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The role of adjuvant therapy in pT4N0 laryngectomized patients: Multicentric observational study

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Abstract

Background: To retrospectively evaluate oncological outcomes in two groups of patients with pT4aN0 glottic SCC treated with total laryngectomy (TL) and neck dissection (ND) who underwent postoperative radiotherapy or exclusive clinical and radiological follow-up.

Methods: It includes patients with pT4N0 glottic SCC who underwent TL and unilateral or bilateral ND with or without PORT. Divided in two comparison groups: the first group underwent adjuvant RT (TL-PORT); the second group referred to clinical and radiological follow-up (TL).

Results: PORT was associated with a better OS while no differences were found in terms of DSS. A better local control is achieved when PORT is administered while no differences in terms of regional and distant control rates were found. Bilateral ND positively impacts on the regional control while the PNI negatively impact the regional control.

Conclusions: A tailored PORT protocol might be considered for pT4N0 glottic SCC treated with TL and ND, both considering the ND's extent and presence of PNI.

KEYWORDS

glottis, head and neck neoplasms, laryngeal neoplasms, laryngectomy, radiotherapy, squamous cell carcinoma of head and neck

1 | INTRODUCTION

The optimal treatment of patients with locally advanced laryngeal squamous cell carcinoma (SCC) is still debated.[1–3] Several strategies have been proposed, ranging from different surgical approaches with or without adjuvant treatments to organ-preserving protocols (OPP).[4,5] However, data from the literature show that the former approach achieves better results in terms of oncological outcomes; therefore, for those patients with locally advanced laryngeal cancers (LALCs), total laryngectomy (TL) with uni- or bilateral neck dissection (ND) should be considered the gold standard.[6–8] In these cases, the optimal adjuvant therapy for pT4 lesions with lymph node-negative neck is to our knowledge not universally acknowledged.[9] The dilemma is to incur in an unnecessary overtreatment that does not lead to an effective improvement in terms of oncological outcomes, impacting on laryngeal function and, therefore, quality of life. In fact, in spite of significant technical refinements in delivery of radiotherapy (RT), complications such as xerostomia, mucositis, esophageal fibrosis, and stricture are still relatively frequent.[10–13]

The lack of reliable scientific data also affects guidelines proposed by various agencies. The criteria approved by the Executive Council of the American Head and Neck Society and the American College of Radiology, in fact, recommend postoperative adjuvant radiotherapy (PORT) for patients with pT3 and pT4 laryngeal cancer, while the National Comprehensive Cancer Network (NCCN) treatment guidelines recommend PORT for patients undergoing TL with glottic cancer showing histopathologic adverse features as extracapsular nodal spreading, positive margins, pT4 primary, pN2 or pN3 nodal disease, perineural invasion, or vascular embolism.[14,15] Nevertheless, no prospective or randomized control trials clearly supporting these criteria do exist.

Aim of this study was therefore to retrospectively evaluate oncological outcomes in two groups of patients with pT4aN0 SCC glottic cancer treated with TL and ND, who were addressed by PORT (TL-PORT) or exclusive clinical and radiological follow-up (TL).

2 | METHODS

This is a retrospective national multicentric study performed in 10 Italian tertiary academic centers. The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee (CER Emilia-Romagna: 0026904/21). It includes patients with pT4N0 glottic SCC who underwent TL and uni- or

bilateral ND (selective neck dissection or modified radical neck dissection) with or without PORT between January 2008 and December 2018.

Patients were divided into two groups: the first underwent adjuvant RT (TL-PORT group), while the second was referred to simple clinical and radiological follow-up after surgery for several reasons such as refusal, inability to perform RT due to general conditions, or excessive time elapsed between surgical treatment and the start of RT (TL group).

Postoperative treatment was based on each center local policies. The external beam radiation therapy was delivered either by 3D conformal RT or by intensity-modulated RT (IMRT).

The irradiation delivered 66–60 Gy on tumor bed and 54–30 Gy in 25 fractions (five fractions per week) either on bilateral or ipsilateral neck nodes.

