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Is there a role for adjuvant radiotherapy after partial laryngectomy? A propensity score matched analysis

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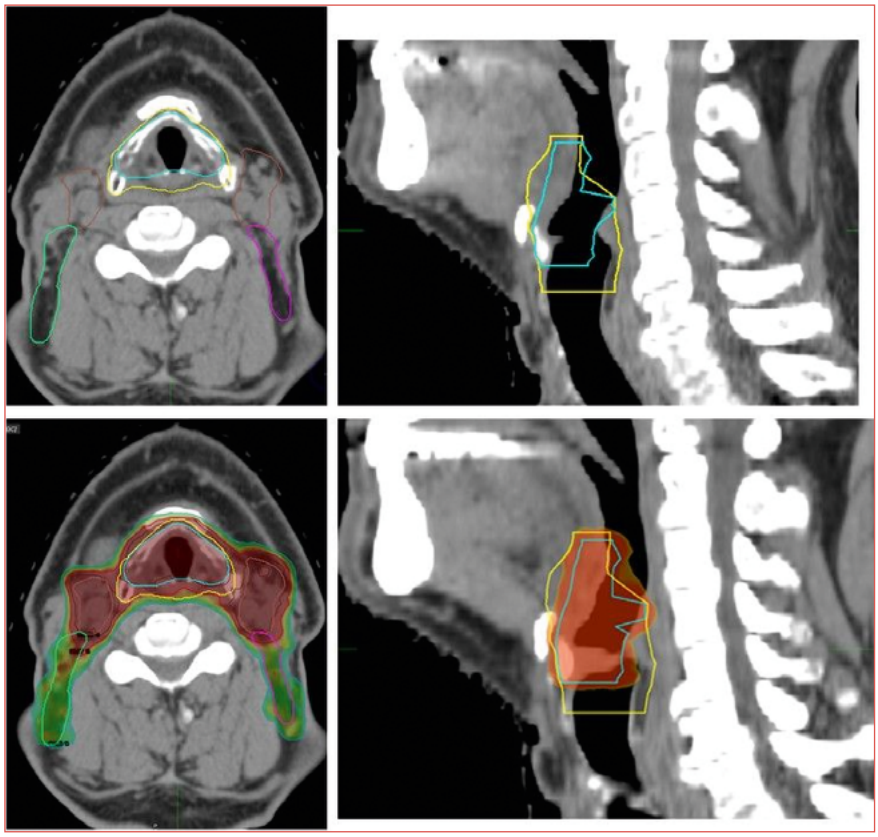
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Cover figure. Radiotherapy target volumes and dose distribution after OPHL type II for pT3-N2c supraglottic carcinoma.

Summary

Objective. To evaluate the impact of postoperative radiotherapy (PORT) on survival outcomes in patients with laryngeal cancer treated with partial laryngectomy.
Methods. In this retrospective multicentre study, 312 patients with supraglottic or glottic squamous cell carcinoma treated with transoral laser microsurgery (TLM) or open partial horizontal laryngectomy (OPHL), with or without PORT between 2005 and 2022 were analysed. Propensity score modelling and inverse probability weighting were applied to balance baseline characteristics. Endpoints included disease-free survival (DFS), overall survival (OS), disease-specific survival (DSS), and locoregional control (LRC).
Results. Of 312 patients, 175 underwent surgery alone and 137 received PORT. Treated patients had more adverse features. PORT significantly improved DFS (hazard ratio [HR] 0.44, 95% confidence interval [CI] 0.25-0.77) and LRC (HR 0.06, 95% CI 0.01-0.25). A significant benefit was also observed for DSS (HR 0.40, 95% CI 0.18-0.92). No statistically significant difference in OS emerged (HR 0.75, 95% CI 0.40-1.37).

Conclusions. PORT significantly improves DFS and LRC after partial laryngectomy in high-risk patients, supporting its role in carefully selected cases.

Keywords: laryngeal cancer, radiotherapy, adjuvant treatment, transoral laser microsurgery, open partial horizontal laryngectomy

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Introduction

Laryngeal cancer (LC) is one of the most frequent malignancies within the head and neck region. Its treatment has not seen notable advancements over the past few years, although therapeutic strategies are becoming more tailored to the stage and characteristics of the disease.

