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Selected laryngeal squamous cell carcinomas with laryngeal mobility impairment are suitable for curative larynx-preservation treatment
A multi-institutional study on 406 patients from the ARYFIX collaborative group

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ABSTRACT

Introduction: Mobility impairment defines a specific subset of laryngeal squamous cell carcinoma (LSCC), with implications for prognosis and treatment. While total laryngectomy (TL) is often considered for mobility-impairing LSCC (MI-LSCC), the role of organ-preserving strategies such as open partial horizontal laryngectomy (OPHL) and non-surgical treatments (NST) remains debated. This study aims to evaluate the outcomes of different treatment strategies for patients with MI-LSCC.

Materials and methods: A retrospective analysis was conducted on 406 MI-LSCC patients using data from the ARYFIX collaborative study. Patients with subglottic tumors or those receiving unimodal radiotherapy (RT) were excluded. Treatment modalities included TL, TL with adjuvant (chemo)radiotherapy ((C)RT), OPHL, OPHL with adjuvant (C)RT, and definitive NST. Survival outcomes, including overall survival (OS), disease-specific survival (DSS), recurrence-free survival (RFS), and laryngo-esophageal dysfunction-free survival (LEDFS), were assessed. Population clustering and propensity score matching (PSM) were used to balance covariates across treatment groups.

Results: The 5-year rates of OS and DSS were 72.0% and 86.2%, respectively. PSM-adjusted analysis indicated that OPHL was associated with the best outcomes. TL with adjuvant (C)RT provided favorable oncologic control, while NST was associated with higher cancer-unrelated mortality and reduced locoregional control. However, NST yielded the best outcomes in patients with N2-3 MI-LSCC. OPHL followed by (C)RT was associated with inferior DSS and unfavorable LEDFS.

Conclusion: In MI-LSCC, OPHL offers satisfactory oncologic and functional outcomes, provided that patient selection is performed carefully. NST, although associated with poorer locoregional control, optimizes outcomes in MI-LSCC with high nodal burden. Treatment for MI-LSCC should be individualized, considering tumor extension, patient fitness, and institutional expertise.

Introduction

Impairment of vocal cord-arytenoid unit (VCAU) mobility, whether partial or complete, characterizes the natural history of laryngeal squamous cell carcinoma (LSCC). The rate of mobility impairment increases from 0 % in T1 to 37.2 % in T2 [1] and 47.6 % in T3 [2]. Several underlying mechanisms have been postulated, with different patterns of involvement of laryngeal structures converging into the clinical finding of VCAU mobility impairment, which can be demonstrated endoscopically and elicits symptoms such as dysphonia and dysphagia [3]. Although this clinical finding has implications in terms of staging, prognosis, and treatment, it is remarkably flawed by poor inter-observer reliability, as demonstrated by a previous study from this collaborative group [4].

Mobility-impairing LSCC (MI-LSCC) is a distinct entity with respect to mobility-intact LSCC, since VCAU mobility is indispensable for the larynx to fulfill functions that have profound systemic implications. A chronically non-functional larynx can severely impact nutritional status, respiratory function, and the cardiovascular apparatus, as observed at both primary presentation and in survivors after treatment of LSCC [5–9]. Thus, the meticulous art of treatment selection in patients affected by LSCC is made even more complex in the subset of MI-LSCC, since several crucial aspects including staging, subclinical disease extension, and reversibility of mobility impairment are poorly elucidated [10].

There is a substantial knowledge gap as to whether MI-LSCC are eligible for larynx-preservation treatment and which therapeutical strategy provides the best outcomes. In fact, non-inferiority of non-surgical treatments (NST), including radiotherapy (RT) with/without chemotherapy (CT), to surgery such as total laryngectomy (TL) or open partial horizontal laryngectomy (OPHL) in patients with MI-LSCC is controversial. Indeed, although the non-inferiority of definitive NST to TL was demonstrated by the Veterans Affairs (VA) Laryngeal Cancer Study Group trial [11], with a rate of cord fixation of 56.6 %, the "*Groupe d'Etude des Tumeurs de la Tête et du Cou*" (GETTEC) trial [12], which included only MI-LSCC, failed to reach the same result and was halted. This discrepancy is coherent with a recent National Cancer Database study on 10,216 patients affected by laryngeal cancer, which reported higher survival with surgery *vs*. NST in those with MI-LSCC [2]. Even within the domain of surgery, eligibility for OPHL in patients with MI-LSCC is debated [13], with selection of patients that can avoid TL being particularly challenging and relying upon a comprehensive assessment of tumor extension, patient's performance status (PS) and comorbidities, availability of a sound pre-treatment and rehabilitation program, adherence to medical indications, and social/family context [3,10].

The present retrospective study primarily aims at assessing the adequacy of larynx-preservation treatment in patients affected by MI-LSCC, in an attempt to unveil relevant elements in terms of decision-making for treatment.

[1] PN, GP, GS, and MF share the last authorship.

Materials and methods

Cohort definition

The updated dataset of ARYFIX, which is a collaborative study detailed in Table 1 [4], was exploited to perform the following analyses. Data were pseudonymized and transferred to the coordinating center (University of Padua – "Azienda Ospedale-Università Padova"; Padova, Italy), where information were aggregated for fully anonymized analysis. Analysis of data was conducted in accordance with the 1964 Helsinki declaration and its later amendments and was endorsed by the Institutional Review Board (approval code: 190n/AO/21). For the present study, patients affected by subglottic LSCC and those receiving unimodal non-surgical treatment (*i.e.*, RT alone) were excluded.

Table 1
Design, inclusion period, and inclusion and exclusion criteria. CRT, chemoradiotherapy; LSCC, laryngeal squamous cell carcinoma; OPHL, open partial horizontal laryngectomy; RT, radiotherapy; TL, total laryngectomy; VCAU, vocal cord-arytenoid unit. *Amended in the present study (declared degree of VCAU impairment was used for the analysis).

