Received: 12 February 2020 | Revised: 10 May 2020 | Accepted: 4 June 2020

DOI: 10.1111/odi.13479

ORIGINAL ARTICLE

ORAL DISEASES WILEY

Histological features and survival in young patients with HPV-negative oral squamous cell carcinoma

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Abstract

Objectives: The frequency of oral squamous cell carcinoma in young adults has increased in the last decades, and there are conflicting results in literature about its prognosis in young subjects. The aim of this study was to analyse the clinical and pathological features of oral squamous cell carcinoma in a cohort of young adults in order to investigate the presence of new independent prognostic markers.

Materials and Methods: Only HPV-negative young patients (under 40-year-old) affected by oral squamous cell carcinoma were considered in this study. Clinical and pathological data were collected. Patients were re-staged according to the 8th edition of AJCC.

Results: Overall, 66 patients were considered in this study. Perineural invasion significant correlated with both 7th and 8th edition of AJCC, and lymphovascular invasion (p-value < .05). The multivariate survival analysis showed that patients with perineural invasion had a significant worse prognosis (HR = 6.384 95% C.I. 1.304–31.252; p-value = .022).

Conclusions: Perineural invasion emerged as an independent prognostic factor for disease-specific survival in young patients with oral squamous cell carcinoma. Furthermore, the evaluation of this parameter is simple, inexpensive and can be used to augment the risk stratification of oral cancer based on the 8th edition of AJCC.

KEYWORDS

8th edition AJCC, disease-specific survival, oral squamous cell carcinoma, perineural invasion, young age

1 | INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most common malignant tumour of the oral cavity, representing the eighth most common cancer worldwide (Shield et al., 2017). Although OSCC usually occurs in males between the age of 60 and 80 years, a rise in OSCC incidence among younger subjects has been reported in recent years (Jeon et al., 2017). In particular, the frequency of OSCC among young adults has increased since the 1980s and to date these patients are 4%–12% of all OSCC cases (Muller, Pan, Li, & Chi, 2008; Udeabor, Rana, Wegener, Gellrich, & Eckardt, 2012). Although young patients represent only a small proportion of all

OSCC cases, there is increasing attention from clinicians and researches on this subgroup of patients. Indeed, several studies have highlighted that young OSCC patients lack of prolonged exposure to known risk factors, mainly tobacco and alcohol (Dahlstrom et al., 2008; Patel et al., 2011). A possible role of HPV infection in the pathogenesis of OSCC has been suggested. Indeed, the patients with HPV-related oropharyngeal tumours are about 10 years younger that HPV-negative patients and without a significant history of tobacco and alcohol use (Martinez et al., 2018). However, recent reports have demonstrated that only a small percentage of OSCC cases is associated with HPV infection (Upile et al., 2014). For this reason, tumour development in younger patients seems to be aetiologically distinct, but there is no consensus about the risk factors involved (Gu et al., 2019; Hirota, Braga, Penha, Sugaya, & Migliari, 2008; Llewellyn, Linklater, Bell, Johnson, & Warnakulasuriya, 2004). Similarly, there are conflicting results in literature about the prognosis of OSCC in young subjects (Gamez et al., 2018; Hyam et al., 2003).

The American Joint Committee on Cancer (AJCC) staging is the most widely used tool for prognostic stratification of OSCC patients. The 8th edition of AJCC cancer staging system has been recently released, and new parameters have been added to stratify OSCC patients, such as depth of invasion (DOI) and extra-nodal extension (ENE) (Amin, Edge, & American Joint Committee on Cancer, 2017). The 8th edition improves the stratification of OSCC patients compared with the previous one; however, accumulating evidence show that this system still needs to be improved to obtain an accurate for the prognostic assessment of young OSCC patients (Kano et al., 2018; Mascitti et al., 2018; Moeckelmann et al., 2018). Therefore, it is necessary to find new prognostic biomarkers in order to better stratify those patients who could benefit from more specific treatments, including young OSCC patients (Frohlich et al., 2018; Kano et al., 2018). There are several well-established molecular techniques to identify new prognostic markers, but the variable results and the high cost hinder their clinical utility (Ho, Wu, Cheng, Yang, & Wu, 2019). For these reasons, the study of morphological features of tumour tissue could be a valuable source of information. Among the morphological features of OSCC, there are some that have gained growing interest in the last years, such as perineural invasion (PNI) and lymphovascular invasion (LVI) (Cassidy et al., 2017; Schmitd, Scanlon, & D'Silva, 2018). Although these parameters have been included in the 8th edition of AJCC cancer staging system as additional prognostic factors, their ability to stratify OSCC patient risk for recurrence or survival is still discussed. There are very few reports that investigated histological and molecular aspects young OSCC patients, with inconclusive results (Farquhar et al., 2018; Jeon et al., 2017).

