

ORIGINAL REPORT

Prognostic Role of Depth of Invasion Stratification Beyond the 10 mm Threshold in Tongue Carcinoma

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ABSTRACT

Objectives: The aim of this study is to define the prognostic role of further stratification in oral tongue and floor squamous cell carcinoma (OTFSCC) with a pathological DOI > 10 mm.

Methods: A retrospective multicenter study was conducted on patients with a pDOI > 10 mm. Patients were stratified into three groups based on pDOI values: Group A (11–20 mm), Group B (21–30 mm) and group C (> 30 mm). The association between stratified pDOI and various histopathological features was investigated, along with disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS). Univariable and multivariable Cox regression analyses were applied to estimate the hazard ratio (HR).

Results: A total of 108 patients were included. Seventy-six patients (70.4%) were in Group A, 22 (20.4%) in Group B, and 10 (9.2%) in Group C. The association between the stratified pDOI and ENE ($p=0.004$), lymph node burden (LNB) ($p=0.011$) and lymph node ratio (LNR) ($p=0.026$) resulted statistically significant. Five-year DSS resulted in 72.5% for Group A, 53.3% for Group B, and 25.9% for Group C. Univariable analysis showed that a pDOI > 30 mm was associated with a statistically significant increased risk of recurrence (HR = 8.32, $p=0.000$) and mortality from disease (HR = 3.61, $p=0.014$).

Conclusion: The stratification of OTFSCCs with a pDOI > 10 mm was statistically significantly associated with ENE, LNB, and LNR. Pathological DOI > 30 mm emerged as a negative prognostic factor for DFS and DSS.

Level of Evidence: Level 3.

1 | Introduction

Oral cavity cancer is the most common malignancy in the head and neck region. The tongue is the most frequently affected site

[1]. Despite advancements in diagnostic techniques, surgical planning, and treatment strategies, prognosis for OTFSCC remains poor, with a 5-year overall survival (OS) and disease-free survival (DFS) of approximately 50% and 60%, respectively [2].

Maria Rosini and Costanza Galloni contributed equally to this work.

Over time, the staging of oral cancer has been subjected to debate, and numerous efforts have been made to update it to improve prognostic accuracy. The 8th edition of the Tumor Node Metastasis (TNM) Staging System, published in 2017, introduced significant changes, incorporating the concept of depth of invasion (DOI) into the pT classification and removing extrinsic tongue muscles involvement from the pT4a category. DOI is one of the most critical factors for predicting lymph node metastasis and locoregional recurrence, and it shows a strong correlation with disease-specific survival (DSS) [3].

In the first version of the 8th edition of the TNM, all tumors with a pDOI greater than 10 mm but without invasion of the cortical bone of the mandible, the maxillary sinus, or the skin of the face were classified as pT3. Subsequently, the pT3 category evolved into a broader, more heterogeneous group. As a result, both the American Joint Cancer Committee (AJCC) and the Union for International Cancer Control (UICC) revised the classification, upstaging tumors with both a size > 4 cm and a pDOI > 10 mm to the pT4a category [4]. However, the 10 mm cutoff for pDOI remains a crucial threshold, and all values > 10 mm are considered equivalent in terms of prognosis.

The main aim of this study is to assess the prognostic impact of further stratification of OTFSCC with pDOI > 10 mm. Secondly, we analyzed the association between stratified pDOI values and the presence of other histopathological risk factors.

2 | Materials and Methods

2.1 | Study Design

This is a retrospective, multicenter study conducted at two tertiary referral centers for this pathology. The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee (CE AVEN Emilia Romagna: 0018649–22).

2.2 | Study Population

We included patients affected by OTFSCC who were treated surgically at the University Hospital of Modena or at the San Maurizio Hospital of Bolzano between January 2015 and May 2023, and who had a pDOI greater than 10 mm.

Exclusion criteria were as follows: history of radiation therapy or chemoradiation therapy for previous head and neck tumors; salvage surgery for recurrent OTFSCC; positive margins (R1) at the histopathological examination; distant metastasis at presentation; follow-up shorter than 12 months; tumor classified as pT4a and p4Tb according to the first version of 8th edition of TNM Staging System (infiltration of adjacent structures, such as the cortical bone of the mandible or maxilla, involvement of the maxillary sinus or skin of the face/invasion of masticator space, pterygoid plates, or skull base and/or encasement of the internal carotid artery). The only pT4a tumors included in the study were those with dimensions greater than 4 cm and pDOI greater than 10 mm.