ARYFIX collaborative study database	
Study design	Retrospective cohort analysis
Inclusion period	2004–2021
Participating centers	• University of Padua – "Azienda Ospedale-Università Padova" (Padova, Italy) • University of Genoa – "IRCCS Ospedale Policlinico San Martino" (Genoa, Italy) • "IRCCS Istituto di Candiolo" (Candiolo, Italy) • "Ospedale San Giovanni Bosco di Torino" (Turin, Italy) • "Ospedale di Vittorio Veneto – ULSS 2 Marca Trevigiana" (Vittorio Veneto, Italy) • University of Bologna – "IRCSS Policlinico Sant'Orsola-Malpighi" (Bologna, Italy) • University of Modena – "Policlinico di Modena" (Modena, Italy) • Erciyes University (Kayseri, Turkey) • University of Cagliari – "Azienda Ospedaliero-Universitaria di Cagliari" (Cagliari, Italy) • University of Brescia – "ASST Spedali Civili di Brescia" (Brescia, Italy) • "IRCCS Istituto Nazionale Tumori Regina Elena" (Rome, Italy)
Inclusion criteria	• Non-recurrent LSCC • Clinical diagnosis of partial or total VCAU mobility impairment made in the center where treatment was delivered • Any of the following treatments with curative intent: o TL w/wo adjuvant RT/CRT o Type II/III OPHL w/wo adjuvant RT/CRT o RT/CRT w/wo salvage TL o Induction CT followed by RT/CRT w/wo salvage TL o Induction CT followed by TL/OPHL w/wo adjuvant RT/CRT (excluded in the present study, see below) • Availability of pre-treatment videolaryngoscopy and/or contrast-enhanced local imaging*
Exclusion criteria	• Previous cancer of the head and neck and/or oncologic treatment involving the head and neck • cM1 at presentation • Hypopharyngeal cancer • Unavailable follow-up information
Additional exclusion criteria of the present study	• Unimodal non-surgical treatment • Subglottic subsite • Induction CT followed by TL/OPHL w/wo adjuvant RT/CRT

Cohort description

The cohort of patients was described in terms of demographic and clinicopathological characteristics, including age, gender, smoking habits, excessive alcohol consumption (*i.e.*, $\geq$1 alcohol unit per day for females, $\geq$2 alcohol unit per day for males), Eastern Cooperative Oncology Group (ECOG) PS, tumor epicenter, grade of differentiation, T category (using cT for patients who did not receive surgery and pT for those who did), presence of nodal metastases, perineural invasion, vascular invasion, and margin status. Since ECOG PS was considered of high relevance for the subsequent analysis, missing data were considered "missing at random" and imputed through multivariate imputation by chained equations including the following covariates: age, gender, smoking habit, excessive alcohol consumption, tumor epicenter, T category, presence of nodal metastases, perineural invasion, vascular invasion, and margin status [14]. Treatment patterns, defined as the combinations and types of treatment modalities, were retrospectively analyzed and margin status was retrieved for patients who received surgery. Differences among patterns of treatment in terms of relevant clinicopathological information including age, tumor epicenter, nodal involvement, margin status, and ECOG PS were assessed through the Kruskal-Wallis (for age) and chi-square tests (for other variables).

Survival analysis

The main aim of the study was to compare different treatment patterns in terms of oncologic outcomes, while adjusting the comparison for clinically-relevant factors potentially acting as confounders. The study hypothesis was that TL is associated with improved oncologic outcomes compared with larynx-preserving treatments (including OPHL and definitive NST) in patients with MI-LSCC.

The following time-to-event outcomes were evaluated: overall survival (OS), disease-specific survival (DSS), cumulative incidence of cancer-unrelated death (CUD), recurrence-free survival (RFS), time-to-recurrence (TTR), locoregional control (LRC), time-to-distant-recurrence (TTDR), and laryngo-esophageal dysfunction-free survival (LEDFS). Events and censors were defined as follows: for OS, death of any cause (event), patient alive at latest evaluation (censor); for DSS, LSCC-specific death (event), patient alive at latest evaluation or dead from a LSCC-unrelated cause (censor); for CUD, LSCC-unrelated death (event), patient alive at latest evaluation or dead from a LSCC-specific cause (censor); for RFS, recurrence of LSCC or death of any cause (event), patient alive with no LSCC recurrence at latest evaluation (censor); for TTR, recurrence of LSCC (event), no LSCC recurrence at latest evaluation, including patient's death (censor); for LRC, local and/or regional recurrence of LSCC (event), no local or regional LSCC recurrence at latest evaluation, including patient's death (censor); for TTDR, distant recurrence of LSCC (event), no distant LSCC recurrence at latest evaluation, including patient's death (censor); for LEDFS, death of any cause or laryngo-esophageal dysfunction (event, defined as any of the following: tracheostomy positioned/persisting $>$ 6 months after treatment, gastrostomy tube positioned/persisting $>$ 6 months after treatment, dysphagia requiring nasogastric tube placement $>$ 6 months after treatment, aspiration unresponsive to rehabilitation with acute/chronic aspiration pneumonia, indication to TL for any reason), patient alive at latest evaluation without laryngoesophageal dysfunction (censor).

Assuming the existence of competitive causes of death, OS was defined as the primary outcome, and DSS, CUD, RFS, TTR, LRC, TTDR, and LEDFS as secondary outcomes. Actuarial estimates and 95 % confidence intervals (CI) were calculated with the Kaplan-Meier method. Unadjusted differences between treatment patterns in terms of survival outcomes were estimated with the log-rank test. The population was then clustered by relevant tumor-related factors (*i.e.*, T and N category, tumor epicenter) and univariate analysis was repeated. In order to balance sub-cohorts with different treatment patterns, a propensity score

matching (PSM) method was utilized with the following technical aspects: matching variable was TL *vs*. any larynx-preserving treatment; distance-determining covariates included age, history of smoke (yes/no), excessive alcohol consumption (yes/no), tumor epicenter (glottic/supraglottic), T category, degree of mobility impairment (hypomobility *vs*. fixation), N status (N0 *vs*. N+), perineural invasion (yes/no), lymphovascular invasion (yes/no), margin status (R0 *vs*. R1 *vs*. NST), and ECOG PS (0 *vs*. 1 *vs*. 2); 1:1 optimal full matching without replacement method was used; propensity score was estimated with logistic regression using a generalized linear model.

Results

From 434 patients of the updated ARYFIX database, 5 affected by subglottic cancer, 4 who received surgery after CT (2 TL, 2 OPHL), and 19 who received unimodal NST were excluded. The latter subgroup was excluded since most (n = 17) patients were undertreated (12 T3N0, 2 T4aN0, 1 T3N2, 2 T4aN2) due to ineligibility to CT. Thus, the study included 406 patients.

