Association of Clinical Appearance with Histopathological Features in Oral Squamous Cell Carcinoma

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Abstract

Oral Squamous Cell Carcinoma (OSCC) is one of the most common malignant epithelial neoplasms affecting the oral cavity. The clinical appearance of oral cancer is highly variable and includes ulceroproliferative, ulcerative, leukoplakic and exophytic. These clinical variants can be graded histopathologically to be a well differentiated, moderately differentiated or poorly differentiated squamous cell carcinoma. The prognosis of the patients varies based on the histopathological grading. Hence, the aim of the study is to associate the clinical appearance of OSCC with the histopathological grading. Data was collected after going through 86,000 patients records from June 2019 to April 2020. Total sample size of the study was 44. The data was exported to SPSS and the variables were verified. Correlation analysis was carried out for the data tabulated. Highest correlation was seen between ulceroproliferative lesions and well differentiated OSCC histopathologically. Hence we can conclude that the clinical appearance of OSCC can give us some clue about its histopathological grade and the study should be extended to a larger sample size in order to give a more comprehensive outcome.

Keywords: *Oral squamous cell carcinoma; Clinical Variants; Ulceroproliferative; Histopathological grade; Oral cancer*

Introduction

Oral squamous cell carcinoma is the most common malignant epithelial neoplasm affecting the oral cavity. Oral cancer includes a group of neoplasms affecting any region of the oral cavity, pharyngeal regions and salivary glands. However, this term tends to be used interchangeably with oral squamous cell carcinoma (OSCC), which represents the most frequent of all oral neoplasms. It is estimated that more than 90% of all oral neoplasms are OSCC [1,2] .Oral squamous cell carcinoma is amongst the most prevalent forms of cancer worldwide with its predominance in the Indian subcontinent due to its etiological, behavioral pattern of tobacco consumption. Late diagnosis, low therapeutic response and aggressive metastasis are the foremost confounders accountable for the poor 5 year survival rate of OSCC. As for the oral cavity OSCCs, many authors reported frequent high-risk HPV involvement by considering the over-expression of p16INK4A as equivalent to HPV infection [3–5]. Risky oral habits (including smoking, alcohol drinking, and betel quid chewing) are major risk factors for OSCC development [6–8].

The cell of origin of OSCC is the oral keratinocyte. OSCC, as any cancer, is caused by DNA mutation, often spontaneous but increased by exposure to any of a range of mutagens – chemical, physical or microbial. The various changes in the DNA can progress from a normal keratinocyte to a pre-malignant or a potentially malignant keratinocyte that is characterised by an ability to proliferate in a less-controlled fashion than normal. The cells become autonomous and a true cancer results, characterised by invasion across the epithelial basement

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membrane and, ultimately, metastasis to lymph nodes, bone, brain, liver and other sites [9–11].

According to the recent data given by WHO, India stands in eleventh position in oropharyngeal cancer[12]. Worldwide, oral cancer accounts for 2%–4% of all cancer cases. In some regions, the prevalence of oral cancer is higher, reaching the 10% of all cancers in Pakistan, and around 45% in India[13,14]. In 2004-2020 over 300,000 new cases of oral and oropharyngeal cancer were diagnosed worldwide. During the same time period, over 7,000 affected individuals died of these cancers [5,15,16].

OSCC may manifest as the following; a red lesion (erythroplakia), a granular ulcer with fissuring or raised exophytic margins, a white or mixed white and red lesion, an indurated lump/ulcer (ie, a firm infiltration beneath the mucosa), a non healing extraction socket,A lesion fixed to deeper tissues or to overlying skin or mucosa, cervical lymph node enlargement, especially if hardness is present in a lymph node or fixation[17].

The clinical appearance of oral cancer is highly variable and includes ulcers, red or white areas, lumps, or fissures[18]. Lesions always must be palpated after inspection to detect induration and fixation to deeper tissues.Erythroplakia is a red and often velvety lesion, which, unlike leukoplakias, may not form a plaque but is level with or depressed below the surrounding mucosa. Of these lesions, 75-90% may show severe epithelial dysplasia, carcinoma in situ, or invasive changes.Red oral lesions usually are more dangerous than white oral lesions. Leukoplakia is a clinical term for a persistent adherent white patch with no histologic connotation and no implied premalignant potential. Some OSCC can also appear as a white patch [19–21]. Late OSCC may manifest as an exophytic lesion or an area of ulceration with induration. The floor of the mouth is the second most common intraoral site for cancer and more commonly is associated with leukoplakia. Carcinomas of the alveolus or gingiva can present as an exophytic mass or a persistent ulcer[22]. The underlying alveolar bone is invaded in 50% of cases, even in the absence of radiographic changes, and adjacent teeth may be loose. Carcinomas of the buccal mucosa are mostly seen at the commissure or in the retromolar area. Most are ulcerated lumps, and some arise in candidal leukoplakias [23–25].