We retrieved patients' information from the analysis of medical records. Among the collected data, we focused on demographics, surgical details, tumor characteristics at the histopathological examination, and follow-up. Tumors were classified according to the most recent version of the 8th edition of the TNM Staging System.

Patients were stratified into three categories according to pDOI: Group A (pDOI 11–20 mm), Group B (pDOI 21–30 mm) and Group C (pDOI > 30 mm).

DOI was defined as the distance between a tangential plane passing through the level of the basement membrane of the healthy adjacent mucosa and the deepest point of tumor invasion [5].

2.3 | Statistical Analysis

Categorical variables were summarized using absolute frequencies and percentages, while continuous variables were summarized using the median, interquartile range (IQR) and range.

The association between the stratified pDOI and perineural and lymphovascular invasion (PNI/LVI), tumor grading (G), pT and pN status, extranodal extension (ENE), lymph node burden (LNB), lymph node ratio (LNR), contralateral neck node metastasis, and ipsilateral level IV and V neck metastasis was investigated through the Chi-square test and the median test depending on the types of variables. LNB was defined as the number of pathologically positive lymph nodes identified after neck dissection. LNR corresponds to the number of involved nodes divided by the number of lymph nodes examined.

We estimated the Kaplan–Meier curves for DFS, DSS, and OS. We used the log-rank test to compare the curves between different groups. Univariable and multivariable Cox regression analyses, adjusting for tumor dimension (> 4 cm) and lymph node status (pN+), were applied to estimate the hazard ratio (HR). A $p < 0.05$ was considered statistically significant. Statistical analysis was performed using STATA/IC 15.1 statistical package (StataCorp LP, Texas, USA).

3 | Results

3.1 | Study Population

A total of 108 patients were eligible for this study according to inclusion and exclusion criteria. General, clinical, and histopathological features, together with staging and treatment details, are reported in Table 1. Sixty-nine patients were men (63.9%), with a median age at the time of surgery of 63 years (IQR = 20.3, range 24–94). The majority of patients had tumors located in the tongue ($n = 92$, 85.2%). In 30 patients (27.8%), the tumor invaded the contralateral tongue, while the oropharynx was affected in 24 patients (22.2%). Compartmental tongue surgery was performed in 84 patients (77.8%). Neck dissection was performed in all patients. Fifty-nine patients (54.6%) underwent a unilateral neck dissection, while 48 patients (44.4%) underwent a bilateral neck dissection. The ipsilateral level IV was dissected in 90

TABLE 1 | General, clinical and surgical details of the study population.

Sex <i>n</i> (%)	108 (100)
Male	69 (63.8)
Female	39 (36.1)
Age median, IQR, range	63, 20.3, 24–94
Smoke <i>n</i> (%)	108 (100)
No	52 (48.1)
Previous	26 (24.1)
Active	30 (27.8)
Alcohol <i>n</i> (%)	108 (100)
No	65 (60.2)
Yes	43 (39.8)
Site <i>n</i> (%)	108 (100)
Tongue	92 (85.2)
Floor of mouth	16 (14.8)
Local extension <i>n</i> (%)	108 (100)
Contralateral tongue	30 (27.8)
Oropharynx	24 (22.2)
Retromolar trigone	2 (1.9)
Surgical technique <i>n</i> (%)	108 (100)
Compartmental tongue surgery	84 (77.8)
Wide margin resection	24 (22.2)
Neck dissection <i>n</i> (%)	108 (100)
Ipsilateral	60 (55.6)
Bilateral	48 (44.4)
Levels of ipsilateral neck dissection <i>n</i> (%)	108 (100)
I-III	18 (16.6)
I-IV	58 (53.7)
I-V	32 (29.6)
Levels of contralateral neck dissection <i>n</i> (%)	48 (100)
I-III	12 (25.0)
I-IV	27 (56.2)
I-V	9 (18.8)
Reconstruction <i>n</i> (%)	108 (100)
Free flap	70 (64.8)
Pedicled flap	19 (17.6)
No flap	19 (17.6)
Grading <i>n</i> (%)	108 (100)

