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# Refining prognostic subcategories in intermediate-advanced glottic cancer: A multicentric study on 637 patients treated by transoral laser microsurgery

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ABSTRACT

*Background:* The current TNM staging system does not fully address the variations in glottic squamous cell carcinoma (SCC) extension and subsites involvement, especially if treated with transoral laser microsurgery (TOLMS). This study aims to evaluate the oncologic outcomes after TOLMS in intermediate-advanced glottic SCC, stratified by prognostic subcategories based on anatomical tumor extension.

*Methods:* This retrospective multicentric study analyzed 637 previously untreated patients with pT2-T3 glottic SCC treated by TOLMS following the same policies at four tertiary European centers. Patients were stratified into 5 subcategories (III, IV, Va, Vb, VI) based on three-dimensional local tumor extension, a refined definition of the previous classification proposed by Piazza et al.

*Results:* Out of 637 patients, 453 (71 %) were pT2, and 184 (29 %) pT3. The 5-year disease-specific survival for the entire cohort was 91 %, LCL 81 %, and LP 87 %. Subcategories Va (anterior paraglottic space [PGS] involvement) and Vb (posterior PGS involvement) showed significantly poorer disease-specific survival (Va: 91 %, Vb: 80 %) and local control with laser alone (Va: 76 %, Vb: 68 %) compared to subcategories III (tumors extending superficially to the supra- and/or subglottis) and IV (tumors infiltrating the vocal muscle). Tumors with posterior PGS involvement demonstrated the highest risk of local recurrence and total laryngectomy (HR: 3.70).

*Abbreviations:* SCC, squamous cell carcinoma; TOLMS, transoral laser microsurgery; DSS, disease-specific survival; LCL, local control with laser alone; LP, laryngeal preservation; OPHL, open partial horizontal laryngectomies; TL, total laryngectomy; RT, radiation therapy; CRT, chemoradiation therapy; PGS, paraglottic space; NBI, Narrow Band Imaging; CT, computer tomography; ELS, European Laryngological Society; HR, hazard ratio; CIs, 95% confidence intervals; IQR, interquartile range.

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*Conclusion:* TOLMS is a viable treatment option for T2-T3 glottic SCC, offering high rates of laryngeal preservation and favorable oncologic outcomes in well-selected patients. Stratification based on tumor subsites involvement provides critical prognostic insights, with posterior PGS invasion serving as a key risk factor for poorer outcomes.

## Introduction

Multiple therapeutic options are now available for intermediate-advanced laryngeal squamous cell carcinomas (SCC), based on clinical staging and the patient's general status. They include both surgical treatments such as transoral laser microsurgery (TOLMS), open partial horizontal laryngectomies (OPHL), and total laryngectomy (TL) [1,2], as well as non-surgical organ preservation protocols, based on radiation (RT) or chemoradiation (CRT) [3,4].

For glottic SCC, the indications for TOLMS, although initially limited to early lesions (Tis-T1b), have been progressively extended to more advanced tumors (T2 and selected T3) [5–10]. Transoral approaches are currently considered a valuable therapeutic option for "early-intermediate glottic cancer" with a mean disease control rate of 81.3 % [11]. However, the three-dimensional involvement of different laryngeal subsites, infiltration of submucosal tissues, and vocal cord mobility represent key points to be considered for adequate selection of patients. When compared to TOLMS treatment for patients with early-stage laryngeal SCC, patients with intermediate-stage SCC, even if well-selected, have a higher likelihood of requiring re-resection of margins or adjuvant radiotherapy [12,13]. The 8th Edition of the TNM staging system [14] only partially addresses these diversities, meaning that the classification of pT2 and pT3 glottic SCC appears oversimplified [15]. For instance, pT2 glottic lesions may include tumors with superficial extension into the supraglottic and/or subglottic regions or deeply infiltrating the muscle with reduced mobility of the vocal cord [16–19]. References to the depth of infiltration, already understood as a pivotal oncologic concept in other head and neck sites like the oral cavity and skin, is so far not included in the TNM staging system of the larynx [20–23]. Moreover, the pT3 category defines glottic tumors causing vocal cord fixation or infiltrating either the inner cortex of the thyroid cartilage or the paraglottic space (PGS). However, it fails to differentiate between fixation of the vocal cord and that of the arytenoid, and between the involvement of the anterior vs. posterior PGS, a well-established anatomic distinction that is known to have an impact on management and prognosis of laryngeal cancer [24–27].

The aim of this retrospective multicentric study was to stratify the oncologic outcomes of a large cohort of patients with pT2-T3 glottic SCC treated by TOLMS at four European tertiary referral centers. Stratification was performed according to disease extension and anatomical subsites, homogeneously evaluated and classified based on an iso-prognostic zones scheme previously described [15], with all centers following a shared diagnostic and therapeutic strategy.

## Materials and methods

### *Study population*

A multicentric observational retrospective study was carried out enrolling a cohort of patients affected by glottic SCC from January 2000 to March 2023 in 4 European tertiary referral Otorhinolaryngology – Head and Neck Units: IRCCS Ospedale Policlinico San Martino – University of Genova (Genova, Italy); Spedali Civili – University of Brescia (Brescia, Italy); European Institute of Oncology, IRCCS (Milan, Italy); and Hospital Clínic – University of Barcelona (Barcelona, Spain). These institutions are high volume centers for TOLMS and share a similar treatment policy. The study was conducted in accordance with the Declaration of Helsinki and approved by the respective local ethics committees (ID LAR_MULTI). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for cohort studies was followed [28].

Inclusion criteria were: (1) histologically-proven, previously untreated glottic SCC; (2) pathologically classified as T2 and T3; (3) successfully submitted to TOLMS with curative intent, with or without neck dissection (ND); (4) availability of related electronical medical records; (5) absence of distant metastasis at presentation. Exclusion criteria were: (1) previous RT administered to the head and neck area; (2) previous head and neck tumor; (3) second-look surgery for revision of margins performed by an open approach.

All patients were adults (≥18 years old). Considering that TOLMS is a relatively brief procedure compared to open-neck surgeries, the sole health-based selection criterion was the anesthesiologist's assessment that the patient was fit to tolerate general anesthesia.

