The Laryngoscope

pT3 N0 Laryngeal Squamous Cell Carcinoma: Oncologic Outcomes and Prognostic Factors of Surgically Treated Patients

Francesco Mattioli, MD; Matteo Fermi, MD; Giulia Molinari, MD; Vincenzo Capriotti, MD; Gabriele Melegari, MD; Federica Bertolini, MD; Elisa D'Angelo, MD; Giancarlo Tirelli, MD; Livio Presutti, MD

Objectives/Hypothesis: To assess the disease control, survival rates, and prognostic factors of exclusive surgical treatment for patients with pT3 N0 laryngeal squamous cell carcinoma (LSCC).

Study Design: Multicentric retrospective cohort study.

Methods: Multicentric retrospective case series of previously untreated patients with pT3 R0N0 LSCC, who received exclusive surgery between 2011 and 2019. Tumor location; subsite involvement; grading; and lymphatic, vascular, and perineural invasion were reported. Overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) were measured.

Results: Fifty-four patients (mean age 67.1; male sex 83.3%; mean follow-up period 37 months) underwent total laryngectomy (48.1%) or partial laryngectomy (51.9%). Ipsilateral or bilateral neck dissection was performed in 46 (85.2%) cases. Perineural invasion was more frequent in case of supraglottic involvement than glottic involvement (85.7% vs. 14.3%, $P = .03$). Five (9.3%) patients experienced recurrence (3 local recurrences, 1 nodal recurrence, 1 distant recurrence). Rate of recurrence differed between glottic (0%), supraglottic (80%), and transglottic (20%) tumors ($P = .01$), with a lower risk yielded by glottic involvement (odds ratio [OR], 0.05, 95% confidence interval [95% CI], 0.01–0.56, $P = .01$). A higher risk was recorded in case of perineural invasion (OR, 66.0, 95% CI, 1.41–3085.3, $P = .03$). The OS, DSS, and DFS were 79.6%, 96.3%, and 90.7%, without differences regarding the type of surgery. The DFS was lower in case of supraglottic involvement when compared to purely glottic LSCC (83.9% vs. 100%, $P = 0.02$).

Conclusions: Exclusive surgery is a safe option for patients with pT3 R0N0 LSCC. Adjuvant treatments or closer follow-up monitoring might be considered in case of supraglottic involvement or perineural invasion.

Key Words: Larynx, laryngeal cancer, laryngectomy, radiotherapy, head and neck cancer.

Level of Evidence: 4

***Laryngoscope*, 00:1–7, 2021**

INTRODUCTION

Laryngeal carcinoma is one of the most common malignant tumors of the upper aerodigestive tract. Currently, conventional management of laryngeal squamous cell carcinoma (LSCC) includes surgery, radiotherapy (RT), and chemoradiotherapy (CRT), either alone or in combination.

In particular, the treatment of locally advanced LSCC (T3 and T4 stages) consists of upfront surgery (total laryngectomy, transoral laser microsurgery [TLM],[1,2] or open partial horizontal laryngectomy [OPHL][3]) possibly followed by RT or laryngeal preservation strategies (RT alone or concurrent CRT).[4]

The guidelines for locally advanced tumors with negative neck lymph node (N0) are not clear regarding the adjuvant treatment after surgery.[5] The National Comprehensive Cancer Network (NCCN) guidelines (version 02.2020) recommend postoperative RT for patients with pT4 N0 disease, close or positive margins, and adverse pathological features, while for those with pT3 disease, the adjuvant treatment is optional.[6] Although various RT techniques have been developed to reduce adverse effects, RT may affect functional outcomes after laryngeal surgery, such as dysphagia, tissue necrosis, laryngeal edema, xerostomia, fibrosis, and eventually decrease quality of life.[7] The change in the laryngeal appearance after RT precludes follow-up clinical examination and endoscopy, since the presence of persistent edema may raise the suspicion of persistent cancer.[8] Therefore, the value of adjuvant treatment is counterbalanced by the potential toxicity, and careful selection of patients requiring additional treatment is essential.

From the Otorhinolaryngology Head and Neck Surgery Department (F.M., M.F., G.M., L.P.), University Hospital of Modena, Modena, Italy; Department of Otorhinolaryngology and Head and Neck Surgery (V.C., G.T.), University of Trieste, Cattinara Hospital, Trieste, Italy; Anesthesiology and Reanimation Department (G.M.), University Hospital of Modena, Modena, Italy; Department of Oncology and Hematology (F.B.), University Hospital of Modena, Modena, Italy; and the Radiation Oncology Unit (E.D.), University Hospital of Modena, Modena, Italy.

Additional supporting information may be found in the online version of this article.