Exclusion criteria were positive neck nodes, histotypes other than SCC, primary SCC of the supraglottis or subglottis, recurrent laryngeal SCC after RT or chemo-RT, follow-up not available or shorter than 3 years, positive surgical margins, and lacking core data (i.e., clinical characteristics at baseline, type and time of outcomes) at medical record analysis.

Primary outcomes were overall survival (OS), disease-free survival (DFS), and disease-specific survival (DSS). Secondary outcomes were local, regional, and distant control rates.

Preoperative study population clinical and radiological features, surgical strategy (i.e., uni-/bilateral ND), and histopathologic characteristics (i.e., laryngeal subsite involvement, tumor grading, perineural and lymphovascular invasion) were retrospectively collected.

2.1 | 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 ± standard deviation (SD) or median and interquartile range (IQR) depending on normality of distribution, which was determined via the Kolmogorov–Smirnov test. Comparisons of datasets of continuous variables with normal distributions were performed with two-tailed Student's *t* test. Paired or independent-samples Student's *t* test was used, as appropriate. Wilcoxon test was performed for datasets with non-normal distributions. Chi-square or Fisher's exact tests were used to compare categorical variables, as appropriate, and odds ratios (OR) for variables affecting survival or recurrence were obtained.

OS, DSS, and DFS were calculated. 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) local, regional, or distant recurrence (DFS). OS, DSS, and DFS curves were represented by Kaplan–Meier graph product limit estimate. A log-rank test was used to compare Kaplan–Meier estimates among different subcategories.

A multivariate Cox proportional hazard model test was run to identify independent prognosticators among factors significantly associated with outcomes at univariate analysis. The estimated hazard ratios (HR) and 95% confidence intervals (CI) were calculated. A two-sided *p*-value of <0.05 was considered statistically significant.

3 | RESULTS

One-hundred and twenty-seven patients treated for laryngeal SCC with pT4aN0 staging were collected by 10 Italian academic institutions.

The whole cohort of patients was controlled for exclusion criteria and the final study population consisted of 105 patients (mean age, 67.5 years ±9.8 SD; range, 54–83). Forty-six patients were treated with TL alone, while the remaining 59 underwent TL-PORT. A selective neck dissection was performed in most of the cases (166/171, 97.1% NDs), while the remaining five NDs were modified radical neck dissections. Postoperative radiotherapy was delivered either by 3D conformal RT (22.2%) or by IMRT (77.8%).

Median delivered radiation dose was 66 and 54 Gy on tumor bed and neck nodes, respectively. Neck nodes were irradiated bilaterally in all patients (95.1%), but two (4.9%) received radiation therapy only on ipsilateral nodes.

Patients' demographics, clinical and histopathologic features distribution are resumed in Table 1.

Median study population follow-up was 50 (43) months. The whole study population OS, DSS, and DFS were 64.8% (95%CI 80.3–105.5), 85.7% (95%CI 112.1–133.1), and 83.8% (95%CI 108.9–131.1), respectively. Seventeen (16.2%) patients experienced recurrence during the follow-up period, being local in 7 (6.2%), regional in 5 (4.8%), and distant in 11 (10.5%) cases. Median time to recurrence was 10.5 (25) months.

Univariate analysis showed that the only factor associated with recurrent disease was perineural invasion ($p = 0.04$; OR 3.03). Unilateral lymph node dissection tended to be associated with a higher risk of recurrence, albeit not reaching statistical significance ($p = 0.07$). However, the lymph node yield was not associated with recurrent disease ($p = 0.34$).