Demographic and clinicopathological characteristics are detailed in Table 2. Mean age at presentation was 63.9 years (range: 36–90). Briefly, most patients were male (88.9 %), chronic smokers (87.4 %), and affected by a locally advanced (T3 in 57.1 %, T4a in 36.5 %) node-negative (66.3 %) LSCC. Primary treatment included surgery in 349 (86.0 %) patients, of whom 205 (50.5 %) underwent TL and 144 (35.5 %) OPHL. Adjuvant (C)RT followed surgery in 161 (39.7 %) cases. Fifty-seven (14.0 %) patients received a definitive NST. Patterns of treatment are detailed in Table 3. Overall, 5 patterns of treatment were identified: TL (70 patients, 17.2 %), TL followed by (C)RT (135 patients, 33.3 %), OPHL (118 patients, 29.1 %), OPHL followed by (C)RT (26 patients, 6.4 %), and definitive NST (57 patients, 14.0 %). Significant differences among treatment patterns were found in terms of relevant clinicopathological features, as summarized in Table 4.

Overall, 5- and 10-year estimates were 72.0 % (95 % CI: 66.8–77.6) and 56.3 % (95 % CI: 48.7–65.2) for OS, 86.2 % (95 % CI: 82.2–90.5) and 80.2 % (95 % CI: 73.9–87.0) for DSS, 64.7 % (95 % CI: 59.4–70.4) and 51.8 % (95 % CI: 44.5–60.3) for RFS, 80.4 % (95 % CI: 76.0–85.1) and 78.8 % (95 % CI: 73.9–84.0) for TTR, 88.4 % (95 % CI: 84.8–92.2) and 87.4 % (95 % CI: 83.3–91.7) for LRC, 87.8 % (95 % CI: 83.9–91.8) and 87.0 % (95 % CI: 82.9–91.3) for TTDR, 16.5 % (95 % CI: 11.6–21.1) and 29.7 % (95 % CI: 20.6–37.8) for CUD, 84.2 % (95 % CI: 78.8–90.0) and 82.9 % (95 % CI: 77.0–89.2) for LEDFS, respectively. Unadjusted comparison did not show superior outcomes for TL with/without (C)RT *vs*. larynx-preservation treatment of any type (Table 4, Supplementary Fig. 1). Univariable effect of the treatment pattern on OS, DSS, RFS, TTR, LRC, TTDR, CUD (Supplementary Fig. 2), and LEDFS is reported in Table 5.

PSM, based on TL with/without (C)RT *vs*. larynx-preservation treatment of any type as matching variable, resulted in an adequate balance (standardized mean difference: 0.008; Supplementary Fig. 3). The PSM-multivariable-adjusted effect of the treatment pattern on OS, DSS, RFS, TTR, LRC, TTDR, CUD, and LEDFS is reported in Table 6: substantial differences were found when considering treatment patterns separately. Briefly, (i) OPHL not followed by adjuvant treatment was associated with the best prognostic profile; (ii) compared to OPHL, NST was associated with increased CUD, and reduced LRC and TTDR, which translated into significantly reduced OS and DSS; (iii) TL followed by adjuvant treatment was associated with relatively favorable outcomes, in contrast to TL alone.

Univariate subgroup analysis, including all the prognostic outcomes considered in the study (Fig. 1), is reported in supplementary tables as follows: T2N0 and T3N0 patients (Supplementary Table 1), T4aN0 patients (Supplementary Table 2), glottic T2N0 and T3N0 patients (Supplementary Table 3), glottic T4aN0 patients (Supplementary Table 4), supraglottic T2N0 and T3N0 patients (Supplementary Table 5), node-positive patients (Supplementary Table 6), T2 and T3 node-positive patients (Supplementary Table 7), N1 patients (Supplementary Table 8), and N2/3 patients (Supplementary Table 9).

In order to provide a more relevant grouping in terms of index decision-making, a further survival analysis was performed after clustering patients into the following 3 cohorts: OPHL ± (C)RT, NST, and TL ± (C)RT. Overall, this clustering confirmed that: (i) OPHL-based treatment is associated with optimal outcomes, particularly for T2/T3N0 MI-LSCC; (ii) NST implied decreased LRC, but were associated with the best survival outcomes in node-positive MI-LSCC; (iii) TL-based treatment provided the best LRC, but CUD was the highest in this cohort (Supplementary Table 10; Supplementary Fig. 4).

Table 2
Demographic and clinicopathologic information. ENE, extranodal extension; IQR, interquartile range; OPHL, open partial horizontal laryngectomy. *2 chronic smokers with no information on alcohol consumption, 1 subject with no alcohol excessive consumption and no information of smoking; **Distribution after multiple imputation; ***pT in patients who were operated on, cT in patients who received definitive non-surgical treatment. ****In patients who received surgery.

Characteristic		Median (IQR)/distribution (N = 406)
Demographics and risk factors	Age	64 years (57–72)
	Gender	Male: 361 (88.9 %) Female: 45 (11.1 %)
	Smoke and excessive alcohol consumption	None: 36 (8.9 %) Only smokers: 196 (48.3 %) Only alcohol excessive consumption: 3 (0.7 %) Both: 157 (38.7 %) Incomplete information: 14 (3.4 %)*
	ECOG performance status	Class 0: 186 (45.8 %) [285 (70.2 %)]** Class 1: 62 (15.3 %) [103 (25.4 %)]** Class 2: 14 (3.4 %) [18 (4.4 %)]** Unknown: 144 (35.5 %) [0 (0 %)]**
Tumor characteristics	Subsite (epicenter)	Glottis: 278 (68.5 %) Supraglottis: 128 (31.5 %)
	Grade	G1: 32 (7.9 %) G2: 223 (55.9 %) G3: 101 (24.9 %) GX: 50 (12.3 %)
	T category***	T2: 26 (6.4 %) T3: 232 (57.1 %) T4a: 148 (36.5 %)
	Nodal metastases	No: 269 (66.3 %) Yes, without ENE: 86 (21.2 %) Yes, with ENE: 51 (12.6 %)
	Perineural invasion	Pn0: 224 (55.1 %) Pn1: 120 (29.6 %) PnX: 62 (15.3 %)
	Vascular invasion	V0: 249 (61.3 %) V1: 95 (23.4 %) VX: 62 (15.3 %)
Treatment characteristics	Treatment	Total laryngectomy ± (neo) adjuvant therapy: 205 (50.5 %) OPHL ± (neo)adjuvant therapy: 144 (35.5 %) Definitive non-surgical treatment: 57 (14.0 %)
	Margin status (n = 349) ****	R0: 326 (93.4 %) R1: 21 (6.0 %) RX: 2 (0.6 %)

Discussion

The findings of the present study led to the rejection of the hypothesis that TL with or without RT, regardless of other clinicopathological factors, provides the best outcome in patients affected by MI-LSCC.