Editor's Note: This Manuscript was accepted for publication on March 15 2021.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Matteo Fermi, MD, Department of Otorhinolaryngology, Head & Neck Surgery, University Hospital of Modena, Italy. E-mail: matteo.fermi.med@gmail.com

DOI: 10.1002/lary.29528

This multicentric research studied the disease control and survival rates of a group of surgically treated pT3 N0 glottic and supraglottic LSCCs, which did not receive adjuvant treatment. The demographic, clinical, and pathologic parameters were assessed to detect prognostic factors related to the oncologic outcome.

MATERIALS AND METHODS

Patients

Patients who underwent surgical treatment for LSCC with curative intent at the Department of Otorhinolaryngology-Head and Neck Surgery of the University Hospital of Modena and Trieste between 2011 and 2019 were retrospectively reviewed. For this kind of retrospective investigation, the Institutional Review Board (IRB) of the University Hospital of Modena and Trieste does not require a formal ethical assessment. The study was performed according to the Declaration of Helsinki. This study included previously untreated patients that had a final pathological stage of disease pT3 R0 (negative resection margins) N0, according to the eight TNM staging classification.[9]

Patients were considered N0 if: 1) they did not have clinical evidence of neck metastases at the preoperative evaluation (cN0) and did not undergo neck dissection (ND); 2) they had evidence of neck metastases at the preoperatory evaluation (cN+), underwent selective ND and no node metastases were present at pathological evaluation (pN0); 3) they were cN0, underwent ND in light of the extent and location of the disease (cT3 and cT4a, supraglottic involvement, preoperative vocal fold hypomobility or fixation), and pathological examination confirmed pN0 status.

Nonresectable tumors, distant metastases, microscopically or macroscopically involved resection margins (either R close—less than 5 mm of free tissue between the margin and the tumor, R1 - microscopic evidence of tumor on the surgical margin or R2—macroscopic evidence of tumor on the surgical margin), pN+ status, and adjuvant treatment were excluded. Frozen sections were assessed as extra resections to determine the final margin status.

Specifically, among the pT3 N0 patients treated in the selected period, 11 were excluded for having undergone postoperative RT for the following reasons: 3 because of R status (Rclose and R1); 8 because of recurrent disease after laser cordectomy or partial laryngectomy. In particular, there were two supraglottic LSCC with perineural (PN) invasion, both with positive margins.

Preoperative videolaryngoscopy with narrow band imaging and computed tomography (CT) were routinely executed.

The type of surgery was chosen according to the extension of the disease and the patient-related findings (i.e. age, comorbidities, laryngeal exposure), following the NCCN guidelines.[6]

The local ethical committees of the University Hospital of Modena and Trieste do not perform a formal ethical assessment for such retrospective investigations.

Pathological features

The exact tumor extension and the involvement of specific anatomical subsites were assessed through the review of the pathological reports. The grading of the disease was classified according to the World Health Organization Classification of Tumors, as low grade (G1), intermediate grade (G2), and high grade (G3).[10] Microscopic evidence of lymphatic (L), vascular (V), and perineural (PN) invasion was also considered.

Postoperative follow-up

Patients were followed up three times per year during the first 2 years, and twice a year for the following 3 years postoperatively. Neck ultrasound was performed every 6 months, while CT or magenetic resonance imaging was scheduled once a year, during a 5-year follow-up. Local, regional, and distant recurrences were recorded, and the salvage treatments were documented. Death and its causes were also considered. The tracheostomy dependence (solely assessed in the partial laryngectomy subgroup) and the gastrostomy dependence rates were also analyzed.

Statistical analysis

All analyses were conducted with GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA) and IBM SPSS Statistics version 26.0 (IBM Corp, Armonk, NY). Categorical variables were presented as rates (%), while continuous variables as mean $\pm$ SD or median and interquartile range (IQR) depending on normality of distribution, which was determined via the Kolmogorov–Smirnov test. Chi-square test or Fisher exact test was used to compare categorical variables and odds ratios (OR) for variables affecting survival or recurrence were obtained.

Overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) were measured.

The endpoints were obtained as the length of time from the date of diagnosis to the date of i) death by any cause (OS); ii) death from the disease (DSS); iii) the local, regional, or distant recurrence (DFS). OS, DSS, and DFS curves were described with Kaplan–Meier graph product limit estimate. A log-rank test was used to compare Kaplan–Meier estimates among the different subcategories. To evaluate the adverse prognostic factors, univariate and multivariate logistic regression and Cox proportional hazard model were built. The estimated hazard ratios (HR) and 95% confidence intervals (CI) were calculated. A two-sided P-value of $<.05$ was considered statistically significant.

RESULTS

Patients

A total of 54 patients resulted eligible for the present study. The patient's demographic and disease features are reported in Table I. Mean age at surgery was 67.1 (range 46–84 years). All tumors were limited to the larynx and the definition of pT3 stage was distributed as follows (at least one of the mentioned features per patient):

- For tumors with supraglottic involvement: 9 cases showed vocal cord fixation; 1 invasion of postcricoid area; 12 invasion of the pre-epiglottic space; 12 invasion of paraglottic space; and 5 invasion of the inner cortex of the thyroid cartilage
- For tumors with glottic involvement: 26 patients had vocal cord fixation; 27 invasion of paraglottic space; and 8 invasion of the inner cortex of the thyroid cartilage.