The aim of this study was to analyse the clinical and histopathological features of OSCC in a cohort of young adults in order to investigate the presence of new independent prognostic markers in this subgroup of patients.

2 | MATERIAL AND METHODS

2.1 | Study population

The cohort included in this retrospective study consists of young patients, defined as under 40-year-old, affected by OSCC. All the patients were treated for curative intent in two Italian University Hospitals (Complex Operating Unit of Odontostomatology, Department of Interdisciplinary Medicine, Aldo Moro University, Bari; Department of Clinical, Specialistic and Dental Sciences, Marche Polytechnic University, Ancona), between 1991 and 2018. All patients had postoperative follow-up every month for the first year, every 2 months during the second year, every 3 months during the third year and every 6 months thereafter. If a patient had symptoms or signs of suspected recurrence, an immediate postoperative visit was scheduled. For the patients that were lost to follow-up, recalls were made by phone call by two operators (M.M. and L.L.). A maximum follow-up period of 10 years was settled.

Examination of medical records was conducted to obtain pertinent data about each patient (age, sex, tobacco and alcohol use, clinical presentation and clinical staging (cTNM)). Pathological data were obtained from the Sections of Pathology of the two Institutes and included pathological stage (pTNM), Grade, perineural invasion (PNI), lymphovascular invasion (LVI) and surgical margins. The data were retrieved by two operators (L.T. and A.T.), to ensure uniformity of the collected data.

Inclusion criteria were as follows: (a) primary OSCC; (b) age under 40 years; (c) follow-up data of at least 1 year for alive patients. Exclusion criteria were as follows: (a) neoadjuvant therapy (i.e. preoperative chemotherapy or preoperative radiation therapy); (b) human papilloma virus (HPV) infection (HPV status was analysed retrospectively by using HPV 16-specific fluorescence in situ hybridization (FISH) and $p16^{Ink4a}$-specific immunohistochemistry); (c) relapsed or multiple (synchronous/metachronous) primary OSCC; (d) OSCC patients with immediate postoperative death.

Informed consent was obtained from all included patients, and the study was conducted in accordance with the "Ethical Principles for Medical Research Involving Human Subjects" statement of the Helsinki Declaration ("World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects", 2014). This study received ethical approval from the Ethical Committee of University of Bari, Italy (Prot.1442/CE). The study was conducted according to the STROBE guidelines.

2.2 | Histopathological evaluation

All the OSCC patients, who fulfil the inclusion and exclusion criteria, were further stratified by pathological stage (pTNM). The pTNM classifications were revised by 3 expert pathologists (G.F., E.M, and C.R.) blinded to clinical data, according to both the 7th and 8th editions of the AJCC Cancer Staging Manual (Amin, Edge, & American Joint

Committee on Cancer, 2017; Edge & American Joint Committee on Cancer, 2010) and the 4th edition of the World Health Organization (WHO) classification of Head and Neck tumours (El-Naggar, Chan, Rubin Grandis, Takata, & Slootweg, 2017).

Routine haematoxylin-eosin (H&E) stained sections obtained from formalin-fixed, paraffin-embedded blocks of the primary tumour specimens were carried out from the most invasive part of the primary tumour. The DOI and the ENE were measured according to the AJCC 8th edition. Due to the paucity of patients with lymph node metastases, pN2 cases were pooled without distinguishing among pN2a, pN2b and pN2c. The presence of PNI was reported when cancer cells were identified in any of the 3 layers of the nerve sheath and/or tumour was in close proximity to the nerve, involving more than one-third its circumference (Liebig et al., 2009). LVI was defined as foci of tumour surrounded by a clear space and with a well-visualized endothelial lining (Tai, Li, Yang, Chu, & Wang, 2013).

2.3 | Outcomes and statistical analysis

GraphPad Prism software version 7.00 for Windows (http://www.graphpad.com; GraphPad Software, San Diego, CA) and SPSS 21.0 (IBM Corporation, Chicago, IL, USA) were used for statistical analysis.