(Continues)

TABLE 1 | (Continued)

G1	6 (5.6)
G2	56 (51.9)
G3	46 (42.6)
PNI <i>n</i> (%)	108 (100)
PNI–	22 (20.4)
PNI+	86 (79.6)
LVI <i>n</i> (%)	108 (100)
LVI–	65 (60.2)
LVI+	43 (39.8)
Margins <i>n</i> (%)	108 (100)
R0	89 (82.4)
R close	19 (17.6)
Dimension median, IQR, range	31.5, 23.5, 5–76
Dimension stratified <i>n</i> (%)	108 (100)
≤ 4 cm	72 (66.7)
> 4 cm	36 (33.3)
pDOI median, IQR, range	15, 10, 11–59
pDOI stratified <i>n</i> (%)	108 (100)
11–20 mm	76 (70.4)
21–30 mm	22 (20.4)
> 30 mm	10 (9.2)
Neck node metastasis <i>n</i> (%)	108 (100)
pN0	42 (38.9)
pN+	66 (61.1)
ENE <i>n</i> (%)	108 (100)
ENE–	72 (66.7)
ENE+	36 (33.3)
LNB median, IQR, range	1, 3.3, 0–21
LNR (%) median, IQR, range	2.47, 7.77, 0.00–64.7
Contralateral neck node metastasis <i>n</i> (%)	48 (100)
No	29 (60.4)
Yes	19 (39.6)
Level IV or V ipsilateral neck node metastasis <i>n</i> (%)	90 (100)
No	73 (81.1)
Yes	17 (18.9)
pT <i>n</i> (%)	108 (100)
pT3	72 (66.7)

(Continues)

TABLE 1 | (Continued)

pT4a	36 (33.3)
pN n (%)	108 (100)
pN0	42 (38.9)
pN1	10 (9.3)
pN2a	4 (3.7)
pN2b	12 (11.1)
pN2c	8 (7.4)
pN3b	32 (29.6)
Adjuvant therapy	91 (100)
No	51 (56.0)
Yes	40 (44.0)

Abbreviations: ENE, extra-nodal extension; IQR, interquartile range; LNB, lymph node burden; LNR, lymph node ratio; LVI, lymphovascular invasion; pDOI, pathological depth of invasion; PNI, perineural invasion.

patients (83.3%), 32 of whom (29.6% of the total) also underwent level V dissection.

At histopathological examination, PNI occurred in 86 cases (79.6%), while LVI in 43 (39.8%). Median maximal tumor diameter was 31.5 (IQR 23.5, range 5–76). In particular, 36 patients (33.3%) presented a tumor greater than 4 cm. Median pDOI was 15 (IQR = 10, range 11–59).

The majority of patients presented neck node metastasis (pN+) ($n = 66$, 61.1%). Among them, histopathological examination revealed ENE in 36 patients (33.3% of the total). Median LNB was 1 (IQR = 3.3, range 0–21) and median LNR was 2.47% (IQR = 7.77, range 0.00–64.7). Contralateral node metastases were present in 19 patients (39.6%), while neck node metastases at the ipsilateral level IV or V were present in a total of 17 patients (18.9%).

Relatively to staging, most of the patients resulted in pT3 ($n = 72$, 66.7%). Regarding pN stage, the most frequent stage after pN0 ($n = 42$, 38.9%) was pN3b ($n = 32$, 29.6%).

Adjuvant therapy, consisting of exclusive radiotherapy or concurrent chemoradiotherapy, was administered to 51 patients (56.0%). Forty patients (44.0%) did not receive any adjuvant therapy due to the early onset of loco-regional or systemic recurrence, postoperative complications, poor performance status, or patient refusal.

3.2 | Association Between pDOI and Other Histopathological Prognostic Variables

According to pDOI, patients have been stratified into the following three categories:

- Group A (pDOI 11–20 mm): 76 patients (70.4%).
- Group B (pDOI 21–30 mm): 22 patients (20.4%).

- Group C (pDOI > 30 mm): 10 patients (9.2%).

The associations between the stratified pDOI and histopathological variables are summarized in Table 2. We found a statistically significant association between the stratified pDOI and ENE ($p = 0.004$), LNB ($p = 0.011$) and LNR ($p = 0.026$).