Traditionally, early-stage LC has been managed effectively with single-modality therapies such as surgery or radiotherapy (RT). However, the management of locally advanced LC necessitates a more aggressive and multimodal approach, often combining surgery, RT and/or chemotherapy (CHT).

In recent years, there has been a growing emphasis on laryngeal preservation strategies aimed at maintaining laryngeal functions and improving patients' quality of life. This has led to the implementation of organ-preservation strategies, including mainly chemoradiotherapy (CRT). However, in light of the long-term results of overall survival (OS) and laryngectomy-free survival (LFS) of this approach [1], some authors advocate improved patient selection to better tailor therapeutic strategies. Transoral laser microsurgery (TLM) and open partial horizontal laryngectomy (OPHLs) have emerged as surgical laryngeal preservation approaches in selected patients with advanced disease.

According to NCCN guidelines, after partial laryngectomy, in cases where unfavourable risk factors are observed in the definitive pathological specimen, the optimal therapeutic strategy remains controversial and may include total laryngectomy (TL), postoperative radiotherapy (PORT) with CHT, or a watch and wait approach. The decision to administer PORT depends on the presence or absence of adverse pathologic features, such as margin status, nodal staging, and extranodal extension. For cancers of the glottic larynx, subglottic extension is also considered an adverse pathologic feature.

The literature has reported conflicting results on the role of PORT in intermediate laryngeal cancer mainly due to the heterogeneity of treatments, staging, margin assessment, and selection bias due to patient or medical decisions. While a positive correlation of disease-free survival (DFS) and loco-regional control (LRC) with PORT has been found, several studies reported no significant differences in OS [2]. Moreover, the role of PORT is also debated for the increased risk of toxicity and functional impairment.

The present paper aimed to assess the effects of adjuvant treatment on survival of a multicentre cohort of patients with laryngeal cancer who underwent partial laryngectomy in a real-world setting. By focusing on a diverse group of patients treated across 3 tertiary centres, this study seeks to provide a comprehensive analysis of the benefits and potential drawbacks of PORT in the context of partial laryngectomy. This includes examining OS, DFS, LRC, and DSS, using propensity score analysis, thereby offering valuable insights into the effectiveness of adjuvant treatment in improving patient outcomes.

Materials and methods

Data in this retrospective study were collected from medical records of consecutive patients with a diagnosis of squamous cell laryngeal cancer who received partial laryngectomy with or without PO(C)RT from 2005 to 2022, at 3 University Hospitals in Italy.

The 3 institutions involved are all high-volume centres with expertise in multidisciplinary treatment of patients with head and neck cancer and all patients were discussed to evaluate the best therapeutic approach in a multidisciplinary tumour board. Preoperative clinical and radiological evaluation and follow-up were conducted according to the main oncological guidelines.

Inclusion criteria encompassed: (i) supraglottic or glottic cancer, (ii) TLM or OPHL with or without bilateral or unilateral neck dissection and (iii) availability of subsequent clinical and radiological follow-up.

Exclusion criteria were: (i) Stage I-II disease, (ii) distant metastatic disease, (III) prior head and neck RT, (IV) unavailability to sign informed consent and (V) treatment purpose other than curative.

Due to the long accrual period and different staging editions, all patients were converted to the 8th TNM version [3].

All patients underwent OPHL [4] or TLM cordectomies according to the European Laryngology Society (ELS) classification [5,6]. Elective neck dissection was performed according to the policy of each centre.

T3 and T4 tumours were grouped according to 4 prognostic subcategories as defined by Succo et al. [7] as follows: subcategory I (anterior pT3 with normal arytenoid mobility); subcategory II (posterior pT3 with impaired/absent mobility); subcategory III (anterior pT4 with normal mobility); and subcategory IV (posterior pT4 with impaired/absent mobility).

The variables collected included: demographic data; previous surgery (which we defined as "major" in case of OPHL, versus "minor" in case of TLM); type of surgical approach; adjuvant therapy.

