CENTRO UNIVERSITÁRIO DE ANÁPOLIS - UNIEVANGÉLICA
PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA

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# EFICÁCIA DOS SISTEMAS DE GRADUAÇÃO BINÁRIO E OMS NA PREDIÇÃO DE TRANSFORMAÇÃO MALIGNA DA DISPLASIA EPITELIAL ORAL: REVISÃO SISTEMÁTICA E METANÁLISE

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Dissertação apresentada ao Programa de Pós-Graduação em Odontologia do Centro Universitário de Anápolis – UniEVANGÉLICA para obtenção do Título de Mestre em Odontologia.

Área de concentração: Clínica Odontológica.
Orientação: Prof.º Dr. Brunno Santos de Freitas Silva.

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## FOLHA DE APROVAÇÃO

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Dissertação apresentada ao Programa de Pós-graduação em Odontologia - PPGO do Centro Universitário de Anápolis - UniEVANGÉLICA como requisito parcial à obtenção do grau de MESTRE.

Aprovado em 04 de novembro de 2020.

**Banca examinadora**

Prof. Dr. Brunno Santos de Freitas Silva

Profa. Dra. Cyntia Rodrigues de Araújo Estrela

Profa. Dra. Maria Alves Garcia Santos Silva

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Dedico esse trabalho à minha mãe, que é o meu maior exemplo de perseverança.

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## EPÍGRAFE

"Embora ninguém possa voltar atrás e fazer um novo começo, qualquer um pode começar agora e fazer um novo fim."

Chico Xavier

**SUMÁRIO**

## LISTA DE ABREVIATURAS E SIGLAS

COCE Carcinoma Oral de Células Escamosas

DEO Displasia Epitelial Oral

LOPM Lesão Oral Potencialmente Maligna

OMS Organização Mundial de Saúde

## RESUMO

A observação microscópica da presença de displasia epitelial pode indicar, a longo prazo, um potencial de transformação maligna de uma lesão da mucosa oral. A graduação histológica é o método de escolha para a avaliação do potencial de transformação maligna da displasia epitelial oral (DEO). Essa revisão sistemática foi desenvolvida para examinar a evidência existente sobre a capacidade de predição do sistema Binário de graduação histológica e comparar este com o sistema da OMS, em relação ao potencial de predição de transformação maligna da DEO. Foram realizadas buscas em 6 bancos de dados eletrônicos e mais 4 plataformas para a busca da literatura cinzenta. Todas as buscas foram realizadas até o dia 3 de setembro de 2020. Foram selecionados 3.653 artigos, após a exclusão de artigos duplicados. Na fase 1, 13 estudos foram selecionados para a leitura completa, mais 1 estudo selecionado por meio de busca manual. Na fase 2, quatro artigos cumpriram os critérios de elegibilidade e foram incluídos nesta revisão, sendo 2 estudos transversais e 2 coorte. A variação na quantidade das amostras foi entre 68 a 141, totalizando 402 espécimes de DEO. Todos os estudos compararam os sistemas de graduação da OMS e Binário na predição de transformação maligna. A habilidade de predição do sistema da OMS foi de 16% a 80% e a do sistema Binário, entre 5% a 80%. A concordância inter-observadores foi avaliada em 3 estudos e foi classificada entre baixa e satisfatória para os dois sistemas. O risco de viés dos estudos foi classificado entre baixo a moderado. A concordância inter-observadores foi de baixa a satisfatória tanto para o sistema da OMS quanto para o sistema Binário. A metanálise foi realizada em 3 estudos e a taxa de transformação maligna em lesões classificadas como displasia severa ou carcinoma *in situ* foi de 40%, pelo sistema da OMS, e de 31% nas lesões classificadas como baixo risco no sistema Binário. Conclui-se que o sistema Binário possibilita maior concordância inter-observadores, porém não há evidências de que é superior ao da OMS na previsão de transformação maligna da DEO.



**Palavras-chave**: Câncer oral; Gradação histológica de neoplasias; Carcinoma de células escamosas; Revisão Sistemática; Metanálise.

## ABSTRACT

The microscopic presence of oral epithelial dysplasia (OED) may indicate long-term risk of malignant transformation. The histologic grading of these cellular and architectural abnormalities is the available method to evaluate the malignant transformation potential of OED. This systematic review was designed to examine the research evidence of the predictive ability of Binary histologic grading system and to compare it with the WHO system for predicting malignant transformation. Detailed individual search strategies for 6 electronic bibliographic databases were implemented. Additional grey literature search was made using 4 databases. All searches were conducted up to September 3rd, 2020. A hand search of the references of the selected articles was also conducted. A total of 3,653 studies were selected, after exclusion of the duplicates. In phase 1, 13 studies were selected for full-text reading and 1 additional study were included after a hand search in their reference list. In phase 2, four articles met the eligibility criteria and were included in this systematic review. Sample size ranged from 68 to 141, totaling 402 OED specimens. OED was assessed by WHO and Binary grading systems in all studies. The ability to predict malignant transformation ranged from 16% to 80% for WHO grading system and from 5% to 80% for Binary system. The data about the interobserver agreement was low to good agreements for the WHO and Binary systems. Overall, the methodology of the studies presented “low” to “moderate” risk of bias. Meta-analysis was performed in 3 of the 4 selected studies. The pooled malignant transformation rate of lesions classified as severe dysplasia or carcinoma in situ by the WHO grading was 40% while the lesions classified as high-risk by the Binary grading system, presented a malignant transformation rate of 31%. In conclusion, despite there is evidence that the Binary system present a less interrater variability when grading OED, there is no confirmation that this system is superior to the WHO system in predicting malignant transformation.



