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Compartmental tongue surgery for intermediate-advanced squamous cell carcinoma: A multicentric study

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Abstract

Background: A multicentric study was conducted on technical reproducibility of compartmental tongue surgery (CTS) in advanced tongue cancers (OTSCC) and comparison to standard wide margin surgery (SWMS).

Methods: We studied 551 patients with OTSCC treated by CTS and 50 by SWMS. Oncological outcomes were analyzed. A propensity score was performed to compare survival endpoints for the two cohorts.

Results: In the CTS group, survival and prognosis were significantly associated with positive lymph-nodes, extranodal extension, depth of invasion and involvement of the soft tissue connecting the tongue primary tumor to neck lymph nodes (T-N tract), independently from the center performing the surgery. SWMS versus CTS showed a HR Cause-Specific Survival (CSS) of 3.24

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(95% CI: 1.71–6.11; $p < 0.001$); HR Loco-Regional Recurrence Free Survival (LRRFS) of 2.54 (95% CI: 1.47–4.40; $p < 0.001$); HR Overall Survival (OS) of 0.11 (95% CI: 0.01–0.77; $p = 0.03$).

Conclusion: Performing the CTS could provide better CSS and LRRFS than SWMS regardless of the center performing the surgery, in advanced OTSSC.

KEYWORDS

anatomic-based surgery, compartmental surgery, oral tongue cancer, oral tongue SCC, tongue surgery

1 | INTRODUCTION

Oral squamous cell carcinoma (OSCC) represents the 18th most common neoplasm worldwide, with almost 355 000 new cases/year and over 177 000 deaths, as estimated in 2018.[1,2] The most frequent OSCC subsite involved is the mobile oral tongue (OT)[3] and an increasing incidence has been observed among people aged <45 years in the last decades.[4–7]

Surgery represents the first-choice treatment for OTSCC,[8] even though a reliable and standardized procedure has not been universally recognized so far.

The gold standard for stages I-II OTSCC is transoral surgical excision with elective neck dissection if the pathological depth of invasion (DOI) is more than 4 and up to 9 mm.[9,10] Stages III-IV OTSCC, with a DOI ≥10 mm, should be managed by "en-bloc" tumor removal and concomitant neck dissection carrying out a so called standard wide margins surgery (SWMS) or, alternatively, a compartmental surgery (CTS) approach.[11] SWMS is performed removing the tumor with clinically disease-free margins (variably defined as in between 1 and 2 cm), not considering the anatomical structures or preferential tumor cell spreading pathways.[11,12] On the other side, the principles of CTS as proposed by Calabrese et al. in 2011 follow the concept of an "anatomy-based oncologic compartment" containing the primary tumor with all its potential muscular, vascular, nervous, and lymphatic pathways of neoplastic spread.[13]

In CTS, the extrinsic muscles of the tongue, even though partially infiltrated by the neoplasm, are completely dissected from their bony insertions and the concept of "en-bloc" removal is extended to all anatomical structures and stromal tissues connecting the primary to the cervical lymph nodes identified as the "T-N tract."[13–15] A comprehensive clearance of the T-N tract represents the main difference with the SWMS, in which the continuity with cervical lymph nodes is obtained only by dissecting the sublingual area. The first study by Calabrese et al. reported that CTS ensured a better local, loco-regional disease control, overall, and disease-free survivals compared with SWMS.[16]

This study aims to evaluate the oncologic outcomes on a larger cohort of patients affected by OTSCC treated uniformly by CTS in four Italian referral centers, thus also assessing its reproducibility among different Hospitals. To study the prognostic gain obtained applying this kind of standardized surgery, we performed a propensity score (PS) matching evaluation between patients treated by SWMS versus CTS, analyzing OTSCC-related specific outcomes as cause-specific and loco-regional disease control.

2 | METHODS

To evaluate the reproducibility of CTS, a retrospective multicenter cohort study was conducted on a consecutive series of 551 patients with OTSCC undergoing CTS from January 2000 to December 2018 in four centers with significant oncological expertise: the European Institute of Oncology IRCCS (IEO, Milan), the San Maurizio Hospital of Bolzano (BZ), the National Cancer Institute IRCCS (INT, Milan), and the ASST Spedali Civili University Hospital of Brescia (BS).

To compare the prognosis between CTS and SWMS, a control group consisting in a series of 50 consecutive patients with clinical intermediate-advanced OTSCC submitted to SWMS at the Otolaryngology – Head and Neck Surgery Department of a single center (IEO) from January 1995 to December 1999, was selected.

All clinical and socio-demographic, surgical, histopathological, and follow-up data were extracted and collected.

Inclusion criteria were: (1) intermediate-advanced clinical stage III–IV OTSCC; (2) primary head and neck cancers; (3) CTS with or without extension to adjacent oropharyngeal subsites (ipsilateral palatine tonsil and/or base of tongue).

CTS performed were defined according to the Ansarin et al. classification including glossectomies Type III to V.[17]

A written informed consent was signed by all patients.

2.1 | Follow-up

It was scheduled for all patients for at least 5 years from the end of treatment according to the NCCN guidelines.[8] To conduct the PS, we reviewed the follow-up data of the 50 patients treated by SWMS at IEO before 2000, updating their clinical status at the end of 2020.

2.2 | Statistical analysis

Demographic and clinical–pathological characteristics were expressed as relative frequencies and percentages according to the related treating center (IEO, BS, INT, BZ) for categorical variables, and median and interquartile range for continuous variables. χ^2 and Kruskal–Wallis tests were used to assess differences across the four centers for categorical and continuous variables, respectively. Two main analyses were carried out: on the CTS cohort alone, and by comparing CTS versus SWMS cohorts.