Table 3
Patterns of treatment. CRT, chemoradiotherapy; iCT, induction chemotherapy; OPHL, open partial horizontal laryngectomy; RT, radiotherapy.

Treatment distribution (N = 406)
• Total laryngectomy (70, 17.2 %)
• Total laryngectomy + adjuvant therapy (135, 33.3 %)
o Adjuvant RT (98, 24.1 %)
o Adjuvant CRT (37, 9.1 %)
• OPHL (118, 29.1 %)
o Type IIA (76, 18.7 %)
o Type IIB (18, 4.4 %)
o Type IIIA (23, 5.7 %)
o Type IIIB (1, 0.2 %)
• OPHL + adjuvant therapy (26, 6.4 %)
o Type IIA + adjuvant RT (9, 2.2 %)
o Type IIA + adjuvant CRT (0, 0 %)
o Type IIB + adjuvant RT (7, 1.7 %)
o Type IIB + adjuvant CRT (4, 1.0 %)
o Type IIIA + adjuvant RT (5, 1.2 %)
o Type IIIA + adjuvant CRT (0, 0 %)
o Type IIIB + adjuvant RT (1, 0.2 %)
o Type IIIB + adjuvant CRT (0, 0 %)
• Definitive non-surgical treatment (57, 14.0 %)
o CRT (40, 9.9 %)
o iCT + RT (5, 1.2 %)
o iCT + CRT (12, 3.0 %)

Thus, a proportion of MI-LSCC patients can be successfully treated with conservative strategies, and the identification of good candidates for such treatment is the logical next goal in this research field. As reported in other studies [15,16], LEDFS was relied on to weigh relevant functional impairment in outcomes, thus conceptually distinguishing mere anatomical maintenance from functional preservation of the larynx [17,18].

MI-LSCC represents a distinct entity compared with mobility-intact LSCC, as functional impairment at presentation also implies extension to prognostically relevant areas [3,19,20] and difficulty in achieving functionality of the (neo-)larynx after treatment [16,21,22]. A spectrum of clinical presentations ranging from mildly reduced mobility of the true vocal cord to fixed VCAU characterizes patients with MI-LSCC. However, the weak inter-observer reliability of such an endoscopic finding prevents granular distinction of MI patterns relative to the entity (*i.e.*, paresis *vs.* paralysis) and location (*i.e.*, true vocal cord *vs.* arytenoid) of motion loss [4]. Although impaired mobility may influence decision-making at different levels [23,24], previous studies have not identified an optimal strategy for MI-LSCC, and therefore guidelines often rely upon scientific evidence for LSCC in general [25,26]. Moreover, as for any LSCC, patient preferences and orientation of the local multidisciplinary team are likely to play an important role in treatment decisions. In the present cohort, treatments were equally distributed between TL (50.5 %) and conservative treatments (49.5 %). Within the latter group, however, OPHL was overrepresented (35.5 %) compared to NST (14.0 %), mirroring the propensity towards conservative surgery in the institutions that contributed to the study. A recent study based on a North American cancer registry observed a higher representation of NST compared to conservative surgical strategies in a large cohort of cT3 MI-LSCC [2]. Compared to the present series, this discrepancy suggests a diversity of larynx-preservation policies in different geographical areas. Of note, imbalance in the distribution of conservative strategies introduces a bias, which must be considered when interpreting the results. Moreover, to maintain adequate statistical power, sequential (*i.e.*, induction CT + (C)RT) *vs.* concomitant (*i.e.*, CRT) combination of non-surgical modalities could not be assessed separately. Thus, response to induction CT could not be ascertained as a predictor of radiosensitivity in MI-LSCC. Considering the advantages after CT-induced laryngeal

Table 4
Main clinicopathological differences between the five patterns of treatment and comparison in terms of oncologic outcomes between patients receiving upfront total lateryngectomy (TL)-based treatment *vs.* open partial horizontal laryngectomy (OPHL)-based treatment *vs.* non-surgical treatment. 5y/10y, estimate at 5/10 years; (C)RT, radiotherapy with/without chemotherapy; IQR, interquartile range; NA, not applicable; PS, performance status; n, numerosity of sample/population. *pT in patients who were operated on, cT in patients who received definitive non-surgical treatment; **$p < 0.001$ also when comparing groups in terms of pre-imputation distribution of ECOG PS.

Characteristic		TL	TL+(C)RT	OPHL	OPHL+(C)RT	Non-surgical treatment	P-value
Median age in years (IQR)		69.5 (60.3 – 78.0)	65.0 (55.5 – 73.0)	61.0 (57.0 – 67.0)	61.0 (54.0 – 65.8)	67.0 (61.0 – 72.0)	**<0.001**
Subsite (%)	**Glottis (n = 278)**	51 (72.9 %)	81 (60.0 %)	102 (86.4 %)	16 (61.5 %)	28 (49.1 %)	**<0.001**
	Supraglottis (n = 128)	19 (27.1 %)	54 (40.0 %)	16 (13.6 %)	10 (38.5 %)	29 (50.9 %)	
T category* (%)	**T2 (n = 26)**	1 (1.4 %)	3 (2.2 %)	21 (17.8 %)	0 (0.0 %)	1 (1.8 %)	**<0.001**
	T3 (n = 232)	48 (68.6 %)	35 (25.9 %)	81 (68.6 %)	18 (69.2 %)	50 (87.7 %)	
	T4 (n = 148)	21 (30.0 %)	97 (71.9 %)	16 (13.6 %)	8 (30.8 %)	6 (10.5 %)	
N status (%)	**N0 (n = 269)**	57 (81.4 %)	64 (47.4 %)	103 (87.3 %)	8 (30.8 %)	37 (64.9 %)	**<0.001**
	N+ (n = 137)	13 (18.6 %)	71 (52.6 %)	15 (12.7 %)	18 (69.2 %)	20 (35.1 %)	
Margin status (%)	**R0**	70 (100.0 %)	125 (92.6 %)	112 (94.9 %)	19 (73.1 %)	NA	**<0.001**
	R1	0 (0.0 %)	10 (7.4 %)	4 (3.4 %)	7 (26.9 %)	NA	
	NA	0	0	2 (1.7 %)	0	NA	
ECOG PS (%)	**0**	39 (55.7 %)	80 (59.3 %)	103 (87.3 %)	21 (80.8 %)	47 (82.5 %)	**<0.001****
	1	21 (30.0 %)	45 (33.3 %)	15 (12.7 %)	5 (19.2 %)	9 (15.8 %)	
	2	10 (14.3 %)	10 (7.4 %)	0 (0.0 %)	0 (0.0 %)	1 (1.7 %)	