According to NCCN guidelines, indications for PORT are pT3-T4 tumours, any tumour with positive surgical margins, and at least one of the following features: close margins, perineural invasion (PNI), lympho-vascular invasion (LVI); in case of positive margins or extranodal extension (ENE) concurrent cisplatin-based CHT was added to PORT. RT was delivered with 3D-conformal (3D-CRT) or intensity modulated (IMRT) technique, and standard doses for adjuvant intent (i.e. 60-70 Gy to the surgical tumour bed and 50-54 Gy for elective treatment of neck lymph nodes).

Statistical analysis

Records before the year 2005 (n = 1) and patients with primary subglottic tumours (n = 2) were excluded. Due to the low number of subjects per strata we combined tumour size and extent (T), lymph node status (N) and grading (G) into 2 groups each (Tab. I). Absolute and relative frequencies were used to summarise discrete variables. G, minor surgery, LVI and PNI missing data were imputed using fully conditional specification method based on linear discriminant analysis modelling of all other available variables.

We used standardised mean difference (SMD) to inspect the imbalance between adjuvant treatment groups.

Propensity score (PS) to receive the treatment was estimated with covariate balancing PS (CBPS) model. As PS predictors, we included variables: (1) related to treatment decision, (2) imbalanced among treatment group and also (3) prognostic for the outcome. For each subject we computed the inverse of the probability of receiving the treatment actually received to weight observations (IPW) in the outcome models and estimated the average treatment effect on treated (ATT). A threshold of 10% was applied to determine residual imbalances after weighting procedure.

Raw, adjusted, weighted and weighted-and-adjusted Cox proportional hazard models were fit to estimate the impact of the treatment on OS, LRC, DSS and DFS.

Endpoints

The main outcome analysed was DFS, while secondary endpoints were OS, LRC and DSS. DFS was defined as the time from partial laryngectomy to death or to progression for subjects who died from any cause or had a local or distant relapse, and the time from partial laryngectomy to the last available follow-up for subjects alive and without local or distant relapse. OS was defined as the time from partial laryngectomy to death for subjects who died, and the time from partial laryngectomy to the last available follow-up for censored subjects. LRC was defined as the time from partial laryngectomy to local recurrence for subjects with local (or locoregional) recurrence, the time from partial laryngectomy to the last available follow-up or to distant recurrence for subjects alive and without local recurrence, and the time from major surgery to death for subjects died by any cause without any recurrence.

Cox models residuals were inspected and tested to assess violations of the proportional hazards assumption and where violations occurred we used stratification of the covariate. Hazard ratio (HR) and 95% confidence interval (CI) were used to quantify the relative risks and median difference in survival with their 1000-replica based bootstrap 95% CI were used to quantify the absolute risks. SAS Version 9.4 and R version 4.3.0 were used for all analyses.

Results

A total of 312 patients were registered in the database and available for analysis according to the inclusion criteria. Among these, 271 patients were males (86.8%) and the median age was 66 years.

Of these, 175 (56%) patients were treated by surgery alone (Group 1- Surgery Group), and 137 (44%) underwent surgery followed by adjuvant treatment (Group 2- PORT Group); 15% of patients underwent previous endoscopic resection (minor surgery) and during follow-up required TLM or OPHL. According to the subsite, 130 (41.6%) and 182 (58.3%) were supraglottic and glottic cancers, respectively.

Factors associated with prognosis were as follows: ENE in 20/312 (6.4%), LVI in 130/312 (41.7%), PNI in 119/312

Table I. Patient characteristics.

