Oral epithelial dysplasia: Classifications and clinical relevance in risk assessment of oral potentially malignant disorders

Kannan Ranganathan, Loganathan Kavitha

Department of Oral and Maxillofacial Pathology, Ragas Dental College and Hospital, Chennai, Tamil Nadu, India

INTRODUCTION

Oral cancer is the 11th most common cancer in the world, with an estimated 300,000 new cases and 145,000 deaths in 2012.[1,2] In India, 20/100,000 population are affected by oral cancer, which accounts for around 30% of all types of cancer.[3] Most cases of oral cancer are associated with habits (tobacco/areca nut) and are preceded by asymptomatic clinical lesions collectively referred to as oral potentially malignant disorder (OPMD).[4] OPMDs include leukoplakia, erythroplakia, reverse smoker’s palate, erosive lichen planus, oral submucous fibrosis, lupus erythematosus and actinic keratosis.[5,6]

The worldwide prevalence rate of OPMDs ranges from 1% to 5%. Estimates provided by individual studies vary depending on the country, the population under investigation, the pattern of tobacco use and the clinical definition used for leukoplakia. One of the early epidemiological studies assessing the risk of OPMDs in India reported that 80% of oral cancers were preceded by OPMDs.[7] The global prevalence (1986 to 2002) of leukoplakia was estimated to be 1.49% to 2.60%.[8,9] The prevalence of erythroplakia among populations in India and Malaysia is estimated to be 0.02%.[10‑13] Reported incidence rates of OPMDs in the Indian subcontinent

Keywords: Cancer, epithelial, grading, histopathology, oral dysplasia, potentially malignant, precancer
have ranged between 0.6/1000 and 30.2/1000 with a regional variation in prevalence from 0.2% in Bihar state in the north to 4.9% in Andhra Pradesh in the east. This difference in the range is attributed to the prevalence and type of tobacco use."

OPMD is a clinical diagnosis for which the histological diagnosis may be hyperplasia, hyperkeratosis, oral epithelial dysplasia (OED) or oral squamous cell carcinoma (OSCC). OED is characterized by cytological and architectural alterations reflecting the loss of normal maturation and stratification pattern of surface epithelium.

This review aims to discuss the different classifications of OED, their limitations and relevance in determining the risk of malignant transformation. Understanding this relation between the clinical diagnosis of OPMD and histopathological diagnosis of OED is essential for early diagnosis and clinical management.

**MALIGNANT TRANSFORMATION OF ORAL POTENTIALLY MALIGNANT DISORDER/ORAL EPITHELIAL DYSPLASIA TO ORAL SQUAMOUS CELL CARCINOMA**

Oral leukoplakia is reported to carry up to 2-fold increased risk of developing oral cancer depending on the site and habits. The MTR of leukoplakia varies from 1.4% to 7%. A recent systematic review of the observational studies in OPMD reported an MTR of 0.13%–34% across 24 studies. The variation in rates between studies is attributed to differences in follow-up times, study group definition and selection and tobacco habits.

**Oral epithelial dysplasia – Terminology**

The word dysplasia denotes abnormal growth. The dysplastic alterations may revert to normal when the underlying inciting stimulus is removed. Dysplastic features in stratified squamous epithelium are characterized by cellular atypia and loss of normal maturation and stratification. The World Health Organization (WHO) monograph on head and neck tumors (2005) uses the term “epithelial precursor lesions” and defines it as “altered epithelium with an increased likelihood for progression to squamous cell carcinoma.”

**Grading of oral epithelial dysplasia**

The current evidence recognizes carcinogenesis of the epithelium as a multistep, progressive, cumulative process of genetic mutations which culminate in tumor formation, and ultimately invasion and metastasis. In this model, simple epithelial hyperplasia progresses through mild OED, to more severe dysplastic changes with increasing genetic aberrations.

Grading of OED is used to assess the probability of malignant transformation. OED is observed in nearly all cases of erythroplakia and 1%–30% of oral leukoplakia cases at the time of diagnosis.

The criteria used for diagnosing dysplasia include architectural changes (tissue changes) and cytological changes (individual cell changes/cytological atypia). The WHO three-tier grading of oral dysplasia is traditionally used by pathologists, in which OED is graded as mild, moderate and severe.