Univariate models were performed to evaluate the associations of potential prognostic factors (e.g., T-N tract, type of surgery, differences in staging between the 7th [7TNM] and 8th TNM Edition [8TNM], extra-nodal extension [ENE], margins, type of adjuvant treatment, and smoking pack/year) with clinical outcomes (overall [OS], cause-specific [CSS], loco-regional recurrence free [LRRFS], and distant metastasis free survivals [DMFS]). Survival curves were estimated using the Kaplan–Meier method, and differences between groups were investigated by the Log-rank test. We also assessed the independent prognostic role of significant clinical variables with multivariable Cox Proportional Hazard models, adjusting for different centers to account for the possible heterogeneity coming from multicentric data. Hazard ratio (HR) with 95% confidence intervals (CI) from multivariable Cox Proportional Hazard models was reported for each variable.

To investigate factors associated with loco-regional relapse, a survival analysis considering competing risks was adopted: all events other than loco-regional were considered competitive and analyzed within a competing risk framework applying the Gray test.[18]

We calculated a PS using multivariable logistic models to compare CTS and SWMS cohorts, including factors that resulted significantly associated with the treatment (CTS vs. SWMS) in univariate logistic analysis. PS reflect the probability that a patient received CTS or SWMS based on baseline characteristics related to his prognostic factors. We evaluated differences between the types of surgery in the whole cohort, stratifying for PS. We stratified patients into mutually exclusive subsets based on the estimated PS by choosing the quantiles of the PS distribution as thresholds.[19]

Since each stratum identifies similar values of PS for both CTS and SWMS groups, the effects of type of surgery can be observed on the outcomes. To produce an overall risk, we used the average off each subset.

The two treatment groups had a significantly different median follow-up, thus the time to events was censored at 2 years. PS was calculated by using the R package "MatchIt."[20] All analyses were carried out with R 4.0 software (http://cran.r-project.org/), and p values <.05 were considered statistically significant.

2.3 | Sensitivity analysis

By using PS, patients receiving SWMS were matched on a one-to-two basis with subjects receiving CTS. Thus, we identified a subgroup of 150 patients (100 CTS vs. 50 SWMS) with similar prognostic factors such as pathological (p) tumor (T), pathological node (N), multifocality, and adjuvant treatments in terms of (chemo) radiotherapy (C)RT (Table S1).

A multivariable sensitivity analysis was also conducted on the whole cohort (601 patients) adjusting for PS and type of surgery (SWMS vs. CTS).

Moreover, we built a second score based on the clinical stage (cTNM score) as it determines the type of surgical approach. One hundred subjects identified from the CTS group were matched with 50 SWMS patients, maintaining the original proportions among centers: IEO = 75% of patients; INT = 3% of patients; BZ = 3% of patients, and BS = 19% of patients.

3 | RESULTS

Clinical–pathological characteristics of the whole study population (CTS and SWMS) are reported in Table 1.

3.1 | Survival outcomes comparing CTS versus SWMS for the whole cohort stratified for PS and for the 150 matched subgroup

For the SWMS 50 patients, the median follow-up was 1.7 years (0–20.1), with a follow-up recorded up to

TABLE 1 Clinical-pathological and tumor characteristics of the study population ($N = 601$ patients).