TABLE 1 Summary of patient's features by pT4 pN0 LSCC treatment modality

	All	Treatment modality		*p*-value
		Total laryngectomy	Total laryngectomy + PORT	
Number of subjects (%)	105	46	59	
Age, mean ± SD, years	66.8 ± 10.9	70.1 ± 11.3	64.8 ± 10.1	**0.014**
Male, *n* (%)	92 (87.6)	40 (87.0)	52 (88.1)	0.856
Bilateral tumor, *n* (%)	57 (54.3)	17 (37.0)	40 (67.8)	**0.002**
Bilateral neck dissection, *n* (%)	69 (65.7)	19 (41.3)	50 (84.7)	**<0.001**
Lymph node yield, mean ± SD	51.2 ± 30.7	38.7 ± 28.9	60.7 ± 28.7	**<0.001**
Central compartment (VI-VII) dissection, *n* (%)	52 (51.0)	23 (51.1)	29 (50.9)	0.981
Pharyngocutaneous fistula, *n* (%)	12 (12.8)	5 (11.4)	7 (14.0)	0.702
Outer thyroid cartilage cortex invasion, *n* (%)	40 (38.1)	16 (34.8)	24 (40.7)	0.537
Prelaryngeal soft tissue invasion, *n* (%)	73 (69.5)	31 (67.4)	42 (71.2)	0.675
Anterior commissure involvement, *n* (%)	80 (77.7)	38 (84.4)	42 (72.4)	0.146
Subglottis involvement, *n* (%)	53 (50.5)	25 (54.3)	28 (47.5)	0.484
Posterior to the magic line[a]	38 (38.0)	17 (38.6)	21 (37.5)	0.907
Lymphovascular infiltration, *n* (%)	41 (39.8)	16 (34.8)	25 (43.9)	0.349
Perineural infiltration, *n* (%)	50 (48.5)	18 (40.0)	32 (55.2)	0.126
Follow-up duration, mean ± SD, months	52.1 ± 30.9	51.3 ± 30.6	54.3 ± 31.6	0.630

Note: The results which are statistically significant are marked in bold.
Abbreviation: PORT, postoperative radiotherapy.
[a]Plane perpendicular and tangential to the vocal process of arytenoid cartilages.

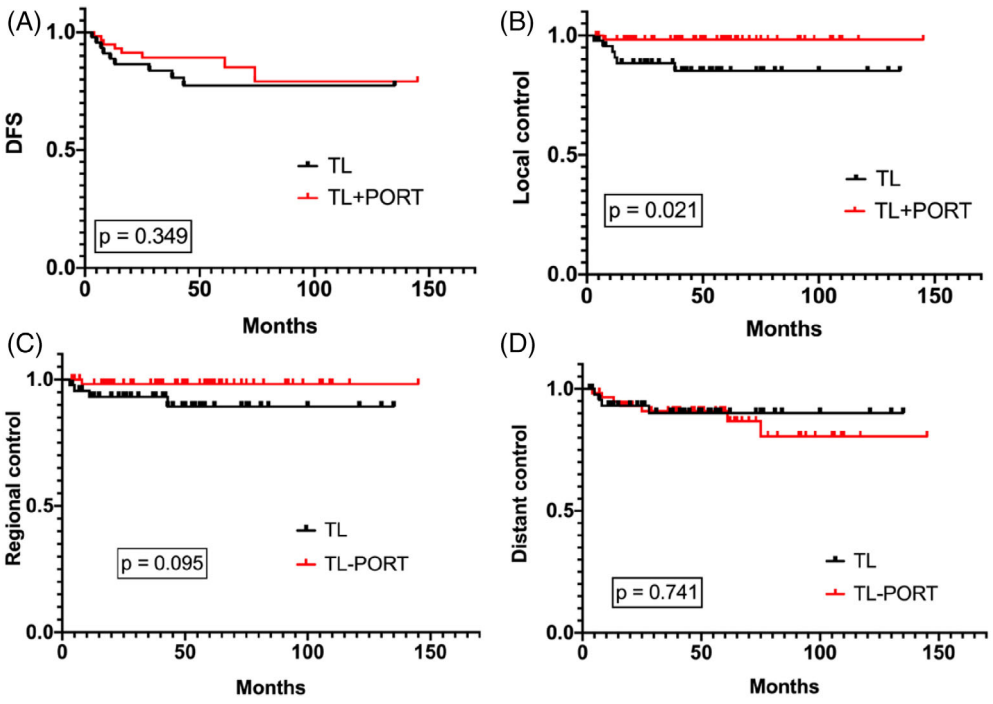

FIGURE 1 Kaplan–Meier analysis of (A) disease specific survival (DSS) comparing TL-PORT and TL group; (B) local control (LC) comparing TL-PORT and TL group; (C) regional control (RC) comparing TL-PORT and TL group; (D) distant control (DC) comparing TL-PORT and TL group [Color figure can be viewed at wileyonlinelibrary.com]