### *Diagnostic protocol*

Preoperative flexible transnasal videolaryngoscopy was used to assess superficial tumor margins under white light and bioendoscopy, i.e. Narrow Band Imaging (NBI, Olympus Medical System Corporation, Tokyo, Japan) or Storz Professional Imaging Enhancement System (SPIES, Karl-Storz, Tuttlingen, Germany, or i-Scan high-definition, Pentax videoendoscopic system, Japan). Preoperative imagining was performed either with neck computer tomography (CT) or magnetic resonance. Anterior and posterior PGS invasion was assessed by retrospectively reviewing CT or as reported by the intraoperative findings according to previously published criteria [29]. Patients with negative nodes at preoperative imaging received TOLMS alone. In cases of clinical and radiological suspicion, patients underwent neck dissection following the NCCN guidelines [1].

### *Treatment and follow-up*

Prior to tumor resection, the surgeon performed an intraoperative laryngoscopy with 0°, and/or 30° and 70° rigid endoscopes, under white light and NBI, SPIES or i-Scan, evaluating superficial tumor margins and the laryngeal subsites involved. Carbon dioxide laser was always used for resection.

Tumor resection was categorized following the European Laryngological Society (ELS) classification of cordectomies [30,31], using en-bloc or multi-bloc resections according to specific tumor features, extension, and laryngeal exposure. All tumors were excised with radical intent, and the specimen immediately oriented by the surgeon inking it at the level of the margins of resection or fixing it with needles on a sponge support. The marked margins varied depending on the type of resection performed, with the primary aim being to ensure precise orientation of the specimen for final histopathological examination. In less extensive cordectomies, at least one superficial margin was typically marked. In more extensive procedures, such as multi-block surgeries the specimen was reconstructed and marked on a support, or additional margins were taken from the surgical bed. The method used to mark the margins could have varied slightly depending on the surgeons' preferences and collaboration with the pathologist.

Based on the final histological examination, the four centers followed a unified strategy. Specifically, if a single positive superficial margin is identified, follow-up is recommended. In cases of multiple positive superficial margins or a positive deep margin, additional treatments were indicated. Options included re-excision through TOLMS, open-neck surgery, or adjuvant radiotherapy. The choice of the most suitable

approach was tailored through multidisciplinary discussion, taking into account factors such as the extent of the initial excision, tumor stage, laryngeal exposure, as well as the patient's comorbidities and preferences. Adjuvant radiotherapy was considered in cases with multiple risk factors or when patients were unable or unwilling to undergo more extensive surgery to address positive margin(s).

Transoral re-excision was carried out after healing within 2 months from the first surgery in case of deep or more than one superficial positive margins, or in case of suspicious findings after the end of the healing process. Adjuvant treatments (RT or CRT) were discussed by local tumor boards based on the presence of persistent tumor after re-excision, perineural invasion, lympho-vascular invasion, multiple positive lymph nodes, or extracapsular spread after neck dissection. Follow-up was conducted in accordance with the ELS guidelines [32].

Tumors were classified according to Piazza et al. [15] into the following subcategories: (III) pT2 extending superficially to the supraglottis and/or subglottis; (IV) pT2 infiltrating the vocal muscle; (Va) pT3 involving the anterior PGS; (VI) pT2 or pT3 with *trans*-anterior commissure (AC) extension with or without involvement of the pre-epiglottic space. We further introduced a new subcategory (Vb) for pT3 extending into the posterior PGS.

### *Data collection and outcome measures*

Surgical margins were classified as "positive" if carcinoma was detected at the inked margin of the specimen, "close" if the tumor was found within 1 mm of the resection margins, and "uncertain" when resection extended to the subperichondral plane of the cartilage or when no margins were available for analysis due to vaporization of the resection bed. The final status of margins was determined after every possible re-resection. In case of "uncertain" margins, some patients were considered to have undergone radical surgery based on intraoperative assessment and a comprehensive review of the pathological report, in conjunction with preoperative radiological findings (e.g. when the tumor was in touch with the inner thyroid lamina without signs of its invasion). These patients were typically placed under close follow-up. When the pathologist identified "uncertain" margins with a suspected presence of microscopic residual tumor, the multidisciplinary team recommended either re-excision (if feasible) or adjuvant therapy, depending on the extent of the initial resection and the degree of laryngeal exposure. Lymph nodes status (pN) was re-staged according to the 8th TNM Edition [14]for all patients.

The primary endpoints were: (1) disease specific survival (DSS), defined as the time between the date of surgery and that of cancer-related death/last follow-up; (2) local control with laser alone (LCL), defined as the time between the date of the surgery and that of any further open or non-surgical treatment for relapse; and (3) laryngeal preservation (LP), defined as the number of patients surviving without TL at a given time point. Overall survival (OS) was considered as a secondary endpoint.

### *Statistical analysis*

Categorical variables were summarized as counts and percentages, while continuous variables were reported as medians and interquartile ranges (IQR: 25th and 75th). To assess differences in distribution of variables among the different pT subcategories, Kruskal-Wallis rank sum test and Chi squared or Fisher's exact test were used as appropriate. The Kaplan-Meier method was used to estimate the survivals while differences among the subcategories groups were assessed with the log-rank test.

A multivariable survival analysis was conducted using the Cox proportional hazards regression model to identify factors associated with the primary outcomes. The selection of variables to be included in the model was made *a priori* based on clinical relevance considering a maximum of 58 events for DSS limiting the number of covariates in the model. Variables were chosen using the prognostic subcategories as a surrogate for the primary T category considering their collinearity (*Spearman's correlation coefficient = 0.7)*, presence of positive lymph nodes, and final margin status as the most relevant postoperative risk factors, and adjuvant therapy administration as the main postoperative confounding factor. No other tumor related variable was included in the regression model to avoid any redundancy since the concept of subcategory stratification itself was accounting for all of them. The results were summarized with hazard ratios (HR) and 95 % confidence intervals (CIs).

