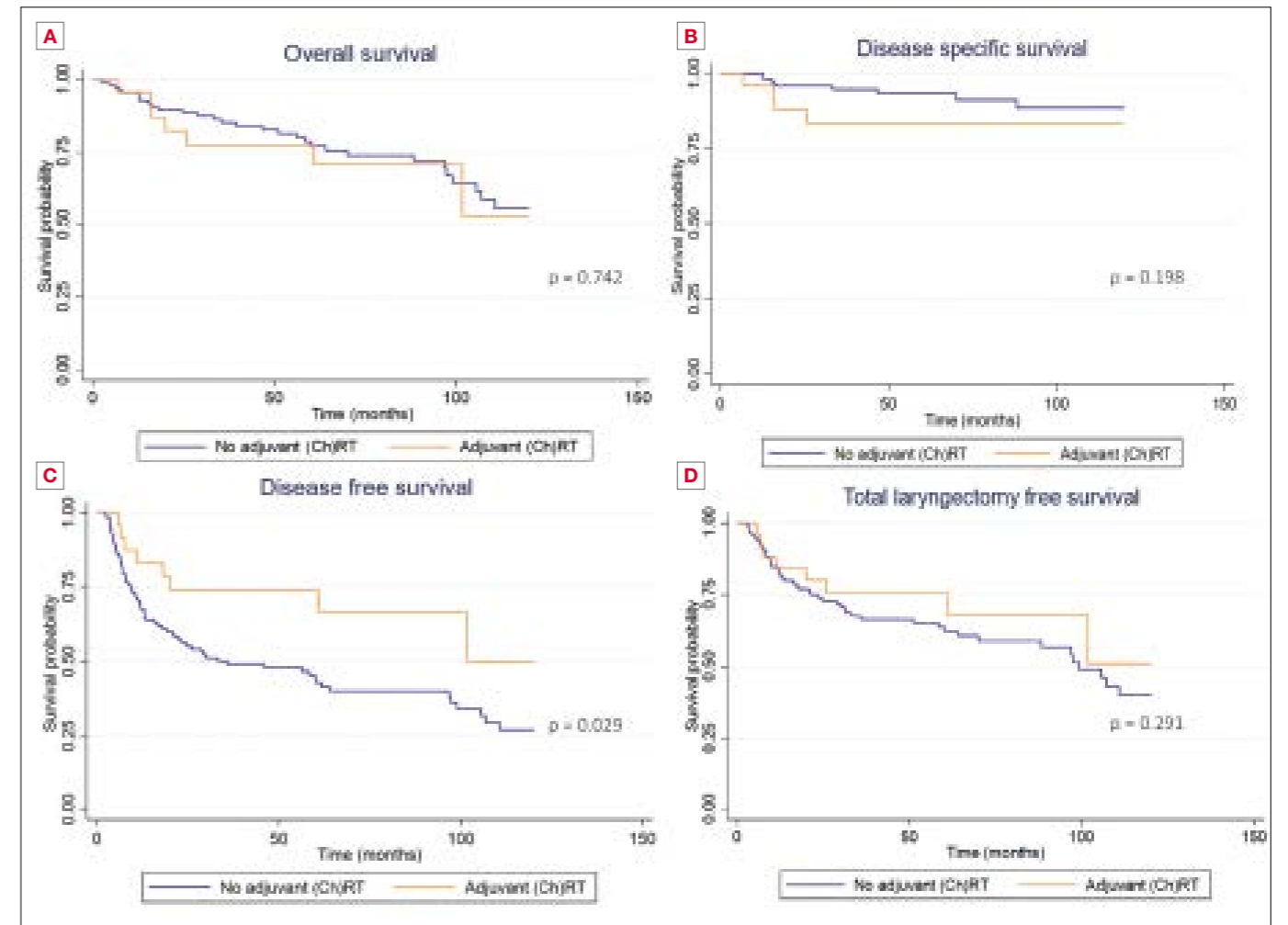


Figure 1. Kaplan-Meier survival estimates for overall, OS (A), disease-specific, DSS (B), disease-free, DFS (C), and total laryngectomy-free survival, TLFS (D), according to adjuvant treatment(s) with (C)RT. (C)RT: (chemo-)radiotherapy.

Table III. Uni- and multivariate Cox survival analysis for overall (OS), disease-free (DFS), and total laryngectomy-free survival (TLFS).