		Group 1-Surgery	Group 2-PORT group	p	SMD
N		175	137		
Mean age in years (SD)		66.2 (10.7)	63.6 (8.5)	0.025	-0.26
Gender (%)	M	152 (86.9)	119 (86.9)	1.000	-0.00
	F	23 (13.1)	18 (13.1)		
Tumour site (%)	Glottic	111 (63.4)	71 (51.8)	0.051	0.24
	Supraglottic	64 (36.6)	66 (48.2)		
Year of major surgery (%)	2005 to 2014	75 (42.9)	51 (37.2)	0.190	-0.12
	2015 to 2018	71 (40.6)	52 (38)		-0.05
	2019 to 2022	29 (16.6)	34 (24.8)		0.20
Type of surgery (%)	OPHL	90 (51.4)	108 (78.8)	< 0.001	-0.60
	TLM	85 (48.6)	29 (21.2)		
Neck dissection (%)	Unilateral	49 (28)	37 (27)	< 0.001	-0.02
	Bilateral	48 (27.4)	71 (51.8)		0.52
	None	78 (44.6)	29 (21.2)		-0.51
Margin status (%)	R0	121 (69.1)	78 (56.9)	0.019	-0.25
	Close	25 (14.3)	18 (13.1)		-0.03
	R1	29 (16.6)	41 (29.9)		0.32
Grading (%)	G1-G2	132 (75.4)	70 (51.1)	< 0.001	0.52
	G3	43 (24.6)	67 (48.9)		
T category (%)	pT0-2	74 (42.3)	40 (29.2)	0.024	0.28
	pT3-4	101 (57.7)	97 (70.8)		
N category (%)	pN1-3	21 (12)	72 (52.6)	< 0.001	-0.96
	c/pN0	154 (88)	65 (47.4)		
Perineural invasion (%)	No	137 (78.3)	56 (40.9)	< 0.001	0.82
	Yes	38 (21.7)	81 (59.1)		
Lympho-vascular invasion (%)	No	134 (76.6)	48 (35)	< 0.001	0.92
	Yes	41 (23.4)	89 (65)		
T subcategory (according to Succo et al. [7])	I	154 (88)	65 (47.4)	< 0 .001	
	II	14 (8)	24 (17.5)		0.29
	III	3 (1.7)	22 (16.1)		0.52
	IV	4 (2.3)	26 (19)		0.56

(38%), and both LVI and PNI in 58/312 (18.5%). Regarding T category, 107/312 (34%) were pT2**,** and 160/312 (51%) were pT3. Only 39/312 (12%) of patients had pT4a disease (20 and 18 were respectively glottic and supraglottic primaries): 12/39 (31%) were in the Surgery Group and 27/39 (69%) in the PORT Group. Globally, pT3-T4 were 101/312 (32.3%) in the Surgery Group and 97 (31%) in the PORT Group. Margins were negative in 199/312 (63.7%) and PORT was delivered in 78 of these cases; 113/312 (36%) patients presented close or positive margins and in 54 (17%) PORT was not performed. In 9% of patients with R1 disease, PORT was not performed due to poor PS. The median follow-up time, estimated by reverse Kaplan-Meier method, was 44.4 months.

There was a clear direction in treatment bias: patients with more severe disease were more likely to receive adjuvant treatment. Higher G, higher T category, higher lymph node status, and presence of PNI, LVI, or ENE were all associated with a higher propensity to receive adjuvant treatment. Absolute SMD for unadjusted variables ranged from 0 to 96% with 15 of 16 explored variables showing a value above 10%. Accordingly, mitigating such baseline

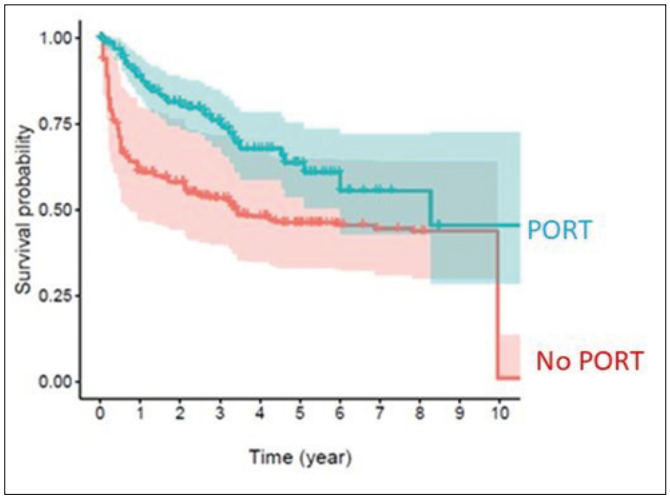


Figure 1. DFS according to adjuvant treatment.