Comparing clinical and pathological staging, 4 (7.4%) lesions appeared to have been erroneously staged as cT4a, while 7 (12.9%) as cT1a (2 cases) and cT2 (5 cases). In total, 50 (92.6%) patients had been classified

TABLE I.
Patients' General Information.

	n (%)
Gender	
Male	45 (83.3)
Female	9 (16.7)
Ethnicity	
Caucasian	53 (98.1)
African	1 (1.9)
Smoking history	
Active	23 (42.6)
Previous	29 (53.7)
N/A	2 (3.7)
Pack-years	
≤20	9 (16.7)
20–59	25 (46.3)
≥60	14 (26)
N/A	6 (11)
Alcohol consumption	
Yes	19 (35.2)
No	31 (57.4)
N/A	4 (7.4)
cT stage	
cT1a	2 (3.7)
cT2	5 (9.2)
cT3	43 (79.7)
cT4a	4 (7.4)
cN stage	
cN0	50 (92.5)
cN1	1 (1.9)
cN2b	2 (3.7)
cN2c	1 (1.9)

n = number of patients; N/A = data not available.

as cN0, whereas the remaining 4 (7.4%) classified as cN+, resulted pN0 after ND.

The distribution of cancer location in the laryngeal sites and the details of involved anatomical subsites, according to the pathological report, are reported in Figure 1. Twenty-six (48.1%) patients underwent total laryngectomy, whereas the remaining 28 (51.9%) were treated by partial laryngectomy, in particular OPHL type 1, 2, 3[3] and horizontal glottectomy.[11,12] The distribution of the enrolled patients according to the treatment choice is resumed in Table II.

ND was simultaneously performed in 46 (85.2%) cases, ipsilateral in 20 (43.5%) cases, and bilateral in the remaining 26 (56.5%). Eight patients (14.8%) did not undergo ND, of which 4 (7.4%) were glottic and 4 (7.4%) had supraglottic involvement. Among the latter, 1 was staged as cT1a cN0 and 2 were staged as cT2 cN0, thus ND was not indicated. The remaining patient had a cT3cN0 tumor, and was 83 years old at the time of diagnosis, so after multidisciplinary discussion it was decided to limit the extent and time of surgery to T.

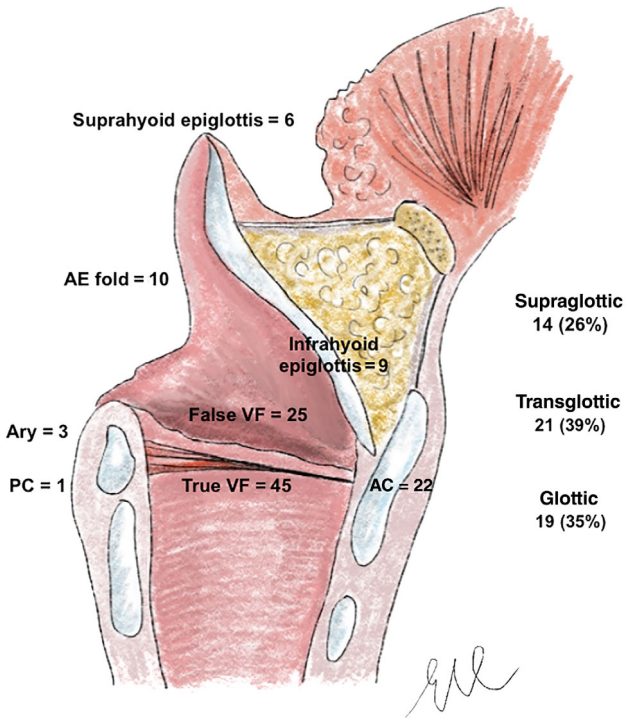

Fig 1. Distribution of laryngeal site and subsite involvements according to clinical and pathological features. Percentages on the total number of patients are reported for sites involvement only, since more than one subsite could be involved at the same time. AC = anterior commissure; AE = aryepiglottic; VF = vocal fold; PC = posterior commissure. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Postoperative course and treatment-related morbidity

Four patients (15.3%) among the total laryngectomy group had to undergo revision surgery for persistent salivary fistula, complicated by hemorrhage in two of them. The mean hospital stay was 27 days (range 9–95 days).

At last follow-up, the tracheotomy-dependance rate among the partial surgery group was 0%. Fifty-three patients (98.1%) fully recovered oral intake diet. One patient only remained dependent on enteral nutrition via gastrostomy after OPHL-2a (overall gastrostomy-dependence rate of 1.9%).