Risk factor	OS				DFS				TLFS					
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate			
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value		
Age	1.09 (1.06-1.13)	0.000	1.09 (1.06-1.13)	< 0.001	1.04 (1.01-1.06)	0.003		1.04 (1.01-1.06)	0.006	1.06 (1.03-1.09)	< 0.001	1.06 (1.03-1.10)	< 0.001	
Thyroid cartilage involvement (inner cortex)	1.34 (0.31-2.94)	0.462			1.51 (0.84-2.70)	0.167				1.45 (0.73-2.88)	0.290			
Posterior PGS invasion	0.68 (0.34-1.36)	0.279			1.03 (0.63-1.67)	0.909				1.23 (0.71-2.15)	0.456			
Margins	Uncertain	1.49 (0.73-3.06)	0.276	1.54 (0.74-3.19)	0.245	1.55 (0.91-2.62)	0.104		1.55 (0.91-2.64)	0.106	1.36 (0.74-2.51)	0.327	1.21 (0.65-2.28)	0.545
	Positive	1.50 (0.69-3.28)	0.309	1.19 (0.45-3.12)	0.727	1.26 (0.72-2.19)	0.415		1.66 (0.90-3.08)	0.104	1.15 (0.59-2.22)	0.680	1.12 (0.52-2.43)	0.772
Adjuvant (C)RT	1.14 (0.53-2.46)	0.742	1.16 (0.44-3.06)	0.770	0.46 (0.23-0.92)	0.029		0.38 (0.17-0.81)	0.013	0.67 (0.32-1.41)	0.291	0.65 (0.27-1.57)	0.334	

Legend: (C)RT: (chemo-)radiotherapy; PGS: paraglottic space; hazard ratios (HR) associated with p values < 0.05 are reported in bold.

mon complication after CO₂ TOLMS, with an incidence of approximately 1.1-2.9% in glottic tumours^{25,34,35}. In our study, complications related to surgery were reported in 10 patients (8.9%), due to local bleeding in 8 cases and subcutaneous emphysema in 2. Similar complication rates were previously reported³⁴, which were 8% for bleeding and 1% for emphysema and cervical fistula.

Organ preservation protocols based on (C)RT, which are alternative treatments to surgery, also have significant associated morbidity, including a 33% rate of severe late toxicity, pharyngeal dysfunction ranging from 17% to 25%, and a treatment protocol-associated mortality of 7%^{22,36,37}. Forastiere et al.³⁸, in their study evaluating concurrent CRT for organ preservation in advanced laryngeal cancer, reported grade 3-4 late toxic effects in 24% of patients receiving induction cisplatin plus fluorouracil followed by RT, 30% in those receiving RT with concurrent cisplatin, and 36% in those treated by RT alone. The total rates of severe toxic effects (acute and late) were 81%, 82%, and 61%, respectively, in patients receiving induction cisplatin plus fluorouracil followed by RT, RT with concurrent cisplatin, and RT alone. Potentially treatment-related deaths were 3%, 5%, and 3%, respectively. Five-year OS did not differ significantly according to treatment and was 55% for induction cisplatin plus fluorouracil followed by RT, 54% for RT with concurrent cisplatin, and 56% for RT alone. Five-year DFS was 38% for induction cisplatin plus fluorouracil followed by RT, 36% for RT with concurrent cisplatin, and 27% for RT alone.

Adding postoperative RT in patients undergoing surgical laryngeal-preserving treatment is associated with a 5-10% rate of severe late laryngeal complications, including laryngeal chondroradionecrosis and stenosis^{22,36,37}. In addition, it may affect functional outcomes and cause dysphagia, laryngeal oedema, tissue necrosis, fibrosis, and adverse effects such as xerostomia, with a decreased quality of life (QoL)^{22,37}. Moreover, the resulting modified laryngeal appearance might preclude adequate follow-up by clinical and endoscopic evaluation²⁰. In our study population, only one of 26 patients who received adjuvant treatment presented a laryngeal stenosis that could be managed without tracheostomy.

Vilaseca et al.³⁹ investigated the prognostic factors affecting QoL after CO₂ TOLMS in laryngeal cancer using the University of Washington-QoL v4 questionnaire. The study included 401 consecutive disease-free patients evaluated one year after treatment, with tumours of different stages and laryngeal subsites, and found that RT and neck dissection were both negative factors for disease-specific QoL. Olthoff et al.⁴⁰ specifically addressed this issue in locally advanced tumours using the EORTC QLQ-C30 and QLQ-H&N35 questionnaires

(developed by the European Organization for Research and Treatment of Cancer) and reported a good QoL.