**Classification systems for grading oral epithelial dysplasia**

The main purpose of a classification and grading system is to promote uniform reporting and management. It should also serve as a means for assessing lesions in epidemiological studies. More than 20 classification systems have been proposed in the past two decades in an attempt to standardize OED grading systems. For any grading system to be clinically useful, it should be reproducible, and the histological assessment should reflect the malignant potential of the lesion. Many of these systems are based on the classification of precursor lesion in other sites, including Squamous Intraepithelial Neoplasia (SIN) of the cervix and the Ljubljana classification of larynx.

**Smith and Pindborg photographic methods (1969)**

Smith and Pindborg described the first system for grading epithelial dysplasia of oral mucosa in the year 1969. They evaluated 13 histologic features, which were standardized by a set of photographs. Each feature was graded as absent, slight and marked. A grading of absent was scored as zero, whereas grading of slight or marked was allocated a score between 1 and 10. The scores are added to give the epithelial atypia index (EAI) (0 to 75).

In this system, the diagnosis of epithelial dysplasia is objective and semi-quantitative as the microscopic features are allocated a weighted score. However, the accuracy of weightage given to each of the histologic characteristics was subjective, and it was found to be difficult for routine use.

**Ljubljana classification (2003)**

The Ljubljana classification was first described by laryngeal pathologists Kambic and Lenart in 1971 for laryngeal hyperplastic lesions. Zerdoner in 2003 proposed the use of Ljubljana classification of laryngeal precancer for grading...
hyperplastic epithelial lesions of the oral cavity in four grades [Tables 1 and 3]." [34,32]

The Ljubljana classification includes all histopathological changes that progress to squamous cell carcinoma each of which entails different treatment options. In this system, carcinoma in situ (CIS) is distinct from atypical hyperplasia, as these two entities differ in morphology and their progression to invasive carcinoma. [24]

Gale and Warnakulasuriya observe that the Ljubljana classification cannot categorize certain oral lesions such as oral submucous fibrosis and oral lichen planus, which have atrophic epithelium and are without significant atypia. Furthermore, this system is considered complex and time-consuming and needs to be validated for oral lesions. [24,26,30,33,34]

Squamous Intraepithelial Neoplasia/dysplasia (SIN/dysplasia) classification (2005)

SIN is a concept derived from cervical intraepithelial neoplasia. It has been extended with some modification of the WHO classification as “oral intraepithelial neoplasia.” It is also used for all sites of the upper aerodigestive tract (UADT). This system proposed

1. Unifying all the histological changes as “Oral Intra-epithelial Neoplasm”
2. Grading lesions as high grade and low grade.

However, it was argued that in UADT, surface maturation/keratinization can occur in the presence of dysplastic layers in the lower strata of epithelium, which is not a feature of cervical intraepithelial neoplasm. Hence, in UADT, a classification of SIN/dysplasia was introduced. It was a modification of 2005 WHO grading system [Table 1]. [24,32,33] The important considerations of this classification are:

1. Dysplasia is a spectrum
2. One end of the spectrum is hyperplastic keratinizing SIN/dysplasia and the other end is atrophic SIN/dysplasia
3. Hyperplastic keratinizing SIN/dysplasia is called keratinized dysplasia
4. Atrophic SIN/dysplasia is similar to the WHO type dysplasia.

The hyperplastic keratinizing SIN/dysplasia and atrophic SIN/dysplasia clinically correspond to leukoplakia and
Ranganathan and Kavitha: Oral epithelial dysplasia grading

Oral Intraepithelial Neoplasia/ Carcinoma in situ (Japanese Society for Oral Pathology), OIN/CIS (JSOP) system (2010)

In 2010, the Working Group of the Japan Society for Oral Tumours (WG–JSOT) proposed a new entity—oral intraepithelial neoplasia (OIN)—in the first edition of its “General Rules for Clinical and Pathological Studies on Oral Cancer.” The term OIN was introduced to avoid confusion with the WHO’s term of CIS and to lay emphasis on the characteristics of oral SCC different from those of SCC of the uterine cervix. According to the Working Committee of the Japanese Society for Oral Pathology (JSOP), OIN/CIS system describes oral precursor lesions under three categories: reactive atypical epithelium, OED and OIN/CIS (JSOP) [24] Mucosal resection is recommended for the treatment of OIN/CIS (JSOP), whereas follow-up is recommended for OED in the OIN system.[24,41,42]