Clinical and pathological features of T3 N0 laryngeal cancers

Data on the local extension and pathological behavior of pT3 N0 tumors were assessed (Supplementary material 1). Most of the tumors (57, 90.4%) were confined to the anterior compartment of the larynx. The anterior commissure was involved in 37 (77%) patients. Only 6 tumors (9.6%) were found to involve the posterior laryngeal compartment, behind a vertical plane tangential to the arytenoid vocal process and perpendicular to the ipsilateral thyroid lamina according to Succo et al.[13] The univariate analysis showed a significantly lower risk for recurrence for patients with glottic involvement (P = .01) with an odds ratio of 0.05 (95% CI 0.01–0.56). On the

Table II.
Distribution of Enrolled Patients According to Surgical Strategy.

Variables	*n* (%) Total laryngectomy	*n* (%) Partial laryngectomy	*P*
Sex			
Male	25 (55.6)	20 (44.4)	**.025**
Female	1 (11.1)	8 (88.9)	
Age			
<65	11 (42.3)	15 (57.7)	.408
≥65	15 (57.6)	13 (46.4)	
Tumor extension			
Supraglottic	6 (42.9)	8 (57.1)	.855
Glottic	9 (47.4)	10 (52.6)	
Transglottic	11 (52.4)	10 (47.6)	
Extension to posterior compartment			
No	22 (46.8)	25 (53.2)	.699
Yes	4 (57.1)	3 (42.9)	
Vocal fold motility			
Normal	5 (23.8)	16 (76.2)	**.007**
Hypomobile	2 (40)	3 (60)	
Fixed	19 (67.9)	9 (32.1)	

n = number of patients.
Bold values indicates $p < 0.05$.

contrary, the other tumor's subsites (i.e. anterior commissure, posterior commissure, false vocal cords, infrahyoid and suprahyoid epiglottis arytenoids, and aryepiglottic folds) did not show statistically significant association with recurrence.

There was a statistically significant difference between the glottic (n = 0; 0%), supraglottic (n = 4; 80%) and transglottic (n = 1; 20%) recurrence rate (P = .014). Moreover, the distribution of the histopathological adverse features (i.e. perineural and lymphovascular invasion) was compared between the supraglottic and glottic LSCC, as shown in Table III. Perineural invasion (PNI) was significantly more frequent in the supraglottic subgroup (P = .032).

Follow-up and survival outcomes

The mean observation period of this study was 37 months. The OS, DSS, and DFS of the whole study population was 79.6%, 96.3%, and 90.7%, respectively (Figure 2).

During the follow-up period, 5 (9.3%) patients experienced recurrence (4 supraglottic and 1 transglottic SCC). Three (5.5%) patients had local recurrence, 1 (1.9%) patient had nodal recurrence, and the remaining patient (1.9%) had pulmonary metastases. All local recurrences occurred in the OPHL group and were salvaged by total laryngectomy with postoperative RT. The patient who had right nodal recurrence had undergone bilateral selective ND (II–III–IV levels) concomitant to total laryngectomy for a right supraglottic tumor, and was rescued by radical ND and postoperative RT. The patient with distant metastasis underwent only palliative care. Both the regional and distant metastases occurred in the total laryngectomy subgroup. At last follow-up, 43 (79.6%) patients were alive without evidence of disease, 9 (16.7%) had died of unrelated causes, and 2 (3.7%) died of disease.

TABLE III.
Distribution of Adverse Histopathologic Features According to Disease Location.

Variables	n (%) Supraglottis	n (%) Glottis	*P*
Perineural invasion (PN)			
Yes	9 (90)	1 (10)	**.032**
No	22 (50)	22 (50)	
Lymphatic invasion (L)			
Yes	0 (0)	1 (100)	.426
No	31 (58.5)	22 (41.5)	
Vascular invasion (V)			
Yes	5 (100)	0 (0)	.064
No	26 (53.1)	23 (46.9)	
PN/L/V			
Yes	12 (85.7)	2 (14.3)	**.013**
No	19 (47.5)	21 (52.5)	

For the total laryngectomy group (26 pts—48.1%), the OS, DSS, and DFS were 65.4% (mean ± SD: 41.9 ± 23.1 months), 92.3% (mean ± SD: 43.2 ± 25 months), and 92.3% (mean ± SD: 43.2 ± 25 months), respectively. For pT3 N0 patients treated with partial laryngectomy (28 pts—51.9%), the OS, DSS, and DFS were 92.9% (mean 4.4–93.8 ± SD: 25.1 months), 100% (mean ± SD: 32.1–25.1 months), and 89.3% (mean ± SD: 28.6 ± 25.1 months), respectively (Figure 3). No statistically significant differences in terms of survivals were found at the log-rank test in relation to the type of surgery. The supraglottic extension significantly influenced the DFS, whereas no statistically significant differences were reported for the OS and DSS. The DFS was significantly lower for pT3 N0 patients with supraglottic disease or supraglottic involvement with respect to those with purely glottic LSCC (DFS: 83.9% vs. 100% P = .02) (Figure 4). At the logistic regression model, patients that showed PNI had a higher chance of recurrence (OR: 66.0, 95% CI: 1.41–3085.3, P = .03), while those with glottic involvement showed the opposite tendency, although not statistically significant (OR: 0.01, 95% CI: 0–1.05, P = 0.05) (Table IV). Cox proportional hazard analysis results are shown in Supplementary material 2.