While tobacco and alcohol use are traditionally the greatest risk factors, it is important to consider other known risk factors, such as betel quid chewing, in certain ethnic populations. Betel quid chewing is popular in Indian and Taiwanese populations and is associated with a significantly increased risk of oral cancer [26–28]. Areca nut, narcotics and cannabis use has also been found to be a risk factor for oral cancer [29–31] .

Treatment of OSCC is made challenging due to the diversity of the anatomic sites in the neck and the critical normal structures that may be near a particular tumour site. Often, the care of a patient requires a multidisciplinary team of surgeons, radiation oncologists, medical oncologists, nutritionists, gastroenterologists, speech and swallowing therapists, amongst others. Despite the availability of aggressive treatments, the 5year survival rate for oral malignancies remains relatively poor at 65%, with only modest gains in the past few years [32–3435].

Very few articles were found in the database regarding clinicopathologic features on various populations based on their ethnicity. Many studies regarding clinical features and histopathological features, molecular studies were reported in literature. The study will help in better understanding of clinical features and histopathological features of OSCC. The aim of the study is to associate the clinical features and histopathological grade of oral squamous cell carcinoma patients in Saveetha Dental College, Chennai.

Materials and Methods

The study was a retro-spective study and was done under a university setting. Total sample size of 44 patients who have undergone the treatment were included in the study. The case sheets were verified with the help of photographs. To minimise the sampling bias, we included all the data available and there was no sorting of data done. Internal validity of the study was done by non-probability inclusion. The external validity of the study includes homogenisation and replication of experimentation. One principal investigator and 2 co-investigators were involved in the study.The study was approved by the scientific review board of the institution.

Data was collected after going through 86,000 patients records from June 2019 to April 2020. The data was obtained from the category of management of Oral

Cancer, clinical features and Histopathological features were data tabulated. Data was verified by one external reviewer. Confidential details were all masked and all the censored data were excluded. The data was imported to SPSS and the variables were verified.

Chi-square test was done on the data obtained using SPSS software by IBM. Age, Gender and ethnicity were considered as independent variables. Patients diagnosed with Oral squamous cell carcinoma and their clinical and Histopathological features were considered as dependent variables.

Results and Discussion

The results showed that out of the total 44 patients, male population was greater than the female population (Figure 1). Most of the population belonged to the age group between 40-60 years old (Figure 2). The percentage of clinical variants and the histopathological grades are represented in Figure 3 and Figure 4 respectively where ulceroproliferative was the most common variant and well differentiated OSCC was the most common histopathological grade. On correlating clinical variants with histopathological grade, ulceroproliferative and exophytic lesions showed highest incidence of well differentiated squamous cell carcinoma histopathologically , Ulcerative lesions showed high incidence of moderately differentiated squamous cell carcinoma (Figure 5).

Statistically significant correlation was established between ulceroproliferative and well differentiated Oral Squamous Cell Carcinoma with $p=0.039(P<0.05)$.

Studies showing the correlation between the clinical variant and Histopathological diagnosis is not present in the literature. Many case reports have also been reported in literature. Van Zyl et al concluded that the most common clinical variant observed in their study was ulceroproliferative lesion, which was in accordance with the current study[36]. The reason associated with this similarity may be due to cultural habits associated with both the populations.

A study done by Jainkittiwong [37], reported that the population involved in the study showed high prevalence of well differentiated squamous cell carcinoma , which was in accordance with the current study. The reason for the similarity is due to the same geographic location shared by the populations involved in the study.

Similarly, on comparing the clinical variant with the histopathological grade, most of the ulceroproliferative variants were diagnosed as well differentiated squamous cell carcinoma histopathologically. This was in accordance with the study by Effiom et al [38], this correlation will help us in determining the prognosis. Compared to poorly differentiated squamous cell carcinoma, well differentiated squamous cell carcinoma are found to have a better prognosis.

