Check for updates

Received: 21 October 2020 | Revised: 24 March 2021 | Accepted: 15 April 2021

DOI: 10.1111/odi.13885

ORIGINAL ARTICLE

ORAL DISEASES Leading in Oral, Maxillofacial, Head & Neck Medicine WILEY

The T-N tract involvement as a new prognostic factor for PORT in locally advanced oral cavity tumors

Daniela Alterio[1] | Matteo Augugliaro[1] | Marta Tagliabue[2,3] | Roberto Bruschini[2] | Sara Gandini[4] | Luca Calabrese[5] | Pietro Belloni[4,6] | Lorenzo Preda[7,8] | Fausto Antonio Maffini[9] | Giulia Marvaso[1,10] | Annamaria Ferrari[1] | Stefania Volpe[1] | Maria Alessia Zerella[1] | Olga Oneta[1,10] | Irene Turturici[1] | Ombretta Alessandro[1,10] | Francesca Ruju[11] | Mohssen Ansarin[2] | Roberto Orecchia[12] | Barbara Alicja Jereczek-Fossa[1,10]

[1]Division of Radiation Oncology, IEO, European Institute of Oncology IRCCS, Milan, Italy

[2]Division of Otolaryngology and Head and Neck Surgery, IEO European Institute of Oncology IRCCS, Milan, Italy

[3]Department of Biomedical Sciences, University of Sassari, Sassari, Italy

[4]Department of Experimental Oncology, IEO, European Institute of Oncology, IRCCS, Milan, Italy

[5]Division of Otorhinolaryngology, San Maurizio" Hospital, Bolzano, Italy

[6]Department of Statistical Sciences, University of Padua, Italy

[7]Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Italy

[8]Diagnostic Imaging Unit, National Center of Oncological Hadrontherapy (CNAO), Pavia, Italy

[9]Department of Pathology, IEO, European Institute of Oncology IRCCS, Milan, Italy

[10]Department of Oncology and Hemato-Oncology, University of Milan, Italy

[11]Department of Radiology, IEO, European Institute of Oncology IRCCS, Milan, Italy

[12]Scientific Directorate, European Institute of Oncology IRCCS, Milan, Italy

Correspondence
Stefania Volpe, Division of Radiation Oncology, IEO, European Institute of Oncology IRCCS, Milan, Italy
Email: stefania.volpe@ieo.it

Marta Tagliabue, Division of Otolaryngology and Head and Neck Surgery, IEO European Institute of Oncology IRCCS, Milan, Italy.
Email: marta.tagliabue@ieo.it

Funding information
This study was partially supported by the Italian Ministry of Health with Ricerca Corrente and 5 × 1000 funds. Many thanks to Donatella Scaglione and Cristiana Fodor. Stefania Volpe MD is a PhD student within the European School of Molecular Medicine (SEMM).

Abstract

Objective: The space comprised between tumor and neck lymph nodes (T-N tract) is one of the main routes of tumor spread in oral cavity tumors. Aim of the study was to investigate the impact of T-N tract involvement on the postoperative radiotherapy (PORT) outcomes.

Materials and Methods: Patients (pts) treated between 2000 and 2016 with indication to PORT were retrospectively retrieved. Inclusion criteria were: (a) locally advanced tumors of the oral cavity, (b) who received with indication to PORT (c) with a minimum follow-up of six months.

Results: One hundred and fifty-seven pts met the inclusion criteria (136 pts treated with PORT and 21 pts not treated with PORT). In the PORT cohort, the T-N tract involvement had no impact on both OS ($p = .09$) and LRFS ($p = .2$). Among the non-PORT cohort, both OS ($p = .007$) and LRFS ($p = .017$) were worse for pts with positive T-N tract compared to those with negative T-N tract. PORT improved both OS

Alterio Daniela and Augugliaro Matteo are equally contributed.

(p = .008) and LRFS (p = .003) in pts with positive T-N tract but not in those with negative T-N tract (p = .36 and p = .37, respectively).

Conclusions: Our results suggest that involvement of T-N tract should be considered as prognostic factors informing the indication to PORT.

KEYWORDS

oral cavity cancers, postoperative radiotherapy, T-N tract

1 | INTRODUCTION

Oral cancer has represented the 17th cause of cancer-related death worldwide in 2020, with a global incidence of 2%, with a significantly higher prevalence in developing countries (Ferlay et al., 2020). The majority of cases present with the locally-advanced disease, with regional involvement in up to 30% of cases (Alvarez Amézaga et al., 2007; Alzahrani et al., 2020; Tromp et al., 2005). The standard of care for locally advanced oral cavity tumors is radical surgery followed by postoperative radiotherapy (PORT) (± concurrent chemotherapy) (National Comprehensive Cancer Network, 2020). To date, the currently accepted surgical technique is excision of the primary tumor with a 1.5–2-cm circumferential macroscopic margin (wide excision, WE) and concomitant or delayed neck dissection according to tumor depth of infiltration (Chong, 2005). Borrowing the concept from the surgery of musculo-skeletal sarcomas, a "compartmental surgery" (CS) technique was proposed for oral tongue tumors in the early 2000s (Calabrese et al., 2009). Among different advantages, this approach provides the unique opportunity to evaluate the presence of cancer cells within the tract between the primary tumor and the neck lymph node echelons (namely, the T-N tract).

The T-N tract, which is not removed with a WE technique, is one of the main routes of tumor spread and its involvement has been already recognized as a prognostic factor for patients' outcomes (Tagliabue et al., 2019). All anatomical structures located between the tongue (T) and the first nodal level (N) constitute the so-called T-N tract, which is a route of dissemination for tumors originating in either the floor of the mouth and the mobile tongue. In detail, it consists of the sublingual and submandibular glands, the mylohyoid muscles, the lingual arteries, veins, and nerves, the hypoglossal nerves, the Warton ducts, the lingual and sublingual nodes, and stromal tissue. Whether the T-N tract involvement could have an impact on PORT efficacy has not been investigated yet.