**Keywords**: Oral cancer; Neoplasm grading; Squamous cell carcinoma; Systematic Review; Meta-analysis.

## 1. INTRODUÇÃO

O carcinoma de células escamosas é um dos tumores orais mais frequentes no mundo, com mais de 300.000 novos casos reportados anualmente (Chi et al., 2015). O carcinoma oral de células escamosas (COCE) representa 90% de todos os tipos de cânceres da cavidade oral (Warnakulasuriya, 2009), e apresenta um prognóstico ruim, com a taxa de sobrevida de 45% a 50% em 5 anos (Omar, 2015). A maioria dos casos de COCE é precedida por uma lesão oral potencialmente maligna (LOPM) (Warnakulasuriya, 2009), principalmente leucoplasia e eritroplasia oral. Ambas podem microscopicamente apresentar displasia epitelial (Woo, 2019).

A displasia epitelial é considerada uma desordem causada por uma proliferação epitelial anormal, resultando em um tecido com distúrbios de diferenciação e maturação, apresentando atipias celulares e distúrbios de arquitetura do epitélio (Tilakaratne et al., 2019). As atipias celulares encontradas são: variação anormal do tamanho e formato dos núcleos e das células, proporção núcleo-citoplasma aumentada, aumento do tamanho do núcleo, figuras de mitose atípicas, aumento do número e tamanho dos nucléolos e hipercromasia. Os distúrbios de arquitetura são caracterizados por: estratificação epitelial irregular, perda de polaridade das células basais, cristas epiteliais em forma de gota, aumento do número de figuras de mitose, presença de mitoses superficiais no epitélio, queratinização prematura de células isoladas e pérolas de queratina na crista epitelial (Warnakulasuriya et al., 2008).

A observação microscópica da presença de displasia epitelial pode indicar um potencial de transformação maligna da lesão a longo prazo (Takata & Slootweg, 2017), e a graduação histológica das atipias celulares e dos distúrbios de arquitetura constituem a base para a avaliação do potencial de transformação maligna de uma lesão (Nankivell et al., 2013). Apesar da existência de vários biomarcadores moleculares capazes de prever corretamente o potencial de transformação maligna de uma lesão, a graduação histológica da displasia epitelial oral (DEO) continua a ser o método de preferência. Isso se deve ao fato de um amplo espectro de aberrações

moleculares estarem presentes nas LOPM, tornando difícil a seleção de um ou mais marcadores para estimar o risco de transformação maligna, impedindo a extrapolação do uso desses biomarcadores fora dos laboratórios de pesquisa (Nikitakis et al., 2018).

Um dos sistemas de graduação histológica da DEO mais utilizado rotineiramente é o proposto pela Organização Mundial da Saúde (OMS) (Barnes et al., 2005). Esse sistema é baseado em uma escala composta de 5 classificações, de acordo com a camada onde se encontram as atipias celulares e os distúrbios de arquitetura do epitélio, dividindo as lesões epiteliais precursoras em: (1) hiperplasia - quando há crescimento celular, mas não há displasia epitelial; (2) displasia leve - quando as alterações estão presentes no apenas no terço inferior do epitélio, nas camadas basal e parabasal; (3) displasia moderada – quando as alterações se encontram nos terços inferior e médio do epitélio, da camada basal até a camada espinhosa; (4) displasia severa – quando as alterações atingem mais de dois terços do epitélio; (5) carcinoma *in situ* – quando as alterações se encontram em todo o epitélio, porém ainda não há invasão para os tecidos adjacentes (Muller, 2018).

Embora o sistema de classificação da OMS seja considerado o "padrão ouro" na predição do potencial de transformação maligna de uma LOPM, ele apresenta grande subjetividade e leva a uma alta variabilidade inter e intra observadores, o que poderia influenciar na predição do risco de transformação maligna de uma LOPM e, consequentemente, o seu tratamento (Abbey et al., 1995). Na tentativa de diminuir essa variabilidade, Kujan et al. (2006) propuseram um sistema de graduação histológica simplificada baseado nos mesmos critérios morfológicos de classificação utilizados pela OMS, o sistema Binário (SB). Esse sistema classifica as lesões em uma de duas categorias: baixo risco ou alto risco para transformação maligna. Nesse sistema, as lesões classificadas como de baixo risco são as que apresentam menos que 5 tipos de atipias celulares e menos que 4 tipos de distúrbios de arquitetura do epitélio. Já as lesões classificadas como de alto risco apresentam 5 tipos de atipias celulares e 4 tipos de distúrbios de arquitetura do epitélio (Kujan et al., 2006).

Apesar de existir alguma evidência de que o sistema Binário promova menor variabilidade inter-observador (Krishnan et al., 2016; Kujan et al., 2006; Nankivell et al., 2013), há falta de evidência de que a capacidade de prognóstico é melhor do que o sistema da OMS, o que demanda validação antes de ser empregado rotineiramente nos casos de DEO (Takata T, Slootweg P, 2017).