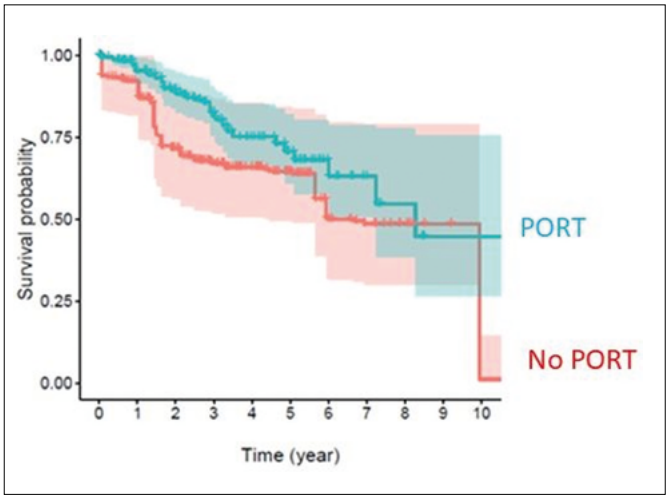


Figure 2. OS according to adjuvant treatment.

imbalances led to larger estimates of the treatment effect compared to unadjusted and unweighted methods. Table I shows the clinical characteristics and baseline imbalances between the 2 groups.

Regarding DFS, patients who received adjuvant treatment had a significant benefit compared to those who did not receive PORT, with a 66% risk reduction compared to the untreated patients (HR: 0.44, 95% CI: 0.25-0.77).

Two- and 5-year DFS were 80.4% (95% CI: 73.2%-88.2%) and 63.6% (95% CI: 53.7%-75.4%) in the PORT Group *versus* 58.1% (95% CI: 44.1%-76.5%) and 46.2% (95% CI: 32.9%-64.9%) in the Surgery Group, respectively (Fig. 1).

However, no significant difference in OS was detected between the 2 groups (HR: 0.75, 95% CI: 0.4-1.37). Two- and 5-year OS were 88.4 % (95% CI: 82.4%-94.8%) and 70.7% (95% CI: 60.8%-82.1%) in PORT Group *versus* 71.6% (95% CI: 56%-91.6%) and 64.6% (95% CI: 49.4%-84.4%) in Surgery Group, respectively (Fig. 2).

The estimation of the average adjuvant treatment effect on OS in this study is largely confounded by the characteristics associated with the treatment assignment. Without adjustments, patients who received adjuvant treatment had a slightly worse OS than those who did not, due to the greater severity of disease. Greater severity of disease in treated patients compared to controls was observed for each known prognostic factor at baseline as covariate imbalance (SMD > 10%). When mitigation techniques for such biases were applied (covariate adjusting and IPW), a larger (but non-significant) benefit of the adjuvant treatment emerged. The HR of 0.75 (95% CI: 0.40 to 1.37) indicates that the average adjuvant treatment benefit if treated (for treated, ATT) is a 25% reduction in the risk of death.

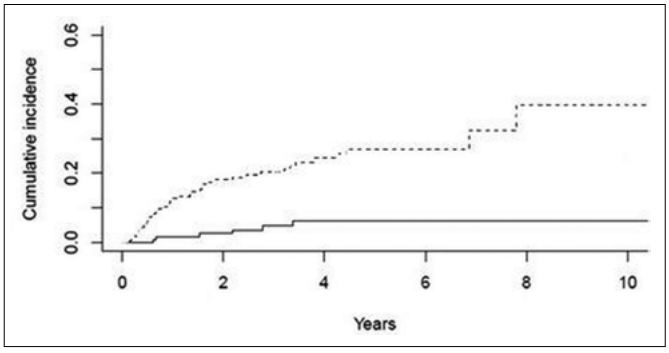


Figure 3. Locoregional relapse rate.

Patients in the PORT Group showed significantly better LRC compared with those who did not receive PORT, with a 94% reduction in risk (HR: 0.06, 95% CI: 0.01-0.25). Two- and 5-year local recurrence rates were 2.5% and 6.5% in PORT Group versus 18% and 26.9% in Surgery Group, respectively (Fig. 3).

Regarding DSS, patients who received PORT had a 60% risk reduction in death from laryngeal cancer compared to those who did not receive it (HR: 0.40, 95% CI: 0.18-0.92). The effect of the adjuvant treatment on DSS is greater than the estimated effect on OS. Without adjustments, patients who received adjuvant treatment already showed a benefit compared to those who did not receive PORT, regardless of the higher severity of disease. When imbalance mitigation techniques were applied (covariate adjusting and IPW) this estimated benefit was enlarged. The HR of 0.68 (95% CI 0.27-1.80) indicates that the average adjuvant treatment

benefit for subjects with characteristics similar to the group receiving it, is about a 30% reduction in the risk of dying from cancer. It should be noted that the competing risk of dying from other causes before dying from cancer was ignored. No different proportion in non-cancer mortality was detected.