Outcome	TL w/wo (C)RT	OPHL w/wo (C)RT	Non-surgical treatment	P-value
Overall survival	5y: 56.8 % 10y: 67.8 %	5y: 86.2 % 10y: 68.8 %	5y: 76.4 % 10y: 67.9 %	**<0.001**
Disease-specific survival	5y: 78.9 % 10y: 78.9 %	5y: 93.6 % 10y: 84.2 %	5y: 85.1 % 10y: 81.4 %	0.055
Recurrence-free survival	5y: 52.3 % 10y: 35.4 %	5y: 79.8 % 10y: 65.7 %	5y: 59.4 % 10y: 56.5 %	**<0.001**
Locoregional control	5y: 92.1 % 10y: 92.1 %	5y: 90.2 % 10y: 85.2 %	5y: 79.8 % 10y: 71.0 %	**0.004**
Time-to-distant-recurrence	5y: 81.8 % 10y: 81.8 %	5y: 94.2 % 10y: 94.2 %	5y: 88.5 % 10y: 84.1 %	**0.021**
Cumulative incidence of cancer-unrelated death	5y: 72.0 % 10y: 48.7 %	5y: 92.0 % 10y: 81.7 %	5y: 89.8 % 10y: 83.4 %	**<0.001**

Table 5
Prognostic outcomes at 5 and 10 years of the different patterns of treatment. (C)RT, radiotherapy with/without chemotherapy; CUD: cancer-unrelated death; DSS, disease-specific survival; LEDFS, laryngoesophageal dysfunction-free survival; LRC, locoregional control; NA, not available; OPHL, open partial horizontal laryngectomy; OS, overall survival; RFS, recurrence-free survival; TL, total laryngectomy; TTDR, time-to-distant-recurrence; TTR, time-to-recurrence. *10-year estimate was not available, 82-month rate is reported.

Treatment pattern	5-year OS	10-year OS	P-value	5-year DSS	10-year DSS	P-value
OPHL (n = 118)	88.2 %	73.8 %	**<0.001**	95.3 %	88.4 %	**0.024**
OPHL + (C)RT (n = 26)	79.0 %	NA (32.9 % *)		86.4 %	NA (48.0 % *)	
NST (n = 57)	76.4 %	67.9 %		85.1 %	81.4 %	
TL (n = 70)	58.0 %	46.4 %		80.5 %	80.5 %	
TL + (C)RT (n = 135)	56.0 %	34.5 %		78.1 %	78.1 %	

Treatment pattern	5-year RFS	10-year RFS	P-value	5-year TTR	10-year TTR	P-value
OPHL (n = 118)	80.3 %	69.5 %	**<0.001**	87.0 %	85.2 %	**0.008**
OPHL + (C)RT (n = 26)	80.0 %	NA (33.3 % *)		84.0 %	NA (84.0 % *)	
NST (n = 57)	59.4 %	56.5 %		68.4 %	65.0 %	
TL (n = 70)	58.4 %	46.7 %		85.6 %	85.6 %	
TL + (C)RT (n = 135)	48.9 %	30.1 %		75.6 %	75.6 %	

Treatment pattern	5-year LRC	10-year LRC	P-value	5-year TTDR	10-year TTDR	P-value
OPHL (n = 118)	89.7 %	87.9 %	0.076	94.4 %	94.4 %	**0.005**
OPHL + (C)RT (n = 26)	87.7 %	NA (87.7 % *)		90.7 %	NA (90.7 % *)	
NST (n = 57)	75.3 %	75.3 %		89.6 %	85.7 %	
TL (n = 70)	91.9 %	91.9 %		87.1 %	87.1 %	
TL + (C)RT (n = 135)	92.3 %	92.3 %		79.2 %	79.2 %	

Treatment pattern	5-year CUD	10-year CUD	P-value	5-year LEDFS	10-year LEDFS	P-value
OPHL (n = 118)	7.5 %	16.6 %	**0.002**	79.1 %	67.2 %	**0.004**
OPHL + (C)RT (n = 26)	8.7 %	NA (31.5 % *)		67.1 %	NA (28.0 % *)	
NST (n = 57)	10.2 %	16.6 %		64.9 %	64.9 %	
TL (n = 70)	28.0 %	42.4 %		NA	NA	
TL + (C)RT (n = 135)	28.3 %	55.8 %		NA	NA	

Table 6
Summary of propensity score-matched, multivariable-adjusted effect of treatment pattern on prognostic outcomes. 95% CI, 95%-confidence interval; (C)RT, (chemo)radiotherapy; CUD: cancer-unrelated death; DSS, disease-specific survival; LEDFS, laryngoesophageal dysfunction-free survival; LRC, locoregional control; OPHL, open partial horizontal laryngectomy; OR, odds ratio; OS, overall survival; RFS, recurrence-free survival; TL, total laryngectomy; TTDR, time-to-distant-recurrence; TTR, time-to-recurrence.