Uma recente revisão sistemática mostrou que o sistema Binário parece ser efetivo na determinação do potencial maligno de LOPM, com maior concordância entre observadores (Yan F, et al., 2020). No entanto, essa revisão não comparou a capacidade de predição do potencial de transformação maligna entre os sistemas de graduação da OMS e o Binário. Portanto, não há evidências de que o sistema Binário de graduação seja mais efetivo do que o sistema da OMS na predição do potencial maligno da DEO.

Essa revisão sistemática foi desenvolvida com o objetivo de examinar a evidência existente sobre a capacidade de predição da transformação maligna do sistema Binário de graduação e compará-lo ao sistema da OMS.

## 2. METODOLOGIA

Esta revisão sistemática foi elaborada de acordo com o critério *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA 2020) (Page et al., 2020). Foi preparado um protocolo baseado no documento de 2015 *Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols* (PRISMA-P) (Shamseer et al., 2015) e registrado na plataforma PROSPERO (*International Prospective Register of Systematic Reviews*) sob o número CRD42020207283.

Pergunta de pesquisa – essa revisão sistemática foi elaborada para responder a seguinte pergunta: O sistema Binário de graduação histológica é mais efetivo do que o sistema da OMS na predição de transformação maligna da DEO?

Foram selecionados estudos usando a estratégia representada pelo acrônimo em inglês PICOS (*Population, Intervention, Comparison, Outcome, Study*). (1) População: biópsias de pacientes com displasia epitelial oral; (2)

Intervenção/exposição: sistema Binário de graduação histológica; (3) Comparação: sistema de graduação histológica da OMS; (4) Desfecho: predição de transformação maligna; (5) Estudos incluídos: estudos observacionais.

### 2.2 Critérios de Elegibilidade:

*Critérios de Inclusão:* Foram selecionados apenas os artigos que compararam o sistema de graduação histológica Binário e da OMS (padrão de referência) na predição de transformação maligna da displasia oral epitelial. Nenhuma restrição de idioma ou tempo foram aplicadas nessa revisão.

*Critérios de Exclusão:* Os critérios de exclusão foram estudos baseados em animais, *in vitro*, modelos *ex vivo*, revisões, cartas, opiniões pessoais, capítulos de livro, resumos de conferências, relato de caso e série de casos; estudos que não usaram o sistema Binário de graduação histológica; que não comparou com o sistema de graduação histológica da OMS; não avaliou a predição de transformação maligna da DEO; estudos que avaliaram a predição de transformação maligna de outras lesões e não da DEO; estudos que não relataram o desfecho para o paciente; ou em que o número de casos transformados nas duas classificações não estava disponível; ou estudos em que os dados reportados não puderam ser usados para analisar a correlação entre a graduação histológica e a transformação maligna; e estudos em que a variação inter e intra-observadores não estava presente (valor do kappa).

### 2.3 Estratégia de buscas nas bases de dados

Foram implementadas estratégias detalhadas de buscas individuais para cada um dos seguintes bancos de dados eletrônicos: PubMed, EMBASE, LILACS, *Web of Science*, Scopus e Livivo. As plataformas *Google Scholar*, *Open Grey* and Proquest foram usadas para a busca da literatura cinzenta. Todas as buscas foram realizadas até o dia 3 de setembro de 2020. Uma busca manual dos artigos selecionados também foi realizada. Estratégias de busca para cada banco de dados foram implementadas usando palavras específicas combinadas e truncadas, com o suporte de uma bibliotecária especializada em ciências da saúde (Apendice 1).

A sequência de buscas abaixo resume a pesquisa inicial feita no PubMed: (“carcinoma in situ"[MeSH Terms] OR "carcinoma in situ" OR "Preinvasive Carcinoma" OR "Intraepithelial Carcinoma" OR "epithelial dysplasia" OR "intraepithelial carcinoma" OR "intraepithelial neoplasm" OR "intraepithelial neoplasms" OR "cytological changes" OR "architectural changes" OR "cellular atypia" OR "dysplastic changes") AND ("binary grading system" OR "scoring system" OR "histopathological grading" OR "histological diagnosis" OR "histologic grading" OR "WHO grading system" OR "World Health Organization grading system" OR "WHO classification") AND ("prognosis"[MeSH Terms] OR "prognosis" OR "prognostic factors" OR "prognostic factor" OR prognoses OR "assessment of risk" OR "malignant transformation" OR "Mouth Neoplasms"[Mesh] OR "Mouth Neoplasms" OR "mouth neoplasm" OR "oral neoplasm" OR "oral neoplasms" OR "cancer of mouth" OR "mouth cancers" OR "oral cancer" OR "oral cancers" OR "cancer of the mouth" OR "mouth cancer" OR "oral squamous cell carcinoma"). Todas as referências foram gerenciadas por um software de gerenciamento de referências (EndNote Web; Thomson Reuters, Toronto, Canada) e as referências duplicadas foram descartadas utilizando o aplicativo Rayyan-a (Qatar Computing Research Institute, Doha, Qatar) (Ouzzani et al., 2016).