Adjuvant therapy did not show statistically significant association with DFS ($p = 0.41$), being the recurrence rate 13.6% within patients treated with postoperative RT and 19.6% within those who did not (Figure 1). A subanalysis on the variables associated with local, regional, and distant control was also performed (Table 2). Local control was significantly associated with PORT ($p = 0.04$; OR 8.69; DFS TL-PORT 98.2% vs. TL 87.5%). Regional control was significantly associated with ND extent ($p = 0.04$; OR 8.47; unilateral ND 88.9% vs. bilateral ND 98.6%) and

TABLE 2 Univariate and multivariate analysis of local, regional, and distant control

	5-year disease-free survival				5-year disease-specific survival				5-year overall survival			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
Risk factor	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Sex (female)	0.39 (0.04–3.26)	0.68			0.46 (0.05–3.86)	0.68			0.79 (0.22–2.78)	1.00		
Lateral neck dissection												
Ipsilateral												
Bilateral	0.39 (0.13–1.13)	0.07			0.39 (0.13–1.19)	0.09			**0.38 (0.16–0.88)**	**0.02**	0.30 (0.63–2.91)	0.42
Central compartment dissection	1.28 (0.43–3.76)	0.64			1.18 (0.58–6.07)	0.28			0.94 (0.41–2.12)	0.88		
Pharyngocutaneous fistula	2.91 (0.75–11.2)	0.11			3.60 (0.91–14.1)	0.07			1.17 (0.34–4.02)	1.00		
Invasion through outer cortex of the thyroid cartilage	0.63 (0.20–1.94)	0.42			0.54 (0.16–1.84)	0.32			0.46 (0.19–1.11)	0.08		
Invasion of tissue beyond larynx	1.06 (0.34–3.31)	0.91			1.24 (0.36–4.24)	1.00			1.29 (0.53–3.13)	0.57		
Invasion of the anterior commissure	0.45 (0.14–1.39)	0.20			0.51 (0.15–1.69)	0.31			0.83 (0.32–2.17)	0.71		
Invasion of the subglottis	1.49 (0.52–4.28)	0.45			2.18 (0.69–6.90)	0.17			1.05 (0.47–2.35)	0.89		
Tumor posterior to the magic plane[a]	0.63 (0.20–1.95)	0.42			0.78 (0.24–2.51)	0.68			1.52 (0.66–3.52)	0.31		
Lymphovascular invasion	1.89 (0.66–5.41)	0.22			1.39 (0.46–4.18)	0.55			1.04 (0.46–2.38)	0.90		
Perineural invasion	**3.03 (0.98–9.35)**	**0.04**			2.40 (0.75–7.59)	0.12			1.29 (0.57–2.92)	0.52		
Adjuvant radiotherapy	0.54 (0.18–1.55)	0.25			0.52 (0.17–1.58)	0.24			**0.31 (0.13–0.71)**	**<0.01**	0.69 (0.89–4.43)	0.09

Note: The results which are statistically significant are marked in bold.

[a]Plane passing anterior to the vocal processes of the arytenoid cartilages, dividing the glottic plane into two compartments according to Succo et al.[39]