Treatment pattern	OS		DSS	
	OR (95 % CI)	p-value	OR (95 % CI)	p-value
OPHL (n = 118)	Ref		Ref	
OPHL + (C)RT (n = 26)	3.52 (1.20–10.29)	**0.021**	3.53 (0.76–16.37)	0.107
NST (n = 57)	10.46 (3.04–35.96)	**<0.001**	15.48 (3.17–75.73)	**<0.001**
TL (n = 70)	6.62 (2.92–14.99)	**<0.001**	8.49 (2.10–34.31)	**0.003**
TL + (C)RT (n = 135)	1.94 (0.77–4.90)	0.162	1.83 (0.40–8.32)	0.435

Treatment pattern	RFS		TTR	
	OR (95 % CI)	p-value	OR (95 % CI)	p-value
OPHL (n = 118)	Ref		Ref	
OPHL + (C)RT (n = 26)	2.36 (0.66–8.41)	0.185	2.40 (0.43–13.48)	0.320
NST (n = 57)	7.98 (2.22–28.73)	**0.001**	15.52 (2.29–105.01)	**0.005**
TL (n = 70)	3.77 (1.45–9.82)	**0.007**	1.84 (0.36–9.35)	0.462
TL + (C)RT (n = 135)	1.68 (0.63–4.43)	0.297	1.43 (0.28–7.25)	0.665

Treatment pattern	LRC		TTDR	
	OR (95 % CI)	p-value	OR (95 % CI)	p-value
OPHL (n = 118)	Ref		Ref	
OPHL + (C)RT (n = 26)	1.43 (0.23–8.80)	0.698	20.54 (2.50–168.99)	**0.005**
NST (n = 57)	29.58 (3.30–265.43)	**0.002**	32.44 (4.83–218.9)	**<0.001**
TL (n = 70)	1.10 (0.15–8.13)	0.925	27.10 (4.09–179.59)	**<0.001**
TL + (C)RT (n = 135)	0.19 (0.02–1.70)	0.139	12.71 (2.05–78.65)	**0.006**

Treatment pattern	CUD		LEDFS	
	OR (95 % CI)	p-value	OR (95 % CI)	p-value
OPHL (n = 118)	Ref		Ref	
OPHL + (C)RT (n = 26)	2.58 (0.46–14.46)	0.281	2.92 (0.68–12.61)	0.150
NST (n = 57)	8.77 (1.43–53.82)	**0.019**	5.85 (0.99–34.68)	0.052
TL (n = 70)	6.25 (2.18–17.89)	**<0.001**	NA	
TL + (C)RT (n = 135)	2.24 (0.59–8.53)	0.238	NA	

remobilization in patients affected by MI-LSCC [24], this aspect is worth investigating in larger and more balanced series.

In the present study, five patterns of treatment were identified: TL, TL followed by (C)RT, OPHL, OPHL followed by (C)RT, and definitive NST. The distribution of relevant clinicopathological features varied significantly across treatment groups. For instance, T4a MI-LSCC were remarkably more frequent in the TL + (C)RT cohort; node-positive cases were prevalent in patients treated with OPHL + (C)RT or TL + (C)RT; the NST cohort was associated with the highest rate of supraglottic MI-LSCC. Interestingly, performance status was significantly worse in the TL and TL + (C)RT cohorts, with roughly 40 % of patients classified as ECOG PS grade 1 or 2. These differences, thoroughly reported in Table 4, indicate a significant selection of treatment in this population and make cohorts ineligible for crude comparison. The strategies adopted to address this selection bias included: 1) clustering into more homogeneous subgroups based on tumor characteristics; and 2) performing multivariable PSM analyses that comprehensively adjust outcomes for potential confounders.

In T2-3 N0 MI-LSCC, OPHL was associated with the best outcomes, although not reaching statistical significance. Of note, differences among treatment patterns were substantially mitigated when focusing