Oral potentially malignant disorders are a precursor for most of the oral squamous cell carcinoma cases. Oral potentially malignant disorders (OPMD) are relatively common, showing a global prevalence from 1 to 5% and a gender, age and site predilection similar to OSCC[10,39]. Although the exact malignant transformation rate for OPMD is unknown, it is expected that leukoerythroplakic areas can be encountered in association with OSCC[40,41]. This pattern was found in few of the

patients included in the present study. As the mean size of the tumors, independent of affected gender, was lower than 4 cm and more than two thirds of the patients complained of the lesions within less than 6 months, it is acceptable to consider that surveillance directed to OPMD diagnosis and follow-up could have been important in early diagnosis of OSCC in the present population. Additionally, these results reinforce the importance of considering the possibility of OSCC when dealing with leukoplakia and erythroplakia, and the need of obtaining biopsy specimens from all lesions from this group.

OSCC age and gender profile, as well as site predilection, shows a heterogeneous pattern of distribution in different countries, in different regions from the same country and in different ethnic groups from the same region, which can be associated with both genetic factors and cultural habits/behavior[42,43]. Studies focusing on specific regions are welcome as they show the demographic and clinical profile of OSCC in restricted geographic locations, offering an enhanced comprehension of these tumors and the possibility of planning specific strategies of prevention, diagnosis and treatment.

The most representative limitations on the methods and results from the present study are associated with the retrieval of clinical and histological information from respective laboratory records and incisional biopsies. To improve the significance of the study, the study should be done extensively with a large amount of sample size, so that the results are reliable.

Figure 1: This graph shows the gender distribution where blue represents male and red represents female with X axis denoting the genders and Y axis denoting the percentage. This graph shows that most of the population in the study was dominated by male gender(76.2%) and the female gender represented a population of (23.8%).

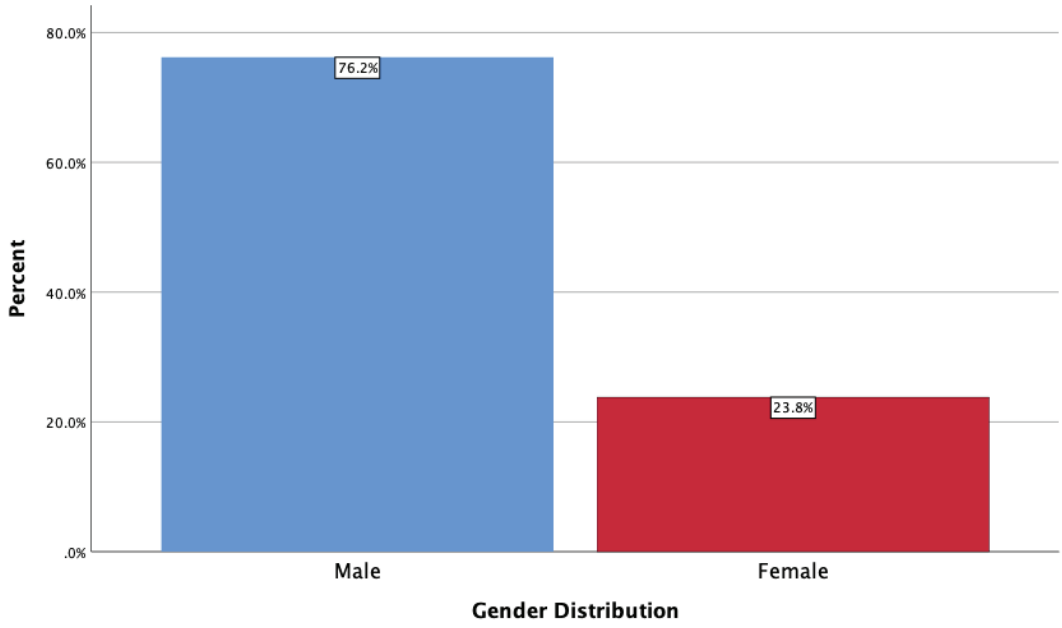


Figure 2: This graph shows the age distribution in the population studied where blue denotes the age group of 40-60 years old and red denotes the age group of 61-80 year old. X axis denotes the two age groups and Y axis denotes the percentage. This graph shows that the most of the population belongs to the age group 40-60 years(69%) and then followed by the age group 61-80 years old(31%)