		TOT ($n = 551$)	IEO ($n = 413$)	INT ($n = 20$)	BZ ($n = 20$)	BS ($n = 98$)	*p*-value
Compartmental Tongue Surgery from January 2000 to December 2018 in 4 Italian Centers							
Median age (IQR)		58 (47–67)	56 (45–65)	57 (47–66)	63 (57–71)	66 (56–76)	<0.001
Gender	F	172 (31.20)	126 (30.50)	8 (40)	4 (20)	34 (34.69)	0.49
	M	379 (68.80)	287 (69.49)	12 (60)	16 (80)	64 (65.30)	
Smoking pack/year	Never	177 (32.12)	117 (28.32)	9 (45)	14 (70)	37 (37.75)	0.004
	<20	78 (14.15)	64 (15.49)	3 (15)	1 (5)	10 (10.20)	
	≥20	296 (53.72)	232 (57.17)	8 (40)	5 (25)	51 (52.04)	
Alcohol	Never	275 (49,9)	205 (49.63)	5 (25)	2 (10)	63 (64.28)	0.001
	Current/former	264 (47.91)	208 (50.36)	14 (70)	7 (35)	35 (35.71)	
	Unknown	12 (2.17)	0 (0)	1 (5)	11 (55)	0 (0)	
Clinical T (Ed. VII)	T1–T2	153 (27.76)	130 (31.47)	8 (40)	7 (35)	8 (8.16)	<0.001
	T3–T4	398 (72.23)	283 (68.52)	12 (60)	13 (65)	90 (91.83)	
Clinical N (Ed. VII)	N0	223 (40.47)	155 (37.53)	13 (65)	7 (35)	48 (48.97)	0.01
	N+	328 (59.52)	258 (62.46)	7 (35)	13 (65)	50 (51.02)	
Pathological T (8TNM)	T1–T2	119 (21.59)	81 (20.09)	8 (40)	6 (30)	22 (22.44)	0.13
	T3-T4	432 (78.40)	330 (79.90)	12 (60)	14 (70)	76 (77.55)	
Pathological N (7TNM)	N0	197 (35.75)	138 (33.41)	10 (50)	8 (40)	41 (41.83)	0.17
	N+	354 (64.24)	275 (66.58)	10 (50)	12 (60)	57 (58.16)	
Pathological stage (8TNM)	I–II	69 (12.52)	46 (11.11	7 (35)	3 (15)	14 (14.28)	0.02
	III–IV	480 (87.11)	336 (81.53)	13 (65)	17 (85)	84 (85.71)	
	Unknown	2 (0.36)	2 (0.48)	0 (0)	0 (0)	0 (0)	
DOI (mm)	≤5	16 (2.90)	12 (2.90)	0 (0)	1 (5)	3 (3.06)	0.25
	5–10	134 (24.31)	97 (23.48)	9 (45)	7 (35)	21 (21.42)	
	>10	401 (72.77)	304 (73.60)	11 (55)	12 (60)	74 (75.51)	
T-N tract	Free from disease	415 (75.31)	343 (83.05)	11 (55)	12 (60)	49 (50.00)	<0.001
	Involved by disease	136 (24.68)	70 (16.94)	9 (45)	8 (40)	49 (50.00)	
Multifocality	No	529 (96.00)	402 (97.33)	19 (95)	19 (95)	89 (90.81)	0.01
	Yes	22 (3.99)	11 (2.66)	1 (5)	1 (5)	9 (09.18)	
Vascular invasion	No	457 (82.94)	372 (90.07)	17 (85)	17 (85)	51 (52.04)	<0.001
	Yes	94 (17.05)	41 (9.92)	3 (15)	3 (15)	47 (47.95)	
Perineural invasion	No	372 (67.51)	328 (78.41)	11 (55)	8 (40)	25 (25.51)	<0.001
	Yes	179 (32.48)	85 (20.58)	9 (45)	12 (60)	73 (74.48)	
ENE	No	371 (67.33)	273 (66.10)	19 (95)	14 (70)	65 (66.32)	0.03
	Yes	180 32.665)	140 (33.89)	1 (5)	6 (30)	33 (33.67)	
Margins	Free	451 (81.85)	349 (84.50)	16 (80)	16 (72.73)	70 (71.42)	0.05
	Microscopic involvement	49 (8.89)	28 (6.77)	2 (10)	2 (9.09)	17 (17.34)	
	Close (<1 mm)	50 (9.07)	36 (8.71)	2 (10)	2 (9.09)	10 (10.20)	
	Unknown	1 (0.18)	0 (0)	0 (0)	0 (0)	1 (1.02)	
Adjuvant RT or CRT	No	169 (30.67)	127 (30.75)	6 (30)	10 (50)	26 (26.53)	0.23
	Yes	382 (69.32)	286 (69.24)	14 (70)	10 (50)	72 (73.46)	
Adjuvant CRT	No	375 (68.05)	285 (69)	16 (80)	15 (68.18)	59 (60.20)	0.21
	Yes	176 (31.94)	128 (31)	4 (20)	5 (22.73)	39 (39.79)	
Median follow-up years (min–max)		5.76 (0–18.38)	7.08 (0–18.38)	2.08 (0–2.92)	1.53 (0–2.97)	2.56 (0–11.74)	

TABLE 1 (Continued)

		TOT ($n = 551$)	IEO ($n = 413$)	INT ($n = 20$)	BZ ($n = 20$)	BS ($n = 98$)	*p*-value
Standard Wide Surgical Margins Surgery at IEO from January 1995 to December 1999							
		$n = 50$ (%)					
Median age (IQR)		55.5 (47.25–66)					
Gender	F	17 (34)					
	M	33 (66)					
Smoking pack/year	Never	19 (38)					
	<20	5 (10)					
	≥20	26 (52)					
Alcohol	Never	18 (36)					
	Current/former	29 (58)					
	Unknown	3 (6)					
Clinical T (7TNM)	T1–T2	22 (44)					
	T3–T4	28 (56)					
Clinical N (7TNM)	N0	17 (34)					
	N+	33 (66)					
Pathological T (7TNM)	T1–T2	25 (50)					
	T3–T4	25 (50)					
Pathological N (7TNM)	N0	16 (32)					
	N+	34 (68)					
Stage (7TNM)	I–II	9 (18)					
	III–IV	41 (82)					
Multifocality	No	45 (90)					
	Yes	5 (10)					
Vascular invasion	No	45 (90)					
	Yes	5 (10)					
Extrinsic muscle invasion	No	14 (28)					
	Yes	35 (70)					
	Unknown	1 (2)					
ENE	No	33 (66)					
	Yes	17 (34)					
Margins	Free	43 (86)					
	Microscopic involvement	1 (2)					
	Close	6 (12)					
Adjuvant RT or CRT	No	26 (52)					
	Yes	24 (48)					
Adjuvant CRT	No	45 (90)					
	Yes	5 (10)					
Median follow-up	Years	1.70 (0–20.11)					

Note: The *p* values are obtained for continuous variable with Kruskal–Wallis test and for categorical value with χ^2 test.
Abbreviations: BS, ASST Spedali Civili, Brescia; BZ, San Maurizio Hospital, Bolzan; CRT, chemoradiotherapy; DOI, deep of invasion; ENE, extranodal extension; IEO, European Institute of Oncology, Milan; INT, National Cancer Institute, Milan; IQR, interquartile range; N, lymph node; RT, radiotherapy; T, tumor.

TABLE 2 Cause specific survival (CSS) on the whole cohort ($N = 601$ patients) and stratified for propensity score.