Primary end point was to detect any significant effect of clinicopathological factors on survival rate; in particular, the clinical end points examined were disease-specific survival (DSS) and disease-free survival (DFS). Follow-up time was calculated from the date of surgical operation to the date of recurrence, whether involving local site or regional lymph node (for DFS), to the date of death due to cancer (for DSS), or the date of the last visit.

In order to evaluate the association between clinicopathological variables, the Mann–Whitney non-parametric test and the chi-square test or the Fisher exact test were used, and then the Spearman rank correlation analysis was performed. Normal distribution of variables was explored through Shapiro–Wilk normality test.

The log-rank test was used to estimate the association among variables and survival outcomes (DSS and DFS). In addition, a multivariate Cox regression hazard models were built in order to assess the association among predictive variables and their influences on the survival outcomes. A p-value <.05 was considered statistically significant.

3 | RESULTS

3.1 | Demographic and clinicopathological variables

The complete clinicopathological data of the OSCC patients are reported in Table 1. Overall, 66 patients with OSCC were considered in this retrospective study. 51 cases (77.3%) were males and 15 (22.7%) females, with a mean age of 32.1 ± 6.2 years (range 10–40). Tobacco and alcohol consumption were reported in 36.4% and 48.5% of the patients, respectively. In particular, 28 patients (42.4%) did not present any major risk factor. Other putative risk factors were reported: 9 patients had first-degree relatives diagnosed with cancer, including head and neck squamous cell carcinoma (HNSCC), and 9 patients were diagnosed with different immune-mediated diseases

TABLE 1 Clinical and pathological characteristics of the patients included in this study

Clinical and pathological data		
Parameters	**No.**	**%**
Sex		
Male	51	77.3
Female	15	22.7
Age (years)	32.1 ± 6.2	
Site		
Oral tongue	52	78.8
Gingival mucosa	6	9.1
Buccal mucosa	4	6.1
Floor of mouth	3	4.5
Retromolar trigone	1	1.5
Clinical presentation		
Ulcer	38	57.6
Leukoplakia	13	19.7
Nodule	9	13.6
Erythroplakia	6	9.1
Grading		
G1	26	39.4
G2	27	40.9
G3	13	19.7
PNI		
No	41	62.1
Yes	25	37.9
LVI		
No	46	69.7
Yes	20	30.3
Margins		
No	44	66.7
Yes	22	33.3
Major risk factors		
Only alcohol use	13	19.7
Only tobacco use	5	7.6
Tobacco + Alcohol	20	30.3
No	28	42.4
Treatment		
Surgery	51	77.3
Surgery + RxT	12	18.2
Surgery + RxT +ChT	3	4.5
Median follow-up	60 months	

Abbreviations: ChT, chemotherapy; RxT, radiotherapy.

but, due to the small number of cases, no significant relationships were found with other variables.

The most common site was oral tongue (52 cases) representing 78.8% of all cases. When considering the anatomical subsites of the tongue, 34 cases occurred on the lateral borders, followed by dorsum (10 cases), ventral surface (6 cases) and the tip (2 cases). The presence of an oral ulcer was the most common clinical presentation (38 cases), followed by leukoplakia (13 cases), nodule (9 cases) and erythroplakia (6 cases). Regarding cTNM, 16 patients were staged as Stage I, 21 as Stage II, 19 as Stage III and 10 as Stage IV. The histological analysis showed the presence of PNI and LVI in 37.9% and 30.3% of cases, respectively.

TABLE 2 Comparison of the pT, pN and Stage classifications according to the 7th and 8th Edition of the AJCC

	Total cases		Recurrences		Deaths	
	7th	8th	7th	8th	7th	8th
pT						
pT1	30	20	8	3	3	0
pT2	23	30	3	8	5	5
pT3	7	10	4	4	5	8
pT4a	6	6	3	3	5	5
pN						
pN0	48	48	10	10	7	7
pN1	14	11	6	6	9	6
pN2	4	7	2	2	2	5
Stage						
I	25	19	5	3	1	0
II	18	22	2	4	4	2
III	11	10	5	5	6	6
IV	12	15	6	6	7	10

The data about pT, pN and Stage groups according to both 7th and 8th AJCC editions are reported in Table 2. The introduction of DOI and ENE determined the upstage in the pT (13 patients) and pN classifications (3 patients), respectively. Overall, 11 patients received an upstage in the Staging score when using the 8th AJCC staging edition (Table 2, Figure and b). Surgery alone was the curative treatment in 51 patients (77.3%), 12 patients (18.2%) received radiotherapy, and 3 patients (4.5%) received a combination of radiotherapy and chemotherapy as part of their treatment (Table 1).