A unidirectional multistate model was built with descriptive purpose to show the percentage of patients experiencing each disease state (disease free, local recurrence, TL, death of disease) over time [33]. Prediction probabilities were estimated using the non-parametric method described by Aalen-Johansen to consider the competing risk between the different events [34]. A $p < 0.05$ was considered to indicate statistical significance for all tests. Statistical analyses were performed using R software for statistical computing (R version 4.0.1). Data were analyzed in March 2024.

## Results

Six-hundred thirty-seven treatment-naïve patients with intermediate-advanced (pT2-T3) glottic SCC treated with TOLMS from January 2000 to March 2023, were retrospectively enrolled: 98 at the University of Genova, 177 at the University of Brescia, 157 at the Hospital Clínic of Barcelona, and 205 at the European Institute of Oncology, Milan. Five hundred and eighty-six (92 %) were males with a median age of 67 years (IQR, 59–74) for the entire group.

According to the final pathology report, 453 (71 %) were staged as pT2 and 184 (29 %) as pT3. The final margins were deemed "free" in 348 (55 %) patients, "close" in 69 (11 %), "uncertain" in 75 (12 %) and "positive" in 145 (23 %). Eighteen patients underwent neck dissection with only 6 having positive nodes (pN1 = 3, pN2b = 1, and pN3b = 2) according to the 8th TNM Edition. A total of 113 patients underwent second-look surgery for margin(s) revision. In 74 cases, no residual carcinoma was detected. Of the 39 cases where re-excision revealed SCC, 18 achieved negative margins, while the remaining 9 did not. Postoperative adjuvant RT was administered in 61 (9.6 %) patients, and among these 10 (1.6 %) received concomitant chemotherapy. The distribution into subcategories is reported in Table 1.

The median follow-up time was 64 months (IQR: 33–113). At the last follow-up, 430 (68 %) patients had no evidence of disease, 58 (9.1 %) were dead of disease, and 146 (23 %) were dead due to other causes. Three patients had a permanent tracheostomy, and 2 were gastrostomy-dependent. For the entire cohort, 3- and 5-year overall survival (95 % CI) were 86 % (83–89) and 78 % (75–82), respectively; 3- and 5-year DSS were 94 % (92–96) and 91 % (89–94), respectively.

A total of 170 patients experienced a local recurrence. The salvage treatments of these patients are reported in Table 2. The 3- and 5-year LCL and LP for the entire cohort were 84 % and 81 %, and 89 % and 87 %, respectively. The rates of DSS, LCL, and LP according to each subcategory are detailed in Table 3.

Kaplan-Meier curves for each primary 5-year survival endpoint (DSS, LCL, and LP) stratified according to each subcategory are depicted in Figs. 1-3. A significant difference at the log-rank test was found for LCL and LP (both $p < 0.001$). A significant difference was found between subcategory III vs. Va ($p = 0.001$; $p = 0.02$), III vs. Vb ($p < 0.001$; $p = 0.014$), III vs. VI ($p < 0.001$; $p = 0.02$), as well as IV vs. Va ($p = 0.03$; $p = 0.02$), IV vs. Vb ($p = 0.004$; $p = 0.0015$), and IV vs. VI ($p < 0.001$; $p = 0.002$) for LCL and LP, respectively.

The Cox proportional hazards multivariable regression analysis showed an approximately 3- and 2-fold increase in the risk of dying due to the cancer, with an HR (95 % CI) of 3.24 (1.01–10.42), and 2.34 (1.00–5.50), respectively, for subcategories Vb and VI, as compared to subcategory III (Fig. 1-3). In addition, subcategories Va, Vb, and VI had a

**Table 1**
Clinical and pathologic characteristics of the cohort. PNI, perineural invasion; LVI, lympho-vascular invasion. IQR, interquartile rate; RT, radiotherapy; CRT, chemo-radiotherapy.

| Variable | Overall, N = 637 | Subcategory III N = 136 | Subcategory IV N = 216 | Subcategory Va N = 98 | Subcategory Vb N = 33 | Subcategory VI N = 154 | p value |
|---|---|---|---|---|---|---|---|
| **Age** | | | | | | | **0.011** |
| Median (IQR) | 67 (59, 74) | 64(57, 72) | 67 (59, 73) | 69 (61, 75) | 63 (58, 69) | 69 (62, 77) | |
| **Gender** | | | | | | | **0.030** |
| Female | 51 (8 %) | 9 (6.6 %) | 23 (11 %) | 9 (9.2 %) | 5 (15 %) | 5 (3.2 %) | |
| Male | 586 (92 %) | 127 (93 %) | 193 (89 %) | 89 (91 %) | 28 (85 %) | 149 (97 %) | |
| **Nodal metastasis** | | | | | | | **0.006** |
| No | 631 (99 %) | 136 (100 %) | 216 (100 %) | 96 (98 %) | 31 (94 %) | 152 (99 %) | |
| Yes | 6 (0.9 %) | 0 (0 %) | 0 (0 %) | 2 (2 %) | 2 (6.1 %) | 2 (1.3 %) | |
| **Grade** | | | | | | | |
| 1 | 63 (11 %) | 23 (19 %) | 25 (12 %) | 6 (6.4 %) | 3 (12 %) | 6 (5.1 %) | |
| 2 | 335 (59 %) | 69 (58 %) | 117 (56 %) | 62 (66 %) | 14 (56 %) | 73 (62 %) | |
| 3 | 167 (30 %) | 27 (23 %) | 67 (32 %) | 26 (28 %) | 8 (32 %) | 39 (33 %) | |
| **PNI** | | | | | | | 0.10 |
| No | 340 (93 %) | 51 (94 %) | 145 (95 %) | 73 (92 %) | 14 (78 %) | 57 (90 %) | |
| Yes | 26 (7.1 %) | 3 (5.6 %) | 7 (4.6 %) | 6 (7.6 %) | 4 (22 %) | 6 (9.5 %) | |
| **LVI** | | | | | | | **0.033** |
| No | 339 (92 %) | 52 (93 %) | 148 (96 %) | 71 (90 %) | 15 (83 %) | 53 (85 %) | |
| Yes | 30 (8.1 %) | 4 (7.1 %) | 6 (3.9 %) | 8 (10 %) | 3 (17 %) | 9 (15 %) | |
| **Final margins** | | | | | | | **<0.001** |
| Free | 348 (55 %) | 84 (62 %) | 129 (60 %) | 49 (50 %) | 11 (33 %) | 75 (49 %) | |
| Close | 69 (11 %) | 5 (3.7 %) | 33 (15 %) | 16 (16 %) | 4 (12 %) | 11 (7.1 %) | |
| Uncertain | 75 (12 %) | 13 (9.6 %) | 3 (1.4 %) | 8 (8.2 %) | 12 (36 %) | 39 (25 %) | |
| Positive | 145 (23 %) | 34 (25 %) | 51 (24 %) | 25 (26 %) | 6 (18 %) | 29 (19 %) | |
| **Adjuvant therapy (RT/CRT)** | | | | | | | **<0.001** |
| No | 576 (90 %) | 129 (95 %) | 202 (94 %) | 81 (83 %) | 24 (73 %) | 140 (91 %) | |
| Yes | 61 (9.6 %) | 7 (5.1 %) | 14 (6.5 %) | 17 (17 %) | 9 (27 %) | 14 (9.1 %) | |