### 2.4 Seleção dos estudos e processo de coleta de dados

A seleção dos estudos foi realizada em duas fases. Na fase 1, dois revisores independentes (BSFS e FPYS), com experiência em patologia oral, utilizaram os critérios de seleção e revisaram os títulos e resumos de todas as referências identificadas. Um terceiro revisor (MAGS), com experiência em medicina oral, foi envolvido quando era necessário obter uma decisão final. Qualquer artigo que não cumpriu o critério de inclusão foi excluído. Na fase 2, os artigos selecionados foram revisados independentemente pelos mesmos revisores (BSFS e FPYS). As listas de referências dos estudos selecionados foram cuidadosamente examinadas por ambos revisores. Todos os desacordos nas suas decisões foram resolvidos em consenso. Quando não foi obtido um consenso, um terceiro revisor (MAGS) foi envolvido para tomar a decisão final.

A seleção final foi sempre baseada no texto completo do artigo publicado. A metodologia de busca completa está demonstrada no fluxograma (Figura 1).

Os dados de todos os artigos incluídos foram registrados na Tabela 1. As seguintes informações foram extraídas: características do estudo (primeiro autor, ano, país), características da amostra (tamanho, padrões e idade), características do observador (número, tipo, calibração, se houve ou não mascaramento), resultados (acompanhamento, dados de transformação maligna, intervalo de confiança (IC) de 95%, *valor de P*, *odds ratio*, kappa) e conclusões. O primeiro revisor coletou a informação necessária dos artigos selecionados. O segundo revisor, conferiu todas as informações obtidas. Novamente, os desacordos foram resolvidos com a discussão e, quando necessário, o terceiro revisor foi solicitado para a decisão final. Quando os dados não estavam completos ou quando os dados presentes não puderam ser calculados, foram realizadas tentativas de contato com os autores para obter as informações omitidas.

### 2.5 Risco de viés nos estudos individualmente

O *checklist* do Instituto *Joanna Briggs* para estudos de prevalência (Munn et al., 2014) foi utilizado para avaliar a qualidade metodológica dos artigos incluídos. Uma adaptação dos 10 critérios usados para avaliar a qualidade metodológica dos estudos de prevalência foi feita obedecendo 9 critérios objetivos. O risco de viés foi classificado em alto quando o estudo apresentava até 49% de marcações “sim”, moderado quando o estudo apresentava de 50 a 69% de marcações “sim”, e baixo quando o estudo apresentava mais de 70% de marcações “sim”. Dois revisores (BSFS e FPYS) avaliaram independentemente a qualidade de cada estudo incluído. O terceiro revisor, quando necessário, resolveu os desacordos entre os revisores.

### 2.6 Medidas sumarizadas

O número de casos transformados de DEO previstos com o sistema Binário e com o sistema da OMS foram considerados como o principal desfecho.

### 2.7 Síntese dos resultados

A metanálise da taxa de transformação maligna em displasia severa/carcinoma *in sit*u (sistema OMS) e de casos classificados como de alto risco (sistema Binário) foi realizada, usando o software MetaXL (Version 5.3, EpiGear *International Pty Ltd, Sunrise Beach, Queensland*, Australia) como complemento do software *Microsoft Excel*. A prevalência combinada de transformação maligna foi expressa por meio de frequências absolutas e relativas e 95% de intervalo de confiança (IC). A heterogeneidade estatística foi calculada por meio de um índice de inconsistência ($I^2$), o qual definiu se um modelo fixo ($I^2 < 50\%$) ou aleatório ($I^2 \geq 50\%$) seria usado.

### 2.8 Confiança em evidência acumulada

Um resumo da certeza das evidências disponíveis foi apresentado utilizando o guia GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) na tabela sumário de achados (*Summary of Findings*) por meio do *software* GRADEpro (Manheimer, 2012).

## 3. CAPÍTULO 1

**Binary and WHO grading systems for the prediction of malignant transformation of oral epithelial dysplasia: A systematic review and meta-analysis**

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**Abstract**

**Objective:** Aim of this systematic review was to examine the evidence of the binary histologic grading system capacity for predicting malignant transformation and to compare it with that of the WHO system.

**Methods:** A systematic review was conducted, using PubMed, EMBASE, LILACS, Web of Science, Scopus, and Livivo databases without any language or timeframe restrictions. Studies were included if they compared the binary and the WHO (reference standard) histologic grading systems in the prediction of malignant transformation of oral epithelial dysplasia. Four articles met the eligibility criteria and were included in qualitative synthesis. Three studies were included in quantitative analysis.

**Results:** The capacity of the WHO and binary grading systems to predict malignant transformation ranged from 16–80% and 5–80%, respectively. The pooled malignant transformation rate of lesions classified as severe dysplasia or carcinoma in situ by the WHO grading was 40% (95% confidence interval [CI], 0.02-0.87, $I^2$=92%, p=0.00), while the corresponding value for lesions classified as high-risk by the binary grading system was 31% (95% CI, 0.00–0.84, $I^2$=97%, p=0.00). Overall, there was no significant difference in prognostication accuracy between the WHO and the binary systems (odds ratio = 2.02, 95% CI, 0.88–4.64). Confidence in cumulative evidence was moderate based on the GRADE criteria.

**Conclusion:** Although some studies suggest that the binary system is associated with lower inter-rater variability when grading OED, the evidence remains inconclusive on whether this system is superior to that of the WHO at predicting malignant transformation.