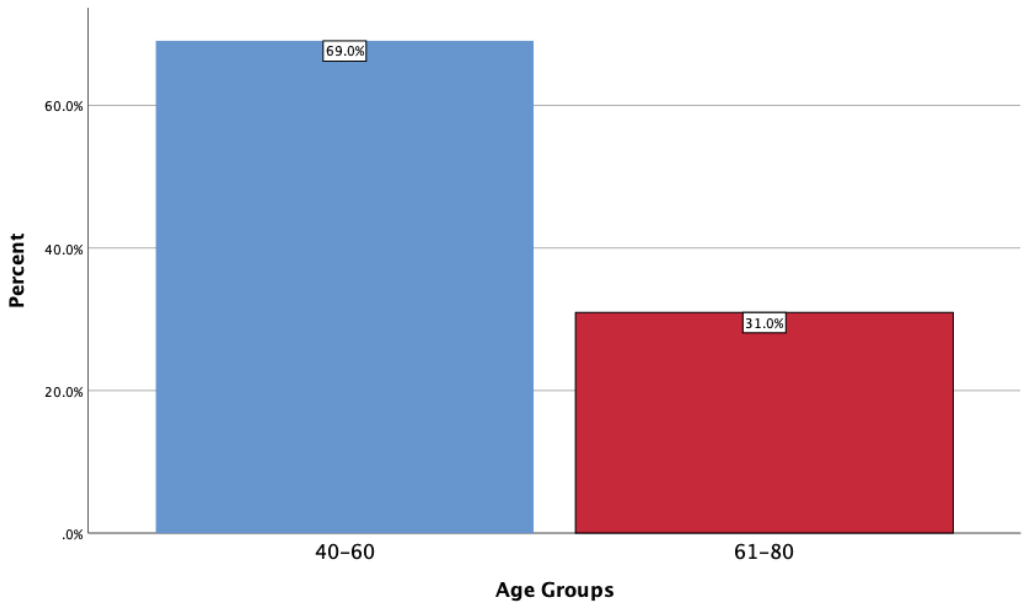


Figure 3: Bar graph representing the distribution of patients based on the clinical variants of oral squamous cell carcinoma where blue represents ulcerative, red represents leukoplakic, green represents exophytic and yellow represents the ulceroproliferative lesions.. X axis depicts the clinical variants and Y axis depicts the percentage. The most number of clinical variants involved in the study was ulceroproliferative (47.6%), followed by exophytic growth (23.8%), followed by ulcerative clinical variant (19%) and the least being leukoplakic clinical variant(9.5%).

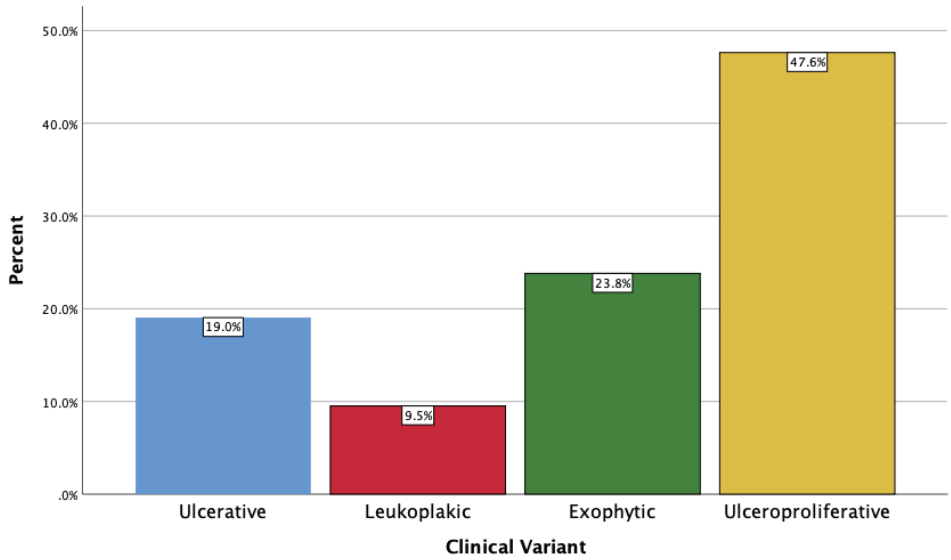


Figure 4: Bar graph depicting the distribution of the various histopathological grades of oral squamous cell carcinoma. Blue represents well differentiated OSCC, red represents moderately differentiated OSCC, green represents poorly differentiated OSCC and yellow represents Verrucous carcinoma. X axis depicts the histopathological grades and Y axis depicts the percentage. Well differentiated OSCC (61.9%) was the most common grade, followed by moderately differentiated OSCC (28.6%), poorly differentiated OSCC and verrucous carcinoma (4.8%).