3.3 | Survival Analysis

The median follow-up time was 26.5 months (IQR = 38.3, range 12–92). At the last follow-up, 49 patients (45.3%) were alive without disease, 9 patients (8.3%) were alive with disease, 34 patients (31.5%) died from disease, and 16 patients (14.8%) died from causes other than OTFSCC.

Kaplan–Meier curves relative to DFS, DSS, and OS are reported in Figure 1. Patients with greater pDOI present statistically significant worse survival curves for DFS and DSS ($p = 0.000$ and $p = 0.031$, respectively) but not for OS ($p = 0.352$).

The estimated 5-year DFS, DSS, and OS for the three groups of stratified pDOI are reported in Table 3.

Univariable and multivariable regression analysis are displayed in Table 4. Patients with a pDOI > 30 mm (Group C) presented a statistically significant increased risk of recurrence (HR = 8.32, $p = 0.000$) and mortality from disease (HR = 3.61, $p = 0.014$) compared to group A. After adjusting for tumor dimension (> 4 cm) and lymph node status (pN+), the increased risk associated with Group C was confirmed for DFS (HR = 5.53, $p = 0.000$).

On the contrary, the association of pDOI with overall mortality was not statistically significant (HR = 1.90, $p = 0.191$; adjusted HR = 1.09, $p = 0.869$).

Lymph node status has been confirmed to be the main independent prognostic factor of recurrence (adjusted HR = 3.15, $p = 0.003$), mortality from disease (adjusted HR = 6.82, $p = 0.002$) and overall mortality (adjusted HR = 2.28, $p = 0.022$) in patients affected by OTFSCC.

4 | Discussion

Over the years, the staging of oral cancer has been frequently debated by several authors, largely due to the limited prognostic value of measuring the two-dimensional surface diameter alone for T1–T3 lesions, and the reliance on extrinsic tongue muscles infiltration to categorize tumors as T4a. As a result, the scientific community proposed incorporating tumor DOI alongside tumor diameter in the 8th edition of the TNM Staging System to provide more accurate prognostic information, as DOI has been widely established as an independent prognostic factor, strongly correlated with nodal metastasis, locoregional recurrence, and survival rates [6]. The pDOI threshold for distinguishing early-stage tumors (pT1–pT2) from advanced ones (pT3) was set at 10 mm [7]. Changes between the 7th and the 8th edition of the TNM Staging System significantly impacted T staging of OTFSCC by reclassifying

TABLE 2 | Association between pathological depth of invasion (pDOI) and other histopathological prognostic variables.

pDOI	Group A (n = 76)	Group B (n = 22)	Group C (n = 10)	p
Grading n (%)				
G1	6 (7.9)	0 (0)	0 (0)	0.439
G2	37 (48.7)	12 (54.5)	7 (70)	
G3	33 (43.4)	10 (45.5)	3 (30)	
PNI n (%)				
PNI–	15 (19.7)	4 (18.2)	3 (30)	0.721
PNI+	61 (80.3)	18 (81.8)	7 (70)	
LVI n (%)				
LVI–	49 (64.5)	12 (54.5)	4 (40)	0.276
LVI+	27 (35.5)	10 (45.5)	6 (60)	
Neck node metastasis n (%)				
N0	32 (42.1)	9 (40.9)	1 (10)	0.144
N+	44 (57.9)	13 (59.1)	9 (90)	
ENE n (%)				
ENE+	55 (72.3)	15 (68.2)	2 (20)	0.004
ENE–	21 (27.6)	7 (31.8)	8 (80)	
LNB n (%)				
≤ median	46 (60.5)	12 (54.5)	1 (10)	0.011
> median	30 (39.5)	10 (45.5)	9 (90)	
LNR n (%)				
≤ median	40 (52.6)	13 (59.1)	1 (10)	0.026
> median	36 (47.4)	9 (40.9)	9 (90)	
Contralateral neck node metastasis n (%)				
No	16 (61.5)	9 (64.3)	4 (50)	0.739
Yes	10 (38.5)	5 (35.7)	4 (50)	
Level IV or V ipsilateral neck node metastasis n (%)				
No	49 (81.7)	19 (90.5)	5 (55.6)	0.080
Yes	11 (18.3)	2 (9.5)	4 (44.4)	
pT n (%)				
pT3	61 (80.3)	9 (40.9)	2 (20)	0.086
pT4a	15 (19.7)	13 (59.1)	8 (80)	
pN n (%)				
pN0	32 (42.1)	9 (40.9)	1 (10)	0.078
pN1	10 (13.2)	0 (0)	0 (0)	
pN2a	2 (2.6)	2 (9.1)	0 (0)	
pN2b	9 (11.8)	2 (9.1)	1 (10)	
pN2c	4 (5.3)	3 (13.6)	1 (10)	
pN3b	19 (25)	6 (7.9)	7 (70)	