To answer these unaddressed questions, we performed a retrospective study on patients who had received CS for locally advanced tumors of the oral cavity, for whom a minimum follow-up of six months was available considering as endpoints: (a) to analyze the prevalence of T-N tract involvement in locally advanced tumors candidate to PORT (b) to evaluate the impact T-N tract involvement on PORT oncological outcomes (5 years overall survival (OS) and loco-regional relapse disease-free survival (LRFS)).

Moreover, we compared patients submitted to CS and PORT (PORT cohort) with a similar group of patients treated with CS not followed by PORT (non-PORT cohort) as stratified per the T-N tract involvement.

2 | PATIENTS AND METHODS

This is a retrospective study approved by the Ethical Committee of the European Institute of Oncology IRCSS (IEO) (notification number: IEO225). The presence of written informed consent for the use of anonymized clinical data for research purposes was verified for every patient screened for the analysis.

2.1 | Clinical characteristics

Consecutive patients with the diagnosis of squamous cell carcinoma of the oral cavity treated with CS at the IEO from June 2000 to May 2016 were analyzed. Inclusion criteria were: (a) locally advanced tumors of the oral cavity (stages III and IV per the TNM seventh ed.), (b) who had received with indication to PORT, and (c) with a minimum follow-up of six months and availability of oncological outcome data; the presence of written informed consent was verified for all patients. Early-stage tumors (stage I and II according to TNM seventh edition) and recurrent/secondary cancers were excluded from the analysis, as well as patients for whom all baseline clinical information was not retrievable from the electronic medical charts. Patient-, tumor- and treatment-related characteristics were retrieved from electronic medical records. The presence of comorbidities was assessed per the Charlson comorbidity index (CCI). Indications for CS were either patients with cT2N+ disease or cT >2 with any nodal stage squamous cell carcinoma of the oral cavity (Calabrese et al., 2009).

2.2 | Pre-operative evaluation

Pre-operative assessment was performed with comprehensive oral cavity and oropharynx examination with clinical exploration, fiber-optic-video pharyngolaryngoscopy and, recently, narrow-band imaging. Loco-regional tumor extension was assessed using contrast-enhanced magnetic resonance (MR) and/or computed

16010825, 2023, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/odi.13885 by Fondazione Irccs Policlinico San Matteo, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

tomography (CT) imaging. In case of suspicious lymph nodes, an ultrasonography-guided fine-needle aspiration was performed. The presence of distant metastases was assessed by position emission tomography (PET)-CT scans or total body CT scans.

2.3 | Pathological findings

For the whole cohort, the following pathological parameters were retrieved: tumor and nodal staging (according to TNM AJCC staging system, seventh ed.), grading, surgical margins status (with margins greater than 5 mm being considered as negative, 1–5 mm as close and <1 mm as positive), tumor grading, number and location of pathological lymph nodes, presence of lymph node extracapsular extension (ECE). The presence of tumor in the T-N tract was already available in most of the retrieved pathologic charts. When missing, a second analysis of the pathologic specimens was retrospectively performed to retrieve this parameter.

2.4 | Indications to adjuvant treatment

Indication to adjuvant treatments was given following multidisciplinary team discussion. According to NCCN (National Comprehensive Cancer Network) guidelines, PORT was indicated in case of advanced-stage tumors (pT3 or pT4) and/or nodal involvement (pN2a or higher and/or ECE) and/or close/positive surgical margins and/or aggressive biologic features (perineural invasion and lymph vascular extension). Indication to add concurrent chemotherapy to PORT was given according to current clinical practice guidelines (Bernier et al., 2005).

In case PORT was not performed despite prior indication to treatment, the reason of omission was verified and reported.

2.5 | Follow-up procedures

Follow-up was performed with clinical and radiological evaluation every three months for the first two years, every four months for the third year, and every six months for the subsequent two years. Subsequently, follow-up was scheduled once a year. A fiber-optic-video pharyngolaryngoscopy was executed at every clinical control. CT/MR and ultrasonography were required according to the pre-treatment evaluation while a whole-body re-staging, by either FDG-PET or total body CT, was required yearly.

2.6 | Statistical analysis

The relative frequencies for the categorical variables were provided to describe the population. The clinical characteristics of the PORT and non-PORT cohorts were compared, and their differences were quantified with Pearson's Chi-square test. Wilcoxon-rank test was performed on continuous variables (time until diagnosis and overall treatment time), while Fisher's exact test or Chi-square were applied to categorical variables (gender, alcohol consumption, tobacco smoke, T-N tract involvement, perineural invasion, ECE, surgical margins status, pT, pN, pathological stage, CCI). Age was considered both as a categorical variable (Fisher's exact test) and a continuous variable (Wilcoxon–rank test). Overall, the time between biopsy and surgery was defined as "time until diagnosis". Overall treatment time was defined as the interval between surgery and the completion of PORT. Follow-up was considered as starting after CS. OS was defined as the time from the surgery until the death from any cause or the last available follow-up; the LRFS was defined as the time from surgery until loco-regional disease progression, death from any cause, or last available follow-up. The survival curves were built with the Kaplan–Meier (KM) method and the Log-rank test was used to compare survival time between the groups. Univariate analyses were carried out to investigate the differences between PORT and non-PORT cohorts in term of outcomes and possible confounding factors (such as age and gender) and other prognostic factors. Variables that were found to be significantly associated with time to events in the univariate model were included in the multivariable Cox proportional hazard models and were kept in the model if they remained significant, following a forward and backward selection variable strategy. A fully adjusted Cox proportional hazard model was used to evaluate the difference between the two groups in terms of OS and LRFS adjusting for significant confounders. Hazard Ratios (HR) with 95% confidence intervals (95CI) obtained from fully adjusted Cox proportional hazard models. All statistical tests were two-sided and $p < .05$ was considered statistically significant. Statistical analysis was performed with R software version 3.6.0–"Planting of a Tree", KM survival plots were obtained with R library survminer (Drawing Survival Curves Using 'ggplot2' • Survminer, n.d.; R: A Language & Environment for Statistical Computing, n.d.).