World Health Organization (WHO) classification systems

World Health Organization (WHO) 1978 classification

A collaborating reference center was established by the WHO in the year 1967, to characterize and define those lesions that should be considered as oral precancer and to determine their relative risk of becoming malignant.[17,33] In its report in 1978, the WHO defined and listed 12 characteristics of epithelial dysplasia and graded epithelial dysplasia as mild, moderate and severe and published the same in the “Histopathological typing of cancer and precancer of the oral mucosa,” in 1997, the characteristic histologic features were listed:

1. Loss of polarity of basal cells
2. Basaloid appearance in more than one layer of cells
3. An increased nuclear–cytoplasmic ratio
4. Drop-shaped rete pegs
5. Irregular epithelial stratification
6. Increased number of mitotic figures
7. Mitotic figures in the superficial half of the epithelium
8. Cellular polymorphism
9. Nuclear hyperchromatism
10. Enlarged nucleoli
11. Reduction of cellular cohesion
12. Keratinization of single cells or cell groups in the prickle cell layer (Kramer et al., 1978).

OED is graded as mild, moderate and severe based on whether dysplastic features were restricted to the lower third, middle third and the upper third of the epithelium, respectively [Table 1].[17,43,44]

World Health Organization (WHO) 2005 classification

The WHO 2005 classification recognizes five histopathological stages in epithelial precursor lesions: Squamous hyperplasia, mild dysplasia, moderate dysplasia, severe dysplasia and CIS. The criteria for diagnosing epithelial dysplasia are architectural and cytological/cellular changes [Table 4].[26]

Based on the architectural and cytological alterations, the epithelium is divided into “thirds,” and the lesions are classified into five categories [Table 1][5,26]

1. Hyperplasia (Squamous hyperplasia): Lesions with an increase in cell number in the spinous layer and/or in the basal/parabasal cell layers. There is presence of regular stratification and no cellular atypia
2. Mild dysplasia: Architectural disturbance present only in the lower third of the epithelium with cytological atypia
3. Moderate dysplasia: The criteria postulate that architectural disturbance extending into the middle third of the epithelium, but the degree of cytological atypia may require upgrading it to “severe dysplasia”
4. Severe dysplasia: Architectural disturbance observed in greater than two thirds of the epithelium, with cytological atypia
5. Carcinoma in situ (CIS): Is a noninvasive carcinoma, classified as a precursor lesion of OSCC. CIS is characterized by full thickness or almost full thickness of epithelial architectural disturbance in the viable cell layers accompanied by pronounced cytological atypia.

Table 4: World Health Organization (WHO) criteria for epithelial dysplasia (2005)

| Architectural changes | Cellular changes |
|-----------------------|------------------|
| Irregular epithelial stratification | Abnormal variation in nuclear size (anisonucleosis) |
| Loss of polarity of basal cells | Abnormal variation in nuclear shape (nuclear pleomorphism) |
| Basal cell hyperplasia* | Abnormal variation in cell size (anisocytosis) |
| Drop-shaped rete ridges | Abnormal variation in cell shape (cellular pleomorphism) |
| Increased number of mitotic figures | Increased nuclear–cytoplasmic ratio |
| Abnormally superficial mitotic figures | Increase in nuclear size* |
| Premature keratinization in single cells (dyskeratosis) | Atypical mitotic figures |
| Keratin pearls within rete ridges | Increased number and size of nucleoli |
| Hyperchromasia | |

*Present in 2005 WHO classification; has been removed in 2017 WHO classification. WHO: World Health Organization
World Health Organization (WHO) 2017 classification
In the recently published 2017 WHO grading system, features of “squamous hyperplasia (acanthosis and basal cell hyperplasia)” and “carcinoma in situ (CIS)” present in the 2005 WHO classification has been dropped from the OED grading [Table 1]. The term CIS is removed from the 2017 WHO classification and used synonymously with severe dysplasia. The cytological/cellular feature, “increase in nuclear size” in the 2005 WHO classification has also been dropped from 2017 WHO diagnostic criteria of OED. The architectural feature “loss of epithelial cell cohesion” has been included in 2017 WHO diagnostic criteria [Table 5].

Binary system (2006)
Warnakulasuriya et al. in their review on OED classification system report that in the workshop conducted on issues related to OPMD in the United Kingdom, the WHO Collaborating Centre for Oral Cancer and Precancer (2005), the working group emphasized the need for two-tier classification – low risk (no / questionable / mild); high risk (moderate / severe) for better reproducibility and clinical utility. However, they added that further studies are needed before the two-tier system can be adopted [Table 1].