**Keywords**: oral cancer; epithelial dysplasia; precancerous lesions; malignant transformation; potentially malignant; prediction; epithelial dysplasia.

## Introduction[1]

Squamous cell carcinoma is among the most common oral malignant tumors worldwide, with over 300,000 new cases reported annually [1]. This type of carcinoma represents 90% of all oral cancer cases [2], with 5-year survival rates ranging between 45% and 50% [3]; most cases are preceded by oral potentially malignant disorders (OPMD) [4], particularly oral leukoplakia and erythroplakia, both of which can microscopically present epithelial dysplasia [5].

Epithelial dysplasia is related to abnormal epithelial proliferation that results in disturbed tissue differentiation and maturation processes; its histologic grading is based on individual cellular features and architectural changes [6,7]. Microscopic presence of epithelial dysplasia may indicate long-term risk of malignant transformation [8]. Histologic grading of these cellular and architectural abnormalities helps evaluate this risk [9]. While several potential molecular biomarkers may help assess the malignant potential of OPMD, histological grading of oral epithelial dysplasia (OED) remains the mainstay of risk evaluation. This practice is partly due to the fact that the wide range of molecular aberrations found in OPMD makes challenging the selection of markers associated with the risk of malignant transformation, restricting their use outside of a research laboratory [10,11].

The World Health Organization (WHO) grading system is currently among the most commonly used systems for OED grading [12]. This system is based on a 5-item classification, dividing the epithelial precursor lesions into hyperplasia; mild, moderate, and severe dysplasia; and carcinoma in situ. Although this classification is regarded as the “reference standard” in the prediction of malignant transformation of OPMD, it is also associated with significant subjectivity and high inter- and intra-observer variability. This uncertainty may influence the accuracy of malignant transformation prediction and, consequently, the management of OPMD [13]. To reduce this variability, Kujan et al. (2006) [14] proposed a simplified histologic grading system based on the same

[1] OPMD, oral potentially malignant disorders; OED, oral epithelial dysplasia; WHO, World Health Organization; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation

morphological criteria as those used by the WHO classification. This system, known as a binary system, involves grading lesions as either at low- or high-risk of malignant transformation [15]. Some evidence suggests that the binary system improves observer variability [9,14,15]; however, the evidence regarding its prognostic ability relative to that of the WHO system remains unclear, demanding validation before entering routine practice [8].

A recent systematic review has shown that the binary system may effectively determine the malignant potential of OPMD, with improved inter-observer agreement [16]. However, this review did not compare the predictive ability of the binary and the WHO grading systems, leaving unresolved the question whether the former is more effective than the latter at predicting the outcome of interest. Consequently, this systematic review was performed to address the following question: Is binary histologic grading system more effective than the WHO grading system at predicting malignant transformation of OED? We selected observational studies that involved patients with OED that underwent a biopsy, assessed using the binary and the WHO grading systems for the prediction of malignant transformation.

## Materials and Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist [17] [27], and registered at the International Prospective Register of Systematic Reviews (registration number CRD42020207283).

### *Eligibility criteria*

Studies were eligible for inclusion in the present review if they compared the binary and WHO (reference standard) histologic grading systems on the prediction of malignant transformation of OED. No language or time restrictions were applied in this review.

Studies were excluded from the present review if they were based on animal, in vitro, or ex vivo models; reviews, letters, personal opinions, book chapters, conference abstracts, case reports and case series; did not use the

binary histologic grading system; did not compare the binary with the WHO histologic grading systems; did not evaluate the prediction of malignant transformation of OED; evaluated the prediction of malignant transformation of diagnoses other than OED; did not report patient outcomes; did not report the number of transformed cases per classification system; reported data in a format that precluded the analysis of a correlation between the grading systems of interest; or did not report the intra- and inter-observer variability estimates (kappa value).

*Information sources*

Detailed searches of the following electronic bibliographic databases were performed: PubMed, EMBASE, LILACS, Web of Science, Scopus and Livivo. Additional grey literature search was performed using Google Scholar, Open Grey, and Proquest.

*Search Strategy*

All searches were conducted up to September 3, 2020. A hand search of the references of the selected articles was also performed. The search strategy for each database involved specific word combinations and truncations and was performed with the support of a health sciences librarian (Appendix 1). All references were managed by reference management software (EndNote Web; Thomson Reuters, Toronto, Canada) and duplicates were discarded using Rayyan software (Qatar Computing Research Institute, Doha, Qatar) [18].

*Study selection and data collection process*

Study selection was conducted in two phases. In phase one, two independent reviewers (BSFS and FPYS) with expertise in oral pathology used the selection criteria to review the titles and abstracts of all identified references. A third author (MAGS) with expertise in oral medicine was involved in making the final decision. Any articles that did not meet the inclusion criteria were excluded at this stage. In phase two, the full text of each selected article was independently reviewed by the same two reviewers (BSFS and FPYS). The reference list of the

selected studies was carefully assessed by both reviewers. Any disagreements were resolved by discussion. When consensus was not reached, a third author (MAGS) made the final decision, which was always based on the review of the full text of a publication. Details of the search methodology are presented in Figure 1.