Results of Spearman's rank correlation analysis are reported in Table 3, showing a significant correlation between PNI, LVI, 7th and 8th editions AJCC. In particular, PNI was correlated with 7th edition AJCC (ρ = .434, p-value < .001), 8th edition AJCC (ρ = 0.584, p-value < .001) and LVI (ρ = 0.301, p-value = .014). Other significant relationships were found: in particular, between tobacco and alcohol use, and between the use of adjuvant therapy and the 7th and 8th editions AJCC (Table 3).

3.2 | Survival analysis

As reported in Table 4, no differences were found between upstaged and non-upstaged patients regarding the number of recurrences and the DFS (p-value > .05). On the contrary, patients who received an

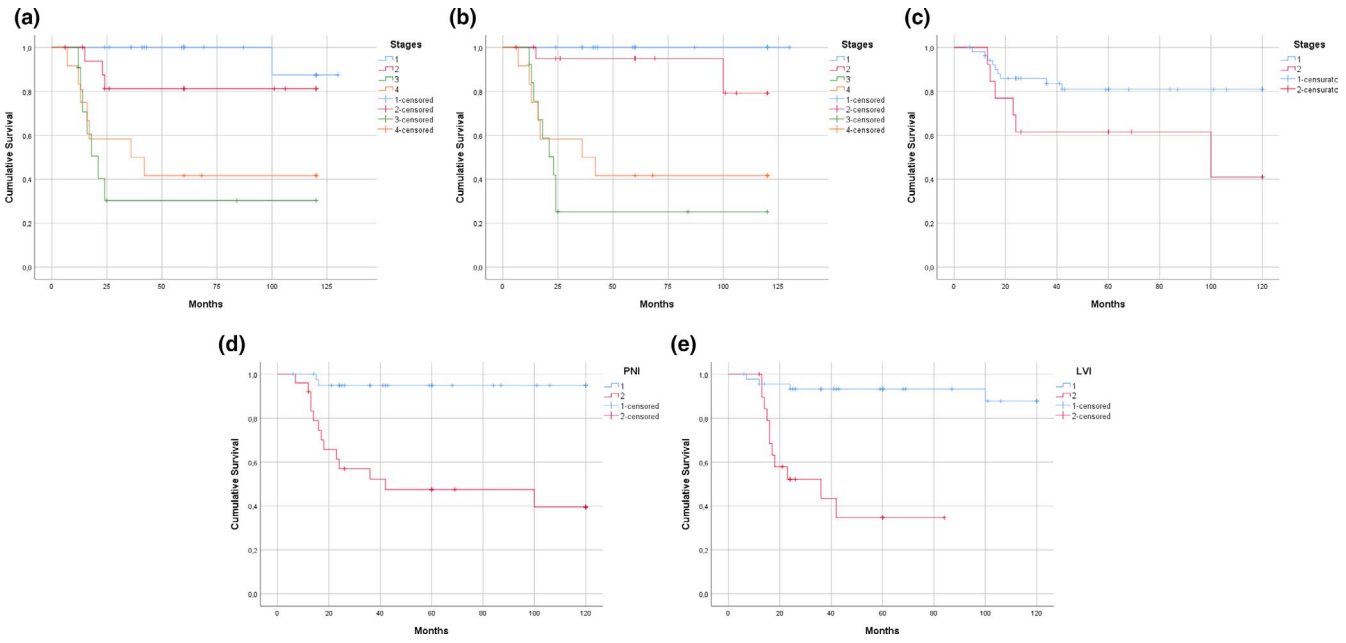

FIGURE 1 Kaplan–Meier analysis. 10-year DSS for patients according to the (a) 7th edition and the (b) 8th edition of the AJCC Cancer Staging Manual. (c) 10-year DSS for upstaged and non-upstaged patients (p-value = .0065). 10-year DSS for patients with and without PNI (p-value < .001) (d). 10-year DSS for patients with and without LVI (p-value < .001) (e) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Spearman's rank correlation for variables evaluated into the cohort of 66 OSCC patients classified according to both the 7th and 8th Edition of the AJCC staging