The binary system for grading epithelial dysplasia categorizes OED into low risk and high risk for undergoing malignant transformation. Kujan et al. in their study show that the binary system that uses four architectural and five cytological features had an increased inter-observer agreement (κ = 0.5) as compared to the WHO (κ = 0.22). Nankivell et al. also contend that the binary system has a superior reproducibility, and a similar prognostic ability when compared to the three-tier WHO system. They showed that the binary system with the use of four architectural features and four cytological features has a higher multi-observer kappa (κ = 0.59) compared with the WHO system (κ = 0.49).

Although the three-tier grading systems (mild, moderate and severe) is widely used, the binary system complements the WHO classification systems, and it has merit as it helps clinicians to make critical clinical decisions particularly in cases with moderate dysplasia. It also facilitates a standardized approach to overcome some difficulty in subjectivity in reporting of epithelial dysplasia. However, the biological significance of this system needs to be validated in longitudinal studies to explore its value in the prediction of malignant transformation risk of OPMDs.

Oral epithelial dysplasia in the clinical context
The histopathologic assessment for the presence of OED is considered the current gold standard for predicting malignant transformation of OPMDs. The presence of epithelial dysplasia is an indicator of the malignant potential of OPMDs, and the risk of these lesions to progress to carcinoma increases with the increasing grades of epithelial dysplasia.

The efficacy and usefulness of histopathological grading of precursor lesions as an indicator of malignant transformation have long been debated in the literatures as malignant transformation of OPMDs can also occur in the absence of OED. Furthermore, wide intra- and inter-observer variability in grading epithelial dysplasia raises the concern of reproducibility.

Accurate clinical classification, supported by objective histopathological examination, will aid follow-up studies that aim to predict malignant transformation of OPMDs. In this context, prospective studies on OPMD/OED with longitudinal follow-up of patients are the need of the hour for clinical validation of the revised three-tier or binary system. Given the difficulty of conducting a longitudinal study, cases pooled from multiple sources are an alternative that needs to be considered.

Besides grading of OED, these studies also need to address clinical determinants and molecular diagnostic aids, which are briefly discussed below.

Clinical determinants of malignant transformation
The risk factors to predict the malignant transformation of OPMDs remains challenging. van der Waal and Lee reported major risk factors for the malignant transformation include:
- Female gender
- Long duration of leukoplasia
- Leukoplasia in non-smokers (idiopathic leukoplasia)
• Site predilection for tongue and/or floor of the mouth
• Size $\geq 200 \text{ mm}^2$
• Non-homogenous type.

Gender predilection
In India, MTRs of leukoplakia are greater in men than in women, possibly because of the association with chewing tobacco and smoking habits\cite{21,62,63} whereas in Europe and other western countries, it is greater in women than men.\cite{4,5,15,64-66}

Duration
Cancers from dysplastic lesions usually develop over a period of 2–5 years, but can occur much later.\cite{50,67,68}
Time frame for this process varies, but it is thought to be a relatively slow process, with malignant transformation occurring over a period of few years.\cite{69}

Smokers versus non-smokers
Lesions in non-smokers are 7.1 times more likely to undergo malignant transformation compared to heavy smokers.\cite{16,19,20,64}

Anatomical location
The floor of the mouth and/or on the lateral tongue has a high risk for malignant transformation.\cite{21,64,70-72}

Homogenous versus non-homogenous leukoplakia
Reibel and Holmstrup considered non-homogenous appearance as an important marker for malignant transformation.\cite{73} Although the most common clinical type of leukoplakia is homogenous, a higher malignant transformation (13.1%) occurs among the non-homogenous clinical types.\cite{23,64,73,74} Speckled and erosive leukoplakia have the highest MTR.\cite{66,75} Homogenous, thick leukoplakia undergoes malignant transformation in 1%–7% of cases. Once the surface becomes granular or verruciform, the malignant transformation potential becomes 4%–15%. Erythroleukoplakia carries an average transformation potential of 28%, but the rates vary from 18% to 47% in different studies.\cite{68}

Other clinical determinants
Large lesions ($\geq 200 \text{ mm}^2$),\cite{64,76,77} multifocal or multiple leukoplakia,\cite{62,63} and proliferative verrucous leukoplakia\cite{20,77-80} are also associated with increased risk of malignant transformation. Advancing age is also shown to be an important determinant of malignant transformation.\cite{19,75,78,81,82} The presence of aneuploidy has been found to signify a high risk of malignant transformation in leukoplakia.\cite{83-86}

