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Incidence of Oral Squamous Cell Carcinoma in Patients Aged 30 Years and Under: A Single Institution Retrospective Analysis

Saja A. Alramadhan, BDS[1*], Sarah G. Fitzpatrick, DDS[1], Donald M. Cohen, DMD, MS, MBA[1], Indraneel Bhattacharyya, DDS, MSD[1], Mohammed N. Islam, DDS, BDS[1]

[1]Department of Oral and Maxillofacial Diagnostic Sciences, University of Florida College of Dentistry, 1395 Center Dr, Gainesville, FL 32610, United States

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***Corresponding author:** Saja A. Alramadhan
Department of Oral and Maxillofacial Diagnostic Sciences, University of Florida College of Dentistry, 1395 Center Dr, Gainesville, FL 32610, United States

Abstract

Background*:** Oral squamous cell carcinoma (OSCC) is a disease typically seen in the elderly, with an established relationship with tobacco and/or alcohol abuse. However, the incidence of OSCC among young adults (defined in this study as ≤ 30 years old) is on the rise. ***Materials and Methods: With IRB approval, a retrospective search was performed at the University of Florida College of Dentistry Oral Pathology Biopsy Service database from 1994-to 2019 for all cases of OSCC affecting patients aged ≤ 30 years. Demographic data were recorded, and the slides were reviewed for diagnostic consensus. ***Results*:** Thirty-one of 3971 OSCC cases (0.76%) were identified. The data show a prominent increase over time. Male patients (54.83%) were more commonly affected. Their ages ranged from 8 to 30 years, with a mean age of 25 years. The lateral border of the tongue is the most frequent site of involvement. A wide spectrum of differential diagnoses were obtained, mostly consisting of reactive lesions. Symptoms were reported in 65.6% of the cases. The histological grades ranged from well to poorly differentiated. ***Conclusion*:** This study underscores the rarity of OSCC in children and young adults. This may potentially lead to a low clinical suspicion, misdiagnosis, and delay in treatment. Further longitudinal multicenter studies with detailed medical history, treatment, genotyping, and prognostic data may help to better understand the etiology of OSCC in young patients, aid in prevention, and improve outcomes.

Keywords: Carcinoma, Squamous Cell, Epithelial Dysplasia, Young adult population, Human Papillomavirus.

INTRODUCTION

Squamous cell carcinoma (SCC) is the most common malignancy of the oral cavity [1-3]. It typically exhibits a peak incidence in the elderly and is strongly associated with smoking and alcohol abuse [1-3]. Oral squamous cell carcinoma (OSCC) rarely occurs in individuals younger than 50 years [1-6]. Nevertheless, as demonstrated by recent global epidemiologic studies, the incidence of SCC, particularly among young adults, is on the rise [1, 4-6].

The etiopathogenesis of oral squamous cell carcinoma (OSCC) in young patients remains unclear, and the traditional risk factors for OSCC, particularly tobacco and alcohol abuse, are assumed to be minimally related to carcinogenesis [1]. Human papillomavirus (HPV) plays a crucial role in the development of anogenital and oropharyngeal malignancies, yet for OSCC is still a matter of debate [1-4]. This study assesses the incidence of OSCC affecting patients 30 years and under over 25 years. The data included in this study were based on a single institution's biopsy service record and are not representative of the countrywide incidence of OSCC in young patients.

MATERIALS AND METHODS

With IRB approval, the archive of the University of Florida Oral Pathology Biopsy Service was retrospectively searched from 1994 to 2019. All patients with OSCC aged ≤ 30 years were identified. Cases with incomplete clinical/pathological data, extraoral locations, and inconclusive diagnoses of squamous cell carcinoma (SCC) were excluded. The cohort included 3971 OSCC cases during the study period. Age, sex, location, clinical presentation, diagnosis, and histological grading were recorded. The

findings of this study were analyzed. In addition, all cases were microscopically reviewed for a diagnostic consensus.

RESULTS

During the span of 25 years, a total of thirty-one cases were identified in patients less than or equal to 30 years of age out of a total of 3971 OSCC cases. The data showed a prominent increase (9.7%) over time (Fig 1). Seventeen patients (54.83%) were men and 14 (45.17%) were women, with a 1.2:1 male to female ratio. The patient age at presentation ranged from 8 to 30 years, with a mean age of 25 years. The youngest patient in this series was an 8-year-old male. This patient presented with an asymptomatic, red, sessile mass of 8 weeks duration on the facial gingiva between the right maxillary lateral and central incisors (teeth 11-12 "*FDI numbering system"*) (Fig 2). The clinical impression was the classic "bump on the gum" lesions, namely pyogenic granuloma, peripheral ossifying fibroma, or peripheral giant cell granuloma.