**Table 2**
Salvage treatments for recurrences according to each subcategory. TOLMS, transoral laser microsurgery; OPHL, open partial horizontal laryngectomy; (C)RT, (chemo-) radiation therapy.

| **Overall,** N = 637 | | **Subcategory III,** N = 136 | **Subcategory IV,** N = 216 | **Subcategory Va,** N = 98 | **Subcategory Vb,** N = 33 | **Subcategory VI,** N = 154 |
|---|---|---|---|---|---|---|
| **No. of local recurrences** | 170 (26 %) | 32 (23 %) | 36 (17 %) | 29 (30 %) | 12 (36 %) | 61 (39 %) |
| **Salvage treatments** | | | | | | |
| **TOLMS** | 46 (27 %) | 16 (50 %) | 7 (19 %) | 9 (31 %) | 1 (8 %) | 13 (21 %) |
| **OPHL** | 21 (13 %) | 2 (6 %) | 10 (28 %) | 3 (11 %) | 0 (0 %) | 6 (9 %) |
| **(C)RT** | 17 (10 %) | 4 (13 %) | 1 (3 %) | 1 (3 %) | 2 (17 %) | 9 (15 %) |
| **Total laryngectomy** | 77 (45 %) | 10 (31 %) | 16 (44 %) | 15 (52 %) | 7 (58 %) | 29 (48 %) |
| **Palliation** | 9 (5 %) | 0 (0 %) | 2 (6 %) | 1 (3 %) | 2 (17 %) | 4 (7 %) |

**Table 3**
Three- and 5-year DSS (Disease-specific survival), LCL (Local control with laser alone), and LP (Laryngeal preservation) rates according to each subcategory.

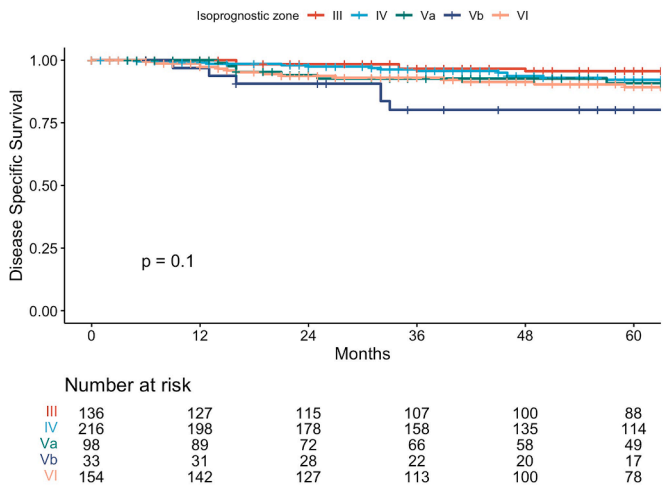
| | **DSS** | | **LCL** | | **LP** | |
|---|---|---|---|---|---|---|
| | **3-year (%)** | **5-year (%)** | **3-year (%)** | **5-year (%)** | **3-year (%)** | **5-year (%)** |
| **Subcategory III** | 97 (93–99) | 96 (92–99) | 91 (87–97) | 90 (85–95) | 96 (92–99) | 94 (90–98) |
| **Subcategory IV** | 96 (93–99) | 92 (88–96) | 88 (84–93) | 86 (81–91) | 94 (90–97) | 92 (88–96) |
| **Subcategory Va** | 93 (87–98) | 91 (84–98) | 76 (67–86) | 76 (67–86) | 81 (73–90) | 81 (73–90) |
| **Subcategory Vb** | 80 (67–96) | 80 (67–96) | 68 (53–86) | 68 (53–86) | 76 (61–93) | 76 (61–93) |
| **Subcategory VI** | 93 (89–97) | 89 (84–95) | 77 (70–85) | 71 (64–79) | 84 (78–90) | 81 (75–88) |

significantly reduced probability to achieve LCL with an HR (95 % CI) of 2.65 (1.37–5.15), 4.03 (1.77–9.18), and 3.79 (2.12–6.67), respectively. Finally, the same subcategories had a significantly increased risk to undergo TL with an HR (95 % CI) of 2.67 (1.18–6.08), 3.70 (1.33–10.32), and 3.46 (1.66–7.22), respectively.

The multistate model demonstrated that the rate of patients experiencing each different disease state (free of disease, local recurrence, TL, death of disease) over time for each subcategory together with the patient's probability to be in each competing disease state at different time points (Fig. 4).