3 | RESULTS

Among the 506 consecutive patients treated with CS in the considered period, 157 met the inclusion criteria. Median time until diagnosis was 39 (absolute range 14–247) days. Median overall treatment time was 114 days (absolute range 83–185).

Of the 157 selected patients included in the present work, 125 were considered in two (88 and 38 patients, respectively) previously published surgically oriented works from our Institution (Calabrese et al., 2011; Tagliabue et al. 2019). Nevertheless, the impact of T-N tract on indication to PORT has not been specifically addressed by neither of the two studies.

3.1 | T-N tract involvement

Microscopic involvement of the T-N tract was found in 40 patients out of 157 (25%). In detail, T-N tract positivity was distributed as

16010825, 2023, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/odi.13885 by Fondazione Irccs Policlinico San Matteo, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 Patients' and tumor- related characteristics of PORT and non-PORT cohorts

	PORT (*n*, %)	Non-PORT (*n*, %)	*p*-Value (Chi-square test)
Total number of patients	136 (87)	21 (13)	
Patients' characteristics			
Gender			
Female	47 (34.5)	5 (23.8)	.47
Male	89 (65.4)	16 (76.2)	
Age, years			
<60	93 (68.4)	9 (42.8)	<.01
60–69	32 (23.5)	5 (23.8)	
>70	10 (7.3)	7 (33.3)	
Alcohol consumption			
Never	69 (50.7)	13 (62.0)	.30
Ever	62 (45.5)	6 (28)	
Tobacco smoke			
Never	45 (33.0)	8 (38.0)	.87
Ever	89 (65.4)	13 (62)	
Charlson Comorbidity Index score			
2	57 (41.9)	5 (23.8)	.02
3	33 (24.3)	4 (19)	
4	26 (19.1)	4 (19)	
5	17 (12.5)	4 (19)	
6	3 (2.2)	4 (19)	
Tumors' characteristics			
pT			
2–3	25 (18.3)	3 (14.3)	.88
4	111 (81.7)	18 (85.7)	
pN			
0	31 (22.8)	10 (47.6)	.03
1–3	105 (77.2)	11 (52.4)	
Pathologic stage (AJCC)			
III	5 (3.7)	2 (9.5)	.52
IV	131 (96.3)	19 (90.5)	
T-N tract involvement			
Negative	101 (74.2)	16 (76.2)	1.00
Positive	35 (25.8)	5 (23.8)	
Perineural invasion			
No	105 (77.2)	20 (95.0)	.10
Yes	31 (22.8)	1 (5.0)	
Extracapsular extension			
No	85 (62.5)	18 (85.7)	.06
Yes	51 (37.5)	3 (14.3)	
Surgical margins			
Negative	119 (87.5)	17 (81.0)	.63
Close/ Positive	17 (12.5)	4 (9.0)	
Grading			
1–2	77 (57.0)	14 (66.7)	.48
3	58 (43.0)	7 (33.3)	

Abbreviations: AJCC, American Joint Committee on Cancer; pN, pathologic nodal stage pT: pathologic tumor stage; PORT, Postoperative radiotherapy.

follows: 4 cases out of 22 (18%), 5 out of 41 (12%) and 31 out of 94 (33%) in pT1-2 N+, pT3-4 N0 and pT3-4 N+ patients, respectively.

3.2 | PORT-Cohort

Among the 157 analyzed patients, 136 were treated with PORT. Patients and tumor characteristics are summarized in Table 1. Overall, the major proportion of patients in both cohorts was male, and the most represented group was below 60 years of age. Most of the included patients had a stage IV disease (96% and 90% in the PORT and non-PORT groups, respectively). Globally, low-intermediate grade tumors (G1-G2) were the most frequent in both cohorts.

Oncological outcomes of patients submitted to PORT according to the T-N tract involvement are visualized in Figure 1a, b and showed no impact of T-N tract involvement on clinical outcomes.

3.3 | Non-PORT cohort

Although having received prior indication to treatment, 21 patients did not undergo PORT. Namely, the reason for adjuvant RT withdrawal was distributed as following: patients' refusal (11 cases, 52%), postoperative complications (four cases, 19%), low-performance status (three cases, 14%), borderline indication (two cases, 10% presenting with pathological staging T3N0 and no concomitant adverse features) and early death for local recurrence (one case, 5%).

Clinical outcomes of the non-PORT cohort are reported in Figure 1c, d and show a statistically significant impact of T-N status on both OS and LRFS.

3.4 | Comparison between the PORT and non-PORT cohorts

The two cohorts were homogeneous according to the majority of relevant patient- and tumor-related characteristics (Table 1). A statistically significant difference between the groups was found only for age (with the older patients being included in the non-PORT group) and nodal status (with the higher rate of positive nodes being

16010825, 2023, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/odi.13885 by Fondazione Irccs Policlinico San Matteo, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