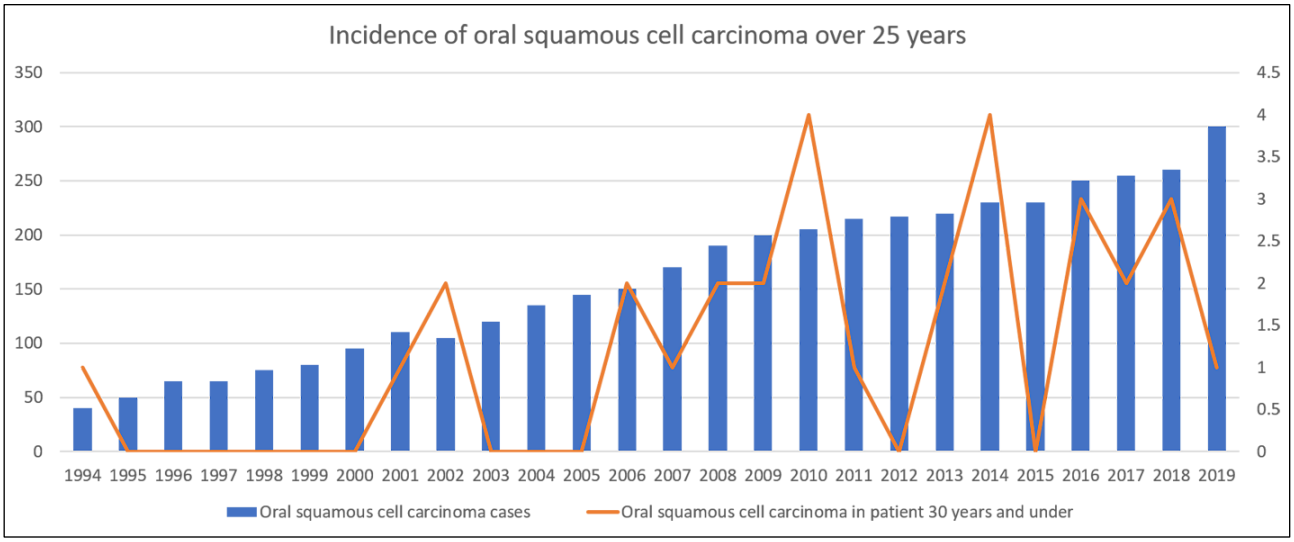

Figure 1: Incidence of oral squamous cell carcinoma over 25 years

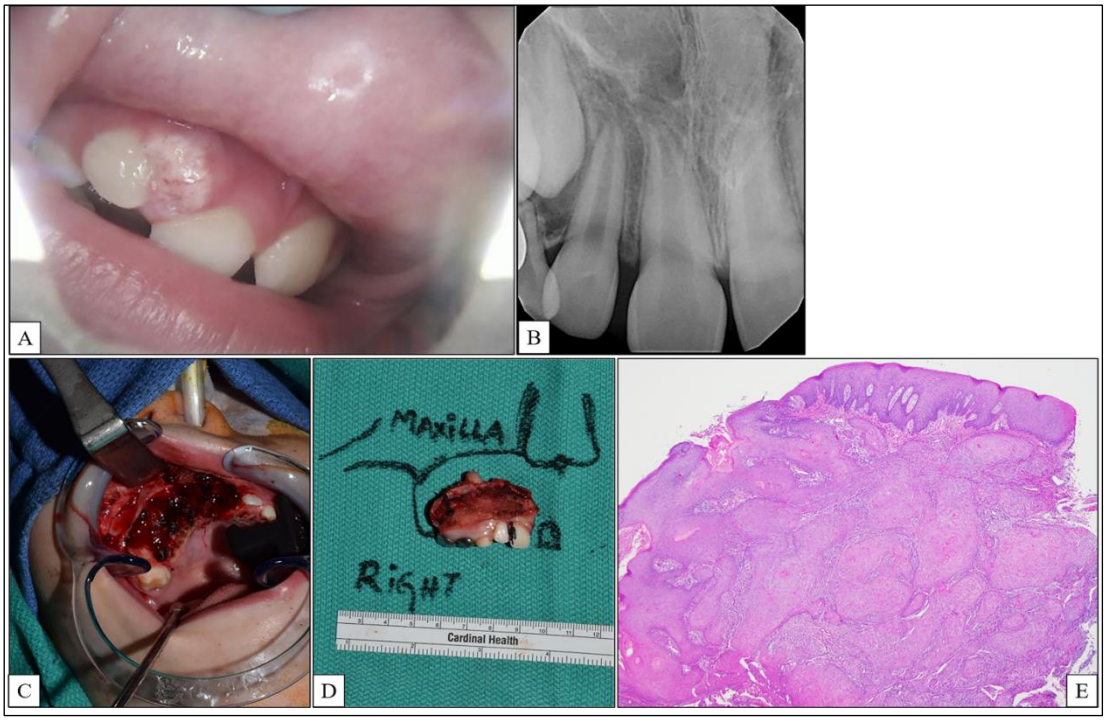

Figure 2: A, Red sessile mass on the facial gingiva between the right maxillary lateral and central incisors (teeth 7- 8). B, The periapical radiograph shows a widening of the periodontal ligament space. C, Intraoperative appearance of the tumor. D, Resected specimen. E, Islands of malignant squamous epithelium invading into the lamina propria, (Hematoxylin-eosin [H&E] staining; original magnification X40)

The oldest patients were a 30-year-old male and female, who presented with symptomatic lateral tongue lesions of 1 month and 6-month duration, and a clinical impression of erosive lichen planus and hyperplastic candidiasis, respectively.

The time elapsed from the onset of the lesion to diagnosis ranged from a few weeks to six years. Four patients were smokers (12.9%). One patient was 13 weeks of pregnancy. The lateral border of the tongue was the most common location (n=19/31), followed by the ventral tongue (n=3/31), and maxillary gingiva (n=2/31). Notably, none of the cases were located on the oropharynx or base of the tongue.