Variable	Contrast	HR	Low.95	Up.95	*p*-value
Age		1.01	1.00	1.02	0.03
T-N tract	Involved by disease vs. not standardly removed + free from disease	2.19	1.42	3.38	<0.001
ENE	Yes vs. no	3.13	2.07	4.73	<0.001
Compartmental surgery (Types III–V glossectomies)	No vs. yes	3.24	1.71	6.11	<0.001

Abbreviation: ENE, extranodal extension.

TABLE 3 Loco-regional recurrence free survival (LRRFS) stratified for propensity score, competing risk: A: on the whole cohort ($N = 601$ patients); B: on the compartmental surgery group ($N = 551$ patients).

Variable	Contrast	HR	Low.95	Up.95	*p*-value
A: LRRFS on the whole cohort (601 patients)					
Age		1.00	0.99	1.02	0.17
Vascular invasion	Yes vs. no	1.71	1.04	2.80	0.03
Extrinsic muscles infiltration	Yes vs. no	1.75	1.04	2.94	0.03
ENE	Yes vs. no	1.75	1.11	2.73	0.01
Adjuvant RT or CRT	Yes vs. no	0.50	0.31	0.80	0.003
Compartmental surgery (Types III–V glossectomies)	No vs. yes	2.54	1.47	4.40	<0.001
B: LRRFS on the compartment surgery group (551 patients)					
pN (7TNM)	N+ vs. N0	4.37	2.53	7.53	<0.001
Vascular invasion	Yes vs. no	1.82	1.08	3.08	0.02
Adjuvant RT or CRT	Yes vs. no	0.33	0.21	0.54	<0.001
DOI (mm)	>10 vs. ≤10	2.34	1.37	4.01	0.001

Note: Adjusted for age and centers.
Abbreviations: CRT, chemoradiotherapy; DOI, depth of invasion; ENE, extranodal extension; N+, pathological lymph nodes; RT, radiotherapy.

December 2020 (Table 1). Table S1 reported the variables included in the PS model. Figure S1 showed 5-years OS and CSS for SWMS.

In the overall cohort of 601 patients (551 CTS and 50 SWMS) stratified by PS, patients treated by SWMS had a 3-time higher risk of dying due to OTSCC (CSS: HR = 3.24, 95% CI: 1.71–6.11; $p < 0.001$; Table 2).

LRRFS on the whole cohort stratified for PS underlined how patients treated by SWMS had more than a two-times higher risk of loco-regional recurrence (LRRFS: HR = 2.54, 95% CI: 1.47–4.40; $p < 0.001$; Table 3A). Therefore, focusing on the T-N tract: regardless of its status (involved or not involved by the disease), if not removed through CTS presented 2.54 times the hazard of developing local recurrences in advanced stage tumors (95% CI: 1.47–4.40; $p < 0.001$; Table 3A).

Concerning the DMFS multivariable analyses on the whole cohort and stratified for PS, no significant difference between the two types of surgery was found (DMFS: HR = 0.68, 95% CI: 0.19–2.41; $p = 0.55$; data not shown).

The results showed that patients belonging to the SWMS group had a 0.11 HR of dying of any cause compared with the CTS group (Table 4).

The sensitivity analysis conducted on the 150 matched subgroup and on the whole cohort adjusted for PS and type of surgery (SWMS vs. CTS), confirmed the same results reported above for CSS and LRRFS. Moreover, the results were confirmed by adopting the cTNM score for identifying the subgroup of 150 patients (100 CTS and 50 SWMS) (data not shown).

TABLE 4 Overall survival (OS) on the whole cohort ($N = 601$ patients) and stratified for propensity score.

Variable	Contrast	HR	Low.95	Up.95	*p*-value
Age		1.03	1.02	1.04	<0.001
T-N tract	Involved by disease vs. not standardly removed + free from disease	1.65	1.16	2.35	0.01
ECE	Yes vs no	2.91	2.05	4.14	<0.001
Compartmental surgery (Types III–V glossectomies)	No vs yes	0.11	0.01	0.77	0.03

Abbreviations: ENE, extranodal extension.