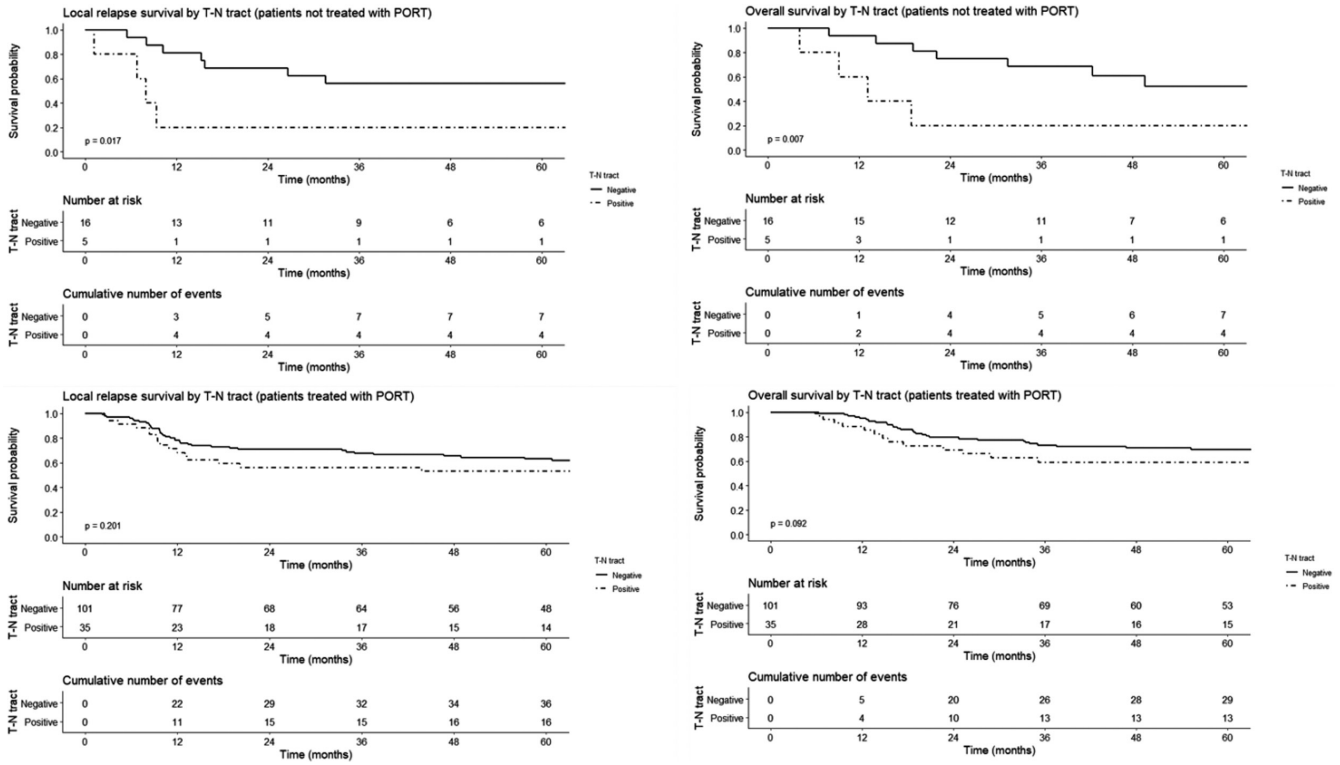


FIGURE 1 Five-year oncological outcomes in PORT and non-PORT cohorts stratified by T-N tract status. Abbreviations: LRFS, Loco-regional Control Free Survival; OS, Overall Survival; PORT, Postoperative Radiotherapy

in the PORT group) and ECE (with more patients in the PORT group presenting with ECE). The comparison between PORT and non-PORT cohorts in terms of OS and LRFS showed better oncological outcome in patients treated with PORT (p = .043 and 0.051, respectively). Multivariate analysis confirmed that PORT remains an independent factor for both OS and LRFS (Table 2). Considering age as a continuous variable, the results do not change, and P-value obtained with the non-parametric Wilcoxon–rank test is 0.018. Time until diagnosis shows no difference by PORT status (p = .73).

After adjusting for the presence of lymph nodes metastases, ECE, and age (dichotomized as under and above 55 years of age) the Cox model indicated that PORT was associated with OS with a hazard ratio of 0.38 (95% confidence interval [CI]: 0.19–0.75; p-value < .01). Therefore, patients who had received the PORT treatment had a 62% lower risk of death. A Cox model with the same adjustments indicated that PORT was associated with LRFS with a hazard ratio of 0.42 (95% CI: 0.22–0.80; p-value = .01) with a resulting reduction in the risk of loco-regional relapse of 57%.

Neither time until diagnosis nor overall treatment time were associated with OS (p = .52 and p = .11, respectively) and LRFS (p = .57 and p = .30, respectively). Also, the CCI did not show any significant association with OS (HR = 1.03, 95% CI: 0.75–1.42, p = .85) and LRFS (HR = 0.93, 95% CI: 0.69–1.25, p = .63); tumor grading was not associated with the considered oncological outcomes, despite a trend towards statistical significance was identified (p = .06 for OS and p = .07 for LRFS).

Considering the T-N tract involvement, patients with positive T-N tract experienced better 5-y OS and 5-y LRFS when treated with PORT compared to the non-PORT group (Figure 2 a,b), p = .07 for OS and p = .05 for LRFS. Notably, the advantage was preserved for the whole duration of the follow-up for both the considered oncological outcomes. Conversely, in case of negative T-N tract, both 5y-OS and 5y-LRFS did not show a statistically significant difference between the two cohorts (p_0.359 and p = .375, respectively) (Figure 2 c,d).

4 | DISCUSSION

The prognostic role of the T-N tract in oral cavity tumors has been investigated in surgical series (Calabrese et al., 2011, Tagliabue et al., 2019); starting from this body of evidence, the aim of this work was to give a more Radiation Oncology-oriented perspective by analyzing the impact of T-N tract involvement on PORT. Results of our analysis suggest that the tumor presence in the T-N tract should be considered–or at least investigated–as a new prognostic factor contributing to inform the indication to PORT. Moreover, pathological findings also indicate the presence of tumor cells within the T-N tract up to one-fourth of patients, which strongly advocates for considering this area (if not surgically removed) for radiation treatment planning purposes.