A review of the submitted clinical impressions of these lesions revealed that only 16.13% of the cases included squamous cell carcinoma (n=3/31) and dysplasia (n=2/32) (Fig 3) in the differential diagnoses. The most frequent clinical impression was a traumatic ulcer (n=7/31) (Fig 4), followed by pyogenic granuloma (n=5/31) and hyperkeratosis (n=4/31). Geographic tongue, granular cell tumor, papilloma, hyperplastic candidiasis, lichen planus, epidermal inclusion cyst, actinic keratosis, scar, and leukoplakia were mentioned once each. These are summarized in Figure 5. Pain, burning, swelling, and dysphagia were mentioned as symptoms in 67.74% of the cases.

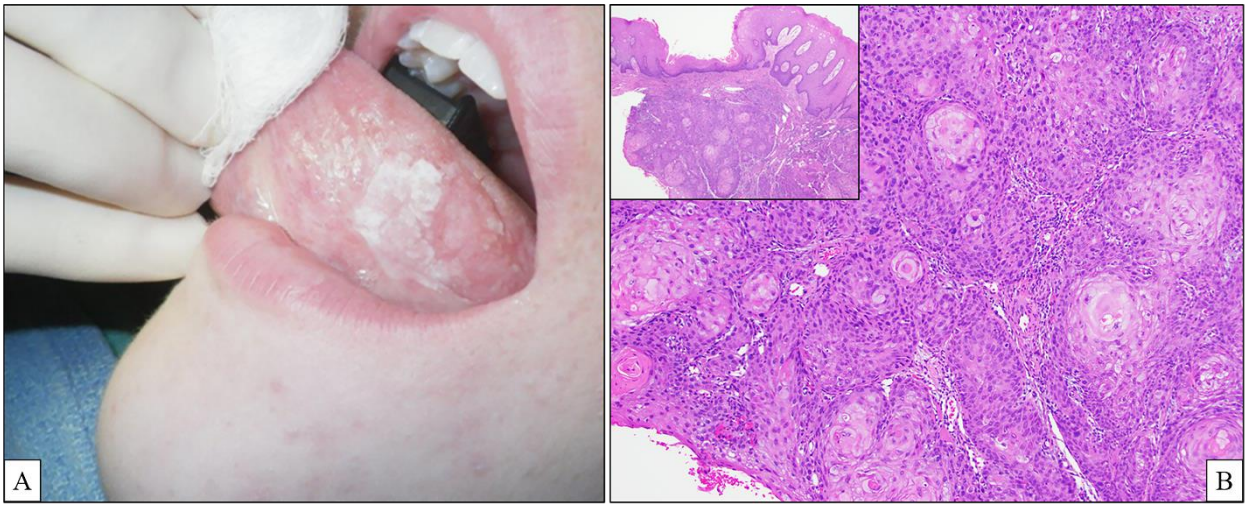

Figure 3: A, A 19-year-old female, with asymptomatic thick erythroleukoplakia on the left lateral tongue, for several months. B, Islands of dysplastic epithelial cells with keratin pearl formation, (H&E stain; original magnification X40)

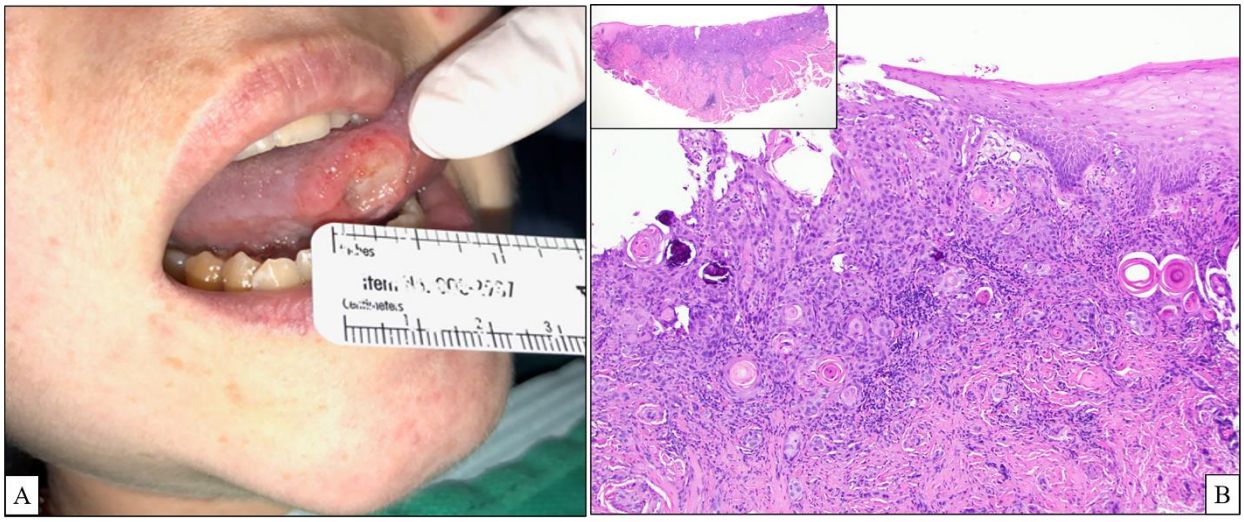

Figure 4: A, A 20-year-old female, with a painful ulcer on the right anterior lateral tongue for 2 months. B, A photomicrograph demonstrating, an ulcer containing infiltrative malignant epithelial islands, (H&E stain; original magnification X100)