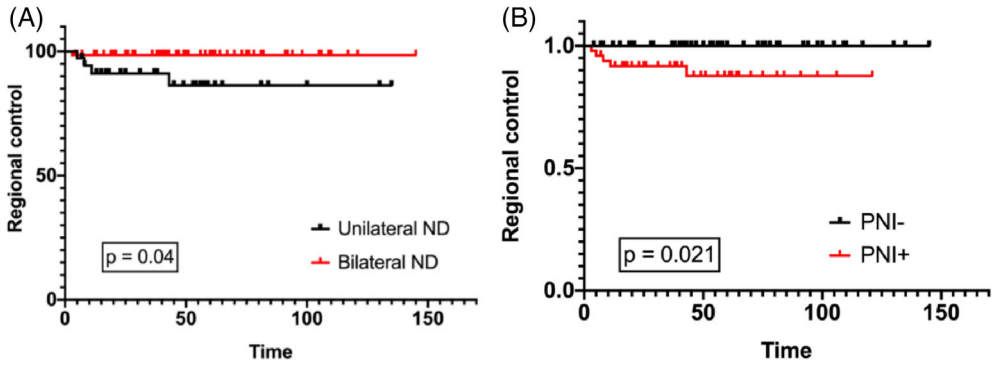

FIGURE 2 Kaplan–Meier analysis of (A) regional control (RC) comparing unilateral with bilateral neck dissection; (B) regional control (RC) comparing absence or presence of perineural invasion (PNI) [Color figure can be viewed at wileyonlinelibrary.com]

perineural invasion ($p = 0.02$; OR 1.11; PNI+ 90% vs. PNI− 100%) (Figure 2). However, PORT seemed to be associated with a better control in this latter group of patients. In fact, the PNI+ patient's subgroup the regional control rate was higher in those patients who underwent PORT (96.7% PNI+ PORT+ vs. 78.9% PNI+ PORT−), even though not reaching statistically significance threshold ($p = 0.06$). No variable was significantly associated with distant metastasis occurrence. No statistically significant difference in terms of DSS was found among patients who underwent TL (79.2%) and those who underwent TL-PORT (87.5%) ($p = 0.22$).

Univariate analysis regarding OS showed a statistically significant association with ND extent ($p = 0.02$; OR 2.63; OS unilateral ND 50% vs. bilateral ND 72.5%) and PORT ($p = 0.004$; OR 3.22; OS TL-PORT 76.8% vs. TL 50%).

PNI was an independent prognostic factor for DFS. Conversely, no independent prognosticator was found at Cox proportional hazard analysis for OS or regional control (Table 3).

4 | DISCUSSION

TL has become the workhorse for management of LALCs, as several authors have repeatedly shown better outcomes in terms of OS, DSS, and DFS compared to OPP, such as exclusive RT or chemo-RT.[4–8] In this setting, the role of adjuvant therapy is still matter of debate, as few studies have shown various results on the role of PORT in LALC.[16–18]

Recent studies focusing on pT3N0 laryngeal cancer have suggested PORT might not be necessary except in high-risk cases with other adverse features.[9,19] However, high-quality data about postoperative management of pT4N0 LALCs treated with TL are still lacking. Li et al. conducted a meta-analysis including only seven studies about the impact of PORT in surgically treated LALCs, reporting better OS and DSS in the TL-PORT group.[17] Graboyes et al. retrospectively reviewed data from the National Cancer Database reporting better OS rates for patients who underwent PORT, but no data were specified concerning DSS and locoregional control rates. Moreover, some biases were underlined by the authors themselves, since patients with advanced age, more comorbidities and treated in academic tertiary centers were less likely to receive PORT.[9] The other main limitations concerning these studies were heterogeneity of the study population in terms of locoregional staging, laryngeal site of primary origin, and type of surgery performed. Conversely, Karatzanis et al. and Kim et al. reported no clear difference in terms of oncologic results among TL and TL-PORT subgroups. However, it was emphasized that comparison was hindered by the unequal distribution of cases among the two subgroups.[20,31]

In our study, PORT was significantly associated with better OS (TL-PORT 76.8% vs. TL 50%) at univariate analysis. However, this finding was not significant at multivariate analysis. Moreover, most of patients who did not undergo PORT did so due to postoperative complications which were related to more advanced age at the time of surgery and heavier burden of medical comorbidities that might have had as well an impact on OS.

Del Bon et al. reported differences in terms of OS, DSS, and RFS between patients with laryngeal cancers extending anteriorly or posteriorly to a horizontal plane passing through the anterior aspect of the arytenoid vocal process, with the latter having worse survival when partial laryngectomy is performed.[21] However, no difference between these two groups has been observed by Marchi et al., when TL is performed.[7] Their results are herein once again confirmed, since we found no significant impact of posterior laryngeal compartment involvement in our cohort of patients treated by upfront TL.