Finally, we evaluated if the type of partial laryngectomy (TLM *vs* OPHL) had an impact on oncological outcomes; we found no significant association between type of surgery and OS (HR: 2.16, 95% CI: 0.8-5.85) and DFS (HR:1.13, 95% CI: 0.51-2.50).

Discussion

This multicentric retrospective study evaluated the role of PORT in a large series of patients addressed by 2 different surgical laryngeal preservation approaches. To our knowledge, this is the only study assessing the impact of adjuvant RT in patients with intermediate stage laryngeal cancer treated with TLM or OPHL by a propensity match score analysis.

In the era of "laryngeal preservation", the meaning of this term should be clearly defined and today covers both the organ and its functions (i.e. no laryngectomy, no long-term tracheotomy, and no long-term feeding tube). The term originates from non-surgical approach based on RT and CHT for intermediate and advanced laryngeal cancers, but currently covers different surgical options.

Intermediate stage (T3-T4, N0 or with limited nodal disease) laryngeal cancer, encompasses a heterogeneous variety of lesions, each characterised by distinct clinical presentation, biological behaviour and prognosis. Thus, neoplastic pathways of tumour spread should be carefully considered in order to perform a non-surgical or surgical preservation approach.

Recent consensus and literature suggest a strict selection of patients to address the surgical approach also in order to avoid PORT and the combination of long-term toxicity [8].

A precise diagnostic staging, mainly addressed to understand the local spread of tumour, particularly regarding the "magic plane" and extension to laryngeal visceral spaces for T3 and beyond cartilages for T4, allows to plan the correct surgical approach and reduce the risk of subsequent PORT.

However, based on clinical and radiological characteristics, the appropriate patient selection for surgical laryngeal preservation rather than non-surgical treatment, is carried out with some limits and about 15-20% of patients suffer from incorrect staging and need for adjuvant treatment, with some studies reporting up to 24%, specifically in pT3N0 [9].

The role of PORT was explored with contrasting results: this is probably due to the retrospective nature of the studies, heterogeneity of cancer staging, different surgical approaches and RT techniques and, finally, patient selection changed throughout the years.

Regarding TLM, Pinacoli et al. recently reported the results of a selected population of pT3 glottic cancer at high risk (positive margins not amenable to re-excision, nodal category ≥ pN2a, presence of PNI and/or LVI): in 141 patients, 18.5% received PORT, 13.5% only RT, and 5% CRT. The 5-year OS was 78.1% (95% CI: 69.3-84.6) and a benefit of PORT for recurrence or death (DFS) at univariate (HR 0.46, p = 0.03) and multivariate (HR 0.38, p = 0.01) Cox analysis was seen [10].

In the recent meta-analysis on OPHL by Locatello et al. [2], on 1,198 patients from 10 studies, no significant OS benefit was observed for those receiving PORT (49.5%) for high-risk (positive or close margin and high nodal burden) features.

Thus, some authors suggest that surgery alone may be a safe option in selected patients with pT3N0 disease (no supraglottic and no PNI) [11].

In 2017, Graboyes et al. evaluated the effect of PORT on survival in a large series of 1490 patients from the National Cancer Data Base with pT3-T4N0 laryngeal cancer surgically managed mainly by total laryngectomy (80%). In a mixed population treated for supraglottic (42.3%), glottic (34.4%) and subglottic tumours, specifically in pT3N0, almost 25% received PORT. The authors concluded that the addition of PORT was not associated with an increased survival for patients with pT3N0 laryngeal SCC (adjusted HR, 0.88; 95% CI 0.64-1.21), whereas patients with pT4aN0 and negative margins did appear to benefit from PORT, with a nearly 40% decrease in the risk of death.

In contrast, Cooper et al. reported a significant difference in mean survival favouring PORT compared to those who received only laryngectomy: for N0 patients, mean survival was 51.6 months (95% CI: 50.3-52.8 months) *versus* 46 months (95% CI 44.4-47.7), while for N1 patients it was 46.8 months (95% CI: 44-49.5 months) *versus* 36.2 months (95% CI: 31.6-40.8) [12].