Studies' characteristics are presented in Table 1. The following information was extracted: study particulars (first author name, year, country), sample characteristics (sample size, setting, participant age), observer characteristics (number, type, instrument calibration, blinding), findings (follow-up, malignant transformation data, 95% confidence interval [CI], P-value, odds ratio, kappa values), and conclusions. The first reviewer extracted the required information from the selected articles. The second reviewer crosschecked all data. Any discrepancies in the extracted data were resolved by discussion and consensus. If consensus was not reached, the third reviewer made the final decision. When data were not complete and could not be derived from the reported values, efforts were made to contact the authors and obtain the required information.

*Risk of bias assessment*

Joanna Briggs Institute Critical Appraisal Checklist for studies reporting prevalence data [19] was used to evaluate the methodologic quality of the included studies (Appendix 2). An adaptation of the 10 criteria used to assess the methodological quality of studies reporting prevalence data was made, yielding 9 objective criteria. Risk of bias was categorized as high, moderate, and low when the study achieved a "yes" score of $\leq$ 49%, 50-69%, and $\geq$ 70%, respectively. Two reviewers (BSFS and FPYS) independently assessed the quality of each included study. The third reviewer resolved any disagreements, as required.

*Effect measures*

The number of transformed OED cases predicted with the binary and WHO systems was considered the main outcome.

*Synthesis methods*

The meta-analyses of malignant transformation rates of severe dysplasia/carcinoma in situ (WHO system) and high-risk lesions (binary system) were conducted using MetaXL (Version 5.3, EpiGear International Pty Ltd, Sunrise Beach, Queensland, Australia) add-on Microsoft Excel software. The pooled prevalence of malignant transformation was expressed as relative or absolute frequencies and 95% CI. Statistical heterogeneity was calculated using an inconsistency index ($I^2$), which determined whether a fixed ($I^2 < 50\%$) or random ($I^2 \geq 50\%$) effects model was used.

*Level of evidence*

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) instrument [20] was used to assess evidence quality; grading of recommendation strength applied to all studies included in the quantitative and qualitative synthesis. This assessment was based on study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias estimates. Evidence quality was reported as high, moderate, low, or very low [20]. The certainty of evidence was rated for OED agreement and malignant transformation. GRADE was used per guidelines available online (http://gradepro.org).

## Results

A total of 4,554 articles were identified from 6 main electronic databases. After excluding ineligible studies and removing duplicates, a total of 3,653 studies remained. Studies from the grey literature were not selected for further assessment because they either did not fulfill the inclusion criteria or had already been identified in other databases. In phase 1, 13 studies were selected for full text reading; the search of their reference lists yielded 1 additional study to be included. In phase two, four articles met the eligibility criteria and were included in qualitative synthesis. Three studies were included in quantitative analysis. The study from Nankivell et al. [9] was excluded because it did not report the number of transformed and non-transformed OED cases independently assessed by the WHO and the binary systems.

*Study characteristics and results of individual studies*

Of four articles selected for qualitative synthesis, two reported on cross-sectional studies [14,21] and two on cohort studies [9,21]. The studies were conducted in the United Kingdom [9,14,22] and Sri Lanka [21]. Sample sizes ranged from 68 to 141, with a total of 402 OED specimens. Patients' age at the time of biopsy ranged from 24 to 94 years, with the mean age in the range of 58 to 62 years. The male/female ratio was 2:1. The studies evaluated the presence of OED in leukoplakia, erythroleukoplakia, and/or erythroplakia specimens obtained for histological analysis by excisional or incisional biopsies. These studies are summarized in Table 1.

OED was assessed by the WHO and binary grading systems in all studies. The accuracy of the WHO grading system at predicting malignant transformation ranged from 16% [22] to 80% [14]. The corresponding values for the binary system ranged from 5% to 80%. Inter-observer agreement was assessed in three studies [9,14,22], presenting low to good agreements for both systems. For the binary system, kappa values were K= 0.756 [22], unweighted (Ks)= 0.5 [14], and K= 0.59 [9]. The unweighted (Ks) and weighted (Kw) kappa values for the WHO grading system were Ks= 0.644 [22]; Ks = 0.22, Kw = 0.63 [14]; and Ks = 0.31, Kw = 0.49 [9].

*Risk of bias in studies*

Overall, the methodology of the studies presented low to moderate risk of bias (Figure 2). The risk of bias assessment is described in detail in Appendix 2.

*Synthesis of results*

Meta-analysis of three selected studies was performed [14,21,22]. The pooled malignant transformation rate of lesions classified as severe dysplasia or carcinoma in situ by the WHO grading was 40% (95% CI, 0.02–0.87, $I^2$=92%, p=0.00) (Figure 3A), while the corresponding value for the lesions classified as high-risk by the binary grading system was 31% (95% CI, 0.00–0.84, $I^2$=97%, p=0.00) (Figure 3B). The overall odds ratio of transformation showed no significant difference between the grading systems (OR = 2.02, 95% CI, 0.88–

4.64) (Figure 4). Among-study heterogeneity was high ($I^2$= 97%) in prevalence meta-analysis and low ($I^2$ = 0) in the odds ratio meta-analysis. Consequently, random and fixed models were applied, respectively.