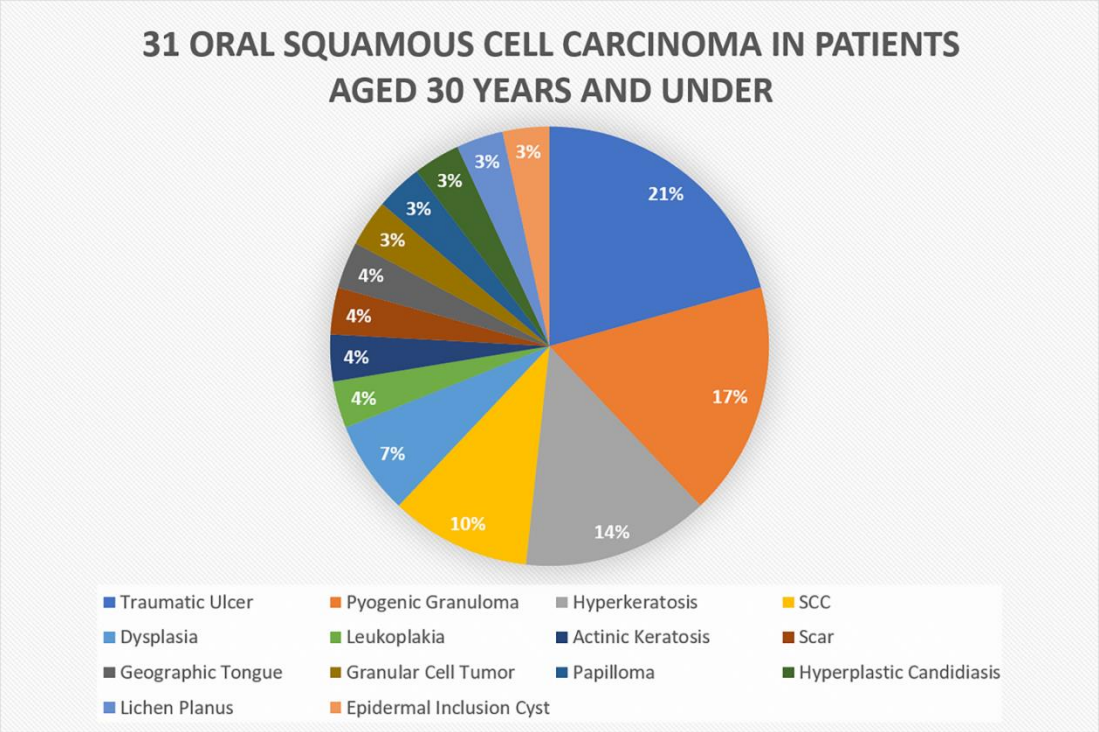

Figure 5: Distribution of the clinical differential diagnoses

The histological grades for the SCC cases ranged from moderately differentiated (n=14/31), well-differentiated (n=12/31), poorly differentiated (n=3/31), and verrucous carcinoma (n=2/31). Perineural invasion (PNI) was observed in about 29.03% (n=9/31) of the specimens examined.

DISCUSSION

Squamous cell carcinoma (SCC) is the most commonly diagnosed malignancy of the oral cavity and the eighth most common malignancy worldwide. OSCC mostly affects older men, with an average age of 62 years, and is strongly associated with tobacco and/or alcohol abuse [1-3]. The incidence of OSCC in youth is rare; however, cases of OSCC in this age group are on the rise, accounting for 3.1% of all cases [1, 4-6].

Our results are in accordance with reports of OSCC in young patients, vis-à-vis male predilection, and a male: female ratio ranging from 1.2:1 to 1.8:1. The literature reports a mean age of twenty-three years. This is lower than our findings [7-10]. However, a higher percentage of never smokers and never drinkers among young females has been reported in some studies [11]. Among the oral cavity sites, the tongue was more commonly involved (41.1%-61.3%) [10].

Patients with OSCC tend to present at an advanced stage and are often misdiagnosed as benign inflammatory or reactive oral conditions [10, 11]. This is congruent with our findings that OSCC is rarely considered in the differential diagnosis. The most frequently considered entity in the differential diagnosis of youthful OSCC is a traumatic ulcer. Therefore, practitioners frequently fail to perform timely follow-ups for persistent ulcers or growth in young patients. This often results in considerable delay in diagnosis. This delay can adversely affect the ultimate outcome and may explain why OSCC in younger patients tend to behave more aggressively and have a poor prognosis [1, 7].

Across all studies, including the present study, OSCCs in young adults were mostly well or moderately differentiated. However, histological grade does not seem to have a significant effect on the clinical outcome and prognosis of the disease [8, 9-15]. De Morais *et al*., (2016) reported no significant difference in relation to the histological grade of OSCC and prognosis in young patients [14].

Recently, there has been a marked increase in OSCC incidence in young women without a history of smoking, as noted in our study [11, 16-18]. Of the 31 cases, one patient was 13 weeks of gestation at the time of OSCC diagnosis. OSCC during pregnancy is extremely rare, accounting for less than 2% of all cancers during gestation [18-20]. The pathophysiology of OSCC associated with pregnancy remains unclear; nevertheless, hormonal changes, immunological suppression, and increased permeability and vascularization may play a role [21]. However, treatment modalities, prognosis, and long-term impact on the developing fetus are also not well established due to the rarity of this diagnosis during pregnancy.