Other prognostic indicators
It has been suggested that the use of molecular markers along with clinical and histological grading can better predict disease progression. Alterations and mutations in the genetic content of oral epithelium are an integral part of “premalignancy.”\cite{87,88} Many genes and signaling pathways have been shown to be involved in the development of OSCC. Molecular markers that correlate OED with malignant transformation\cite{89} include:

a. Overexpression of EGFR,\cite{90} c-Jun,\cite{91} Ki67/Mcm2,\cite{92} Cyclins D and E,\cite{93} p53,\cite{94-96} p63,\cite{97} survivin, MMP-9,\cite{98} TGF alpha,\cite{99,90} COX-1 and-2\cite{100-102}
b. Amplification of Cyclin D1\cite{103,104}
c. Loss of c-erbB2,\cite{105} pRB\cite{106}
d. Upregulation of telomerase (human telomerase reverse transcriptase; hTERT)\cite{107-109}
e. Aneuploidy\cite{84}
f. Loss of heterozygosity (Chromosome loci 3p, 8p, 9p, 4q, 11q, 13q, 17p)\cite{110-112}
g. Cytokeratins (CK 1, CK 8 and CK 18)\cite{113,114}
h. High-risk Human papillomavirus, p16\cite{115}

Progress in molecular oncology has significantly advanced the knowledge on tumorigenesis; however, the clinical utility of these genetic markers in OPMD/OED need to be defined.

CONCLUSION
Oral squamous cell carcinoma is often diagnosed in the late stages of the disease. Delayed diagnosis precludes successful treatment and favorable outcomes. Oral potentially malignant disorders are associated with the variable rate of malignant progression, with the finding of oral epithelial dysplasia on tissue biopsy remaining the gold standard in guiding management.

Long-term prospective studies are imperative to understand the natural history of oral potentially malignant disorders and oral squamous cell carcinoma, to facilitate diagnosis of at an early stage and render appropriate treatment, thereby reducing the morbidity and the mortality associated with advanced stage of oral cancer.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Sankaranarayanan R, Ramadas K, Amarasinghe H, Subramanian S, Johnson N. Oral cancer: Prevention, early detection, and treatment. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, editors. Cancer:
44. Rajendran R, Sivapathasundaram B. Shafer's Textbook of Oral Pathology. 7th ed. India: Elsevier; 2012, p. 88.

45. El-Naggar AK, Chan JK, Grandis JR, Takata T, Slootweg PJ. WHO Classification of Head and Neck Tumors. WHO/IARC Classification of Tumours. 4th ed., Vol. 9. International Agency for Research on Cancer (IARC) press; 2017.

46. Kujan O, Oliver RJ, Khattab A, Roberts SA, Thakker N, Sloan P, et al. Evaluation of a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation. Oral Oncol 2006;42:987-93.

47. Nankivel P, Williams H, Matthews P, Suortamo S, Nead D, McConkey C, et al. The binary oral dysplasia grading system: Validity testing and suggested improvement. Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:87-94.

48. Liu W, Bao ZX, Shi LJ, Tang GY, Zhou ZT. Malignant transformation of oral epithelial dysplasia: Clinicopathological risk factors and outcome analysis in a retrospective cohort of 138 cases. Histopathology 2011;59:733-40.

49. MacDonald DG, Saka SM. Structural indicators of the high risk lesion. In: Johnson NE, editor. Risk Markers for Oral Diseases. Oral Cancer: Detection of Patients and Lesions at Risk. Vol. 2. Cambridge: Cambridge University Press; 1991. p. 163-87.

50. van der Waal I, Avel J. Oral leukoplakia: A proposal for uniform reporting. Oral Oncol 2002;38:521-6.

51. Mehanna HM, Ratnay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia - a systematic review and meta-analysis. Head Neck 2009;31:1600-9.

52. Tilakaratne WM, Sherriff M, Morgan PR, Odell EW. Grading oral epithelial dysplasia: Analysis of individual features and progression to cancer. Head Neck Pathol 2011;4:61-6.

53. Speight PM. Update on oral epithelial dysplasia and progression to cancer. Head Neck Pathol 2007;1:61-6.

54. Dost F, Lé Cao K, Ford PJ, Ades C, Farah CS. Malignant transformation of oral epithelial dysplasia: A real-world evaluation of histopathologic grading. Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:343-52.

55. Pindborg JJ, Reibel J, Holmstrup P. Subjectivity in evaluating oral pre-malignant and malignant lesions. J Oral Pathol Med 1985;14:698-708.