Limitations and strengths

The current study has several limitations, with some inherent to the nature of a retrospective data analysis. Many variables could not be properly obtained because we did not have knowledge of them at the time patients were treated. These include vocal cord motility impairment, posterior PGS involvement, and status of resection margins after CO₂ TOLMS. Histological features such as PNI, LVI, and inner thyroid cartilage invasion were not systematically recorded in some hospitals years ago, and it is now known that they might have affected treatment decisions. The multicentre characteristic of the study also hinders understanding the decision of receiving adjuvant treatment for each patient, mostly for those without clinical and histological adverse features. Adjuvant treatment(s) features as type and dose were also difficult to assess, as many patients received adjuvant treatment in other hospitals. Among the strengths of the study are the large number of patients included, all from centres with experience in CO₂ TOLMS and sharing a similar comprehensive management of laryngeal cancer.

Conclusions

In conclusion, our study suggests that adjuvant treatment with (C)RT has a positive impact on DFS for pT3 glottic SCC treated with CO₂ TOLMS. The absence of significant differences in terms of OS, DSS, and TLFS between pT3 SCC glottic tumours without negative prognosticators treated by surgery alone and those with unfavourable risk-factors treated by transoral resection plus adjuvant treatment(s) seems to reinforce the idea that such a multimodal treatment can help reduce adverse events in terms of loco-regional control of a potentially life-threatening disease. Further prospective studies should be conducted to validate our findings and to confirm the relevance of adjuvant treatment(s) in this specific setting of patients.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

AP, LRS: patient enrolment, study design, drafting the

manuscript; CS: study design, drafting the manuscript; PB: patient enrolment, study design; FM, GZ, FDB: revision of the manuscript; GP, IV,CP: patient care, study design, revision of the manuscript.

Ethical consideration

This study was approved by the Institutional Ethics Committee of the University of Brescia (protocol number 4267). The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each patient for study participation and data publication.