DISCUSSION

The optimal treatment of patients with T3 (LSCC) is highly debated.[14] The standard of care is controversial with CRT, RT alone, and organ preserving surgical techniques (i.e. TLM, OPHL, and total laryngectomy), all claiming to offer equally effective outcomes to patients. The American Society of Clinical Oncology recommends for T3 cancer mainly concurrent CRT protocols. However, there are several experiences reporting that surgical

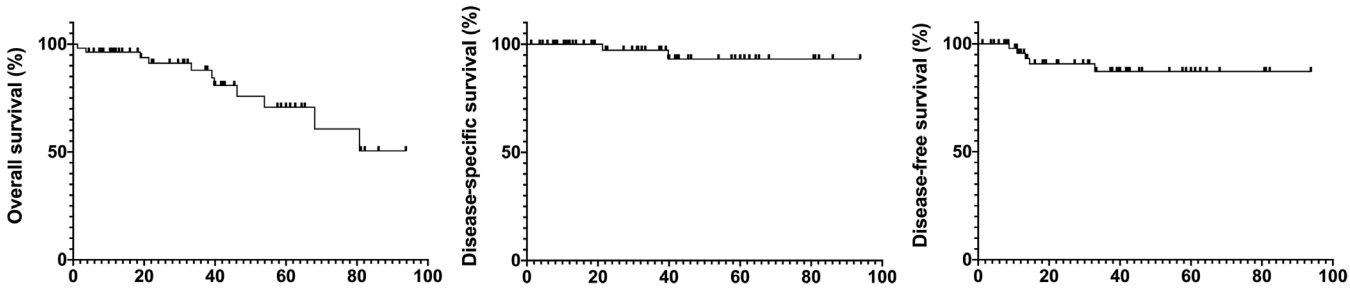

Fig 2. Panel showing overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) of the whole patient's cohort.

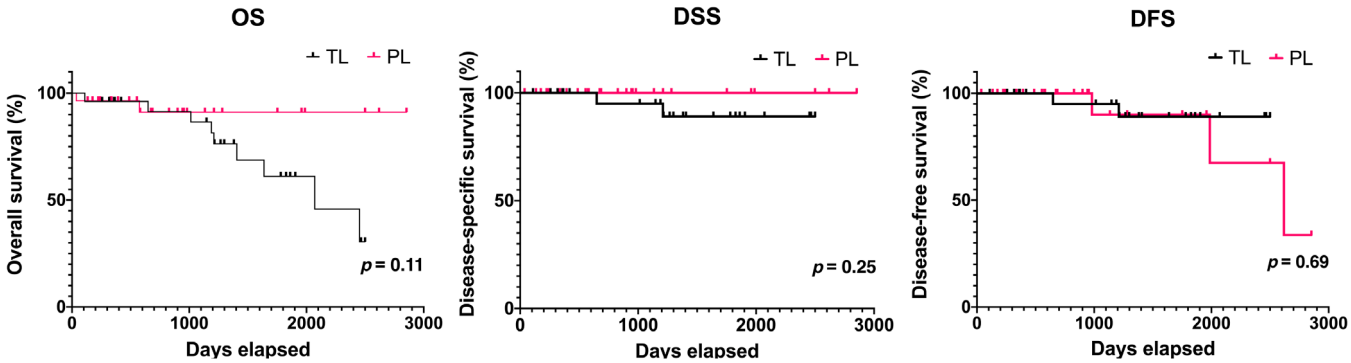

Fig 3. Panel showing overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) of the whole patient's cohort along with the surgical strategy. PL, partial laryngectomy; TL total laryngectomy. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

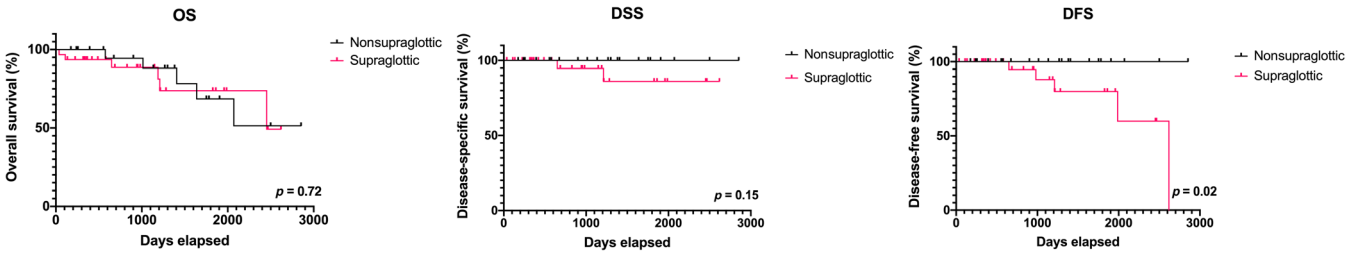

Fig 4. Panel showing overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) of the whole patient's cohort along with the disease extent. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