## Discussion

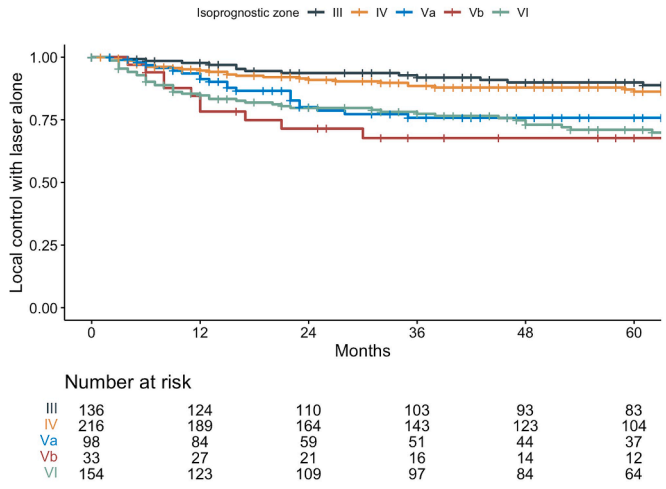
The current study represents a multicentric validation on a larger cohort of patients of previous research in which isoprognostic zones for glottic SCC were delineated according to TOLMS outcomes [15]. In the present analysis, which is focused on pT2-T3 glottic SCC, subcategories III and IV showed favorable outcomes after TOLMS, supporting its role




| Variable | | N | Hazard ratio | p |
|---|---|---|---|---|
| **pT subcategory** | III | 136 | Reference | |
| | IV | 216 | 1.59 (0.68, 3.71) | 0.28 |
| | Va | 98 | 1.75 (0.66, 4.66) | 0.26 |
| | Vb | 33 | 3.24 (1.01, 10.42) | 0.05 |
| | VI | 154 | 2.34 (1.00, 5.50) | 0.05 |
| **Positive nodes** | no | 631 | Reference | |
| | yes | 6 | 3.13 (0.70, 13.98) | 0.14 |
| **Final margins** | free | 348 | Reference | |
| | close | 69 | 0.52 (0.16, 1.74) | 0.29 |
| | uncertain | 75 | 1.15 (0.49, 2.70) | 0.74 |
| | positive | 145 | 1.91 (1.00, 3.62) | 0.05 |
| **Adjuvant therapy** | no | 576 | Reference | |
| | yes | 61 | 1.19 (0.54, 2.63) | 0.66 |



**Fig. 1.** Kaplan-Meier curves and multivariable regression analysis for the survival endpoint DSS (Disease-specific survival) stratified according to each subcategory. No significant differences were observed among the subcategories in the Kaplan-Meier curves. HR (95% CI) of 3.24 (1.01–10.42), and 2.34 (1.00–5.50), respectively, for subcategories Vb and VI showed an increased risk of death of disease.




| Variable | | N | Hazard ratio | p |
|---|---|---|---|---|
| **pT subcategory** | III | 136 | Reference | |
| | IV | 216 | 1.40 (0.75, 2.59) | 0.287 |
| | Va | 98 | 2.65 (1.37, 5.15) | 0.004 |
| | Vb | 33 | 4.03 (1.77, 9.18) | <0.001 |
| | VI | 154 | 3.79 (2.12, 6.77) | <0.001 |
| **Positive nodes** | no | 631 | Reference | |
| | yes | 6 | 2.93 (0.89, 9.68) | 0.078 |
| **Final margins** | free | 348 | Reference | |
| | close | 69 | 1.08 (0.57, 2.03) | 0.812 |
| | uncertain | 75 | 1.51 (0.89, 2.55) | 0.126 |
| | positive | 145 | 2.60 (1.67, 4.06) | <0.001 |
| **Adjuvant therapy** | no | 576 | Reference | |
| | yes | 61 | 0.60 (0.33, 1.08) | 0.089 |



**Fig. 2.** Kaplan-Meier curves and multivariable regression analysis for the survival endpoint LCL (Local control with laser alone) stratified according to each subcategory. Significant differences were observed among the subcategories: III vs. Va ($p = 0.001$; $p = 0.02$), III vs. Vb ($p < 0.001$; $p = 0.014$), and III vs. VI ($p < 0.001$; $p = 0.02$) in the Kaplan-Meier curves. HR (95 % CI) of 2.65 (1.37–5.15), 4.03 (1.77–9.18), and 3.79 (2.12–6.67), respectively for Va, Vb, and VI showed a significantly reduced probability to achieve LCL.

as a primary treatment modality [12]. Previous studies had reported poorer prognosis of pT2 with impaired vocal cord mobility for deep vocal muscle invasion (once defined pT2b, or subcategory IV) compared to pT2 with normal vocal fold mobility and purely superficial extension to the subglottis and/or supraglottis (once defined pT2a, or subcategory III). These results suggest that glottic tumors with impaired cord mobility were much more comparable to those with fixed cord/arytenoid (pT3). In line with such an observation, Peretti et al. [35] reported lower LCL and disease-free survival (DFS) in glottic lesions with muscular infiltration. Canis et al. [36] noted that pT2b behaved like pT3 in terms of LCL and recurrence free survival (RFS). Reviews by Warner et al. [17] and Hendriksma et al. [18] also supported these findings, even when comparing T2 tumors treated with TOLMS versus RT. Similarly, the *meta*-analysis by McCoul et al. [16] confirmed that deep muscular infiltration of the vocal cord causing its reduced mobility is related to an unfavorable outcome after RT. More recently, Forner et al. [19] reported a significant difference in the 5-year local and loco-regional control rates between pT2a and pT2b (75.2 % vs. 57 %, respectively).

Conversely, our study involving 136 patients in subcategory III and 216 patients in subcategory IV indicates that the incidence of local recurrences is quite similar in both categories (23 % and 17 %, respectively) without any significant difference in terms of DSS, LCL, and LP. However, a notable difference is observed in the residual options for salvage surgery in case of tumor relapse. In subcategory III, in fact, 50 % of relapsing patients underwent a second TOLMS, compared to only 19 % in subcategory IV, where patients more commonly received OPHL (28 %) or TL (44 %). These findings have therefore important implications regarding treatment selection, suggesting that the best local control in subcategory IV may be obtained by upfront open surgery [16].