The pathogenesis of OSCC in young patients remains poorly understood. Since the duration of

exposure to tobacco and alcohol is believed to be shorter in young individuals, it has been hypothesized that the pathogenesis of OSCC is probably different from that in older patients [1]. To date, no specific or definitive etiological agent has been identified for OSCC in young adults. Nutritional deficiency, persistent irritation in the oral cavity, immunosuppression, and human papillomavirus (HPV) infections have been suggested as possible contributing factors [11, 25]. However, none of these factors has been proven to be consistently causative. Importantly, the possibility of a genetic predisposition should be considered in patients below 30 years. Rare hereditable syndromes, such as Fanconi anemia, xeroderma pigmentosum, Bloom syndrome, Li-Fraumeni syndrome, and dyskeratosis congenita, have all been linked to an increased risk of OSCC [16, 22, 23]. These syndromes are associated with an increased risk of developing head and neck neoplasms in general, and SCC of the tongue in particular. The incidence of SCC in such conditions is up to 700-1000 times greater than that in the general population [22].

The increase in the incidence of oropharyngeal squamous cell carcinoma (OPSCC) among young individuals has been attributed to high-risk HPV infections; however, for OSCC remains a matter of debate. In fact, OSCC affecting young patients rarely expresses active HPV transcripts despite their smoking/alcohol status [11, 17, 24-26]. Several studies have suggested that HPV infection in young adults is of low significance in the pathogenesis of OSCC [1, 24, 27, 28, 29]. The prevalence of HPV-related OSCC in young patients has not been sufficiently established, with variable results shifting from 0% to 58.3% [1, 14, 24, 30]. This variation in results might be attributed to differences in tumor anatomical locations, geographic heterogeneity, and accuracy of the technique used for HPV detection [1]. Brägelmann *et al*., (2013) did not detect any HPV or other viruses "*i.e. EBV"* in seven young non-smokers with OSCC [31]. Harris *et al*., (2011) found that 44% of SCC of the tongue affecting young patients expressed p16 on immunohistochemistry (IHC) staining. However, HPV expression was absent in these tumors when using in situ hybridization or PCR-based techniques [32]. P16 IHC staining is considered a reliable surrogate marker for HPV-related OPSCC, but less so for OSCC. Immunoexpression of at least 70% of tumor cells (nuclear and cytoplasmic staining) is required to confirm p16 positivity [33]. However, Harris *et al*., (2011) found that p16 expression was independent of the presence of high-risk HPV in OSCC [29]. In addition, the identification of HPV does not imply that it is biologically active nor it is implicated in the etiology of the neoplasm [1, 34]. HPV-related OSCCs have not been shown to have a clinical course similar to that of HPV-positive oropharyngeal carcinomas [28]. The clinical course, pathologic characteristics, survival rates, and immunoexpression are similar to those of cell cycle regulators (i.e., p16) in HPV-positive and HPV-negative OSCC in young patients [29]. Hence, multicentric studies exploring the prognostic status of HPV status in OSCC are warranted.

Additionally, the prognosis of OSCC in younger patients has a scant agreement. Few studies have documented a more aggressive clinical course and poor prognosis for OSCC in younger populations [1, 25]. Other studies reported a better prognosis for such a population, with higher disease-free survival rates [35]. Paradoxically, recent studies have not been able to detect much variation in the clinical course and outcomes in young patients compared to older patients [1, 6]. A study by Udeabor *et al*., (2012) showed that young adults with OSCC did not have a poorer prognosis than older patients [36]. Park *et al*., (2010) reported a higher rate of local regional recurrence of OSCC in a young age group [37]. In contrast, Soudry *et al*., (2010) and Ho *et al*., (2008) reported a higher recurrence rate in older patients [8, 38]. The tendency for delayed diagnosis in young patients may explain their poorer prognosis, as mentioned by some authors [1, 25-27]. Other authors have found that young patients with OSCC are unique only because of their age but are similar in all other aspects of the disease to older patients [26]. The characteristics of SCC in young adults appear to be poorly understood, and the literature lacks consensus regarding demographics, etiology, prognosis, and outcomes in this age group [39]. This inconsistency in the results in the literature is partly explained by the variable definition of "young age," with a wide age range of 30 to 45 years [1, 14, 24-28, 31, 41-44]. Some authors have proposed considering only patients below 30 years of age as young to garner consistency of data [22, 40]. In addition, most studies are based on small sample sizes, which preclude drawing any robust conclusions. Differences in geographical location, as well as differences in study methodology, may also explain the variability observed in the clinical and pathological profiles of these patients.

LIMITATIONS

This study underscores the rarity of OSCC in children and young adults. Unfortunately, significant details pertaining to grading, staging, management, and patient outcomes were not available due to the retrospective nature of this study. After diagnosis, patients were referred to a variety of outside institutions for treatment; consequently, follow-up information was not available because the patients did not return to the initial dental specialist/general dentist.

CONCLUSION

The increased incidence of OSCC in children and young adults in the context of non-traditional risk factors is concerning. This often results in misdiagnosis and delays diagnosis and treatment, causing significant

mortality. Given the potential long-term adverse impact of conventional OSCC therapy, the management of OSCC in young patients must be individualized. Hence, treatment decisions must be directed towards improving quality of life. In addition, OSCC in the younger age group is more prone to be misdiagnosed as benign. Therefore, any lesion suspicious for OSCC should be promptly biopsied and managed, even in young patients. Furthermore, patients under 30 years of age may require detailed genetic counseling to assess additional disease activity and improve outcomes. Additional larger multicenter studies with more detailed medical history, treatment, genotyping, and outcome data are desirable. This will assist in elucidating the etiology, treatment modalities, and outcomes for OSCC in young patients.