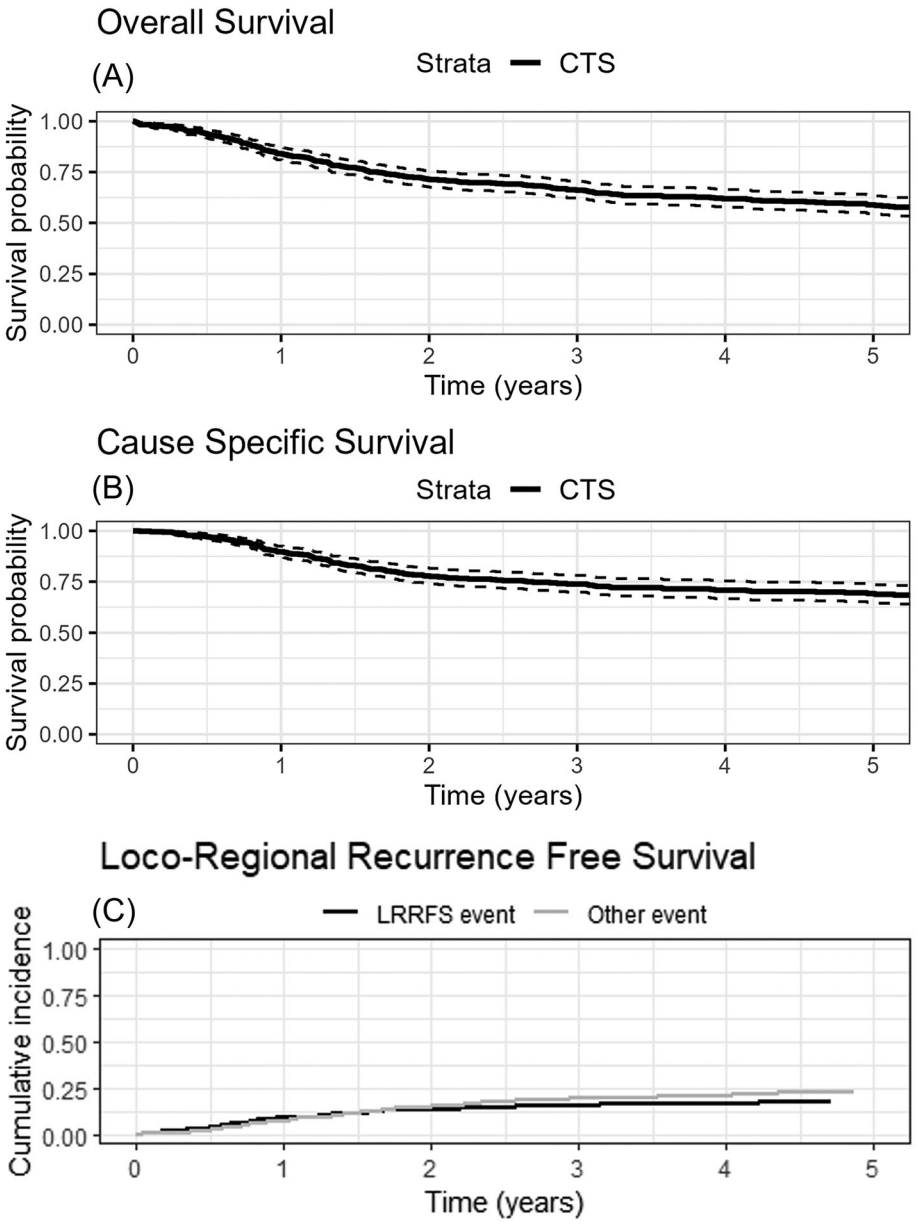

FIGURE 1 Baseline survival probability and cumulative incidence for compartmental tongue surgery (CTS). (A) Overall survival; (B) Cause specific survival; (C) Loco-regional recurrence free survival competing risk.

3.2 | Survival outcomes of patients treated with CTS

According to the inclusion criteria, our sample counted 551 patients, and the median follow-up was 5.7 years (0–18.3), with a follow-up updated to June 2020 (Table 1).

Figure 1 shows the baseline survival probability and cumulative incidence for CTS: at 5 years OS was 58.59% and CSS was 68.78%. The cumulative incidence for LRRFS at 5 years was 17.41%.

3.3 | Patients' characteristics across different hospitals

We observed statistically significant differences in patients' treatment across hospitals in terms of age, cT, cN, pT (according to the 7TNM), presence of multifocality in the specimen, vascular and perineural invasion, and ENE (p values <0.05, Table 1).

Moreover, differences across the four centers were found in case of heavy smokers (pack/year ≥20) and non-drinkers, G2 tumor grading, Stage III–IV in the 8TNM,[21] presence of clinically pathologic lymph nodes (cN+), T-N tract involved by disease, and involvement of the lingual margins (p value <0.05, Table 1).

In Figure S2, only OS showed to be significantly different across the hospitals ($p = 0.0015$). For all the other studied outcomes (CSS and LRRFS), no difference was found ($p = 0.9$ and $p = 0.44$, respectively).

3.4 | Survival outcomes and clinical factors related to tumor prognosis in CTS

T-N tract involvement by disease and advanced stages (III–IV) were significantly associated with worse OS and CSS in univariate analyses (all log-rank test $p < 0.05$).

The multivariable analysis, adjusted for possible heterogeneity among centers, showed a worse OS for the T-N tract involvement by disease and the pathological lymph nodes status (according to the 7TNM). Prognostic factors such as vascular invasion, ENE, perineural invasion, tumor multifocality, DOI >10 mm, and adjuvant treatments (RT or CRT) not performed (Table 5A) were significantly associated with poor survival.

These results were confirmed by multivariable analyses for CSS adjusting for centers and same prognostic

TABLE 5 A: Overall survival (OS) and B: Cause specific survival (CSS) for the compartmental surgery group ($N = 551$ patients).

Variable	Contrast	HR	Low.95	Up.95	*p* value
A: OS for the compartmental surgery group (N = 551 patients)					
T-N tract	Involved by disease vs. free from disease	1.56	1.13	2.16	0.006
pN (7TNM)	N+ vs. N0	2.81	1.94	4.08	<0.001
Vascular invasion	Yes vs. no	1.52	1.06	2.17	0.02
ENE	Yes vs. no	1.68	1.21	2.34	0.001
Perineural invasion	Yes vs. no	1.44	1.05	1.97	0.02
Multifocality	Yes vs. no	2.30	1.35	3.96	0.002
Adjuvant RT or CRT	Yes vs. no	0.44	0.31	0.61	<0.001
DOI (mm)	>10 vs. ≤10	1.83	1.29	2.61	<0.001
B: CSS for the compartment surgery group (N = 551 patients)					
T-N tract	Involved by disease vs. free from disease	2.00	1.34	2.99	<0.001
pN (7TNM)	N+ vs. N0	4.78	2.75	8.30	<0.001
Vascular invasion	Yes vs. no	1.33	0.84	2.10	0.21
Adjuvant RT or CRT	Yes vs. no	0.62	0.39	0.96	0.03
Multifocality	Yes vs. no	2.33	1.12	4.81	0.02
ENE	Yes vs. no	1.73	1.14	2.62	0.009
Perineural invasion	Yes vs. no	1.47	0.99	2.19	0.05
DOI (mm)	>10 vs. ≤10	1.83	1.13	2.96	0.01

Note: Adjusted for age and centers.