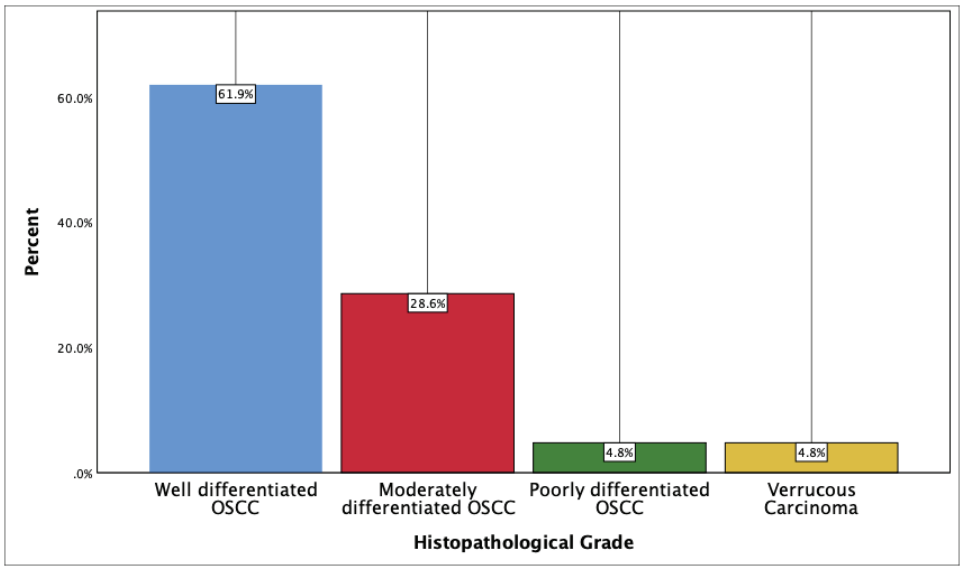
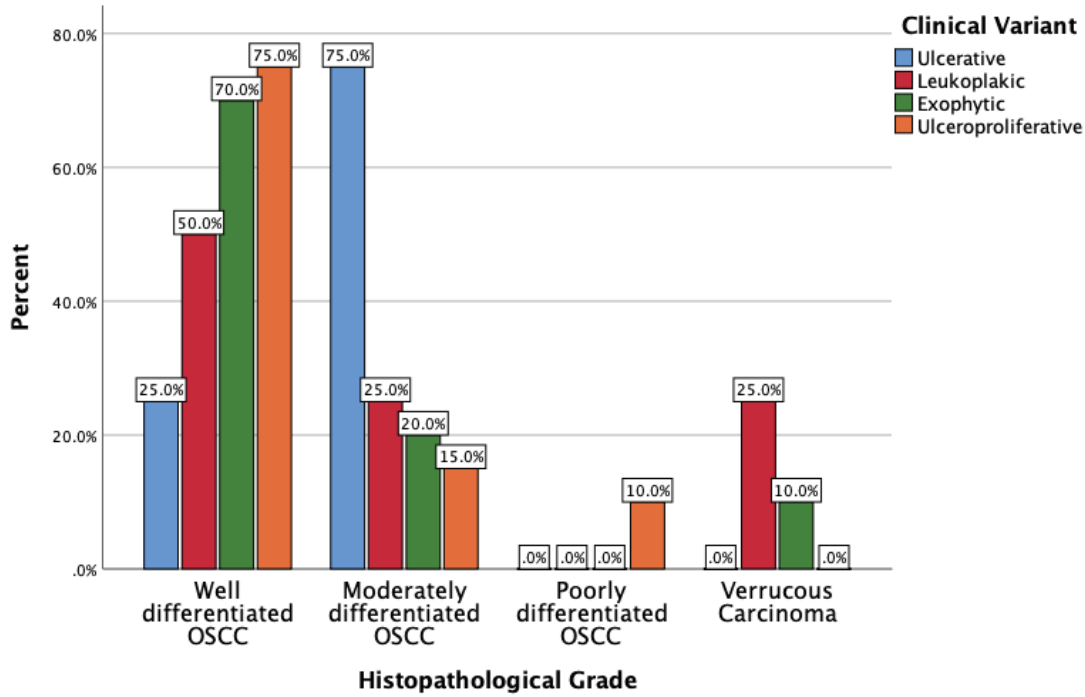