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REFERENCES

1. Dos Santos Costa, S. F., Brennan, P. A., Gomez, R. S., Fregnani, E. R., Santos-Silva, A. R., Martins, M. D., de Castro-Junior, G., Rahimi, S., & Fonseca, F. P. (2018). Molecular basis of oral squamous cell carcinoma in young patients: Is it any different from older patients?. Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology, 47(6), 541–546. https://doi.org/10.1111/jop.12642
2. Siegel, R. L., Miller, K. D., & Jemal, A. (2016). Cancer statistics, 2016. CA: a cancer journal for clinicians, 66(1), 7–30. https://doi.org/10.3322/caac.21332
3. Curado, M. P., Johnson, N. W., Kerr, A. R., Silva, D. R. M. E., Lanfranchi, H., Pereira, D. L., ... & Vargas, P. A. (2016). Oral and oropharynx cancer in South America: incidence, mortality trends and gaps in public databases as presented to the Global Oral Cancer Forum. *Translational Research in Oral Oncology*, *1*, 2057178X16653761.
4. Rushatamukayanunt, P., Morita, K., Matsukawa, S., Harada, H., Shimamoto, H., Tomioka, H., & Omura, K. (2014). Lack of association between high-risk human papillomaviruses and oral squamous cell carcinoma in young Japanese patients. *Asian Pacific journal of cancer prevention: APJCP*, 15(10), 4135–4141. https://doi.org/10.7314/apjcp.2014.15.10.4135
5. Pontes, F. S., Carneiro, J. T., Jr, Fonseca, F. P., da Silva, T. S., Pontes, H. A., & Pinto, D.dosS., Jr (2011). Squamous cell carcinoma of the tongue and floor of the mouth: analysis of survival rate and independent prognostic factors in the Amazon region. The Journal of craniofacial surgery, 22(3), 925–930. https://doi.org/10.1097/SCS.0b013e31820fe1cb
6. Santos-Silva, A. R., Ribeiro, A. C., Soubhia, A. M., Miyahara, G. I., Carlos, R., Speight, P. M., Hunter, K. D., Torres-Rendon, A., Vargas, P. A., & Lopes, M. A. (2011). High incidences of DNA ploidy abnormalities in tongue squamous cell carcinoma of young patients: an international collaborative study. Histopathology, 58(7), 1127–1135. https://doi.org/10.1111/j.1365-2559.2011.03863.x
7. Byers R. M. (1975). Squamous cell carcinoma of the oral tongue in patients less than thirty years of age. American journal of surgery, 130(4), 475–478. https://doi.org/10.1016/0002-9610(75)90487-0
8. Soudry, E., Preis, M., Hod, R., Hamzany, Y., Hadar, T., Bahar, G., Strenov, Y., & Shpitzer, T. (2010). Squamous cell carcinoma of the oral tongue in patients younger than 30 years: clinicopathologic features and outcome. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery, 35(4), 307–312. https://doi.org/10.1111/j.1749-4486.2010.02164.x
9. Hilly, O., Shkedy, Y., Hod, R., Soudry, E., Mizrachi, A., Hamzany, Y., Bachar, G., & Shpitzer, T. (2013). Carcinoma of the oral tongue in patients younger than 30 years: comparison with patients older than 60 years. Oral oncology, 49(10), 987–990. https://doi.org/10.1016/j.oraloncology.2013.07.005
10. Bhanu Prasad, V., Mallick, S., Upadhyay, A. D., & Rath, G. K. (2017). Systematic review and individual patient data analysis of pediatric head and neck squamous cell carcinoma: An analysis of 217 cases. International journal of pediatric otorhinolaryngology, 92, 75–81. https://doi.org/10.1016/j.ijporl.2016.11.005
11. Liu, X., Gao, X. L., Liang, X. H., & Tang, Y. L. (2016). The etiologic spectrum of head and neck squamous cell carcinoma in young patients. Oncotarget, 7(40), 66226–66238. https://doi.org/10.18632/oncotarget.11265
12. Hinchy, N. V., Jayaprakash, V., Rigual, N., Reid, M., Frustino, J. L., Rossitto, R., Groman, A., & Sullivan, M. A. (2016). Progression of gingival squamous cell carcinoma from early to late stage after invasive dental procedure. General dentistry, 64(2), 38–43.
13. Deyhimi, P., Torabinia, N., & Torabinia, A. (2013). A comparative study of histological grade and expression of Ki67 protein in oral squamous cell carcinoma in young and old patients. Dental research journal, 10(4), 514–517.