References

- NCCN head-and-neck. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf, Accessed September 24, 2024.
- Forastiere AA, Ismaila N, Lewin JS, et al. Use of larynx-preservation strategies in the treatment of laryngeal cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2018;36:1143-1169. <https://doi.org/10.1200/JCO.2017.75.7385>
- Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* 2017;67:93-99. <https://doi.org/10.3322/caac.21388>
- Remacle M, Arens C, Eldin MB, et al. Laser-assisted surgery of the upper aero-digestive tract: a clarification of nomenclature. A consensus statement of the European Laryngological Society. *Eur Arch Otorhinolaryngol* 2017;274:3723-3727. <https://doi.org/10.1007/s00405-017-4708-3>
- Ferrari M, Mularoni F, Taboni S, et al. How reliable is assessment of true vocal cord-arytenoid unit mobility in patients affected by laryngeal cancer? A multi-institutional study on 366 patients from the ARYFIX collaborative group. *Oral Oncol* 2024;152:106744. <https://doi.org/10.1016/j.oraloncology.2024.106744>
- Succo G, Crosetti E, Bertolin A, et al. Treatment for T3 to T4a laryngeal cancer by open partial horizontal laryngectomies: prognostic impact of different pathologic tumor subcategories. *Head Neck* 2018;40:1897-1908. <https://doi.org/10.1002/hed.25176>
- Del Bon F, Piazza C, Lancini D, et al. Open partial horizontal laryngectomies for T3-T4 laryngeal cancer: prognostic impact of anterior vs posterior laryngeal compartmentalization. *Cancers (Basel)* 2019;11:289. <https://doi.org/10.3390/cancers11030289>
- Vilaseca I, Aviles-Jurado FX, Valduvicio I, et al. Transoral laser microsurgery in locally advanced laryngeal cancer: prognostic impact of anterior versus posterior compartments. *Head Neck* 2021;43:3832-3842. <https://doi.org/10.1002/hed.26878>
- Peretti G, Piazza C, Mora F, et al. Reasonable limits for transoral laser microsurgery in laryngeal cancer. *Curr Opin Otolaryngol Head Neck Surg* 2016;24:135-139. <https://doi.org/10.1097/MOO.0000000000000240>
- Marchi F, Del Bon F, Chu F, et al. Refining prognostic subcategories in intermediate-advanced glottic cancer: a multicentric study on 637 patients treated by transoral laser microsurgery. *Oral Oncol* 2025;164:107264. <https://doi.org/10.1016/j.oraloncology.2025.107264>
- Maroldi R, Ravaneli M, Farina D. Magnetic resonance for laryngeal cancer. *Curr Opin Otolaryngol Head Neck Surg* 2014;22:131-139. <https://doi.org/10.1097/MOO.0000000000000036>
- Jäckel MC, Ambrosch P, Martin A, et al. Impact of re-resection for inadequate margins on the prognosis of upper aerodigestive tract cancer treated by laser microsurgery. *Laryngoscope* 2007;117:350-356. <https://doi.org/10.1097/01.mlg.0000251165.48830.89>
- Preuss SF, Cramer K, Drebbler U, et al. Second-look microlaryngoscopy to detect residual carcinoma in patients after laser surgery for T1 and T2 laryngeal cancer. *Acta Otolaryngol* 2009;129:881-885. <https://doi.org/10.1080/00016480802441739>
- Vander Poorten V, Meulemans J, Van Lierde C, et al. Current indications for adjuvant treatment following transoral laser microsurgery of early and intermediate laryngeal cancer. *Curr Opin Otolaryngol Head Neck Surg* 2021;29:79-85. <https://doi.org/10.1097/MOO.0000000000000702>
- Bernier J, Dommene C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;350:1945-1952. <https://doi.org/10.1056/NEJMoa032641>
- Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 2004;350:1937-1944. <https://doi.org/10.1056/NEJMoa032646>
- Remacle M, Eckel HE, Antonelli A, et al. Endoscopic cordectomy. A proposal for a classification by the Working Committee, European Laryngological Society. *Eur Arch Otorhinolaryngol* 2000;257:227-231. <https://doi.org/10.1007/s004050050228>
- Remacle M, Van Haverbeke C, Eckel H, et al. Proposal for revision of the European Laryngological Society classification of endoscopic cordectomies. *Eur Arch Otorhinolaryngol* 2007;264:499-504. <https://doi.org/10.1007/s00405-007-0279-z>
- Ravaneli M, Paderno A, Del Bon F, et al. Prediction of posterior paraglottic space and cricoarytenoid unit involvement in endoscopically T3 glottic cancer with arytenoid fixation by magnetic resonance with surface coils. *Cancers (Basel)* 2019;11:67. <https://doi.org/10.3390/cancers11010067>
- Simo R, Bradley P, Chevalier D, et al. European Laryngological Society: ELS recommendations for the follow-up of patients treated for laryngeal cancer. *Eur Arch Otorhinolaryngol* 2014;271:2469-2479. <https://doi.org/10.1007/s00405-014-2966-x>
- Cooper DJ, Davies C, Putnam P, et al. Real-world survival impact and utilization of adjuvant radiation in advanced laryngeal cancer. *Ear Nose Throat J* 2024;1455613241291701. <https://doi.org/10.1177/01455613241291701>
- Graboyes EM, Zhan KY, Garrett-Mayer E, et al. Effect of postoperative radiotherapy on survival for surgically managed pT3N0 and pT4aN0 laryngeal cancer: analysis of the National Cancer Data Base. *Cancer* 2017;123:2248-2257. <https://doi.org/10.1002/cncr.30586>
- Mattioli F, Fermi M, Molinari G, et al. pT3N0 laryngeal squamous cell carcinoma: oncologic outcomes and prognostic factors of surgically treated patients. *Laryngoscope* 2021;131:2262-2268. <https://doi.org/10.1002/lary.29528>
- Kim SH, Lee YS, Kwon M, et al. Adjuvant role of radiation therapy for locally advanced laryngeal cancer without pathological lymph node metastasis. *Acta Otolaryngol* 2016;136:703-710. <https://doi.org/10.3109/00016489.2016.1146827>