The generally considered risk factors for indication to PORT are based on studies using the WE technique (Fan et al., 2017). Comparatively, CS technique is the "en bloc" removal of the primary tumor and the neck lymph nodes, which allows to assess the

16010825, 2023, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/odi.13885 by Fondazione Irccs Policlinico San Matteo, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 Multivariate analysis on overall survival (OS) and Loco-regional control free survival (LRFS) according to the treatment with postoperative radiotherapy (PORT), the presence of lymph node extracapsular extension, the pathologic lymph node stage (pN0 versus pN positive) and patient's age

OS				
Number of patients: 157				
Number of events: 59				
Clinical parameters	**HR**	**lowHR**	**upHR**	***p*-Value**
PORT	1			<.01
No	0.38	0.19	0.75	
Yes				
ECE	1			.03
No	1.83	1.04	3.19	
Yes				
pN	1			.01
0	2.95	1.29	6.75	
>0				
Age	1			.04
≤ 55	1.76	1.03	3.00	
> 55				
LRFS				
Number of patients: 157				
Number of events: 59				
Clinical parameters	**HR**	**lowHR**	**upHR**	***p*-Value**
PORT	1			<.01
No	0.42	0.22	0.80	
Yes				
ECE	1			.02
No	1.81	1.07	3.04	
Yes				
pN	1			.01
0	2.69	1.26	5.74	
>0				
Age				
≤ 55	1			.02
> 55	1.79	1.09	2.95	

Abbreviations: ECE, extracapsular extension; HR, Hazard ratio; OS, Overall survival; pN, Pathologic nodal stage; PORT, Postoperative radiotherapy.

T-N tract involvement. Our results showed that the improvement of clinical outcome achieved by PORT could be even higher in patients with a positive T-N tract compared to those with an uninvolved T-N tract. On the contrary, PORT seems not to improve oncological results in patients presenting with negative T-N tract. Overall, we can speculate that PORT could compensate for the worse prognosis of patients with the microscopic T-N tract involvement. Unfortunately, we could not perform any sub-group analysis due to the low number of patients included in the non-PORT cohort. Nevertheless, according to a personalized medicine-based approach, further investigation is warranted to select low-risk patients for adjuvant de-intensification strategies to optimize the therapeutic index of such multidisciplinary approach. Moreover, PORT still represents the standard of care for patients with locally advanced stage OCSCC. Therefore, information on T-N tract could serve as an additional prognostic factor in defining adjuvant treatments mainly in patients with borderline stages (e.g., T1-T2N1) and no other risk factors.

Recently published guidelines for clinical target volume delineation recommend to consider the following parameters: location of the primary tumor, presence of anatomical barriers, and preferential routes of spread (Grégoire, Evans, et al., 2018).

16010825, 2023, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/odi.13885 by Fondazione Irccs Policlinico San Matteo, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

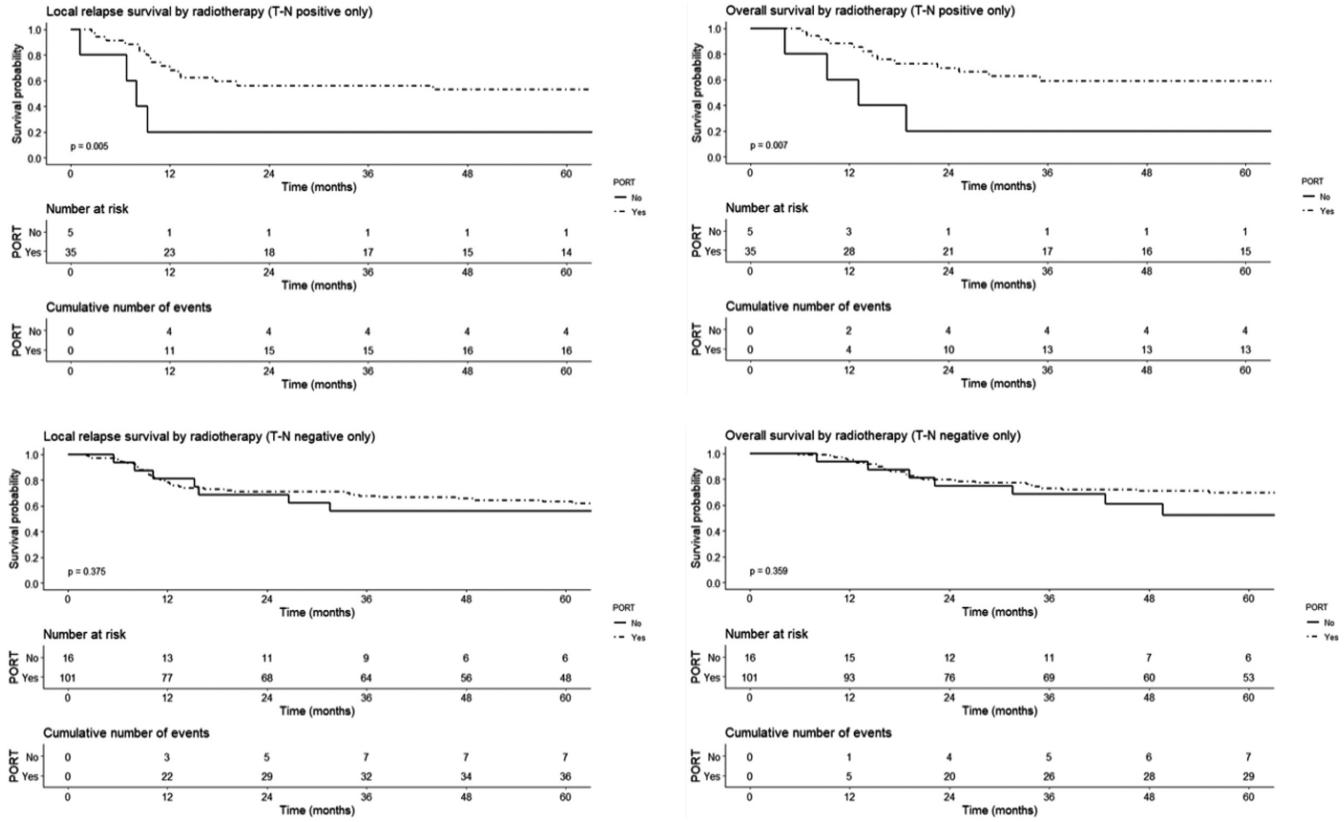
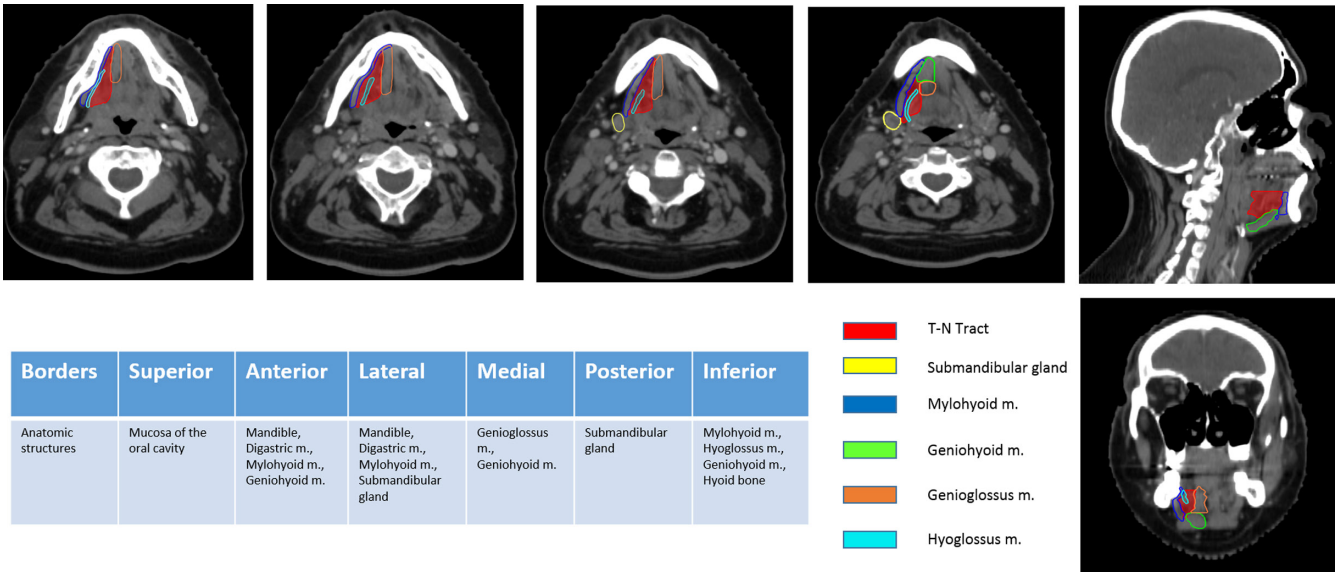