14. de Morais, E. F., Mafra, R. P., Gonzaga, A. K. G., de Souza, D. L. B., Pinto, L. P., & da Silveira, É. J. D. (2017). Prognostic Factors of Oral Squamous Cell Carcinoma in Young Patients: A Systematic Review. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons, 75(7), 1555–1566. https://doi.org/10.1016/j.joms.2016.12.017
15. Fang, Q. G., Shi, S., Liu, F. Y., & Sun, C. F. (2014). Tongue squamous cell carcinoma as a possible distinct entity in patients under 40 years old. Oncology letters, 7(6), 2099–2102. https://doi.org/10.3892/ol.2014.2054
16. Ambele, M. A., Pepper, M. S., van Heerden, M. B., & van Heerden, W. F. P. (2019). Molecular profile of tongue cancer in an 18-year-old female patient with no recognizable risk factor. Laryngoscope investigative otolaryngology, 4(3), 310–313. https://doi.org/10.1002/lio2.266
17. Hussein, A. A., Helder, M. N., de Visscher, J. G., Leemans, C. R., Braakhuis, B. J., de Vet, H. C. W., & Forouzanfar, T. (2017). Global incidence of oral and oropharynx cancer in patients younger than 45 years versus older patients: A systematic review. European journal of cancer (Oxford, England : 1990), 82, 115–127. https://doi.org/10.1016/j.ejca.2017.05.026
18. Boztepe OF, Gun T, Dogru H, Coskunfirat K, Keles Y. A Case of Aggressive Floor of The Mouth Cancer During Pregnancy. Selcuk Med J 2018;34(3): 122-124
19. Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., & Thun, M. J. (2009). Cancer statistics, 2009. CA: a cancer journal for clinicians, 59(4), 225–249. https://doi.org/10.3322/caac.20006
20. Layton, S. A., Rintoul, M., & Avery, B. S. (1992). Oral carcinoma in pregnancy. The British journal of oral & maxillofacial surgery, 30(3), 161–164. https://doi.org/10.1016/0266-4356(92)90148-c
21. Murphy, J., Berman, D. R., Edwards, S. P., Prisciandaro, J., Eisbruch, A., & Ward, B. B. (2016). Squamous Cell Carcinoma of the Tongue During Pregnancy: A Case Report and Review of the Literature. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons, 74(12), 2557–2566. https://doi.org/10.1016/j.joms.2016.06.173
22. Paderno, A., Morello, R., & Piazza, C. (2018). Tongue carcinoma in young adults: a review of the literature. Acta otorhinolaryngologica Italica : organo ufficiale della Societa italiana di otorinolaringologia e chirurgia cervico-facciale, 38(3), 175–180. https://doi.org/10.14639/0392-100X-1932
23. Lee, N. V., Kang, E. T. B., Senger, C., & Poh, C. F. (2020). Oral cancer in a 5-year-old boy: a rare case report and review of literature. Oral surgery, oral medicine, oral pathology and oral radiology, 130(1), e10–e19. https://doi.org/10.1016/j.oooo.2019.12.005
24. Campbell, B. R., Netterville, J. L., Sinard, R. J., Mannion, K., Rohde, S. L., Langerman, A., Kim, Y. J., Lewis, J. S., Jr, & Lang Kuhs, K. A. (2018). Early onset oral tongue cancer in the United States: A literature review. Oral oncology, 87, 1–7. https://doi.org/10.1016/j.oraloncology.2018.10.009
25. Cariati, P., Cabello-Serrano, A., Perez-de Perceval-Tara, M., Monsalve-Iglesias, F., & Martínez-Lara, I. (2017). Oral and oropharyngeal squamous cell carcinoma in young adults: A retrospective study in Granada University Hospital. Medicina oral, patologia oral y cirugia bucal, 22(6), e679–e685. https://doi.org/10.4317/medoral.21755
26. Martinez, R. C., Sathasivam, H. P., Cosway, B., Paleri, V., Fellows, S., Adams, J., Kennedy, M., Pearson, R., Long, A., Sloan, P., & Robinson, M. (2018). Clinicopathological features of squamous cell carcinoma of the oral cavity and oropharynx in young patients. The British journal of oral & maxillofacial surgery, 56(4), 332–337. https://doi.org/10.1016/j.bjoms.2018.03.011
27. Santos, H. B., dos Santos, T. K., Paz, A. R., Cavalcanti, Y. W., Nonaka, C. F., Godoy, G. P., & Alves, P. M. (2016). Clinical findings and risk factors to oral squamous cell carcinoma in young patients: A 12-year retrospective analysis. Medicina oral, patologia oral y cirugia bucal, 21(2), e151–e156. https://doi.org/10.4317/medoral.20770
28. Farquhar, D. R., Tanner, A. M., Masood, M. M., Patel, S. R., Hackman, T. G., Olshan, A. F., Mazul, A. L., & Zevallos, J. P. (2018). Oral tongue carcinoma among young patients: An analysis of risk factors and survival. Oral oncology, 84, 7–11. https://doi.org/10.1016/j.oraloncology.2018.06.014
29. Miranda Galvis, M., Freitas Jardim, J., Kaminagakura, E., Santos-Silva, A. R., Paiva Fonseca, F., Paes Almeida, O., Ajudarte Lopes, M., Lópes Pinto, C., & Kowalski, L. P. (2018). Expression of cell cycle proteins according to HPV status in oral squamous cell carcinoma affecting young patients: a pilot study. Oral surgery, oral medicine, oral pathology and oral radiology, 125(4), 317–325. https://doi.org/10.1016/j.oooo.2018.01.003
30. Blanchard, P., Belkhir, F., Temam, S., El Khoury, C., De Felice, F., Casiraghi, O., Patrikidou, A., Mirghani, H., Levy, A., Even, C., Gorphe, P., Nguyen, F., Janot, F., & Tao, Y. (2017). Outcomes and prognostic factors for squamous cell carcinoma of the oral tongue in young adults: a single-institution case-matched analysis. European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery, 274(3), 1683–1690. https://doi.org/10.1007/s00405-016-4419-1