Abbreviations: CRT, chemoradiotherapy; DOI, depth of invasion; ENE, extranodal extension; N+, pathological lymph nodes; RT, radiotherapy.

factors as above except for vascular invasion ($p = 0.21$, Table 5B).

Focusing on adjuvant treatments, patients treated with RT or CRT had 0.44 times the hazard of dying due to any cause (OS, 95% CI: 0.31–0.61; $p < 0.001$) and presented 0.62 times the hazard of dying due to OTSCC (CSS, 95% CI: 0.39–0.96; $p = 0.03$), compared with not treated with adjuvant therapy patients (Table 5). Moreover, patients treated with RT or CRT after CTS showed 0.33 times the hazard of loco-regional recurrence (LRRFS, 95% CI: 0.21–0.54; $p < 0.001$), (Table 3B).

Considering the LRRFS, pN+, vascular invasion, and lack of adjuvant treatments remained independently associated with local events (Table 3B).

4 | DISCUSSION

This study is the largest case series in the English literature of patients affected by OTSCC treated by a CTS approach.

OS is defined as the time from randomization to death of any cause: the events that are taken into consideration are cancer-related deaths and other death causes such as second cancers, cardiac events, pulmonary complications, or other medical disorders.[22,23] Patients undergoing CTS presented fewer deaths for cancer but a higher number of deaths for other causes. Aware of the limitations of our comparison, we hypothesize that patients undergoing CTS might show a worse OS because of fewer cancer-related deaths but more deaths for other causes.

Focusing on disease-specific cancer outcomes (CSS and LRRFS), CTS seemed to reveal a protective role compared with SWMS.

Regarding the CSS on 601 patients (551 treated by CTS and 50 by SWMS), a worse outcome was related to the involvement of the T-N tract, presence of ENE, and SWMS. The 5-year survival curve of CSS (death closely related to disease) is very low in patients undergoing SWMS (27%).

Our results showed that patients with the T-N tract involved by disease presented a twice higher risk of dying for OTSCC compared with those without such a pathologic finding. On the other hand, patients' prognosis was better even if the removed T-N tract was not involved by disease (3-times better CSS for CTS compared with SWMS). These data support that CTS should be performed for tumors in clinical stages III-IV regardless of clinical involvement of the T-N tract. Concerning SWMS patients' group, the analyses showed a risk >3-times of dying for tongue cancer and more than 2-times higher risk of loco-regional recurrence than those who had undergone CTS.

In multivariable analysis, LRRFS was not significantly associated with the T-N tract status: however, its comprehensive removal according to the CTS technique, allows excising all soft tissues where the loco-regional persistence/recurrence could be localized.[14]

In the multivariable analysis of our CTS cohort, the margins status was not prognostically significant. CTS is a technique based on the pathways of tumor spread, where the high-risk muscular structures are completely removed in continuity with the T-N tract, and the low-risk areas such as the contralateral compartment remain intact regardless of its distance from the tumor.[13,14] The deep margin, the most common technical issue in performing SWMS, is not considered at all in the CTS approach since a complete removal of all the tumor diffusion pathways, even in-depth, is systematically performed with an "en-bloc" technique.

Due to the low numbers of the observed events, the DMFS was not significantly associated with the type of surgery but only with the presence of ENE, confirming previous reports.[24,25] In fact, distant metastases are usually reported to appear later than 2 years after treatment,[26] but in our study the comparison between SWMS and CTS was at 2-year follow-up, having the two cohorts a different median follow up (SWMS 1.7 years and CTS 5.7 years). However, although the clinical manifestation of metastases often takes years, evidence suggests that distant dissemination occurs very early in the malignant progression of cancer. Similarly, to other solid malignancies, the increase in 5-year survival linked to better local control is frequently associated with an increase in late distant metastases.[27,28]

In 2002 Session et al.[29] reported data on 332 patients treated for all stages of OTSCC: an overall 5-year DSS was 57% with CSS 43%, concluding that an improvement in DSS was seen in patients with clear margins, early stages, and negative nodes.[29]

In 2004 Gorsky et al.[30] found a 5-year DSS of 54% and 22% for Stages III and IV, respectively, and a 5-year OS of 40% on 322 consecutive patients with high-stage OTSCC, treated by a standard surgical technique. In 2007, Fan et al.[31] analyzed 201 advanced stage OTSCC (61% Stage IV and 39% Stage III), all treated by SWMS: the 3-year OS and RFS were 48% and 50.8%, respectively. On multivariable analysis, factors as multiple nodes, tumor differentiation, ENE, and adjuvant treatments were independent negative prognostic factors.[31]

In our study, survival was significantly associated in multivariable analyses with the above-mentioned factors such as: lymph nodes status, ENE, T-N tract involvement and lack of adjuvant therapies.