Biological behavior of LALCs strongly differs according to its site of origin, as supraglottic cancers show higher rates of regional metastasis and lower survival, thus requiring a more aggressive management.[22–24] Thus, studies on selected populations of LALCs are required to better define their ideal management and prognosis. In this study, a specific population consisting in a cohort of

TABLE 3 Univariate and multivariate analysis of local, regional, and distant control

	5-year local control				5-year regional control				5-year distant control			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
Risk factor	**OR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Sex (female)	1.19 (0.13–10.7)	1.00			0.94 (0.90–0.93)	1.00			0.88 (0.81–0.94)	0.35		
Lateral neck dissection												
Ipsilateral												
Bilateral	0.36 (0.77–1.72)	0.22			**0.12 (0.01–1.09)**	**0.04**	0.15 (0.02–1.40)	0.09	0.59 (0.16–2.08)	0.50		
Central compartment dissection	0.17 (0.20–1.56)	0.10			4.01 (0.44–37.86)	0.36			2.43 (0.59–10.1)	0.31		
Pharyngocutaneous fistula	**8.77 (1.53–50.13)**	**0.02**	**10.1 (1.99–51.8)**	**<0.01**	5.26 (0.78–35.43)	0.12			0.73 (0.08–6.40)	1.00		
Invasion through outer cortex of the thyroid cartilage	0.25 (0.02–2.12)	0.24			0.39 (0.04–3.62)	0.64			0.92 (0.25–3.36)	1.00		
Invasion of tissue beyond larynx	2.77 (0.32–24.1)	0.67			1.79 (0.19–16.74)	1.00			0.74 (0.20–2.73)	0.73		
Invasion of the anterior commissure	1.09 (1.02–1.17)	0.34			1.15 (0.12–10.89)	1.00			**0.01 (0.05–0.69)**	**0.01**		
Invasion of the subglottis	1.33 (0.28–6.27)	1.00			4.16 (0.44–38.56)	0.36			1.82 (0.50–6.65)	0.52		
Tumor posterior to the magic plane[a]	0.63 (0.11–3.43)	0.70			0.39 (0.04–3.64)	0.64			0.92 (0.25–3.39)	1.00		
Lymphovascular invasion	0.58 (0.10–3.16)	0.70			2.36 (0.37–14.83)	0.38			1.95 (0.55–6.88)	0.33		
Perineural invasion	1.44 (0.30–6.82)	0.71			**1.11 (1.01–1.21)**	**0.02**		0.95	1.99 (0.54–7.28)	0.35		
Adjuvant radiotherapy	**0.12 (0.02–1.09)**	**0.04**	0.12 (0.02–1.13)	0.06	0.20 (0.02–1.85)	0.17			1.03 (0.29–3.62)	1.00		

Note: The results which are statistically significant are marked in bold.

[a]Plane passing anterior to the vocal processes of the arytenoid cartilages, dividing the glottic plane into two compartments according to Succo et al.[39]

pT4N0 glottic SCC, treated with TL and ND with negative surgical margins was selected. Moreover, the distribution of different variables within the TL and TL-PORT has been controlled to check for results reliability.

Studies focusing on PORT in LALCs often report locoregional control without analyzing predictive factors for regional and local recurrences, respectively.[16] In the present study, PORT was associated with local control, being significantly higher in the TL-PORT group (98.2% vs. 87.5%). The improved local control provided by PORT might be explained by the presence of microscopic tumoral foci in the surrounding extralaryngeal tissues that are controlled more effectively with adjuvant therapy. However, further larger studies should investigate the local control gain in patients undergoing TL-PORT, as well as the RT sequelae that may lead to a reduced quality of life and higher risk of intra- and perioperative complications whenever further salvage surgery is needed.