therapy led to better survival outcomes than nonsurgical therapy for patients with advanced LSCC.[15,16] In addition, some epidemiological studies reported a decline in survival for patients with LSCC, possibly attributable to the increased use of RT and CRT protocols.[17,18] RT is considered an important adjunct for most of head and neck tumors, since it can address the residual microscopic tumor burden after the excision, but there are several factors related to the laryngeal anatomic disease that may reduce the likelihood of locoregional residual disease,[19] in particular, fascial barriers surrounding larynx that provide natural fence to tumor spread, the relatively poor lymphatic network from the glottis, and the wide margins achievable with interventions like total laryngectomy.[19] Differently from other head and neck tumor subsites, postoperative RT is not recommended for patients with T3 N0-1 glottic cancer treated with total laryngectomy or T3 N0 glottic cancer treated with partial laryngectomy, in the absence of other high-risk features (i.e. positive or close margins, close margins, PNI, vascular invasion, lymphatic invasion).[6] However, T3 N0 supraglottic cancers treated with partial or total laryngectomy, postoperative RT (or CRT) should be discussed, especially if high-risk features are present.[6] Despite these recommendation for selective use of postoperative RT in patients with locally advanced LSCC, many patients who underwent surgery are still treated with adjuvant RT.[19] Several authors have already questioned the role of postoperative RT for patient with T3 N0-1 LSCC treated with primary surgery,[5,20,21] mainly because RT may deeply affect functional outcomes after laryngeal surgery, eventually decreased quality of life.[7] Moreover, the change in the laryngeal appearance might undermine follow-up clinical examination and endoscopy.[8,16] Therefore, careful

TABLE IV.
Logistic Regression Model for Disease Recurrence.

Variables	Recurrence HR (95% CI)	*P*
Age	1.24 (0.96–1.60)	.10
Male	Ref	—
Female	0.08 (0–18.8)	.37
Supraglottic involvement	Ref	—
Glottic involvement	0.01 (0–1.05)	.05
Total laryngectomy	Ref	—
Partial laryngectomy	16.8 (0.06–5124.0)	.33
PN0[a]	Ref	—
PN1	66.0 (1.41–3085.3)	.03
LMV0[b]	Ref	—
LMV1	1.26 (0.02–83.3)	.91

[a]PN: perineural invasion.
[b]LMV: lymphovascular invasion.

selection of patients requiring additional treatment is essential.

In this study, we evaluated the survival outcome of a population of glottic and supraglottic pT3 pN0 LSCCs to investigate whether total laryngectomy and partial laryngectomy alone represented an adequate treatment modality. More importantly, we aimed to underline the prognostic factors related to the oncologic outcome of these tumors.

The OS, DSS, and DFS of the whole study population were 79.6%, 96.3%, and 90.7%, respectively. Interestingly, there were no statistically significant differences in terms of these rates between the total laryngectomy and the partial laryngectomy (i.e. OPHL or horizontal glottectomy) groups. The survival outcomes reported in the present case series are comparable to other case series reported in the literature.[13,14,22] However, in most of them, adjuvant RT is variably employed and reported outcomes might be misunderstood due to the multimodal treatment. In addition, most of the studies contained stage III and IV "advanced" LSCCs with different combinations of tumor extension and lymph node involvement.[23,24] We believe that T3 laryngeal cancers represent a distinct subset with moderate tumor load, especially if without nodal involvement, that requires a more individualized treatment.

Moreover, experiences regarding histopathologically confirmed T3 N0 LSCCs are still lacking, since most of the published case series include cT3 N0 LSCCs.[14]

Kim et al. retrospectively studied 60 patients with T3-4 LSCC evaluating the impact of the postoperative RT on the 5-year cumulative OS, DSS, and DFS, reporting 84%, 92.1%, and 92.6%, respectively[25] without statistically significant difference between the patients who underwent adjuvant RT and those undergoing primary surgery alone. However, the authors did not differentiate the surgical strategy (total vs. partial laryngectomy) or the histopathologic adverse features (PNI, L, V). In the present study, the recurrence rate was significantly lower in the glottic SCCs than for the supraglottic SCCs. This finding seems to be reinforced by the analysis of the adverse histopathologic features distribution, since the rate of PNI was significantly higher in the supraglottic group.