In our data, patients who underwent post-operative RT or CRT according to NCCN guidelines based on their pathological tumor stage[8] benefitted from a better OS, compared with patients at the same pathological tumor stage not receiving adjuvant treatments showing an HR OS of 0.44 (95% CI: 0.31–0.61; $p < 0.001$), independently from other considered risk factors. Similar results were found for both CSS and LRRFS. Among the 169 patients not treated with adjuvant therapies (according to the 7TNM), 4 were Stage III with no other risk factors in the CTS group. At the same time, 98 were Stage III–IV, and 67 were staged as I–II. The 98 Stage III–IV patients were candidates for adjuvant treatments according to NCCN guidelines.[8] Still, they were considered unfitted due to general comorbidities or suffered from postoperative complications that critically delayed the beginning of (C)RT.[32] Among the remaining 67 patients who did not receive adjuvant (C)RT since pathologically staged as I–II, 33 were down-staged by definitive histopathological examination. Thirty-four underwent CTS after an invasive diagnostic incisional biopsy that caused a morphological and radiological alteration of the peritumoral tissues thus explaining a clinical preoperative overstaging.

There have been many changes in adjuvant head and neck cancer treatments in the last 20 years.[33] The results of our multivariate analyses underlined how the role of the type of surgery performed is an independent prognostic factor for the patient's prognosis independently of other elements, such as adjuvant treatments, in the sense that, even if the therapies have changed over time, the protective role of compartment surgery was independently significant. Moreover, our data demonstrate that the same positive results were achievable in each center adopting the CTS technique and participated in this study. The Kaplan–Meier survival curves for tongue cancer-specific outcomes (CSS and LRRFS), among all centers, underlined that no difference was found in applying such a surgical approach.

The different result for OS, not confirmed in multivariable analysis, could be explained by the fact that OS includes death for OTSCC together with death for other causes and one of the four centers is characterized by a median age higher than the others. Moreover, multivariable analyses (adjusted for prognostic and confounding factors) showed that OTSCC survival and prognosis in patients treated with CTS were not related to the single center. These data confirmed that the anatomically based approach of CTS is a highly reproducible surgical technique and can be codified by already published surgical steps based on tongue and floor of the mouth anatomy.[15,34]

Focusing on functional results of patients treated with CTS, removing the lingual extrinsic muscles from their bone insertion could result in a larger excision than the SWMS, but as already reported in some published works on this topic, a dissected muscle does not maintain functionality and, a good reconstruction fills the excision gap.[13] It is already reported that CTS could offer superior oncologic results without reducing functional outcomes compared with SWMS. Our findings were compared with a systematic review published in 2013 by Lam and Samman, focused on speech and swallowing for tongue cancer surgery and free flap reconstruction in the time laps from 2000 to 2012.[35] In total, 21 articles were included in this systematic review, and according to the provided results, SWMS seems to cause the same morbidity when compared with CTS.[36]

We are aware of the limitations of our work: the retrospective and multicentric nature of the study analysis, which may imply some inclusion criteria and data collection biases. Moreover, the comparison among the two types of surgery (SWMS and CTS) included a small number of cases (50) treated by SWMS in a historical series (1995–1999), performed at a single center (IEO) and with different years of comparison (2000–2018 CTS, 1995–1999 SWMS).

Unfortunately, although we are aware that entering the data on SWMS of all four centers would have been optimal, this was not possible as the data were not available.

Furthermore, it was not possible for us to insert more recent patients in the SWMS group as, when the CTS was conceived and applied, the SWMS was no longer carried out. Therefore, the years compared cannot be parallel but consecutive. To overcome these important issues, we ensured that the groups were comparable through PS, mimicking randomized controlled trials, thus reducing confounding factors and selection bias.

5 | CONCLUSION

Our data confirmed that CTS showed good reproducibility among different centers applying the standardized concept of tongue surgical compartment and following codified surgical steps. This study on the largest case series of patients affected by OTSCC treated by a CTS approach seems to confirm that CTS ensures better specific survival outcomes (CSS and LRRFS) compared with SWMS. Multivariable analysis confirmed the T-N tract and lymph nodal status, ENE, and adjuvant treatments were variables affecting the survival outcomes. Although our data confirmed that CTS showed good reproducibility among different centers and improved oncological outcomes, further studies are needed to validate and confirm these findings.

AUTHOR CONTRIBUTIONS

Luca Calabrese: designed the study, wrote manuscript, approved final manuscript; **Marta Tagliabue** and **Alberto Grammatica**: writing – original draft; **Rita De Berardinis**: data curation and review; **Federica Corso** and **Sara Gandini**: formal analysis; **Luca Gazzini, Monir Abousiam, Enrico Fazio, Davide Mattavelli, Walter Fontanella, Lorenzo Giannini** and **Lorenzo Bresciani**: data curation; **Roberto Bruschini, Cesare Piazza** and **Mohssen Ansarin**: approved final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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.