Note: Bold indicates statistically significant p-values.

Abbreviations: ENE, Extra-nodal extension; LNB, lymph node burden; LNR, lymph node ratio; LVI, Lymphovascular invasion; PNI, Perineural invasion.

many pT4a tumors infiltrating extrinsic tongue muscles as pT3, resulting in the new pT4a category being sparsely populated, as infiltration of the mandible, maxilla, and skin of the face is rare [8]. On the other hand, the pT3 category became a repository for a heterogeneous group of tumors with varying aggressiveness and prognoses, prompting several proposals to further subclassify these tumors.

In February 2018, the third printing of the 8th edition of the AJCC TNM classification introduced an update to oral cancer staging, which included tumors with bilateral tongue involvement and/or DOI > 20 mm in the pT4a category. However, only 4 months later, a further revision removed these criteria. The update reclassified tumors larger than 4 cm and with DOI > 10 mm as pT4a [4]. The result was a more uniform redistribution of pT3 and pT4a stages compared to the initial version of 8th edition. However, the 10 mm pDOI cut off has remained a fixed threshold since 2017, and even the new classification does not account for the varying prognostic impact of increasing pDOI values.

By stratifying tumors with a pDOI > 10 mm, our results demonstrate a progressive decline in DFS, DSS, and OS as DOI values increase, as shown by the Kaplan–Meier curves. The association was statistically significant only for DFS and DSS, but not for OS, which can be explained by the high number of patients in the first group who died from causes unrelated to cancer. This result was validated by the univariable Cox regression analysis estimating the hazard ratio of group C compared to group A.

In the multivariable analysis, adjusting for pN status (pN0/pN+) and tumor size (≤ 4 cm / > 4 cm) as confounding factors, a pDOI > 30 mm was confirmed as an independent risk factor positively associated with DFS. On the other hand, the correlation did not significantly persist for DSS. However, it is important to specify how the small sample size strongly influenced the results of the multivariable analysis, which, with a larger number of patients, could yield different results.

The prognostic impact of a pDOI greater than 10 mm has already been investigated by other authors. For example, Mattavelli et al. found that, in a cohort of patients affected by oral cancer, OS continues to be independently affected by thickness of invasion even beyond 10 mm, and therefore suggested introducing a pDOI cut off of 20 mm to determine a shift to the T4a category [8]. In 2019, Liao et coworkers analyzed the prognostic impact of three criteria used to identify pT4a disease (tumor > 4 cm / pDOI > 10 mm [AJCC 2018, second revision], pDOI > 20 mm [AJCC 2018, first revision] and through mandible and maxillary cortex/skin invasion [AJCC from third to eighth editions]) in a large cohort of patients with buccal, gum, hard palate, and retromolar SCC. Their results showed that all three criteria identified high-risk patients who deserved to be classified in the pT4a category, but pDOI > 20 mm was the strongest prognostic factor compared to the others [9].

The role of DOI as an independent predictor of cervical lymph node metastasis is well-established and well-documented [3, 10, 11]. Nodal metastases have a profound and detrimental impact on prognosis, leading to a 50% reduction in 5-year DSS [3]. In our study, the associations between stratified pDOI and