In our analysis, the reported 5-year OS in the PORT group was 70.7%, which seems higher than previous findings, particularly for a population with intermediate-high risk disease. However, in our study, no benefit in OS from the addition of PORT was observed. This is a further interesting finding because patients with a worse prognosis for high-risk features (who received PORT) are expected to have poorer OS. Therefore, achieving survival rates similar to those of subjects with better prognostic features (Surgery

Group) could already indicate a therapeutic improvement. Another factor to consider that might explain the lack of impact of PORT on OS is that patients with local recurrence can be salvaged by total laryngectomy and this may not influence survival.

These data cannot be easily compared with those derived from our analysis, as the surgical approach and population differ both for T and N categories. In our series, not exclusively pT3N0 patients were included and a subgroup analysis was not performed.

As seen in other studies, in our series 31% of patients with pT4 did not receive adjuvant RT: the reasons for not performing adjuvant treatment include poor PS, surgical complications, and patient refusal.

Our cohort also included patients with pT4a disease, because in most cases they were clinically staged as cT3 but upstaged to pT4a at definitive histological examination. This is consistent with other authors' experience who report that many pT4a derived from upstaging of tumours previously labelled as cT3 [13]. Considering the small sample size (12.5% of all patients), it was not possible to perform a subgroup analysis, but we believe that this group of patients deserves special comment as we consider adjuvant treatment of primary importance in this setting. Some literature data demonstrate its important benefit on OS based only on T category regardless of other risk factor (margin status, PNI, and LVI) [9].

Conversely, a recent paper from Bertolin et al. found no difference in terms of regional recurrence, DFS, DSS, and OS comparing pT4a patients who underwent adjuvant PO(C) RT to those who did not, with increased decannulation time after PORT. Their conclusion is based on 29 patients, of whom 13 received adjuvant therapy, which seems too weak to translate into daily clinical practice. However, we are aware that in the future, the number of patients with cT4 disease who will undergo partial laryngectomy will likely increase, but attention should be paid to the omission of adjuvant therapy.

Our study showed an impressive benefit of PORT in terms of LRC with a 94% reduction in risk (HR: 0.06, 95% CI: 0.01-0.25), and an important impact on DFS and DSS, with a 66% risk reduction compared to the untreated (HR: 0.44, 95% CI: 0.25-0.77) and a 60% risk reduction (HR: 0.40, 95% CI: 0.18-0.92), respectively. This benefit is in line with those observed in pT3 laryngeal cancer by Pinacoli et al. [10] and Cooper et al. [12]

According to guidelines, the reasons for PORT are often, in the intermediate stage, positive or close margins. Many literature studies have shown the impact of positive margins in terms of local recurrence, such Gallo et al. [14] and Dufour et al. [15] In Crosetti et al. [16], even though it was a significant predictor at univariate analysis, it did not remain significant at multivariate analysis. Recently Crosetti et al. [17] conducted a meta-analysis exploring the prognostic role of margins in OPHL: even though a significant heterogeneity of studies was included, the definition and management of close or positive margins are linked to an increased risk of local recurrence. Less clear was the impact on OS. Therefore, margin status is probably not the only risk factor in terms of LRC.

Interestingly, in our study, only 19% of patients presented positive or close margins, and it did not appear to be significantly correlated with prognosis. The low rate of R1 in our series confirms the accurate diagnostic process and appropriate selection of patients for different treatment strategies. This also strengthens the role of OPHL in highly selected pT4 patients, while historically these were addressed by total laryngectomy.

Considering the role of PORT in the N-positive scenario, in our series 202 patients received neck dissection (64.7%). Globally, 72 pN positive cases (23%) received PORT, of whom 28 had glottic tumours: these data are consistent with the literature.

While in supraglottic cancer the risk of occult nodal involvement is high, pT3-T4 glottic cancers have a lower risk. With the widespread use of surgical laryngeal preservation approach, some clinicians advocate to avoid an elective neck dissection.