56. Abbey LM, Kaugars GE, Gunsolley JC, Burns JC, Page DG, Svrisky JA, et al. Intraexaminer and interexaminer reliability in the diagnosis of oral epithelial dysplasia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995;80:188-91.

57. Karahalioğlu A, Reibel J, Therkildsen MH, Praetorius F, Nielsen HW, Dabelsteen E, et al. Observer variability in the histologic assessment of oral premalignant lesions. J Oral Pathol Med 1995;24:198-200.

58. Fischer DJ, Epstein JB, Morton TH, Schwartz SM. Interobserver reliability in the histopathologic diagnosis of oral pre-malignant and malignant lesions. J Oral Pathol Med 2004;33:65-70.

59. Scully C. Challenges in predicting which oral mucosal potentially malignant disease will progress to neoplasia. Oral Dis 2014;20:1-5.

60. van der Waal I, Axell T. Oral leukoplakia: to treat or not to treat. A long-term study of thirty patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1979;80:188-91.

61. Lee JJ, Hong WK, Hittelman WN, Mao L, Lotan R, Shin DM, et al. Predicting cancer development in oral leukoplakia: Ten years of translational research. Clin Cancer Res 2000;6:1702-10.

62. Hamadah O, Goodson MI, Thomson PJ. Clinicopathological behaviour of multiple oral dysplastic lesions compared with that of single lesions. Br J Oral Maxillofac Surg 2010;48:503-6.

63. Yang SW, Tsi CN, Lee YS, Chen TA. Treatment outcome of dysplastic oral leukoplakia with carbon dioxide laser – Emphasis on the factors affecting recurrence. J Oral Maxillofac Surg 2011;69:78-87.

64. Napier SS, Speight PM. Natural history of potentially malignant oral lesions and conditions: An overview of the literature. J Oral Pathol Med 2008;37:1-10.

65. Ray JG, Ranganathan K, Chattopadhyay A. Malignant transformation of oral submucous fibrosis: Overview of histopathological aspects. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:200-9.

66. Silverman S, Bhargava K, Smith LW, Malawalla AM. Malignant transformation and natural history of oral leukoplakia in 57,518 industrial workers of Gujarat, India. Cancer 1976;38:1790-5.

67. Jerjes W, Upile T, Hamdooz Z, Al-Khawaldeh M, Morcos M, Mosse CA, et al. CO2 laser of oral dysplasia: Clinicopathological features of recurrence and malignant transformation. Lasers Med Sci 2012;27:169-79.

68. Neville B, Damm D, Allen C, Bouquot J. Oral and Maxillofacial Pathology. 2nd ed. Philadelphia: W.B. Saunders; 2002.

69. Bouquot JE, Speight PM, Farthing PM. Epithelial dysplasia of the oral mucosa – Diagnostic problems and prognostic features. Curr Diagn Pathol 2006;12:11-21.

70. Kramer IR, Lucas RB, el-Labbab N, Lister L. The use of discriminant analysis for examining the histological features of oral keratoses and lichen planus. Br J Cancer 1970;24:673-83.

71. Waldron CA, Shafer WG. Leukoplakia revisited. A clinicopathologic study. 3256 oral leukoplakias. Cancer 1975;36:1386-92.

72. Wannakuwala S. SCC and precursor lesions: Prevention. Periodontology 2011;57:38-50.

73. Reibel J, Holmstrup P. Premalignant disorders and cancer of the oral mucosa. Ugeskr Laeger 2010;172:3040-2.

74. Holmstrup P, Vedtofte P, Reibel J, Stoltze K. Long-term treatment outcome of oral premalignant lesions. Oral Oncol 2006;42:461-74.

75. Chiesa F, Sala L, Costa I, Moglia D, Maurit M, Podrecca S, et al. Excision of oral leukoplakias by CO2 laser on an out-patient basis: A useful procedure for prevention and early detection of oral carcinomas. Tumori 1986;72:307-12.

76. Cowan CG, Gregg TA, Napier SS, McKenna SM, Kee F. Potentially malignant oral lesions in Northern Ireland: A 20-year population-based perspective of malignant transformation. Oral Dis 2001;7:18-24.

77. Shiu MN, Chen TH, Chang SH, Hahn LJ. Risk factors for leukoplakia and malignant transformation to oral carcinoma: A leukoplakia cohort in Taiwan. Br J Cancer 2000;82:1871-4.