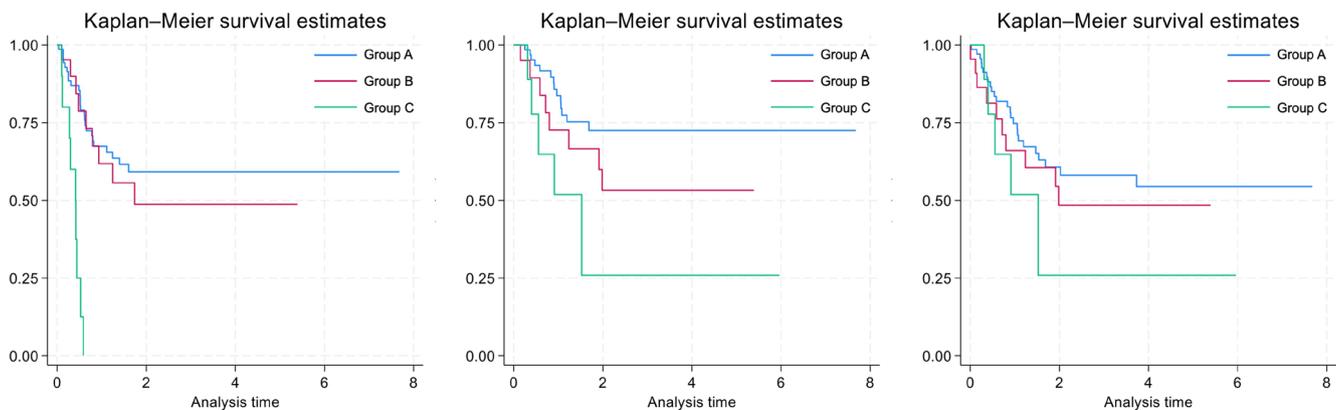


FIGURE 1 | Kaplan–Meier curves for (a) disease free survival (DFS) ($p=0.000$), (b) disease specific survival (DSS) ($p=0.031$) and (c) overall survival (OS) ($p=0.352$).

TABLE 3 | Estimated 5-year disease free survival (DFS), disease specific survival (DSS) and overall survival (OS) for the three groups of stratified pathological depth of invasion (pDOI).

	DFS	DSS	OS
Group A	59.2% (95% CI [45.5–70.6])	72.5% (95% CI [57.6–82.9])	54.4% (95% CI [39.2–67.4])
Group B	48.7% (95% CI [24.0–69.6])	53.3% (95% CI [27.5–73.6])	48.4% (95% CI [24.9–68.5])
Group C	0% (95% CI [0.0–0.0])	25.9% (95% CI [1.5–64.9])	25.9% (95% CI [1.5–64.9])

Abbreviation: CI, Confidence interval.

LNB, LNR, and ENE were found to be statistically significant. To the best of our knowledge, no studies have investigated the association between DOI and LNB before. However, several authors have found that LNB has a stronger prognostic impact on mortality compared to the size or laterality of nodal metastasis, which are currently included in the TNM Staging System [12, 13]. The development of nodal metastases in multiple lymph nodes and the extracapsular spreading of neoplastic cells in OTFSCC with increasing pDOI are facilitated by the prolonged tumor growth period and its biological aggressiveness.

Currently, the NCCN guidelines recommend prophylactic neck dissection for oral cancer when the DOI is ≥ 4 mm [14]. Other DOI values have been described in the literature for defining the risk of nodal metastasis, all of which are below 10 mm [11, 15–17]. In our study, we did not find an association between increasing pDOI values greater than 10 mm and the presence of nodal metastasis. This aligns with previous findings, which suggest that the presence of metastasis is primarily influenced by pDOI values below 10 mm, and that the risk of nodal metastasis does not continue to increase significantly above this threshold.

Elective contralateral neck dissection for OTFSCC is recommended in cases of floor of mouth involvement and tumors reaching or crossing the midline [14]. Our results did not show

a significant association between pDOI stratification and the risk of contralateral metastasis. In a recent study conducted by Grammatica et al., it was found that tumors with pDOI > 10 mm have their deepest point of invasion located less than 5 mm from the median raphe, suggesting that some patients of group A could also have tumors approaching the midline and therefore be at risk of contralateral neck metastasis [18].

From our results, no statistical significance was found regarding the association between increasing pDOI and the involvement of ipsilateral level IV and V lymph nodes. Several risk factors have been identified, including tongue localization, pN2 and pN3 staging, moderate or poor differentiation, tumor size > 2.5 cm, and DOI > 8 mm [19–22]. Nevertheless, the decision to include lower level cervical nodes during elective neck dissection for OTFSCC remains controversial [23, 24].