In the analysis of Sanabria et al. [18], the pooled incidence of occult metastases in glottic and supraglottic pT3 were 14.4% (95% CI: 6.9-21.8, I2 = 11%) and 23.8% (95% CI: 18.6-28.9, I^2 = 0%), respectively.

The rate increases in pT4, where in glottic tumours the pooled incidence was 32.7% (95% CI: 16.6-48.8, I2 = 0) and 34% (95% CI: 26.1-41.9, I2 = 0) for supraglottic lesions. Considering a cutoff of 20% for occult nodal metastasis, in supraglottic cancer elective treatment of the neck should be undertaken for pT2 or higher disease. Due to the different anatomy, in glottic cancer the risk of occult metastasis does not exceed 20% until tumours are staged as T3, and elective neck dissection should not be routinely performed. However, it should be noted that patients with pN+ disease were at higher risk (RR = 3.1) to develop recurrences [16], so it is important to not underestimate the risk of occult nodal metastases.

Importantly, in the era of surgical laryngeal preservation, it is important to select patients in the intermediate stage in order to avoid a multimodal treatment that could affect the functional outcome.

This study has several limitations, primarily its retrospective design and the heterogeneity of the population analysed, along with the lack of functional and toxicity data that prevents a precise risk-benefit assessment of PORT.
The unclear definition of the toxicity profile of PORT can also be deduced from the literature. Some series reported worsening in function of residual larynx outcomes after PORT, such as longer tracheostomy dependence, longer time to resume oral intake and more frequent need to place a permanent feeding tube.
However, it is extremely difficult to understand the exact contribution of PORT to these symptoms as functional recovery depends on several factors related to treatment (including the type of surgery performed) and patients (age, comorbidities, etc.). On the other hand, some adverse events are ascribed to PORT with greater security such as chondronecrosis or laryngeal stenosis.
To date, one clear conclusion from the literature is that it is extremely difficult to quantify any deterioration on laryngeal function attributable with certainty to adjuvant treatment. The available series in most cases are retrospective, analysing patients treated over wide time ranges who consequently were managed by both surgical and radiotherapy techniques not fully comparable to modern ones. Moreover, most studies do not present an assessment of laryngeal function at baseline to be compared with that after treatment.
Even if this study lack of functional data, the strength of our cohort is that all patients were discussed in a multidisciplinary board and clear selection criteria were applied in order to treat them using different approaches. Moreover, all patients were managed with modern RT techniques (IMRT or VMAT) and followed in a multidisciplinary way .
Moreover, the appropriate statistical method on over 300 patients, all treated in high-volume centres, allowed us to compare 2 groups of patients with different prognosis, and led to strong and solid results on the importance of adjuvant therapy on outcomes after partial laryngectomy.

Conclusions

To our knowledge this is the first propensity score-matched analysis on a large cohort of patients treated with 2 different partial laryngectomy techniques, with or without PORT. Our work confirms that PORT is an effective treatment in a real-world setting of patients who underwent partial laryngectomy with high-risk factors; specifically, from our analysis, patients who received PORT achieved a significant and strong benefit in terms of DFS. Moreover, the average treatment effect on local recurrence strongly and consistently favoured the PORT Group. This is an important finding that is consistent with previous reports in the literature. Although we did not observe a statistically significant benefit in OS, this should be interpreted considering the higher baseline risk of the PORT Group and the possibility of salvage treatment, as obtaining similar OS in patients with more adverse features may already represent a clinically relevant effect. In contrast, an accurate staging despite the limits of clinical and radiological assessment, together with thorough multidisciplinary discussion, are necessary in order to avoid, whenever possible, multimodal treatments and combined toxicity in intermediate stage lesions without high risk factors.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

LB, EDA, ID: conceived and designed the study; LB, ID, MF, AI, FM, FM, AB, CG, GP, FM, MF, LP: contributed to patient enrollment and data collection; LB, : performed the statistical analysis and methodology development; LB, EDA, ID: drafted the manuscript; GP, AT, EDA: supervised the study and critically revised the manuscript for important intellectual content. All authors contributed to data interpretation, reviewed the manuscript, and approved the final version for publication.

Ethical consideration

This study was approved by the Institutional Ethics Committee of CER Liguria (protocol number: 370/2022). The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from each patient for study participation and data publication.

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