78. Hanssen LS, Olson JA, Silverman S Jr. Proliferative verrucous leukoplakia. A long-term study of thirty patients. Oral Surg Oral Med Oral Pathol 1985;60:285-98.

79. Cabay RJ, Morton TH Jr, Epstein JB. Proliferative verrucous leukoplakia and its progression to oral carcinoma: A review of the literature. J Oral Pathol Med 2007;36:255-61.

80. Holmstrup P, Dabelsteen E. Oral leukoplakia-to treat or not to treat. Oral Dis 2016;22:494-7.

81. Gupta PC, Mehta FS, Daftary AK, Bahl N, Blomgren RS, et al. Incidence rates of oral cancer and natural history of oral precancerous lesions in a 10-year follow-up study of Indian villagers. Community Dent Oral Epidemiol 1980;8:283-333.

82. Bánočky J. Follow-up studies in oral leukoplakia. J Maxillofac Surg 1977;5:69-75.

83. Bremmer JF, Brakenhoff RH, Broeckaert MA, Beliën JA, Leemans CR, Bloemen E, et al. Prognostic value of DNA ploidy status in patients with oral leukoplakia. Oral Oncol 2011;47:956-60.

84. Torres-Rendon A, Stewart R, Craig GT, Wells M, Speight PM. DNA ploidy analysis by image cytometry helps to identify oral epithelial dysplasias with a high risk of malignant progression. Oral Oncol 2009;45:468-73.

85. Bradley G, Odell EW, Raphael S, Ho J, Le IW, Benchmark S, et al. Abnormal DNA content in oral epithelial dysplasia is associated with increased risk of progression to carcinoma. Br J Cancer 2010;103:1432-42.

86. Sperandio M, Brown AL, Lock C, Morgan PR, Coupland VH, Madden PB, et al. Predictive value of dysplasia grading and DNA ploidy in malignant transformation of oral potentially malignant disorders. Cancer Prev Res (Phila) 2011;4:822-31.