- ²⁵ Chien PJ, Hung LT, Wang LW, et al. Oncologic results and quality of life in patients with T3 glottic cancer after transoral laser microsurgery. *Eur Arch Otorhinolaryngol* 2021;278:2983-2992. <https://doi.org/10.1007/s00405-020-06445-2>
- ²⁶ Mattioli F, Serafini E, Lo Manto A, et al. The role of adjuvant therapy in pT4N0 laryngectomized patients: multicentric observational study. *Head Neck* 2023;45:197-206. <https://doi.org/10.1002/hed.27225>
- ²⁷ Expert Panel on Radiation Oncology – Head and Neck; Salama JK, Saba N, Quon H, et al. ACR appropriateness criteria[®] adjuvant therapy for resected squamous cell carcinoma of the head and neck. *Oral Oncol* 2011;47:554-559. <https://doi.org/10.1016/j.oraloncology.2011.05.002>
- ²⁸ Cervinka BP, Rao S, Farwell DG, et al. Efficacy of laryngectomy alone for treatment of locally advanced laryngeal cancer: a stage- and subsite-specific survival analysis. *Clin Otolaryngol* 2018;43:544-552. <https://doi.org/10.1111/coa.13018>
- ²⁹ Sessions DG, Lenox J, Spector GJ, et al. Management of T3N0M0 glottic carcinoma: therapeutic outcomes. *Laryngoscope* 2002;112:1281-1288. <https://doi.org/10.1097/00005537-200207000-00026>
- ³⁰ Li M, Zhang T, Tan B, et al. Role of postoperative adjuvant radiotherapy for locally advanced laryngeal cancer: a meta-analysis. *Acta Otolaryngol* 2019;139:172-177. <https://doi.org/10.1080/00016489.2018.1542159>
- ³¹ Ko HC, Harari PM, Chen S, et al. Survival outcomes for patients with T3N0M0 squamous cell carcinoma of the glottic larynx. *JAMA Otolaryngol Head Neck Surg* 2017;143:1126-1133. <https://doi.org/10.1001/jamaoto.2017.1756>
- ³² Succo G, Peretti G, Piazza C, et al. Open partial horizontal classification by the working committee on nomenclature of the European Laryngological Society. *Eur Arch Otorhinolaryngol* 2014;271:2489-2496. <https://doi.org/10.1007/s00405-014-3024-4>
- ³³ Al-Gilani M, Skillington SA, Kallogjeri D, et al. Surgical vs nonsurgical treatment modalities for T3 glottic squamous cell carcinoma. *JAMA Otolaryngol Head Neck Surg* 2016;142:940-946. <https://doi.org/10.1001/jamaoto.2016.1609>
- ³⁴ Vilaseca-González I, Bernal-Sprekelsen M, Blanch-Alejandro J-L, et al. Complications in transoral CO₂ laser surgery for carcinoma of the larynx and hypopharynx. *Head Neck* 2003;25:382-388. <https://doi.org/10.1002/hed.10207>
- ³⁵ Ellies M, Steiner W. Peri- and postoperative complications after laser surgery of tumors of the upper aerodigestive tract. *Am J Otolaryngol* 2007;28:168-172. <https://doi.org/10.1016/j.amjoto.2006.08.008>
- ³⁶ Laccourreye O, Hans S, Borzog-Grayeli A, et al. Complications of postoperative radiation therapy after partial laryngectomy in supraglottic cancer: a long-term evaluation. *Otolaryngol Head Neck Surg* 2000;122:752-757. [https://doi.org/10.1016/S0194-5998\(00\)70210-5](https://doi.org/10.1016/S0194-5998(00)70210-5)
- ³⁷ Steiniger JR, Parnes SM, Gardner GM. Morbidity of combined therapy for the treatment of supraglottic carcinoma: supraglottic laryngectomy and radiotherapy. *Ann Otol Rhinol Laryngol* 1997;106:151-158. <https://doi.org/10.1177/000348949710600211>
- ³⁸ Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* 2003;349:2091-2098. <https://doi.org/10.1056/NEJMoa031317>
- ³⁹ Vilaseca I, Bernal-Sprekelsen M, Him R, et al. Prognostic factors of quality of life after transoral laser microsurgery for laryngeal cancer. *Eur Arch Otorhinolaryngol* 2015;272:1203-1210. <https://doi.org/10.1007/s00405-014-3030-6>
- ⁴⁰ Olthoff A, Ewen A, Wolff HA, et al. Organ function and quality of life after transoral laser microsurgery and adjuvant radiotherapy for locally advanced laryngeal cancer. *Strahlenther Onkol* 2009;185:303-309. <https://doi.org/10.1007/s00066-009-1967-y>