Variable	Age	Sex	Grade	PNI	Stage (7th AJCC)	Stage (8th AJCC)	LVI	Margins	Tobacco	Alcohol	Adjuvant therapy
Age	$\rho = 1$	−0.058	−0.141	0.044	−0.241	−0.200	−0.063	0.156	0.062	−0.104	−0.208
	p-value = 1	.644	.257	.724	.051	.107	.614	.212	.622	.404	.094
Sex		$\rho = 1$	−0.092	0.051	0.231	0.131	−0.036	0.153	−0.135	−0.053	0.105
		p-value = 1	.463	.685	.062	.293	.776	.219	.282	.675	.404
Grade			$\rho = 1$	0.207	0.103	0.130	−0.053	0.201	−0.064	−0.108	0.289
			p-value = 1	.096	.410	.298	.672	.106	.611	.388	.019*
PNI				$\rho = 1$	0.434	0.584	0.301	0.044	0.150	−0.070	0.130
				p-value = 1	.000**	.000**	.014*	.725	.229	.576	.299
Stage (7th AJCC)					$\rho = 1$	0.934	0.326	0.182	0.054	−0.027	0.552
					p-value = 1	.000**	.008**	.144	.667	.827	.000**
Stage (8th AJCC)						$\rho = 1$	0.438	0.165	0.163	−0.020	0.564
						p-value = 1	.000**	.186	.191	.874	.000**
LVI							$\rho = 1$	0.023	0.174	−0.053	0.222
							p-value = 1	.853	.569	.714	.073
Margins								$\rho = 1$	−0.045	−0.043	0.105
								p-value = 1	.720	.732	.402
Tobacco									$\rho = 1$	0.436	0.009
									p-value = 1	.000**	.940
Alcohol										$\rho = 1$	0.016
										p-value = 1	.900
Adjuvant therapy											$\rho = 1$
											p-value = 1

*$p < .05$.

**$p < .001$.

TABLE 4 Comparison between upstaged and non-upstaged patients for pT and Stage

	pT			Staging		
	Same	Upstaged	*p*-value	Same	Upstaged	*p*-value
5-year recurrences	11/52	3/14	>.05[a]	13/55	1/11	>.05[a]
5-year DFS	77.3%	78.6%	>.05[b]	74.9%	90.9%	>.05[b]
10-year recurrences	13/52	5/14	>.05[a]	16/55	2/11	>.05[a]
10-year DFS	64.4%	0%	>.05[b]	57.6%	0%	>.05[b]
5-year deaths	9/53	5/13	>.05[a]	9/55	5/11	**.0461** [a]
5-year DSS	80.8%	61.5%	>.05[b]	81.7%	54.5%	**.0380** [b]
10-year deaths	11/53	6/13	>.05[a]	11/55	7/11	**.0065** [a]
10-year DSS	80.8%	30.8%	**.0267** [b]	81.7%	0%	**.0064** [b]

Note: Cases with recurrences or death are reported as number of cases/total cases. Bold values indicate statistical significance.

[a]χ^2 test or Fisher's exact test.

[b]Log-rank test.

TABLE 5 Results of Cox proportional hazard analysis for the young patients with OSCC

Variables	Risk ratio	95% confidence interval	*p*-value
Stage 8th edition	2.428	1.221–4.829	**.011**
PNI	6.384	1.304–31.252	**.022**
LVI	2.532	0.857–7.480	.093

Note: Bold values indicate statistical significance.

upstage in the Staging score showed a significantly higher number of deaths after 5 and 10 years (*p*-value = .0461 and .0065, respectively). To confirm this, the 5-year and 10-year DSS were significantly lower in upstaged patients (*p*-value = .038 and .0064, respectively) (Figure 1c).

The prognostic significance of PNI and LVI in young OSCC patients were initially analysed with log-rank test, showing a significant worse prognosis in patients with PNI (*p*-value < .001) (Figure 1d) or LVI (*p*-value < .001) (Figure 1e).

In order to test the usefulness of PNI and LVI as independent prognostic markers in young OSCC patients, Stage groups according to 8th AJCC edition were considered the best risk of death factor available. The Cox proportional hazard model, including Stage, PNI and LVI as variables, confirmed these results, showing that patients with PNI had a significant worse DSS (HR = 6.384 95% C.I. 1.304–31.252; *p*-value = .022) than those without PNI (Table 5).