In case of pT3 tumors, we introduced a novel subcategory for lesions extending into the posterior PGS (Vb). In fact, anterior vs. posterior compartmentalization of the PGS has been recently reported to be a crucial point in the selection of patients for partial surgery of the larynx, although the series published to date are still limited [26,36]. In 2009, Vilaseca et al. [37] reported oncological results of 147 patients treated for pT3 glottic and supraglottic tumors with TOLMS, stratifying the cohort in terms of pre-epiglottic space involvement, thyroid cartilage

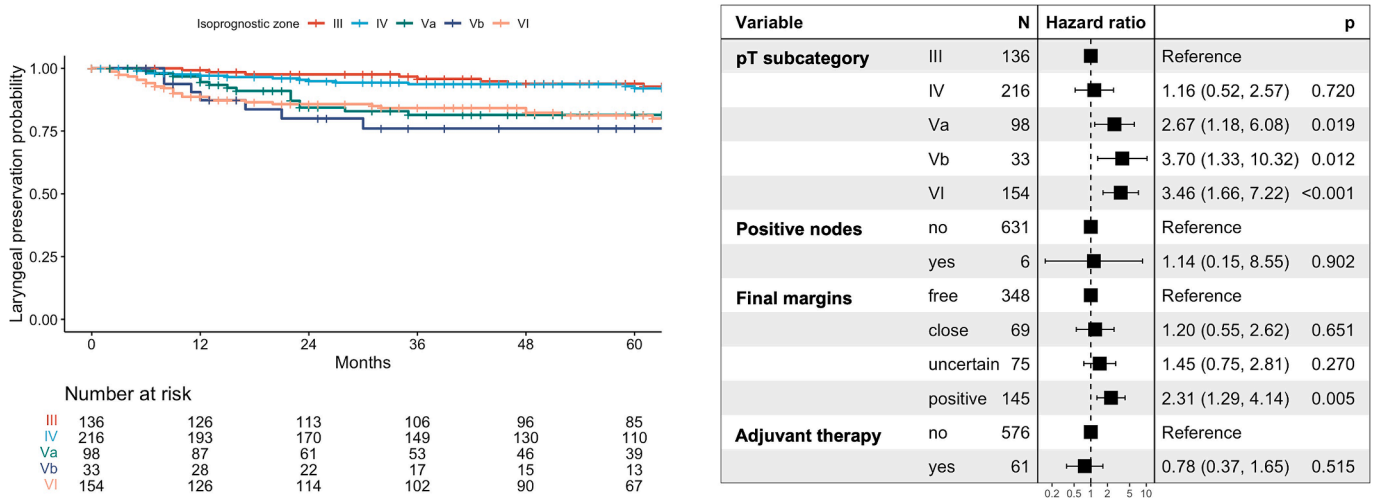



**Fig. 3.** Kaplan-Meier curves and multivariable regression analysis for the survival endpoint LP (Laryngeal preservation) stratified according to each subcategory. Significant differences were observed among the subcategories: IV vs. Va ($p = 0.03$; $p = 0.02$), IV vs. Vb ($p = 0.004$; $p = 0.0015$), and IV vs. VI ($p < 0.001$; $p = 0.002$) in the Kaplan-Meier curves. The HRs (95 % CI) of 2.67 (1.18–6.08), 3.70 (1.33–10.32), and 3.46 (1.66–7.22), respectively for Va, Vb and VI showed a significantly increased risk to undergo total laryngectomy for these subcategories.

infiltration, and arytenoid fixation. The authors reported a 5-year OS, DSS, and LP of 73.1 %, 86.3 %, and 51 %, respectively, for glottic SCC. Moreover, the presence of arytenoid fixation in multivariate analysis was found to be an independent negative prognosticator for recurrence, and for organ and function preservation. In the same year, Peretti et al. [38] reported a series of 120 glottic SCC, 109 pT2 (56 with normal, 53 with impaired vocal fold mobility), and 11 pT3 with posterior PGS involvement, all treated with TOLMS. Five-year DSS, LCL, and LP were 98.3 %, 85.6 %, and 96.1 % for pT2, and 100 %, 71.6 %, and 72.7 % for pT3, thus confirming the worse outcome of the latter category.

In the same way, Ansarin et al. [39] reported in 2016 similar oncological outcomes: for pT2 and pT3, the RFS was 75.3 % and 68.6 %, respectively (p < 0001). Furthermore, the authors showed that in selected pT3 without fixed arytenoid, RFS remained lower independently of postoperative RT. Similar to the literature, fixed arytenoid was significantly related to worse survival rates with a 10-year OS of 66.7 %. Canis et al. [36] investigated 391 patients treated by TOLMS and categorized as pT2a, pT2b, and pT3, further confirming the worse outcomes of the pT3 category in terms of OS, DSS, and LP. Following this trend, Vilaseca et al. in 2021 [26] reviewed 262 locally advanced glottic and supraglottic SCC (pT3-T4a) treated with TOLMS. In multivariate analysis, anterior and posterior PGS involvement were independent risk factors for TL. In our cohort, tumors extending into the anterior PGS (subcategory Va) and particularly those infiltrating the posterior PGS (subcategory Vb) showed significantly poorer DSS and LCL compared to subcategories III and IV. Moreover, tumors with PGS involvement (subcategories Va and Vb) demonstrated a higher probability of requiring TL, with an HR (95 % CI) of 2.67 (1.18–6.08) and 3.7 (1.33–10.32), respectively, highlighting the challenges in achieving organ preservation in these cases.

When compared with the survival outcomes provided by other surgical modalities such as OPHL and TL [40–42], our results for pT3 with TOLMS represents a sound treatment, capable of yielding survival outcomes comparable to more invasive surgeries. This is especially true for selected patients with pT3 involving anterior PGS, and the outcomes are also similar to those reported for cT3 tumors treated with non-surgical methods like CRT [27]. However, our study shows that involvement of the posterior PGS with arytenoid fixation is associated with poorer outcomes in all endpoints, underlying that TOLMS with curative intent should be considered with caution in this subgroup of lesions. As a matter of fact, we have to acknowledge that in our cohort category Vb was the least represented (33 cases) and this could have led to the slightly wider CIs for this category in the multivariable analysis. The lower number of patients in this category can be ascribed to the fact that a predictive factor for infiltration of the posterior PGS is arytenoid fixation, and, as already stated in literature [8], indications for TOLMS are limited in such scenario.