Figure 5: The bar graph represents the association between the clinical variants and the histopathological grade of oral squamous cell carcinoma, where blue denotes ulcerative lesions, red denotes leukoplakic lesions, green denotes exophytic lesions and orange denotes ulceroproliferative lesions. X axis represents the various histopathological grades and Y axis represents the percentage of clinical variants. This graph shows that the cases diagnosed with well differentiated OSCC appear clinically mostly as ulceroproliferative(75%) or exophytic(70%), whereas moderately differentiated OSCC appear clinically as ulcerative lesions(75%). Correlation between clinical variants and histopathological grades was done using Chi-square test, Pearson Chi-square value is 17.662-p value - 0.039(<0.05) was found to be statistically significant. There was a significant association of moderately differentiated OSCC with ulcerative lesions and well differentiated

OSCC with ulceroproliferative lesions.



Conclusion

Within the limits of the study, the highest correlation is seen between ulceroproliferative lesion and well differentiated Oral Squamous Cell Carcinoma. Similarly ulcerative lesions with moderately differentiated oral squamous cell carcinoma histopathologically. The results of the study will act as a guide for the clinicians and surgeons to establish the correct treatment planning and thus predict the prognosis of the patient. Hence we can conclude that the clinical appearance of OSCC can give us some clue about its histopathological grade and the study should be extended to a larger population in order to give a more comprehensive outcome.

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References

1. Thangaraj SV, Shyamsundar V, Krishnamurthy A, Ramani P, Ganesan K, Muthuswami M, et al. Molecular Portrait of Oral Tongue Squamous Cell Carcinoma Shown by Integrative Meta-Analysis of Expression Profiles with Validations [Internet]. Vol. 11, PLOS ONE. 2016. p. e0156582. Available from: http://dx.doi.org/10.1371/journal.pone.0156582
2. Dharahaas, Dharahaas, Saveetha dental college India. Oral cancer: a systematic review [Internet]. Vol. 6, International Journal of Current Advanced Research. 2017. p. 2967–70. Available from: http://dx.doi.org/10.24327/ijcar.2017.2970.0156
3. Don KR, Ramani P, Ramshankar V, Sherlin HJ, Premkumar P, Natesan A. Promoter hypermethylation patterns of P16, DAPK and MGMT in oral squamous cell carcinoma: a systematic review and meta-analysis. Indian J Dent Res. 2014 Nov;25(6):797–805.
4. Gupta V, Ramani P. Histologic and immunohistochemical evaluation of mirror image biopsies in oral squamous cell carcinoma. Journal of Oral Biology and Craniofacial Research. 2016

Sep 1;6(3):194–7.