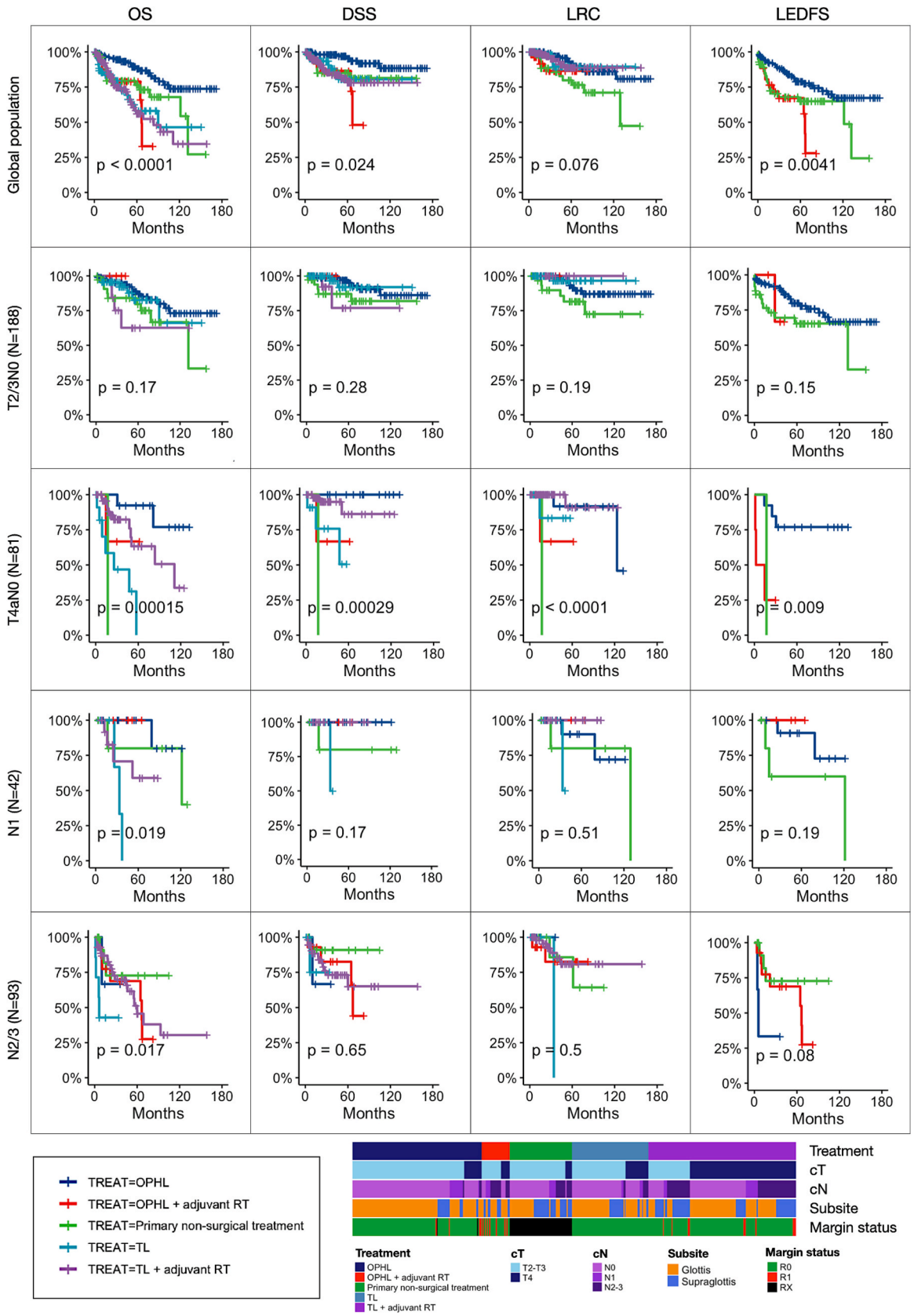

Fig. 1. Panel displaying pattern of treatment-specific outcomes, including overall survival (OS), disease-specific survival (DSS), locoregional control (LRC), and laryngoesophageal dysfunction-free survival (LEDFS), in the entire population and clinically relevant cohorts. The heatmap shows the distribution of relevant variables in the different treatment groups. The exact N category could not be retrieved in 1 patient with node-positive laryngeal squamous cell carcinoma.

on DSS. In this subgroup, NST showed a mild, non-significant increase in locoregional relapse. Interestingly, distant failure was significantly more frequent in patients who received TL with adjuvant (C)RT. While LEDFS at 5 years was lower in patients treated with NST compared with OPHL, no significant differences were found at 10 years. However, functional results were substantially worsened when adjuvant treatment was added to OPHL. Results observed in T2-3 N0 MI-LSCC did not substantially differ when considering glottic and supraglottic tumors separately. Overall, one can conclude that multiple treatments are available for T2-3 N0 glottic and supraglottic MI-LSCC, with outcomes being rather similar after proper selection. This means that even in MI-LSCC, OPHL and NST should be considered as potential treatment options for patients who would be otherwise considered good candidates for conservative treatments if diagnosed with normal laryngeal mobility.

In the T4aN0 MI-LSCC cohort, the large majority of patients underwent TL with adjuvant (C)RT, as per standard of care. Few patients received TL alone, and the high cancer-unrelated mortality in this group suggests that general conditions and/or complications following TL played a role in the decision of omitting adjuvant RT. Interestingly, a small cohort of patients who received OPHL (n = 13) showed very good outcomes, with >75 % of these subjects being alive with a functional neo-larynx at 10 years after surgery. As previously demonstrated by Succo et al., highly selected patients with low-volume T4a LSCC might be considered for OPHL as a single-modality treatment in the absence of other risk factors such as positive margins and nodal metastases [27]. Although standard of care should be considered as the first choice, the very good outcomes shown in the present and other studies [28–30] mandate researching and validating factors that could reliably identify candidates for conservative surgery, even in the presence of limited extralaryngeal extension.

Node-positive MI-LSCC represented one-third of the population and showed significant differences in treatment-specific outcomes. N1 MI-LSCC were mostly treated conservatively (54.8 %) and showed relatively similar outcomes in different treatment groups. N2-3 MI-LSCC received TL with/without adjuvant therapy in most cases. Remarkably, N2-3 MI-LSCC treated with NST (n = 14) were associated with the best prognosis in terms of both survival and LEDFS. Moreover, while for other treatments a decrease in outcomes could be observed when comparing node-negative *vs.* node-positive MI-LSCC, outcomes of patients treated with NST were rather constant regardless of nodal status. These findings are consistent with those reported by Choi et al., where the survival benefit of TL over NST in cartilage-invading T4a disease was not significant in patients with N2 or N3 LSCC [31].

When focusing on treatment-specific outcomes adjusted by potential confounders, OPHL showed an optimal profile in terms of all the prognostic endpoints, which was confirmed also when considering all OPHL patients regardless of adjuvant (C)RT. This also applies to LEDFS, which, though with loss of significance at multivariable PSM analysis, was the highest in patients treated with OPHL. Although OPHL constitutes an acute functional injury to the pharyngo-laryngeal axis, harvesting of the "pexy", which stably mimics laryngeal elevation that occurs during physiological deglutition, provides the patient with a "safer" (*i.e.*, aspiration-inhibiting) anatomy. This is consistent with the observations by Crosetti et al. [32] and Cantaffa et al. [33] that after OPHL the neo-larynx is relatively resistant to functional aging phenomena that are observed in healthy individuals. Indeed, the rate of persistent dysphagia and need for functional laryngectomy were relatively low in a population of 100 elderly patients who underwent OPHL [34]. These findings reinforce the concept that OPHL represents a very robust choice in adequately selected patients, even if larynx mobility is impaired. Nonetheless, it is worth specifying that in centers participating in this study OPHL was indicated after a meticulous and comprehensive assessment of the patient, with neither LSCC extension [35] nor laryngeal mobility constituting sufficient elements for appropriate decision making if other relevant aspects such as general conditions, comorbidities, social context, feasibility of rehabilitation, and patient preferences are neglected [13]. Moreover, the type of OPHL also has important implications on post-operative functionality of the neo-larynx and thus plays a role in the decision-making process [36].

The Achille's tendon of OPHL in this population is evident when focusing on patients who received adjuvant (C)RT after conservative surgery. The latter cohort displayed a combination of high cancer-unrelated mortality and poor DSS, which, coherently with results of a multi-institutional study on 130 LSCC patients treated with OPHL + (C)RT [37], was evident only beyond 5 years of follow-up. Comparing clinicopathological factors of the OPHL and OPHL + (C)RT groups, the main reasons that led to indicate adjuvant therapy were positive margins and nodal metastases. Of note, roughly one-fifth (18.1 %) of patients treated with upfront OPHL underwent (C)RT after surgery, highlighting that a non-negligible proportion of OPHL indications would probably have been reconsidered in retrospect. However, if one considers the indications to adjuvant (C)RT in head and neck cancer [38,39], some high-risk features such as positive/close margins, perineural invasion, lymphovascular invasion, and occult nodal disease become known only after surgery. This fact demonstrates that the current clinical practice is characterized by the unmet need of predictive means to obtain such clinically-relevant information before initiating treatment of LSCC [40,41]. On the other hand, risk for primary tumor and nodal mis-staging can be substantially mitigated via systematic interaction with dedicated radiologists [35] and by meticulously selecting candidates for conservative treatment (Supplementary Table 10) [10]. Overall, OPHL should be avoided in patients with MI-LSCC at high risk of positive margins and/or when clinical nodal burden makes it likely that adjuvant (C)RT would be indicated after surgery.