FIGURE 2 Five-year oncological outcomes according to T-N tract status stratified by adjuvant treatment (PORT versus non-PORT). Abbreviations: LRFS, Loco-regional control free survival, OS, overall survival, PORT, Postoperative radiotherapy



Borders	Superior	Anterior	Lateral	Medial	Posterior	Inferior
Anatomic structures	Mucosa of the oral cavity	Mandible, Digastric m., Mylohyoid m., Geniohyoid m.	Mandible, Digastric m., Mylohyoid m., Submandibular gland	Genioglossus m., Geniohyoid m.	Submandibular gland	Mylohyoid m., Hyoglossus m., Geniohyoid m., Hyoid bone

FIGURE 3 Anatomical boundaries of the T-N tract identified on computed tomography (CT) images

Specifically, generous margins are suggested in case of oral cavity tumors to minimize the risk of marginal recurrences (Metcalfe et al., 2017). As data on the incidence of microscopic disease in the T-N tract are lacking, the delineation of this region as a target volume is generally not specifically addressed or even not recommended in current guidelines (Grégoire et al., 2018; Liu et al., 2015; Merlotti et al., 2014). Specifically, some authors do not recommend, in clinical practice, irradiation of the area encompassed between the primary tumor and pathologically positive lymph nodes[17]. The importance of irradiating this tumor root of spread could be therefore underestimated, potentially leading to unexpected loco-regional recurrences. Our results suggest

16010825, 2023, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/odi.13885 by Fondazione Irccs Policlinico San Matteo, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

that the risk of T-N tract involvement correlates with tumor and lymph node staging. Interestingly, in our series, 12% of patients with pathologically negative lymph nodes still had tumor cells within the T-N tract. Overall, our results strongly suggest including the T-N tract as a target volume in patients with locally advanced oral cavity tumors receiving curative RT or submitted to a WE with indication to PORT. To complement this information, we herein provide the anatomical boundaries of the T-N tract identified on computed tomography and magnetic resonance images, as depicted in Figure 3. Further details are provided in Figures S1 and S2.

Calabrese et al. (2009) firstly described the CS technique for head and neck cancers. Compared to the traditional WE, advantages of CS consist in (a) removal of the tumor routes of spread (b) higher standardization of the surgical procedure (c) better pre-operative definition of the surgical procedure which should translate in a more favorable impact on both reconstruction and rehabilitation. Whether PORT could maintain its role in improving oncological outcomes after CS has not been specifically investigated. A retrospective analysis comparing patients treated with CS with a historical cohort of patients treated with traditional WE showed a statistically significant improvement of local disease-free survival ($p = .006$) and OS ($p = .0007$) in favor of CS. Multivariate analysis suggested that PORT plus concurrent chemotherapy remained an independent prognostic factor for the 5-years local recurrence rate ($p = .054$) (Calabrese et al., 2011). Nevertheless, in that series, early-stage tumors were also included with T2N0 tumors (which generally have no indication to PORT) representing the 18% and 17% of the WE and CS groups, respectively. Conversely, in their cohort of patients with pT4 (per TNM 7ed) oral cavity tumors treated with CS, Piazza et al. (2019) did not find any difference in 2y-OS between patients who had received with PORT and those who had not. Of note, the authors did not provide any justification for PORT omission. Moreover, interpretation of their results on PORT efficacy is at least partially impaired, as both primary and recurrent tumors were included in the analysis. In the present study, we included only locally advanced tumors who had indication to PORT (thus excluding early-stage tumors and recurrences). Among our population, we found that 13% of patients did not perform any adjuvant treatment for non-oncological reasons. Therefore, this cohort of untreated patients permitted to have a sort of control group to be compared with the one treated with PORT. Despite patients treated with PORT had a significantly higher rate of positive lymph nodes and ECE, both OS and LRFS compared favorably to those of patients in the non-PORT group. Multivariate analysis confirmed that PORT remains an independent prognostic factor for both OS and LRFS. These findings should be interpreted with caution due to the low number of patients in the non-PORT group and the relatively high prevalence (28%) of declining performance status and/or postoperative complications, which could represent independent negative prognostic factors. Therefore, while our data suggest that PORT could improve oncological outcomes following CS, further investigations are warranted to confirm these results.