In the subcategory VI (pT2/T3 for anterior *trans*-commissural extension) a diminished likelihood of obtaining local control was demonstrated with TOLMS alone, with an increased probability of patients requiring TL, compared to subcategories III and IV. Analogous results are documented in the literature for comparable tumors that have been treated with RT [43–45]. Moreover, subcategory VI showed an approximately 2-fold increase in the risk of dying for laryngeal cancer in multivariate analysis. Furthermore, subcategory VI, like the Vb, exhibited a significantly decreased probability of achieving LCL.

According to the conventional TNM staging [14], the oncological outcomes for pT2-pT3 glottic SCC treated with TOLMS are 5-year DSS 98.3 %, 5-year LCL 85.6 %, and 5-year LP 95.1 % for pT2, and 5-year DSS 100 %, 5-year LCL 71.6 %, and 5-year LP 72.7 % for pT3 [38]. Alternatively, as reported in other studies, for pT2, the 5-year DSS is 94.9 % and 5-year OP is 89.8 % [46], while for pT3, 5-year OS is 58.6 %, 5-year RFS is 57.8 %, and 5-year DSS is 84.1 % [36].

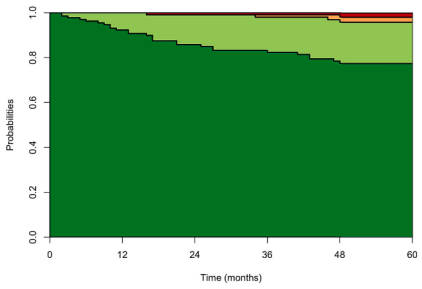
In our study, the oncological outcomes are consistent with literature. However, as previously emphasized, there were no statistically significant differences between the subcategories constituting T2 (III vs VI) or those constituting T3 (Va vs Vb). It is important to note that category VI includes both T2 and T3 *trans*-commissural tumors, and the prognostic values for this category (subcategory VI: 5-year DSS 89 %, 5-year LCL 71 %, 5-year LP 81 %) deviate notably from those reported for T2, but are closer to those of T3.

Regarding the treatment of recurrences after TOLMS, the worst scenario is seen for subcategory Vb, almost exclusively managed by TL, and subcategory VI, mainly salvaged with TL. Concerning lymphatic spread, our study confirmed that in pT2-T3 glottic SCC, neck metastasis is rare, accounting for less than 1 % of cases. Therefore, prophylactic neck dissection in pT2-T3 cN0 glottic SCC remains questionable. [47].

Conversely, recurrent tumors in subcategories III and IV are managed with OPHL in 6 % and 28 % of patients, and with TL in 31 % and 44 %, respectively. Also Chien et al. [48] reported a 5-year LP rate of 80 %. Among recurrences, 44 % underwent TL and 22 % were salvaged by TOLMS.

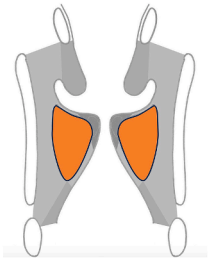
Our study highlights that achieving optimal oncological and functional outcomes hinges on meticulous pre- and intraoperative

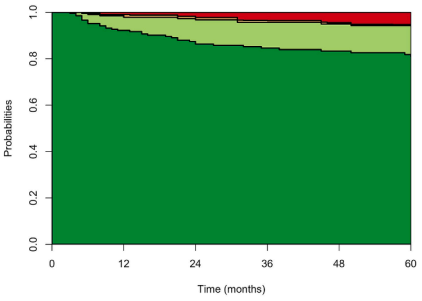
SUBCATEGORY III




| Time (Months) | 24 | 36 | 60 |
|---|---|---|---|
| Death of disease | 0.01 | 0.01 | 0.02 |
| Total Laryngectomy | 0.00 | 0.01 | 0.02 |
| Local Recurrence | 0.13 | 0.16 | 0.18 |
| Disease free | 0.86 | 0.82 | 0.78 |

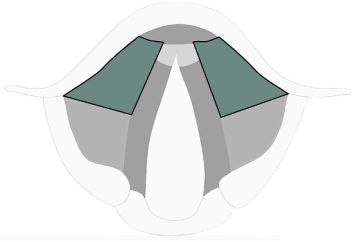
SUBCATEGORY IV

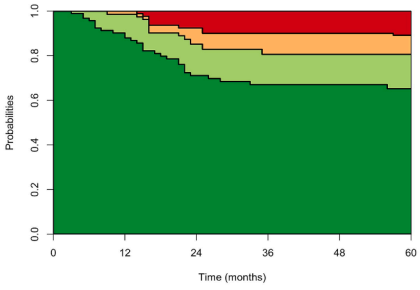





| Time (Months) | 24 | 36 | 60 |
|---|---|---|---|
| Death of disease | 0.03 | 0.04 | 0.05 |
| Total Laryngectomy | 0.01 | 0.01 | 0.01 |
| Local Recurrence | 0.10 | 0.10 | 0.13 |
| Disease free | 0.86 | 0.85 | 0.81 |

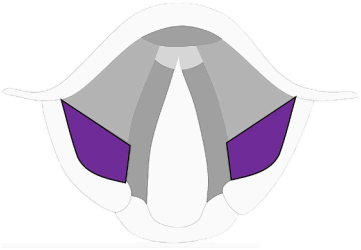
SUBCATEGORY Va

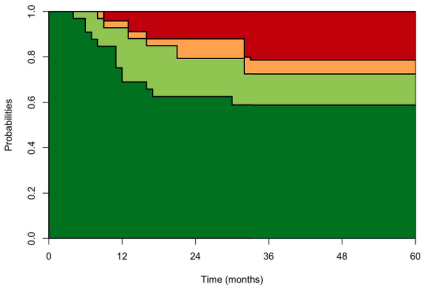





| Time (Months) | 24 | 36 | 60 |
|---|---|---|---|
| Death of disease | 0.08 | 0.11 | 0.11 |
| Total Laryngectomy | 0.07 | 0.09 | 0.09 |
| Local Recurrence | 0.14 | 0.13 | 0.16 |
| Disease free | 0.71 | 0.62 | 0.59 |