Perineural invasion (PNI) in oral cancer has been largely described and is currently considered a risk factor for aggressive disease [25]. Newman et al. found that pT3 oral tongue SCC with a DOI > 10 mm had a higher rate of PNI compared to tumors with a lesser DOI [26]. Similarly, Sudhakar et al. reported that in a cohort of 108 patients affected by OTFSCC, 40.5% of patients with a DOI < 10 mm had PNI, compared to 82.4% of tumors with a DOI > 10 mm [27]. LVI represents an independent prognostic factor for reduced OS in patients with oral cancer SCC [28]. Barret et al. found a highly significant association between LVI and increasing pT stage in a cohort of 335 patients with tongue SCC [29]. Krishnamurthy et al. found that the average pDOI in patients with positive LVI was greater, at 11 mm, compared to 6.4 mm in those without LVI ($p=0.00$) [30]. One possible explanation proposed by Huang et al. is that tumor emboli might be harder to form in the small-caliber lymphatics of superficial regions compared to the larger lymphatics found in deeper tissues [31]. In contrast to the previous studies, we focused on the association between progressively greater pDOI, beyond 10 mm, and PNI and LVI. However, no statistically significant association was found between stratified pDOI and PNI and LVI. This lack of significance may be explained by the fact that the neurovascular bundle, which travels in the paramedian septum, located between the genioglossus muscle medially and the inferior longitudinalis, hyoglossus, and styloglossus muscles laterally, can be easily reached once the tumor's pDOI exceeds 10 mm [32]. Therefore, there is no significant difference between tumors

TABLE 4 | Univariable and multivariable regression analysis relative to disease-free survival (DFS), disease specific survival (DSS) and overall survival (OS).

	Univariable			Multivariable		
	HR	95% IC	<i>p</i>	HR	95% IC	<i>p</i>
DFS						
pDOI Group B vs A	1.20	0.56–2.55	0.643	1.13	0.51–2.47	0.766
pDOI Group C vs A	8.32	3.70–18.75	0.000	5.53	2.22–13.82	0.000
> 40 mm				1.38	0.70–2.74	0.353
pN+				3.15	1.49–6.69	0.003
DSS						
pDOI Group B vs A	1.85	0.78–4.42	0.165	1.77	0.73–4.31	0.208
pDOI Group C vs A	3.61	1.29–10.09	0.014	2.12	0.69–6.57	0.192
> 40 mm				1.60	0.70–3.69	0.265
pN+				6.82	2.03–22.94	0.002
OS						
pDOI Group B vs A	1.28	0.62–2.65	0.511	1.05	0.49–2.25	0.903
pDOI Group C vs A	1.90	0.73–4.97	0.191	1.09	0.39–3.05	0.869
> 40 mm				2.20	1.12–4.31	0.021
pN+				2.28	1.12–4.64	0.022

Note: Bold indicates statistically significant *p*-values.
Abbreviation: CI, Confidence interval.

with a pDOI of 11–20 mm and those with a pDOI > 30 mm, as both have likely reached the nerve and vascular branches.

This study points out for the first time that OTFSCC with a pDOI > 30 mm is not equivalent to other pT3 tumors in terms of survival rates. Despite the improvements achieved by the various revisions of the TNM Staging System for oral cavity tumors, further modifications could be considered to account for the different prognostic impact of additional pDOI stratification for pT3 OTFSCC.

Moreover, an interesting finding is represented by the direct association between pDOI > 10 mm and LNB or ENE, which deserves to be explored further. We hope to motivate the interest in the argument and the development of future studies.

The limitations of our study include its retrospective design and the relatively small sample size, which particularly affects patient stratification and multivariable analysis.

5 | Conclusions

In conclusion, pDOI stratification beyond 10 mm revealed a positive association with ENE, LNB, and LNR, which are factors strongly associated with worse outcomes.

Moreover, from the survival analysis, pDOI > 30 mm emerged as a negative prognostic factor for DFS and DSS. Therefore, pDOI > 30 mm could serve as an additional criterion for differentiating

tumors within the pT3 category. However, further large-scale, multicenter, and prospective studies are required to provide robust evidence that can be applied in clinical practice and guide future revisions of the TNM Staging System.

Conflicts of Interest

The authors declare no conflicts of interest.

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