We are aware of some limitations of our work, including its retrospective nature, long study period and the relatively limited number of patients (especially in the non-PORT group), and unavailability of details on PORT. Moreover, the depth of infiltration (DOI) for the primary tumor was not available for a significant proportion of patients, as well as the HPV status, which is a recognized prognosticator for this subset of HN cancers (Calabrese et al., 2020). To address this issue, we are currently reviewing all pathological specimens to quantify the impact of DOI on PORT following PORT. Despite the above-mentioned limitations, we strongly believe that our series has the full potential of providing the radiation oncologist with clinically meaningful information for the management and target volume delineation in patients with advanced cancer of the oral cavity, especially for those who are not suitable for surgery. Admittedly, further studies on wider cohorts are warranted to support our results. Arguably, a more refined knowledge of risk factors–and patterns of failure according to baseline characteristics, would contribute to integrate these findings, and complement currently adopted contouring guidelines for radiation oncology clinical practice.

5 | CONCLUSION

Results of the present analysis suggest that the presence of tumor within the T-N tract could represent an additional risk factor to be considered for the indication to PORT. Nevertheless, prospective studies are warranted to confirm our preliminary results. Moreover, due to the high incidence of microscopic disease found within the T-N tract, we suggest considering this region as a target volume for radiation treatment planning purposes.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTION

Daniela Alterio: Conceptualization; Supervision; Writing-review & editing. **Matteo Augugliaro:** Conceptualization; Writing-original draft; Writing-review & editing. **Marta Tagliabue:** Conceptualization; Methodology; Supervision; Visualization; Writing-review & editing. **Roberto Bruschini:** Conceptualization; Data curation; Investigation; Methodology. **Sara Gandini:** Data curation; Formal analysis; Validation; Writing-review & editing. **Luca Calabrese:** Supervision; Writing-review & editing. **Pietro Belloni:** Data curation; Formal analysis; Validation. **Lorenzo Preda:** Data curation; Visualization; Writing-review & editing. **Fausto Antonio Maffini:** Formal analysis; Validation; Visualization. **Giulia Marvaso:** Supervision; Visualization; Writing-review & editing. **Annamaria Ferrari:** Investigation; Validation; Writing-review & editing. **Stefania Volpe:** Conceptualization;

16010825, 2023, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/odi.13885 by Fondazione Irccs Policlinico San Matteo, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methodology; Writing-original draft; Writing-review & editing. **Maria Alessia Zerella:** Conceptualization; Writing-original draft; Writing-review & editing. **Olga Oneta:** Investigation; Validation; Writing-review & editing. **Irene Turturici:** Investigation; Writing-review & editing. **Ombretta Alessandro:** Visualization; Writing-review & editing. **Francesca Ruju:** Investigation; Methodology; Visualization. **Mohssen Ansarin :** Supervision; Validation. **Roberto Orecchia:** Supervision; Writing-review & editing. **Barbara Alicja Jereczek-Fossa:** Supervision; Writing-review & editing.

ETHICAL APPROVAL

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In this research, no animals were involved. All patients signed written informed consent for radiation therapy and written informed consent for the use of the anonymized data for research or educational purpose.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/odi.13885.

DATA AVAILABILITY STATEMENT

Research data not shared.

ORCID

Marta Tagliabue https://orcid.org/0000-0002-7879-4846
Fausto Antonio Maffini https://orcid.org/0000-0002-4554-8956
Giulia Marvaso https://orcid.org/0000-0002-5339-8038
Stefania Volpe https://orcid.org/0000-0003-0498-2964

REFERENCES

Alvarez Amézaga, J., Barbier Herrero, L., Pijoan del Barrio, J. I., Martín Rodríguez, J. C., & Romo Simón, L., Genolla Subirats, J., Rios Altolaguirre, G., de los Ríos, A., Arteagoitia Calvo, I., Landa Llona, S., Arruti González, J. A., López Cedrún, J., & Santamaría Zuazua, J. (2007). Diagnostic efficacy of sentinel node biopsy in oral squamous cell carcinoma. Cohort study and meta-analysis. *Medicina Oral, Patologia Oral Y Cirugia Bucal*, *12*(3), E235–E243.

Alzahrani, R., Obaid, A., Al-Hakami, H., Alshehri, A., Al-Assaf, H., Adas, R., Alduhaibi, E., Alsafadi, N., Alghamdi, S., & Alghamdi, M. (2020). Locally advanced oral cavity cancers: What is the optimal care? *Cancer Control*, *27*(1), 107327482092072. https://doi.org/10.1177/1073274820920727

Bernier, J., Cooper, J. S., Pajak, T. F., Van Glabbeke, M., Bourhis, J., Forastiere, A., Ozsahin, E. M., Jacobs, J. R., Jassem, J., Ang, K. K., & Lefèbvre, J. L. (2005). Defining risk levels in locally advanced head and neck cancers: A comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). *Head and Neck*, *27*(10), 843–850. https://doi.org/10.1002/hed.20279

Calabrese, L., Bizzoca, M. E., Grigolato, R., Maffini, F. A., Tagliabue, M., Negro, R., Leuci, S., Mignogna, M. D., & Lo Muzio, L. (2020). From bench to bedside in tongue muscle cancer invasion and back again: Gross anatomy, microanatomy. Surgical treatments and basic research. *Life*, *10*(9), 197. https://doi.org/10.3390/life10090197

Calabrese, L., Bruschini, R., Giugliano, G., Ostuni, A., Maffini, F., Massaro, M. A., Santoro, L., Navach, V., Preda, L., Alterio, D., Ansarin, M., & Chiesa, F. (2011). Compartmental tongue surgery: Long term oncologic results in the treatment of tongue cancer. *Oral Oncology*, *47*(3), 174–179. https://doi.org/10.1016/j.oraloncology.2010.12.006

Calabrese, L., Giugliano, G., Bruschini, R., Ansarin, M., Navach, V., Grosso, E., Gibelli, B., Ostuni, A., & Chiesa, F. (2009). Compartmental surgery in tongue tumours: Description of a new surgical technique. *Acta Otorhinolaryngologica Italica*, *29*(5), 259–264.