Lymph nodes metastasis has widely been described as one of the main prognostic factors of laryngeal cancer and is associated with an increased risk of regional recurrence.[25–28] Different studies have investigated the importance of ND including an adequate number of lymph nodes in improving regional control and survival rates, however no consensus exists on superiority of bilateral versus unilateral ND for glottic LALC yet.[25,29,30]

The analysis of predictive factors for regional recurrence in this study showed that pN0 patients have a relatively small 5-year risk of nodal recurrence, which is significantly smaller when a bilateral ND is performed (11.1% vs. 1.4%). These results could be explained by the extralaryngeal tissue invasions encountered in pT4 SCC that might determine more diffuse and bilateral lymphatic drainage. Therefore, we deem appropriate to consider bilateral ND in this subset of patients.

The role of PORT in preventing nodal recurrence has also been debated,[31] with some authors suggesting it only in high-risk cases.[25,32] A clear standard about the RT dosage and field should be established since the typical treatment field used in PORT for LALCs includes bilateral neck as well as the surgically addressed primary tumor site. However, it remains unclear if both sites need to be within the RT field. According to observations from this study, PORT on lymph nodes stations might not be necessary in cases of pT4N0 glottic LALC when bilateral ND has been performed, thus reducing RT short- and long-term side effects. However, further prospective trials need to ascertain this assumption.

Perineural invasion has already been described as an adverse histopathologic feature for laryngeal cancer, heavily impacting survival rates. A recent matched-pair analysis on a surgically treated heterogeneous cohort of patients with laryngeal cancer reported that PNI is significantly associated with poorer prognosis in terms of OS, DSS, and DFS.[33] However, wide heterogeneity is present in the current literature, with several studies suggesting that PNI is an independent factor that predicts cervical lymph nodes metastases in head and neck SCC, while others describing no association between PNI and regional recurrence.[34–37] Our results seem to confirm the former results correlating PNI to a worse regional control. In this setting, performing bilateral ND should be strongly advised to obtain better oncological outcomes. Methods to reliably predict PNI before surgery would be therefore more than useful in such a respect.

Lastly, neither PORT nor the extent of ND were related to better distant control, showing that the rate of distant metastasis could be related only to cancer biological behavior and locoregional stage when TL is performed. However, most of our recurrences (10.5%) were distant metastases, implying the importance of a close follow-up of distant sites after treatment of LALCs.

Interestingly, no difference was observed between TL-PORT and TL alone in terms of DSS. This finding might be related to the efficacy of salvage treatment in managing selected local and regional recurrences.

A deep understanding of the efficacy and risks correlated to PORT is critical. Quantifying the exact benefits and comparing them with patient age, will, comorbidities, RT side effects, and possible complications after salvage surgery provides the best therapeutic planning in terms of oncological outcomes and quality of life.[38] National or international prospective multicenter studies should address such aspects in the near future to further refine both patient counseling and multidisciplinary board decisions.

The strength of this study is related to the inclusion of a well-selected group of glottic pT4a R0 N0 SCC operated on with TL and ND, who were subsequently treated with PORT (TL-PORT group) or were exclusively followed-up clinically and radiologically for several reasons such as refusal, inability to perform RT due to general conditions, or excessive time elapsed between surgical treatment and the start of RT (TL group). On the other hand, study limitations include its multicentric nature (with potential differences within the therapeutic strategies adopted and referral biases), and the relatively low number of included patients, possibly affecting the statistical power of our analyses. This could be attributed to the highly selective inclusion criteria and relative rarity of pT4N0 glottic SCC.

5 | CONCLUSION

Patients with pT4N0 glottic SCC treated by TL and ND have better local control when PORT is administered.

However, no difference in terms of regional, distant control, and DSS have been herein reported.

Bilateral ND positively impacts on regional control while PNI negatively impact on regional control. A tailored PORT protocol should be considered for pT4N0 glottic SCC treated by TL and ND, both considering ND extent (uni- vs. bilateral), and presence of PNI. Moreover, until stronger evidences are available, pros and cons should be openly discussed within the multidisciplinary team and during patient counseling, properly balancing tumor control possibility and long-term RT consequences on post-treatment quality of life.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

All the procedures performed in the study were in accordance with the ethical standards of the institution at which the study was conducted.

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