5. Kumar A, Sherlin HJ, Ramani P, Natesan A, Premkumar P. Expression of CD 68, CD 45 and human leukocyte antigen-DR in central and peripheral giant cell granuloma, giant cell tumor of long bones, and tuberculous granuloma: An immunohistochemical study. Indian J Dent Res. 2015 May;26(3):295–303.
6. Mathews LM, Krishnan M. Oral cancer and smokeless tobacco--A review. Drug Invention Today [Internet]. 2019;12(6). Available from: https://pdfs.semanticscholar.org/d8bb/df292523429d5e5f86379327b29c6d1bc5a4.pdf
7. Choi S, Myers JN. Molecular pathogenesis of oral squamous cell carcinoma: implications for therapy. J Dent Res. 2008 Jan;87(1):14–32.
8. Premkumar J, Ramani P, Chandrasekar T, Natesan A, Premkumar P. Detection of species diversity in oral candida colonization and anti-fungal susceptibility among non-oral habit adult diabetic patients. J Nat Sci Biol Med. 2014 Jan;5(1):148–54.
9. Nazar SA, Student FY, saveetha dental college and hospitals, saveetha university, Road PH, India. C 600 077, et al. Awareness Of Early Detection And Prevention Of Oral Cancer among Dentists - A Review [Internet]. Vol. 13, IOSR Journal of Dental and Medical Sciences. 2014. p. 10–2. Available from: http://dx.doi.org/10.9790/0853-13151012
10. Maheswari TNU, Venugopal A, Sureshbabu NM, Ramani P. Salivary micro RNA as a potential biomarker in oral potentially malignant disorders: A systematic review. Ci Ji Yi Xue Za Zhi. 2018 Apr;30(2):55–60.
11. Ahad M, Gheena S, Year B 1st. Awareness of Tooth Brushing Techniques and Proper Oral Hygiene among School Children. Available from: https://www.jpsr.pharmainfo.in/Documents/Volumes/vol7Issue06/jpsr07061525.pdf
12. Institute NC, National Cancer Institute. World Health Organization [Internet]. Definitions. 2020. Available from: http://dx.doi.org/10.32388/xo5awv
13. Mehrotra R, Yadav S. Oral squamous cell carcinoma: etiology, pathogenesis and prognostic value of genomic alterations. Indian J Cancer. 2006 Apr;43(2):60–6.
14. Gupta PC, Nandakumar A. Oral cancer scene in India [Internet]. Vol. 5, Oral Diseases. 2008. p. 1–2. Available from: http://dx.doi.org/10.1111/j.1601-0825.1999.tb00055.x
15. Kadiyala SV, Saveetha Dental College, Saveetha University, Chenna, Jayaraj G, Saveetha Dental College, et al. Awareness of oral cancer among non medical students: a survey [Internet]. Vol. 6, International Journal of Current Advanced Research. 2017. p. 2707–10. Available from: http://dx.doi.org/10.24327/ijcar.2017.2710.0083
16. Ashok Kumar MD, Gheena S. Incidence of Dry Socket after Third Molar Extraction. Available from: https://www.jpsr.pharmainfo.in/Documents/Volumes/vol7Issue07/jpsr07071515.pdf
17. Silverman S Jr. Early diagnosis of oral cancer. Cancer. 1988 Oct 15;62(8 Suppl):1796–9.
18. Sivaramakrishnan SM, Ramani P. Study on the Prevalence of Eruption Status of Third Molars in South Indian Population. Early Pregnancy. 2015;7(4):1.
19. Sridharan G, Ramani P, Patankar S, Vijayaraghavan R. Evaluation of salivary metabolomics in oral leukoplakia and oral squamous cell carcinoma. J Oral Pathol Med. 2019 Apr;48(4):299–306.
20. Sridharan G, Ramani P, Patankar S. Serum metabolomics in oral leukoplakia and oral squamous cell carcinoma. J Cancer Res Ther. 2017 Jul;13(3):556–61.
21. Gheena S, Ezhilarasan D. Syringic acid triggers reactive oxygen species-mediated cytotoxicity in HepG2 cells. Hum Exp Toxicol. 2019 Jun;38(6):694–702.
22. Depprich RA, Handschel JG, Fritzemeier CU, Engers R, Kübler NR. Hybrid verrucous carcinoma of the oral cavity: A challenge for the clinician and the pathologist. Oral Oncology Extra. 2006 Feb 1;42(2):85-90.
23. Jayaraj G, Sherlin HJ, Ramani P, Premkumar P, Anuja N. Cytomegalovirus and Mucoepidermoid carcinoma: A possible causal relationship? A pilot study. J Oral Maxillofac Pathol. 2015 Sep;19(3):319–24.
24. Viveka TS, Shyamsundar V, Krishnamurthy A, Ramani P, Ramshankar V. p53 expression helps identify high risk oral tongue pre-malignant lesions and correlates with patterns of invasive tumour front and tumour depth in oral tongue squamous cell carcinoma cases. Asian Pac J Cancer Prev. 2016;17(1):189–95.

25. Swathy S, Gheena S, Varsha SL. Prevalence of pulp stones in patients with history of cardiac diseases. Research Journal of Pharmacy and Technology. 2015;8(12):1625–8.

26. Anuthama K, Sherlin HJ, Anuja N, Ramani P, Premkumar P, Chandrasekar T. Characterization of different tissue changes in normal, betel chewers, potentially malignant lesions, conditions and oral squamous cell carcinoma using reflectance confocal microscopy: correlation with routine histopathology. Oral Oncol. 2010 Apr;46(4):232–48.