Chong, V. (2005). Oral cavity cancer. *Cancer Imaging*, *5*(special issue A), S49–S52. https://doi.org/10.1102/1470-7330.2005.0029

Drawing Survival Curves using 'ggplot2' • survminer. (n.d.). Retrieved 4 March 2020, from https://rpkgs.datanovia.com/survminer/index.html

Fan, K. H., Chen, Y. C., Lin, C. Y., Kang, C. J., Lee, L. Y., Huang, S. F., Liao, C. T., Ng, S. H., Wang, H. M., & Chang, J. T. C. (2017). Postoperative radiotherapy with or without concurrent chemotherapy for oral squamous cell carcinoma in patients with three or more minor risk factors: A propensity score matching analysis. *Radiation Oncology*, *12*(1), 184. https://doi.org/10.1186/s13014-017-0910-0

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., Znaor, A., Soerjomataram, I., & Bray, F. (2020). *Global Cancer Observatory (GLOBOCAN): Cancer Today, 2020*. https://gco.iarc.fr/today

Grégoire, V., Evans, M., Le, Q.-T., Bourhis, J., Budach, V., Chen, A., Eisbruch, A., Feng, M., Giralt, J., Gupta, T., Hamoir, M., Helito, J. K., Hu, C., Hunter, K., Johansen, J., Kaanders, J., Laskar, S. G., Lee, A., Maingon, P., … Grau, C. (2018). Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO. TROG Consensus Guidelines. *Radiotherapy and Oncology*, *126*(1), 3–24. https://doi.org/10.1016/j.radonc.2017.10.016

Grégoire, V., Grau, C., Lapeyre, M., & Maingon, P. (2018). Target volume selection and delineation (T and N) for primary radiation treatment of oral cavity, oropharyngeal, hypopharyngeal and laryngeal squamous cell carcinoma. *Oral Oncology*, *87*, 131–137. https://doi.org/10.1016/j.oraloncology.2018.10.034

Liu, S. H., Chao, K. S. C., Leu, Y. S., Lee, J. C., Liu, C. J., Huang, Y. C., Chang, Y. F., Chen, H. W., Tsai, J. T., & Chen, Y. J. (2015). Guideline and preliminary clinical practice results for dose specification and target delineation for postoperative radiotherapy for oral cavity cancer. *Head and Neck*, *37*(7), 933–939. https://doi.org/10.1002/hed.23692

Merlotti, A., Alterio, D., Vigna-Taglianti, R., Muraglia, A., Lastrucci, L., Manzo, R., Gambaro, G., Caspiani, O., Miccichè, F., Deodato, F., Pergolizzi, S., Franco, P., Corvò, R., Russi, E. G., & Sanguineti, G. (2014). Technical guidelines for head and neck cancer IMRT on behalf of the Italian association of radiation oncology - head and neck working group. *Radiation Oncology*, *9*(1), 264. https://doi.org/10.1186/s13014-014-0264-9

Metcalfe, E., Aspin, L., Speight, R., Ermiş, E., Ramasamy, S., Cardale, K., Dyker, K. E., Sen, M., & Prestwich, R. J. D. (2017). Postoperative (chemo)radiotherapy for oral cavity squamous cell carcinomas: Outcomes and patterns of failure. *Clinical Oncology*, *29*(1), 51–59. https://doi.org/10.1016/j.clon.2016.09.008

National Comprehensive Cancer Network (2020). *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)Head and Neck Cancer.*

Piazza, C., Grammatica, A., Montalto, N., Paderno, A., Del Bon, F., & Nicolai, P. (2019). Compartmental surgery for oral tongue and floor of the mouth cancer: Oncologic outcomes. *Head and Neck*, *41*(1), 110–115. https://doi.org/10.1002/hed.25480

16010825, 2023, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/odi.13885 by Fondazione Irccs Policlinico San Matteo, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

R: a language and environment for statistical computing. (n.d.). Retrieved 4 March 2020, from https://www.gbif.org/tool/81287/r-a-language-and-environment-for-statistical-computing

Tagliabue, M., Gandini, S., Maffini, F., Navach, V., Bruschini, R., Giugliano, G., Lombardi, F., Chiocca, S., Rebecchi, E., Sica, E., Tommasino, M., Calabrese, L., & Ansarin, M. (2019). The role of the T-N tract in advanced stage tongue cancer. *Head and Neck*, *41*(8), 2756–2767. https://doi.org/10.1002/hed.25761

Tromp, D. M., Brouha, X. D. R., Hordijk, G.-J., Winnubst, J. A. M., & de Leeuw, R. J. (2005). Patient and tumour factors associated with advanced carcinomas of the head and neck. *Oral Oncology*, *41*(3), 313–319. https://doi.org/10.1016/j.oraloncology.2004.09.008

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Alterio D, Augugliaro M, Tagliabue M, et al. The T-N tract involvement as a new prognostic factor for PORT in locally advanced oral cavity tumors. *Oral Dis*. 2023;29:128–137. https://doi.org/10.1111/odi.13885

16010825, 2023, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/odi.13885 by Fondazione Irccs Policlinico San Matteo, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License