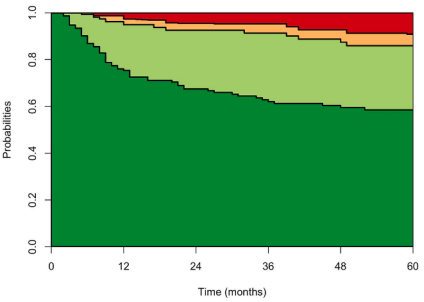
SUBCATEGORY Vb






| Time (Months) | 24 | 36 | 60 |
|---|---|---|---|
| Death of disease | 0.12 | 0.21 | 0.21 |
| Total Laryngectomy | 0.09 | 0.06 | 0.06 |
| Local Recurrence | 0.16 | 0.14 | 0.14 |
| Disease free | 0.62 | 0.59 | 0.59 |

SUBCATEGORY VI




| Time (Months) | 24 | 36 | 60 |
|---|---|---|---|
| Death of disease | 0.05 | 0.05 | 0.09 |
| Total Laryngectomy | 0.03 | 0.04 | 0.05 |
| Local Recurrence | 0.25 | 0.28 | 0.28 |
| Disease free | 0.67 | 0.62 | 0.58 |

**Fig. 4.** Multistate models for each subcategory coupled with the patient's probability to be in each competing disease state at different time points. At 36 months, there is a higher probability of being in a disease-free survival status for subcategories III and VI, while death of disease status is more frequently encountered for Vb, and finally, total laryngectomy probability is higher for category Va followed by Vb. Local recurrence is more prevalent for category VI but it requires less total laryngectomy compared to categories Va and Vb.

diagnostics, along with specialized skills and expertise through a multidisciplinary decision-making process. Suboptimal patient and tumor selection can increase the likelihood of recurrence or the need for multimodal treatments, leading to increased toxicity and higher complication rates. In our study, only a small proportion of patients (9.6 %) required adjuvant treatment, with data in the literature ranging from 2 % to 27.9 % [7,26,36–38,49,50]. These discrepancies may be justified by different patient profiles with an increased nodal burden in some series. However, it demonstrates that TOLMS can be applied as unimodal treatment in a large percentage of intermediate-advanced glottic SCC, especially when careful preoperative patient selection is performed.

Incorporating subcategorization of tumors based on specific three-dimensional anatomical involvement may aid in prognostication and treatment selection, guiding personalized therapeutic strategies while preserving laryngeal function. Among our patients, only 3 had a permanent tracheostomy, and 2 remained gastrostomy-dependent. This trend has been confirmed in other studies, with a range of 0–1.3 % of permanent gastrostomy after TOLMS and 0–2 % of permanent tracheotomy [7,36,38,49,50].

Our results underscore the importance of considering tumor extension beyond conventional TNM staging to predict oncological outcomes. The current study benefitted from collaboration with multiple high-volume referral centers, enhancing the generalizability and robustness of our isoprognostic zones. The retrospective nature of this study also represents its main limitation. However, this should not constrain its applicability to alternative treatment modalities. Rather, it presents an opportunity for an insightful prospective comparative analysis across various therapeutic modalities, particularly within the context of a multidisciplinary tumor board to validate our findings and elucidate the optimal management strategies for T2-T3 glottic tumors.

## Conclusion

TOLMS is confirmed to be a valuable option for intermediate-advanced pT2-T3 glottic SCC, and is associated with favorable oncological outcomes and a high laryngeal preservation rate. In this study, we refined the existing classification by introducing subcategories that are specific to these tumor stages thus facilitating the selection of suitable candidates for TOLMS. Our experience indicates that while tumors with superficial extension show favorable oncologic outcomes, deeper involvement, particularly in the posterior PGS, results in poorer results, highlighting the necessity for targeted and personalized therapeutic approaches. Further prospective and comparative analyses are necessary to validate and optimize such management strategies.

## CRediT authorship contribution statement

**Filippo Marchi:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Francesca Del Bon:** Visualization, Supervision, Investigation, Conceptualization. **Francesco Chu:** Writing – original draft, Investigation, Data curation. **Claudio Sampieri:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Elisa Bellini:** Writing – original draft, Investigation, Data curation. **Davide Lancini:** Supervision, Data curation, Conceptualization. **Stefano Zorzi:** Writing – original draft, Data curation, Conceptualization. **Laura Ruiz-Sevilla:** Writing – original draft, Investigation, Data curation. **Marta De Vecchi:** Writing – original draft, Investigation, Data curation. **Aurora Pinacoli:** Writing – original draft, Investigation, Data curation, Conceptualization. **Giacomo Pietrobon:** Writing – original draft, Investigation, Data curation. **Rosa-Delia Ramirez:** Writing – original draft, Investigation, Data curation. **Pietro Benzi:** Writing – original draft, Investigation, Data curation. **Jacopo Di Domenico:** Writing – original draft, Investigation, Data curation. **Francesc Xavier Aviles-Jurado:** Supervision, Methodology, Investigation. **Marta Filauro:** Validation, Supervision, Data curation, Conceptualization. **Gabriele Zigliani:** Writing – original draft, Investigation, Data curation. **Francesco Mora:** Writing – original draft, Investigation, Data curation. **Alessandra Sordi:** Writing – original draft, Investigation, Data curation. **Claudia Montenegro:** Writing – original draft, Investigation, Data curation. **Isabel Vilaseca:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Cesare Piazza:** Writing – review & editing, Validation, Supervision, Conceptualization. **Mohssen Ansarin:** Writing – review & editing, Validation, Supervision, Conceptualization. **Giorgio Peretti:** Writing – review & editing, Validation, Supervision, Conceptualization.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgement

Given the subject matter and the scope of our study, we cannot but take this opportunity to commemorate and acknowledge the recent passing of Dr. Wolfgang Steiner, one of the pioneers in the field of transoral laser microsurgery. His contributions have been invaluable in shaping the landscape of laryngeal cancer treatment, and his legacy continues to inspire advancements in surgical techniques and patient care. Dr. Steiner's pioneering work laid the foundation for the current knowledge, the development and refinement of TOLMS, revolutionizing the approach to countless laryngeal cancer patients worldwide. His vision and dedication will be sorely missed but enduringly remembered within the medical community.

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