NST showed a decreased LRC relative to other treatment strategies. This is consistent with other studies: (i) the VA trial showed similar 2-year OS between TL with adjuvant RT *vs.* NST in an advanced stage LSCC population with vocal cord fixed in 56.6 % of cases. However, the rate of salvage laryngectomy was as high as 41 % in patients with vocal cord fixation (*vs.* 29 % in those with mobility-intact LSCC) [42]; (ii) the GETTEC trial, which was halted before completing the planned accrual, reported better 2-year OS (84 %) in patients undergoing TL with adjuvant RT compared with NST (69 %) in a population of 68 patients with MI-LSCC [12]; (iii) a recent National Cancer Database study on 4,861 cases of cT3M0 MI-LSCC reported higher survival in patients receiving surgery *vs.* NST, irrespective of age, gender, ethnicity, insurance status, income, comorbidity, treatment facility, tumor epicenter, and nodal status [2]. Moreover, cancer-unrelated mortality was significantly higher in patients treated with NST. Since the majority of these patients received definitive CRT, this finding is coherent with the long-term observations of the RTOG 91–11 trial, which led to hypothesize a higher rate of long-term toxicity (*e.g.*, chronic aspiration) in subjects treated with a concomitant regimen [43,44].

Conclusions

The present study suggests that TL with/without adjuvant (C)RT does not necessarily provide a survival advantage in all patients with MI-LSCC. Thus, this research confirms that treatment of MI-LSCC, like LSCC in general [10], needs to be individualized based on tumor- and patient-related factors. In patients who are otherwise good candidates for OPHL, the presence of mobility impairment should not be considered an absolute contraindication, provided that local expertise is adequate and tumor extension is comprehensively analyzed by combining endoscopy and imaging. In patients with MI-LSCC who have adequate conditions for conservative treatment but a high risk for positive margins and/or a clinical nodal status suggesting multiple nodal metastases and/or extranodal extension, NST should be preferred over OPHL. This collaborative group's next aims will be (i) to expand the cohort of patients with MI-LSCC who received NST, (ii) in order to separately analyze sequential and concomitant combination of RT and CT in terms

of prognostic outcomes, and (iii) to evaluate the role of transoral laser microsurgery for MI-LSCC.

CRediT authorship contribution statement

Francesca Mularoni: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Filippo Marchi:** Writing – original draft, Investigation, Data curation. **Piergiorgio Gaudioso:** Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Stefano Taboni:** Supervision, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Erika Crosetti:** Visualization, Validation, Supervision, Methodology, Investigation, Data curation. **Andrea Luigi Camillo Carobbio:** Visualization, Validation, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Giovanni Bamfi:** Formal analysis, Data curation. **Giuseppe Anile:** Supervision, Methodology, Data curation. **Luigia Bandolin:** Visualization, Validation, Formal analysis, Data curation. **Maria Baldovin:** Validation, Investigation, Formal analysis, Data curation. **Ilaria Bertotto:** Investigation, Formal analysis, Data curation. **Fabio Busato:** Visualization, Funding acquisition, Formal analysis, Data curation. **Sedat Cağli:** Investigation, Funding acquisition, Formal analysis, Data curation. **Simone Caprioli:** Investigation, Formal analysis, Data curation. **Filippo Carta:** Visualization, Validation, Formal analysis, Data curation. **Giacomo Contro:** Methodology, Investigation, Formal analysis, Data curation. **Francesca Del Bon:** Investigation, Formal analysis, Data curation. **Serap Doğan:** Validation, Investigation, Formal analysis, Data curation. **Matteo Fermi:** Validation, Investigation, Funding acquisition, Formal analysis. **Marta Filauro:** Visualization, Investigation, Funding acquisition, Formal analysis, Data curation. **Milena Fior:** Formal analysis, Data curation. **Francesca Gennarini:** Methodology, Investigation, Data curation. **Chiara Gottardi:** Validation, Investigation, Formal analysis, Data curation. **Mete Gündoğ:** Supervision, Formal analysis, Data curation. **Alessandro Ioppi:** Validation, Methodology, Investigation, Formal analysis, Data curation. **Davide Lancini:** Formal analysis, Data curation. **Marco Lionello:** Visualization, Validation, Supervision, Formal analysis, Data curation. **Alfredo Lo Manto:** Data curation. **Vincenzo Maiolo:** Validation, Data curation. **Cinzia Mariani:** Investigation, Formal analysis, Data curation. **Gino Marioni:** Validation, Supervision. **Valeria Marrosu:** Data curation. **Francesco Mazzola:** Visualization, Data curation. **Nausica Montalto:** Data curation. **Francesco Missale:** Visualization, Investigation, Data curation. **Carlotta Pessina:** Visualization, Validation, Formal analysis, Data curation. **Alberto Paderno:** Visualization, Supervision, Data curation. **Marco Ramanzin:** Data curation. **Marco Ravanelli:** Validation, Supervision, Data curation. **Francesco Rigoni:** Visualization, Investigation, Formal analysis, Data curation. **Alessandra Ruaro:** Data curation. **Tommaso Saccardo:** Visualization, Supervision, Data curation. **Claudio Sampieri:** Validation, Investigation, Formal analysis, Data curation. **Melania Tatti:** Validation, Resources, Data curation. **Alberto Vallin:** Data curation. **Chiara Varago:** Data curation. **Imdat Yüce:** Validation, Data curation. **Elisabetta Zanoletti:** Visualization, Validation, Supervision. **Andy Bertolin:** Writing – review & editing, Visualization, Supervision. **Paolo Bossi:** Writing – review & editing, Visualization, Supervision. **Maria Grazia Ghi:** Writing – review & editing, Validation, Supervision. **Roberto Maroldi:** Writing – review & editing, Validation, Supervision. **Francesco Mattioli:** Writing – review & editing, Validation, Supervision. **Cesare Piazza:** Writing – review & editing, Visualization, Validation. **Raul Pellini:** Writing – review & editing, Validation, Supervision. **Livio Presutti:** Writing – review & editing, Validation, Supervision. **Roberto Puxeddu:** Writing – review & editing, Validation, Supervision. **Alperen Vural:** Writing – review & editing, Visualization, Validation. **Piero Nicolai:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Conceptualization. **Giorgio Peretti:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Giovanni Succo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Marco Ferrari:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2025.107466.

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