87. Scully C, Sudbo J, Speight PM. Progress in determining the malignant...
potential of oral lesions. J Oral Pathol Med 2003;32:251-6.
88. Lingen MW, Pinto A, Mendes RA, Franchini R, Czarinski R, Tilakaratne WM, et al. Genetics/epigenetics of oral premalignancy: Current status and future research. Oral Dis 2011;17 Suppl 1:7-22.
89. Piriyage G, Tilakaratne WM, Tavassoli M, Warnakulasuriya S. Molecular markers in oral epithelial dysplasia: Review. J Oral Pathol Med 2009;38:737-52.
90. Srinivasan M, Jewell SD. Evaluation of TGF-alpha and EGFR expression in oral leukoplakia and oral submucous fibrosis by quantitative immunohistochemistry. Oncology 2001;61:284-92.
91. Turatti E, da Costa Neves A, de Magalhães MH, de Sousa SO. Assessment of c-jun, c-fos and cyclin D1 in premalignant and malignant oral lesions. J Oral Sci 2005;47:71-6.
92. Torres-Rendon A, Roy S, Craig GT, Speight PM. Expression of Mem2, geminin and Ki67 in normal oral mucosa, oral epithelial dysplasias and their corresponding squamous-cell carcinomas. Br J Cancer 2009;100:1128-34.
93. Oliver RJ, MacDonald DG. G1 cyclins in oral epithelial dysplasia. J Oral Pathol Med 2001;30:80-6.
94. Murti PR, Warnakulasuriya KA, Johnson NW, Bhonsle RB, Gupta PC, Daftry DK, et al. P53 expression in oral precancer as a marker for malignant potential. J Oral Pathol Med 1998;27:191-6.
95. Cruz IB, Snijders PJ, Meijer CJ, Braakhuis BJ, Snow GB, Walboomers JM, et al. p53 expression above the basal cell layer in oral mucosa is an early event of malignant transformation and has predictive value for developing oral squamous cell carcinoma. J Pathol 1998;184:360-8.
96. Kövesi G, Szende B. Prognostic value of cyclin D1, p27, and p63 in oral squamous cell carcinoma, oral leukoplakia and oral submucous fibrosis. J Investig Clin Dent 2014;5:214-9.
97. Oliver RJ, MacDonald DG. G1 cyclins in oral epithelial dysplasia. J Oral Pathol Med 2001;30:80-6.
98. Mutirangura A, Supiyaphun P, Trirerekapan S, Sriuranpong V, Sakuntabhai A, Yenrudi S, et al. Telomerase activity in oral leukoplakia and head and neck squamous cell carcinoma. Cancer Res 1996;56:3530-3.
99. Kannan R, Bijur GN, Mallery SR, Beck FM, Helliwell T, Mehanna H. Biomarkers in oral lesions. J Oral Pathol Med 2003;32:251-6.
100. Shibata M, Kodani I, Osaki M, Adachi H, Ryoke K, Adachi H, et al. Cyclin D1 and cancer development in laryngeal premalignancy patients. Cancer Prev Res (Phila) 2009;2:14-21.
101. Kilpi A, Rich AM, Konttinen YT, Reade PC. Expression of c-erbB-2 protein in keratinocytes of oral mucosal lichen planus and subsequent squamous cell carcinoma. Eur J Oral Sci 1996;104:278-84.
102. Soni S, Kaur J, Kumar A, Chakravarti N, Mathur M, Bahadur S, et al. Alterations of Rb pathway components are frequent events in patients with oral epithelial dysplasia and predict clinical outcome in patients with squamous cell carcinoma. Oncology 2005;68:314-25.
103. Palani J, Lakshminarayanan V, Kannan R. Immunohistochemical detection of human telomerase reverse transcriptase in oral cancer and pre-cancer. Indian J Dent Res 2011;22:362.
104. Murirangura A, Supiyaphun P, Trirerekapan S, Sriuranpong V, Sakuntabhai A, Yenrudi S, et al. Telomerase activity in oral leukoplakia and head and neck squamous cell carcinoma. Cancer Res 1996;56:3530-3.
105. Kannan S, Tahara H, Yokozaki H, Mathew B, Nalinakumari KR, Nair MK, et al. Telomerase activity in premalignant and malignant lesions of human oral mucosa. Cancer Epidemiol Biomarkers Prev 1997;6:413-20.
106. Rosin MP, Cheng X, Poh C, Lam WL, Huang Y, Lovas J, et al. Use of allelic loss to predict malignant risk for low-grade oral epithelial dysplasia. Clin Cancer Res 2000;6:357-62.
107. Mao L, Lee JS, Fan YH, Ro JY, Batsakis JG, Lippman S, et al. Cyclin D1 and cancer development in laryngeal premalignancy patients. Cancer Prev Res (Phila) 2009;2:14-21.
108. Kilpi A, Rich AM, Konttinen YT, Reade PC. Expression of c-erbB-2 protein in keratinocytes of oral mucosal lichen planus and subsequent squamous cell carcinoma. Eur J Oral Sci 1996;104:278-84.
109. Soni S, Kaur J, Kumar A, Chakravarti N, Mathur M, Bahadur S, et al. Alterations of Rb pathway components are frequent events in patients with oral epithelial dysplasia and predict clinical outcome in patients with squamous cell carcinoma. Oncology 2005;68:314-25.
110. Partridge M, Emilion G, Falworth M, A‘Hern R, Phillips E, Pateromichelakis S, et al. Patient-specific mutation databases for oral cancer. Int J Cancer 1999;84:284-92.
111. Nanda KD, Ranganathan K, Devi U, Joshua E. Increased expression of CK8 and CK18 in leukoplakia, oral submucous fibrosis, and squamous cell carcinoma: An immunohistochemistry study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;82:69-74.
112. Shibata M, Kodani I, Osaki M, Adachi H, Ryoke K, et al. Cyclo-oxygenase-1 and -2 expression in human oral mucosa, dysplasias and squamous cell carcinomas and their pathological significance. Oral Oncol 2003;41:304-12.
113. Sun XJ, Ma J, Zhang H, Wang XQ, Li JH. The expressions of cyclooxygenase-2 (Cox-2), VEGF in oral squamous cell carcinoma and precancerous lesions and their significances. Shanghai Kou Qiang Yi Xue 2005;14:173-6.
114. Zhang S, Du Y, Tao J, Wu Y, Chen N. Expression of cytosolic phospholipase A2 and cyclooxygenase 2 and their significance in human oral mucosa, dysplasias and squamous cell carcinomas. ORL J Otorhinolaryngol Relat Spec 2008;70:242-8.
115. Lerman MA, Almazrooa S, Lindeman N, Hall D, Villa A, Woo SB, et al. HPV-16 in a distinct subset of oral epithelial dysplasia. Mod Pathol 2017;30:1646-54.