4 | DISCUSSION

A worldwide increasing trend in the incidence of OSCC in young adults has been observed in the last decades, although the exact incidence is still uncertain (Borba Ribeiro et al., 2019). Moreover, the cut-offs reported in the literature defining the "young age" range from 30 to 45 years, highlighting the lack of standardization (de Morais et al., 2017; Oliver et al., 2019; Teixeira et al., 2019). Besides, the role of tobacco and alcohol consumption in the development of OSCC in young adults is still debated. A possible involvement of HPV infection in the pathogenesis of OSCC in young adults was initially suggested, but as widely reported in literature, only a small proportion of oral cancers are related to HPV infection (Upile et al., 2014). Recently, substantial evidence support the hypothesis that young patients affected by HNSCC are more associated with HPV-negative status (Ryu, Kim, Cho, & Yoon, 2019). For this reason, we focused on HPV-negative patients; therefore, our results exclude this viral infection as a possible aetiological factor and further emphasize the need to identify the risk factors related to young OSCC patients.

The negligible role of traditional risk factors in the development of OSCC in young adults led to formulate other pathogenetic hypotheses. Specific hereditary influences and familial risk factors have been suggested, but recent studies failed to find substantial genetic differences between younger and older OSCC patients (Lingen et al., 2000; Pickering et al., 2014). Indeed, in the present study, only 3 patients reported to have first-degree relatives diagnosed with HNSCC. Another hypothesis is related to the ability of cancer cells to avoid destruction from the host immune system (Chen & Mellman, 2017). Indeed, recent studies have increasingly shown that tumour immune microenvironment plays a critical role in cancer progression, although significant results in young OSCC patients has not yet emerged (Huang et al., 2019; Ryu et al., 2019; Teixeira et al., 2019; Vincent-Chong et al., 2018).

The recent implementation of clinicopathological parameters of the 8th edition of the AJCC cancer staging system, allows for better stratification of OSCC patients, even if the prognostic prediction for OSCC in young patients still unreliable (Amin et al., 2017; Mascitti et al., 2018). This may partly due to the use of differing survival end points and unstandardized cut-off age for defining young patients (Campbell et al., 2018). To the best of our knowledge, this is the first study to evaluate the 8th edition of the AJCC cancer staging system in young OSCC patients. The comparison between upstaged and non-upstaged patients showed a significantly higher number of

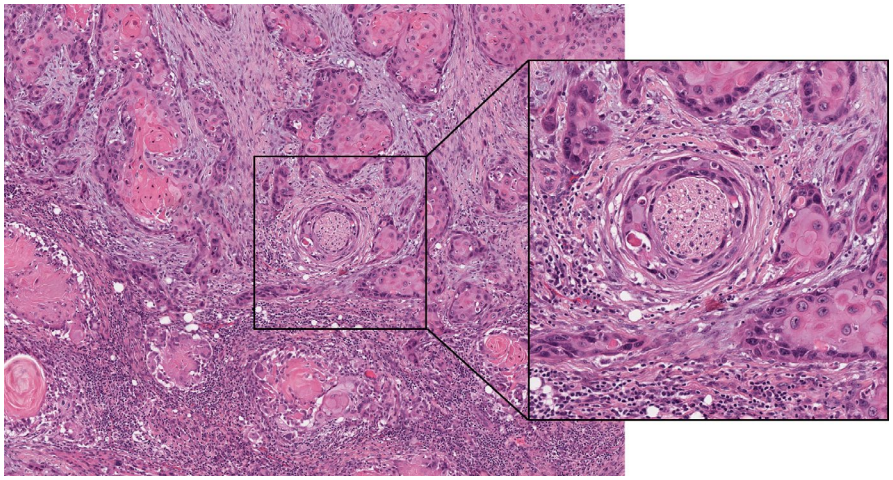

FIGURE 2 Perineural invasion in OSCC: haematoxylin-eosin stained section showing the carcinoma cells encircling a nerve trunk [Colour figure can be viewed at wileyonlinelibrary.com]

deaths and a worse DSS (Table 4, Figure 1c), confirming that the 8th edition of the AJCC cancer staging system provides a better stratification of young OSCC patients.