*Overall risk of bias*

All studies presented limitations associated with sample size estimation and confounding control, with the latter considered inherent to observational studies. The selected articles presented the mean of 22–60 months of case follow-up, which ranged from 6 to 120 months. This lack of standardization of the follow-up period could bias the pooled evaluation of OED outcomes, as the follow-up duration might have been insufficient to observe a malignant transformation.

*Level of evidence*

According to the GRADE criteria, confidence in the cumulative evidence for the comparison of both systems was moderate (Appendix 3). Inconsistency and imprecisions were judged as not serious. For OED agreement the system showed a very low certainty of evidence. Heterogeneity of the studies' methodology and design (observational studies) was mainly responsible for the limited level of evidence and the limited suitability for a meta-analysis.

## Discussion

Overall, the present systematic review findings suggest that the binary and WHO grading systems have a similar ability to predict malignant transformation of OED. We observed that the worst grades of OED in both grading systems corresponded to a malignant transformation rate in the range of 31–40%. These findings suggest that these grading systems have a similar capacity to predict malignant transformation, considering that the presence of OED does not guarantee that malignancy will occur [23]. The main weakness of both systems remains the lack of objective histopathological analysis or inter-observer agreement [9,24,25].

The binary grading system was designed to simplify the WHO system and improve the associated observer variability and prognostic ability [14]; there is some data that suggests a higher inter-observer agreement of the former than that of the latter systems [9,21]. Kujan et al. [14] suggested that the binary system could improve the prognostication in cases classified as moderate in the WHO system. However, this premise is not a consensus in the literature, as the binary system is not always able to differentiate between the cases graded as moderate in the WHO classification [9].

Predictive ability is the essence of any diagnostic test, in particular, assessing the risk of malignant transformation. Decisions regarding diagnostic tests should account for their purpose, diagnostic accuracy in practice, and ease of use, including any need to train users [26]. Consequently, obtaining extensive data about the diagnostic accuracy of both grading systems is crucial, in particular, since the level of training of the examining pathologist may influence the outcome of the examination. This systematic review has shown that studies reporting on the accuracy of the binary and WHO grading systems are rare, while rarer are the studies that compare the performance of these systems, precluding sensitivity and specificity analyses. At the time of writing, there are no published studies investigating the impact of regular calibration of pathologists on the assessment of OED grading. Finally, studies on how this may influence the inter- and intra-observer variability or improve the accuracy of the available grading systems in predicting malignant transformation are also lacking.

One of the main limitations of the WHO classification is its assessment of moderate dysplasia, which is associated with poor inter-observer agreement among pathologists [14]. Another limitation of the moderate dysplasia category is the lack of clear guidelines on its management, including whether or not such a lesion should be removed [6]. To reduce the bias associated with the 5-item system, in 2017, the WHO proposed a three-tiered scale (differentiating mild, moderate, and severe dysplasia), which puts severe dysplasia and carcinoma in situ in the same category [8]. However, this did not seem to benefit moderate dysplasia management.

Simplicity is among the advantages of the binary system. In addition, its reproducibility may assist clinicians in decision-making [14]. However, it is not a commonly used method among pathologists, many of whom have been trained in the WHO classification. The pathologist's familiarity with the WHO system may influence the accuracy of this method, which should be considered before recommending an alternative grading system.

*Limitations*

Only four studies included in the present systematic review directly compared the WHO system with the binary system on the prediction of malignant transformation of OED; two of these studies were retrospective and none presented sample size calculations, while only one seemed to have adequately controlled for the impact of confounding factors. Considering only the evidence from the observational studies, the GRADE criteria suggest the cumulative evidence may be approached with moderate confidence. Although showing a very low evidence, the overall inter-observer agreement estimates were better for the binary than for the WHO system.

*Future research*

The present study highlights the potential role of the binary system in improving OED grading. However, this potential remains to be verified in studies involving high quality evidence. Future research should include comparative prospective studies with sample sizes derived from suitable calculations, and accounting for calibration among pathologists, follow-up information, major confounding factors (e.g., by excluding OED cases positive for fungi of Candida species, histologic epithelial changes related to inflammation, and cases of proliferative verrucous leukoplakia), and diagnostic accuracy (sensitivity and specificity) assessments.

## Conclusion

Both grading systems have a similar capacity to predict malignant transformation. There is no evidence to suggest that the binary system is superior

to the WHO system at predicting malignant transformation; available evidence is considered of moderate certainty. However, the binary system presents better inter-observer agreement than does the WHO system when grading OED.

## Registration and Protocol

A systematic review protocol based on the 2015 Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement was prepared [27] and registered at the International Prospective Register of Systematic Reviews (PROSPERO), under the number CRD42020207283.

## Acknowledgements

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## Conflict of interest

The authors deny any conflicts of interest related to this study.