31. Brägelmann, J., Dagogo-Jack, I., El Dinali, M., Stricker, T., Brown, C. D., Zuo, Z., Khattri, A., Keck, M., McNerney, M. E., Longnecker, R., Bieging, K., Kocherginsky, M., Alexander, K., Salgia, R., Lingen, M. W., Vokes, E. E., White, K. P., Cohen, E. E., & Seiwert, T. Y. (2013). Oral cavity tumors in younger patients show a poor prognosis and do not contain viral RNA. *Oral oncology*, 49(6), 525–533. https://doi.org/10.1016/j.oraloncology.2013.02.003
32. Harris, S. L., Thorne, L. B., Seaman, W. T., Hayes, D. N., Couch, M. E., & Kimple, R. J. (2011). Association of p16(INK4a) overexpression with improved outcomes in young patients with squamous cell cancers of the oral tongue. *Head & neck*, 33(11), 1622–1627. https://doi.org/10.1002/hed.21650
33. Lewis J. S., Jr (2020). Human Papillomavirus Testing in Head and Neck Squamous Cell Carcinoma in 2020: Where Are We Now and Where Are We Going?. *Head and neck pathology*, 14(2), 321–329. https://doi.org/10.1007/s12105-019-01117-y
34. Grønhøj Larsen, C., Gyldenløve, M., Jensen, D. H., Therkildsen, M. H., Kiss, K., Norrild, B., Konge, L., & von Buchwald, C. (2014). Correlation between human papillomavirus and p16 overexpression in oropharyngeal tumours: a systematic review. British journal of cancer, 110(6), 1587–1594. https://doi.org/10.1038/bjc.2014.42
35. van Monsjou, H. S., Lopez-Yurda, M. I., Hauptmann, M., van den Brekel, M. W., Balm, A. J., & Wreesmann, V. B. (2013). Oral and oropharyngeal squamous cell carcinoma in young patients: the Netherlands Cancer Institute experience. *Head & neck*, 35(1), 94–102. https://doi.org/10.1002/hed.22935
36. Udeabor, S. E., Rana, M., Wegener, G., Gellrich, N. C., & Eckardt, A. M. (2012). Squamous cell carcinoma of the oral cavity and the oropharynx in patients less than 40 years of age: a 20-year analysis. *Head & neck oncology*, 4, 28. https://doi.org/10.1186/1758-3284-4-28
37. Park, J. O., Sun, D. I., Cho, K. J., Joo, Y. H., Yoo, H. J., & Kim, M. S. (2010). Clinical outcome of squamous cell carcinoma of the tongue in young patients: a stage-matched comparative analysis. *Clinical and experimental otorhinolaryngology*, 3(3), 161–165. https://doi.org/10.3342/ceo.2010.3.3.161
38. Ho, H. C., Lee, M. S., Hsiao, S. H., Hwang, J. H., Hung, S. K., Chou, P., & Lee, C. C. (2008). Squamous cell carcinoma of the oral cavity in young patients: a matched-pair analysis. European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery, 265 Suppl 1, S57–S61. https://doi.org/10.1007/s00405-007-0496-5
39. Frare, J. C., Sawazaki-Calone, I., Ayroza-Rangel, A. L., Bueno, A. G., de Morais, C. F., Nagai, H. M., Kunz, R., & Lopes, M. A. (2016). Histopathological grading systems analysis of oral squamous cell carcinomas of young patients. *Medicina oral, patologia oral y cirugia bucal*, 21(3), e285–e298. https://doi.org/10.4317/medoral.20953
40. Zhang, Y. Y., Wang, D. C., Su, J. Z., Jia, L. F., Peng, X., & Yu, G. Y. (2017). Clinicopathological characteristics and outcomes of squamous cell carcinoma of the tongue in different age groups. *Head & neck*, 39(11), 2276–2282. https://doi.org/10.1002/hed.24898
41. Campbell, B. R., Sanders, C. B., Netterville, J. L., Sinard, R. J., Rohde, S. L., Langerman, A., ... & Lang Kuhs, K. A. (2019). Early onset oral tongue squamous cell carcinoma: Associated factors and patient outcomes. *Head & neck*, *41*(6), 1952-1960. doi:10.1002/hed.25650
42. Gamez, M. E., Kraus, R., Hinni, M. L., Moore, E. J., Ma, D. J., Ko, S. J., Rwigema, J. C. M., McGee, L. A., Halyard, M. Y., Buras, M. R., Foote, R. L., & Patel, S. H. (2018). Treatment outcomes of squamous cell carcinoma of the oral cavity in young adults. *Oral oncology*, 87, 43–48. https://doi.org/10.1016/j.oraloncology.2018.10.014
43. Kapila, S. N., Natarajan, S., & Boaz, K. (2017). A Comparison of Clinicopathological Differences in Oral Squamous Cell Carcinoma in Patients Below and Above 40 Years of Age. Journal of clinical and diagnostic research: JCDR, 11(9), ZC46–ZC50. https://doi.org/10.7860/JCDR/2017/27828.10600
44. Oliver, J. R., Wu, S. P., Chang, C. M., Roden, D. F., Wang, B., Hu, K. S., Schreiber, D., & Givi, B. (2019). Survival of oral tongue squamous cell carcinoma in young adults. *Head & neck*, 41(9), 2960–2968. https://doi.org/10.1002/hed.25772