In recent years, several studies have been conducted with the aim to improve the prognostic stratification of OSCC based on the TNM criteria by including other histopathological factors (Lee et al., 2019). Among these morphological parameters, the PNI has attracted increasing interest as a poor prognostic factor in OSCC (Tai et al., 2013). The PNI is a histological parameter, defined as the dissemination of cancer cells in and along nerve bundles due to tropism of cancer cells for these tissues (Chatzistefanou, Lubek, Markou, & Ord, 2017) (Figure 2). This parameter is distinct from the "perineural spread," defined as the dissemination of cancer cells along the nerves that can be detected with imaging (Ginsberg, 1999). PNI can be considered as a distinct form of metastatic spread independent of vascular and lymphatic invasion, and its occurrence in OSCC is quite high, ranging from 12% to 50% of all specimens (Lee et al., 2019). The PNI has long been recognized as an indicator of poor prognosis in OSCC patients, but currently it is not required for stage grouping (Amin et al., 2017). Therefore, the use of PNI as a criterion to guide treatment decisions is debated. Our results revealed the usefulness of PNI as an independent prognostic marker in young OSCC patients, confirmed by both univariate and multivariate analysis. Indeed, young OSCC patients with PNI reported a significant worse DSS (HR = 4.983 95% C.I. 1.029–24.119; *p*-value = .046). These results are in agreement with several studies conducted among OSCC and HNSCC patients (Ling, Mijiti, & Moming, 2013; Nair et al., 2018; Ryu et al., 2019; Tai et al., 2013). In particular, a recent work of Ryu et al. found that HNSCC patients under 45 years of age were more commonly affected by PNI (Ryu et al., 2019). There is no consensus about the prognostic significance of unifocal (one nerve affected) and multifocal (two or more nerves affected) PNI. Furthermore, the presence of the different evaluation methods and the potential confounders for assessing PNI continue to be debated (Aivazian et al., 2015). Indeed, different classifications of PNI have been investigated, such as the diameter, the location and the number of infiltrated nerves, but the inherent subjectivity of these methods hinders their clinical utility (Miller et al., 2012; Wei, Li, & Tai, 2019). For these reasons, and due to the small sample size, in our study, we used a dichotomous score (the presence or the absence of PNI) for the evaluation of this parameter. These findings suggest that OSCC in young patients with PNI may represent a more aggressive subtype. Indeed, as the cancer cells spread along the bundle nerves may extend beyond the tumour mass, there is a higher risk of recurrence even after radical surgery (Nair et al., 2018).

Our study failed to demonstrate LVI as an independent prognostic marker in young OSCC patients in multivariate analysis (HR = 2.532 95% C.I. 0.857–7.480; *p*-value = .093), LVI has been identified as a useful histological marker of aggressiveness in OSCC (Campbell et al., 2018). Although several reports suggested a higher presence of LVI in young OSCC patients, the prognostic role of this parameter is debated (Farquhar et al., 2018). A possible explanation could be related to the small number of cases reported. Indeed, LVI seems to be more rare than other histological parameters in young OSCC patients (Jeon et al., 2017). Other reasons could be related to the number of sections of tumour examined or variability in criteria used in to define LVI (Beggan et al., 2016).

The main limitation of the present study is the low sample size and its retrospective nature. However, our results provide significant insights about the prognostic role of PNI in young OSCC patients. In conclusion, the age is a complex variable that can influence the tumour progression by multiple mechanisms, and its role on OSCC progression has not been extensively studied. Our results showed that PNI emerged as an independent prognostic factor for DSS in young OSCC patients. Furthermore, the evaluation of PNI is simple, inexpensive and can be used to augment the risk stratification of OSCC based on the 8th edition of the AJCC cancer staging system.

AUTHOR CONTRIBUTION

Marco Mascitti: Conceptualization; Data curation; Writing-original draft. **Angela Tempesta:** Data curation; Writing-original draft. **Lucrezia Togni:** Data curation; Writing-original draft. **Saverio Capodiferro:** Methodology; Supervision; Writing-review & editing. **Giuseppe Troiano:** Formal analysis. **Corrado Rubini:** Investigation.

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How to cite this article: Mascitti M, Tempesta A, Togni L, et al. Histological features and survival in young patients with HPV-negative oral squamous cell carcinoma. *Oral Dis*. 2020;26:1640–1648. https://doi.org/10.1111/odi.13479