Similarly, the rate of V was also high, even though it did not reach statistical significance (P = .064). At the logistic regression model, PNI was also significantly (P = .039; OR 9.0; CI 95% 1.26–63.89) associated with the development of recurrent disease during the follow-up period. Thus, adverse histopathologic features (i.e. PNI and V) should be thoroughly considered as a possible indication for adjuvant RT for pT3 N0 LSCCs.

Zhou et al. conducted a retrospective study on a total of 202 T3 supraglottic SCCs stating that partial laryngectomies can achieve satisfactory outcomes.[20] However, their 5-year OS, DSS, and DFS were 73.4%, 73.4%, and 64.5%, respectively,[20] slightly worse than the ones herein reported for supraglottic patients. Nevertheless, all the local recurrences of this cases series occurred in LSCCs with supraglottic extension treated with OPHLs and, even if not reaching statistical significance, presumably some of those could have been prevented by performing up-front total laryngectomy. Thus, in such cases, a closer postoperative monitoring would be advised due to a higher risk of local recurrence.

On the other hand, the oncologic outcomes achieved for pT3 glottic LSCCs were satisfactory, independent from the chosen surgical strategy, even though no postoperative RT was administered. Our data agree with those reported by Session et al. that showed no significant difference in the OS and DSS of cT3 N0 glottic SCCs between several treatment groups (total laryngectomy, total laryngectomy with adjuvant RT, and definitive RT).[22]

Following the NCCN guidelines, when considering the possibility for occult nodal metastasis in cT3 LSCC, elective ND would be recommended.[6] Accordingly, in our case series, ND was performed in 85.2% of the cases. Considering the supraglottic subgroup of tumors, none experienced recurrence if bilateral or unilateral (all tumors limited to one side of the larynx) elective ND was performed. Among those who (4 patients) did not undergo ND, none developed nodal recurrence. Since supraglottic tumors are known to be at a higher risk of nodal metastases, and it has been reported that occult metastases are present in up to 26% of the cN0 patients, with an increase by pT category (from 10% in pT2 to 40% in pT4), a more aggressive policy including bilateral ND even in cN0 patients is advocated, especially if adjuvant RT is not administered.[26] This underlines that indication to neck management should take both tumor stage and tumor location into account. The treatment efficacy of additional adjuvant RT for a node-eliminated neck area requires further debate.[25,27] High nodal yield is related to better survival outcomes after ND. Thus, the removal of micrometastasis proportionally increases with the resection of regional lymph nodes. This issue has not been addressed in the present study, since the cohort size and the amount of the selected events (i.e. death and recurrence) are not large enough to assess the impact of such

covariate in influencing the oncologic outcome. Further studies will guarantee the understanding of the role of nodal yield on survival and disease-control of LSCCs.

This study has some limitations. First, despite being multicentric, the number of included patients is low, possibly affecting the statistical power of our analyses. This could be attributed to the highly selective inclusion criteria and the relative rarity of pT3 pN0 tumors, as underlined by other authors, especially those with supraglottic involvement.[25,27]

The patient selection process was designed to collect a group of patients with homogeneous tumor stage, consistently with the aim of the present research of assessing the disease control and survival rates of a pathologic condition for which the best treatment strategy, as well as the role of adjuvant RT, is still debated. Moreover, the only clinically relevant and statistically significant difference found among the total versus partial laryngectomy groups was the preoperative vocal fold mobility (Table II), demonstrating that the study population subgroups were also uniform.

Second, the retrospective design made the results prone to recall bias or misclassification bias. Since there are no reliable guidelines to choose among total laryngectomy and OPHLs, a selection bias for the surgical strategy could be considered, as related to the experience of the two centers involved in the present study. Eventually, survival trends would need to be confirmed through a longer follow-up period, ideally of 5 years.

To define the ideal management of T3 N0 LSCC, different factors must be taken into account, preferably through studies with larger cohorts, prospective setting or randomization of various treatment modalities, including nonsurgical strategies.

CONCLUSIONS

The oncologic outcome of pT3 N0 LSCCs treated by primary open surgery is satisfactory, even without adjuvant treatment. Patients treated by total laryngectomy and OPHLs showed a comparable OS, DSS, and DFS. A significantly higher rate of recurrence was reported in patients with purely supraglottic SCC or supraglottic extension. PNI, which was more frequently found in supraglottic cancers, was associated with a higher rate of recurrence at the logistic regression analysis. These features might depict a specific subgroup of patients that deserves adjuvant RT or a closer follow-up monitoring, especially for supraglottic cancers treated with less-than-total laryngectomy.