27. Ko YC, Huang YL, Lee CH, Chen MJ, Lin LM, Tsai CC. Betel quid chewing, cigarette smoking and alcohol consumption related to oral cancer in Taiwan. J Oral Pathol Med. 1995 Nov;24(10):450–3.

28. Jayaraj G, Ramani P, Herald J. Sherlin, Premkumar P, Anuja N. Inter-observer agreement in grading oral epithelial dysplasia – A systematic review [Internet]. Vol. 27, Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology. 2015. p. 112–6. Available from: http://dx.doi.org/10.1016/j.ajoms.2014.01.006

29. Alexander AJ, Ramani P, Sherlin HJ, Gheena S. Quantitative analysis of copper levels in areca nut plantation area - A role in increasing prevalence of oral submucous fibrosis: An in vitro study. Indian J Dent Res. 2019 Mar;30(2):261–6.

30. Warnakulasuriya S. Areca nut use: an independent risk factor for oral cancer [Internet]. Vol. 324, BMJ. 2002. p. 799–800. Available from: http://dx.doi.org/10.1136/bmj.324.7341.799

31. Jayaraj G, Sherlin HJ, Ramani P, Premkumar P, Natesan A. Stromal myofibroblasts in oral squamous cell carcinoma and potentially malignant disorders. Indian J Cancer. 2015 Jan;52(1):87–92.

32. Chaitanya NC, Muthukrishnan A, Babu DBG, Kumari CS, Lakshmi MA, Palat G, et al. Role of Vitamin E and Vitamin A in Oral Mucositis Induced by Cancer Chemo/Radiotherapy- A Meta-analysis. J Clin Diagn Res. 2017 May;11(5):ZE06–9.

33. Subramaniam N, Muthukrishnan A. Oral mucositis and microbial colonization in oral cancer patients undergoing radiotherapy and chemotherapy: A prospective analysis in a tertiary care dental hospital. J Investig Clin Dent. 2019 Nov;10(4):e12454.

34. Hannah R, Ramani P, Sherlin HJ, Ranjith G, Ramasubramanian A, Jayaraj G, et al. Awareness about the use, ethics and scope of dental photography among undergraduate dental students dentist behind the lens. Research Journal of Pharmacy and Technology. 2018;11(3):1012–6.

35. Jangid K, Alexander A, Jayakumar N, Varghese S, Ramani P. Ankyloglossia with cleft lip: A rare case report [Internet]. Vol. 19, Journal of Indian Society of Periodontology. 2015. p. 690. Available from: http://dx.doi.org/10.4103/0972-124x.162207

36. Van Zyl AW, Bunn BK. Clinical features of oral cancer: clinical review. S Afr Dent J. 2012;67(10):566–9.

37. Jainkittivong A, Swasdison S, Thangpisityotin M, Langlais RP. Oral squamous cell carcinoma: a clinicopathological study of 342 Thai cases. J Contemp Dent Pract. 2009 Sep 1;10(5):E033–40.

38. Effiom OA, Adeyemo WL, Omitola OG, Ajayi OF, Emmanuel MM, Gbotolorun OM. Oral squamous cell carcinoma: a clinicopathologic review of 233 cases in Lagos, Nigeria. J Oral Maxillofac Surg. 2008 Aug;66(8):1595–9.

39. Venugopal A, Uma Maheswari TN. Expression of matrix metalloproteinase-9 in oral potentially malignant disorders: A systematic review. J Oral Maxillofac Pathol. 2016 Sep;20(3):474–9.

40. Sharon CV, Priya VV, Gayathri R. Role of milk on X-linked inhibitors of apoptosis gene expression in oral cancer. Drug Invention Today [Internet]. 2018;10(8).

41. Hema Shree K, Ramani P, Sherlin H, Sukumaran G, Jeyaraj G, Don KR, et al. Saliva as a Diagnostic Tool in Oral Squamous Cell Carcinoma - a Systematic Review with Meta Analysis. Pathol Oncol Res. 2019 Apr;25(2):447–53.

42. Zhen W, Karnell LH, Hoffman HT, Funk GF, Buatti JM, Menck HR. The National Cancer Data Base report on squamous cell carcinoma of the base of tongue. Head Neck. 2004 Aug;26(8):660–74.

43. Scott SE, Grunfeld EA, McGurk M. Patient's delay in oral cancer: A systematic review. Community Dent Oral Epidemiol. 2006 Oct;34(5):337–43.