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REFERENCES

1. Anwar N, Pervez S, Chundriger Q, Awan S, Moatter T, Ali TS. Oral cancer: clinicopathological features and associated risk factors in a high risk population presenting to a major tertiary care center in Pakistan. *PloS One*. 2020;15(8):e0236359.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
3. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin*. 2011;61(4):212-236.
4. Brown LM, Check DP, Devesa SS. Oral cavity and pharynx cancer incidence trends by subsite in the United States: changing gender patterns. *J Oncol*. 2012;2012:649498.
5. Patel SC, Carpenter WR, Tyree S, et al. Increasing incidence of oral tongue squamous cell carcinoma in young white women, age 18 to 44 years. *J Clin Oncol*. 2011;29(11):1488-1494.
6. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87-108.
7. Moyses RA, López RV, Cury PM, et al. Significant differences in demographic, clinical, and pathological features in relation to smoking and alcohol consumption among 1,633 head and neck cancer patients. *Clinics (Sao Paulo)*. 2013;68(6):738-744.
8. NCCN Guidelines Version 2.2023 – May 15, 2023, Head and neck cancers. Accessed June 2023. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf
9. Mann J, Julie D, Mahase SS, et al. Elective neck dissection, but not adjuvant radiation therapy, improves survival in stage I and II oral tongue cancer with depth of invasion >4 mm. *Cureus*. 2019;11(12):e6288.
10. Terada H, Sasaki E, Suzuki H, Nishikawa D, Beppu S, Hanai N. An examination of the cutoff value of the depth of invasion for prophylactic neck dissection in stage I/II tongue cancer. *Acta Otolaryngol*. 2020;140(5):422-426.
11. Bradley PJ, MacLennan K, Brakenhoff RH, Leemans CR. Status of primary tumour surgical margins in squamous head and neck cancer: prognostic implications. *Curr Opin Otolaryngol Head Neck Surg*. 2007;15(2):74-81.
12. DiNardo LJ, Lin J, Karageorge LS, Powers CN. Accuracy, utility, and cost of frozen section margins in head and neck cancer surgery. *Laryngoscope*. 2000;110(10 Pt 1):1773-1776.
13. Calabrese L, Bruschini R, Giugliano G, et al. Compartmental tongue surgery: long term oncologic results in the treatment of tongue cancer. *Oral Oncol*. 2011;47(3):174-179.
14. Tagliabue M, Gandini S, Maffini F, et al. The role of the T-N tract in advanced stage tongue cancer. *Head Neck*. 2019;41(8):2756-2767.
15. Calabrese L, Giugliano G, Bruschini R, et al. Compartmental surgery in tongue tumours: description of a new surgical technique. *Acta Otorhinolaryngol Ital*. 2009;29(5):259-264.
16. Calabrese L, Tagliabue M, Maffini F, Massaro MA, Santoro L. From wide excision to a compartmental approach in tongue tumors: what is going on? *Curr Opin Otolaryngol Head Neck Surg*. 2013;21(2):112-117.
17. Ansarin M, Bruschini R, Navach V, et al. Classification of glossectomies: proposal for tongue cancer resections. *Head Neck*. 2019;41(3):821-827.
18. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med*. 2007;26(11):2389-2430.

19. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46(3):399-424.
20. Ho D, Imai K, King G, Stuart EA. MatchIt: nonparametric preprocessing for parametric causal inference. *J Stat Softw*. 2011;42(8):1-28.
21. Amin MB, Edge SB, Greene FL, et al. *AJCC Cancer Staging Manual*. 8th ed. Springer; 2017.
22. Delgado A, Guddati AK. Clinical endpoints in oncology – a primer. *Am J Cancer Res*. 2021;11(4):1121-1131.
23. Lebwohl D, Kay A, Berg W, Baladi JF, Zheng J. Progression-free survival: gaining on overall survival as a gold standard and accelerating drug development. *Cancer J*. 2009;15:386-394.
24. Carta F, Quartu D, Mariani C, et al. Compartmental surgery with microvascular free flap reconstruction in patients with T1-T4 squamous cell carcinoma of the tongue: analysis of risk factors, and prognostic value of the 8th edition AJCC TNM staging system. *Front Oncol*. 2020;10:984.
25. Piazza C, Grammatica A, Montalto N, Paderno A, Del Bon F, Nicolai P. Compartmental surgery for oral tongue and floor of the mouth cancer: oncologic outcomes. *Head Neck*. 2019;41(1):110-115.
26. Balasubramanian D, Subramaniam N, Missale F, et al. Predictive nomograms for oral tongue squamous cell carcinoma applying the American joint committee on cancer/union internationale contre le cancer 8th edition staging system. *Head Neck*. 2021;43(4):1043-1055.
27. Ansarin M, De Berardinis R, Corso F, et al. Survival outcomes in oral tongue cancer: a mono-institutional experience focusing on age. *Front Oncol*. 2021;11:616653.
28. Klein CA. Cancer progression and the invisible phase of metastatic colonization. *Nat Rev Cancer*. 2020;20(11):681-694.
29. Sessions DG, Spector GJ, Lenox J, Haughey B, Chao C, Marks J. Analysis of treatment results for oral tongue cancer. *Laryngoscope*. 2002;112(4):616-625.
30. Gorsky M, Epstein JB, Oakley C, Le ND, Hay J, Stevenson-Moore P. Carcinoma of the tongue: a case series analysis of clinical presentation, risk factors, staging, and outcome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2004;98(5):546-552.
31. Fan KH, Lin CY, Kang CJ, et al. Combined-modality treatment for advanced oral tongue squamous cell carcinoma. *Int J Radiat Oncol Biol Phys*. 2007;67(2):453-461.
32. Ghanem AI, Schymick M, Bachiri S, et al. The effect of treatment package time in head and neck cancer patients treated with adjuvant radiotherapy and concurrent systemic therapy. *World J Otorhinolaryngol Head Neck Surg*. 2019;5(3):160-167.
33. Bhatia A, Burtness B. Treating head and neck cancer in the age of immunotherapy: a 2023 update. *Drugs*. 2023;83(3):217-248.
34. De Berardinis R, Tagliabue M, Belloni P, et al. Tongue cancer treatment and oncological outcomes: the role of glossectomy classification. *Surg Oncol*. 2022;42:101751.
35. Lam L, Samman N. Speech and swallowing following tongue cancer surgery and free flap reconstruction—a systematic review. *Oral Oncol*. 2013;49(6):507-524.
36. Grammatica A, Piazza C, Montalto N, et al. Compartmental surgery for oral tongue cancer: objective and subjective functional evaluation. *Laryngoscope*. 2021;131(1):E176-E183.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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