BIBLIOGRAPHY

1. 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.
2. 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.
3. Succo G, Peretti G, Piazza C, et al. Open partial horizontal laryngectomies: a proposal for classification by the working committee on nomenclature of the European Laryngological Society. *Eur Arch Otorhinolaryngol* 2014; 271:2489–2496.
4. Bussu F, Miccichè F, Rigante M, et al. Oncologic outcomes in advanced laryngeal squamous cell carcinomas treated with different modalities in a single institution: A retrospective analysis of 65 cases. *Head Neck* 2012; 34:573–579.
5. Graboyes EM, Zhan KY, Garrett-Mayer E, Lentsch EJ, Sharma AK, Day TA. Effect of postoperative radiotherapy on survival for surgically managed pT3N0 and pT4aN0 laryngeal cancer: Analysis of the National Cancer Data Base: PORT for T3-T4N0 Laryngeal SCC. *Cancer* 2017;123: 2248–2257.
6. National Comprehensive Cancer Network. NCCN guidelines for head and neck cancer care. Available at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck_blocks.pdf Accessed August 9, 2020.
7. Laccourreye O, Hans S, Borzog-Grayeli A, Maulard-Durdux C, Brasnu D, Housset M. Complications of postoperative radiation therapy after partial laryngectomy in supraglottic cancer: a long-term evaluation. *Otolaryngol Head Neck Surg* 2000;122:752–757.
8. Sanguineti G, Adapala P, Endres EJ, et al. Dosimetric predictors of laryngeal edema. *Int J Radiat Oncol Biol Phys* 2007;68:741–749.
9. Amin MB, Edge S, Greene F, et al., eds. *AJCC Cancer Staging Manual*. 8th ed.: Cham, Switzerland: Springer; 2017.
10. El-Naggar AK, JKC C, Grandis JR, Takata T, Slootweg PJ, eds. *WHO Classification of Head and Neck Tumours*. 4th ed.: Lyon, France: International Agency for Research on Cancer; 2017.
11. Calearo CV, Teatini G. Horizontal Glottectomy. *Laryngoscope* 1978;88: 1529–1535.
12. Alicandri-Ciufelli M, Molteni G, Mattioli F, et al. Horizontal glottectomy: is it an out-of-date procedure? *Am J Otolaryngol* 2011;32:578–582.
13. 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.
14. Riga M, Chelis L, Danielides V, Vogiatzaki T, Pantazis T-L, Pantazis D. Systematic review on T3 laryngeal squamous cell carcinoma; still far from a consensus on the optimal organ preserving treatment. *Eur J Surg Oncol* 2017;43:20–31.
15. Megwalu UC, Sikora AG. Survival outcomes in advanced laryngeal cancer. *JAMA Otolaryngol Head Neck Surg* 2014;140:855–860.
16. Al-Gilani M, Skillington SA, Kallogjeri D, Haughey B, Piccirillo JF. Surgical vs nonsurgical treatment modalities for T3 glottic squamous cell carcinoma. *JAMA Otolaryngol Head Neck Surg* 2016;142:940.
17. Hoffman HT, Porter K, Karnell LH, et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. *Laryngoscope* 2006;116:1–13.
18. Cosetti M, Yu G-P, Schantz SP. Five-year survival rates and time trends of laryngeal cancer in the US population. *Arch Otolaryngol Head Neck Surg* 2008;134:370–379.
19. Cervenka BP, Rao S, Farwell DG, Bewley AF. Efficacy of laryngectomy alone for treatment of locally advanced laryngeal cancer: a stage- and subsite-specific survival analysis. *Clin Otolaryngol* 2018;43:544–552.
20. Zhou J, Zhou L, Tao L, et al. Oncological outcomes of surgical treatment for T3 supraglottic laryngeal squamous cell carcinoma patients. *Acta Otolaryngol* 2018;138:1028–1034.
21. Sanguineti G, Vidiri A, Pellini R. Is postoperative radiotherapy routinely indicated after total laryngectomy for pT3N0-1 supraglottic carcinoma? *Oral Oncol* 2020;107:104825.
22. Sessions DG, Lenox J, Spector GJ, et al. Management of T3N0M 0 glottic carcinoma: therapeutic outcomes. *Laryngoscope* 2002;112:1281–1288.
23. Bussu F, Paludetti G, Almadori G, et al. Comparison of total laryngectomy with surgical (cricohyoidopexy) and nonsurgical organ-preservation modalities in advanced laryngeal squamous cell carcinomas: a multicenter retrospective analysis. *Head Neck* 2013;35:554–561.
24. de Vincentiis M, De Virgilio A, Bussu F, et al. Oncologic results of the surgical salvage of recurrent laryngeal squamous cell carcinoma in a multicentric retrospective series: emerging role of supracricoid partial laryngectomy: treatment modalities in recurrent laryngeal SCC. *Head Neck* 2015;37:84–91.
25. 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.
26. Redaelli de Zinis LO, Nicolai P, Tomenzoli D, et al. The distribution of lymph node metastases in supraglottic squamous cell carcinoma: therapeutic implications. *Head Neck* 2002;24:913–920.
27. Bussu F, Almadori G, De Corso E, et al. Endoscopic horizontal partial laryngectomy by CO_2 laser in the management of supraglottic squamous cell carcinoma. *Head Neck* 2009;31:1196–1206.