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## Figure captions

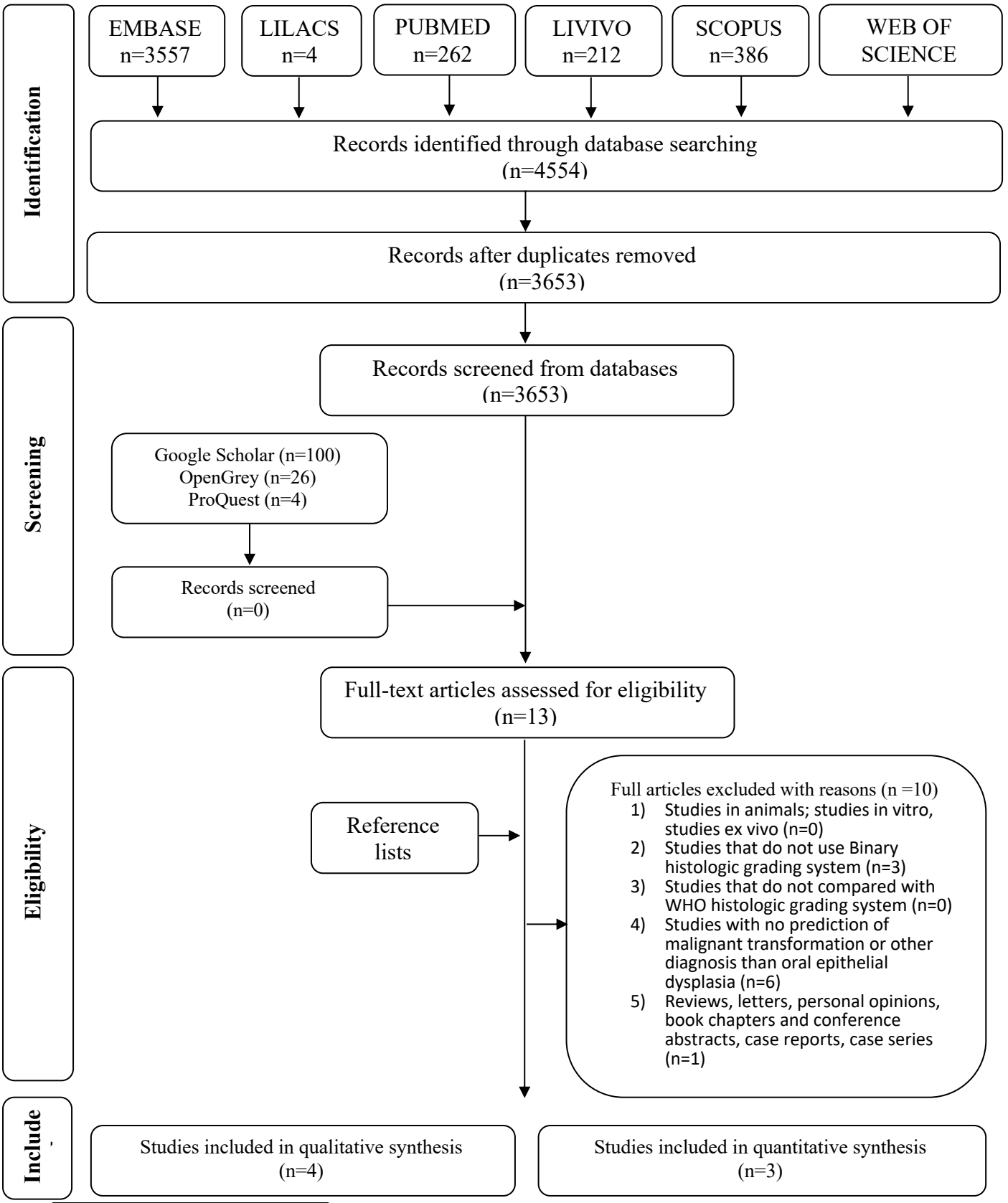
**Figure 1 -** Flowchart of literature search and selection criteria.[2]

**Figure 2 -** Results from Joanna Briggs Institute Critical Appraisal Checklist for studies reporting prevalence data (Munn et al. Int J Health Policy Manag. 3(3), 123–128, 2014).

**Figure 3 - (**A) Forest plot of malignant transformation of severe dysplasia/carcinoma in situ (WHO grading). (B) Forest plot of malignant transformation of high-risk lesions (binary grading).

**Figure 4 -** Forest plot of malignant transformation of severe dysplasia/carcinoma in situ (WHO grading) and of high-risk lesions (binary grading).

**Figure 1 -** Flowchart of literature search and selection criteria.[3]




[3] Adapted from PRISMA.

**Table 1.** Summary of descriptive characteristics of included articles (n= 4 cohorts).

| Author, Year, Country | Sample size (M/F) | Sample Settings | Age (y) Mean (range) | Data collection (Observers) | | | | | Main results | | | | Conclusions |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Number | Specialty | Calibration | Blinding | Follow-up (months) | Malignant transformation BS | Malignant transformation WHO | OED agreement (Kappa) | Clinical features | |
| Diajil et al., 2013 UK | 100 (68/32) | Excisional biopsy ($CO_2$ laser excision) | 68 male patients: 58 (30–81)<br><br>32 female patients 59 (33–94) | 2 | Oral Pathologist | Standardised histopathology examination | Independent assessment | Mean: 60 Range 24 – 120 | Low = 2<br>High = 3<br><br>Low= Reference category<br><br>High= OR 2.828 (1.182–6.678) P = 0.020<br><br>Chi-square | Severe/CIS = 5<br><br>Mild= Reference category<br><br>Moderate= OR 1.129 (0.350–3.641) P =0.839<br><br>Severe= OR 4.622 (1.527–13.990) P = 0.007<br><br>CIS= OR 4.800 (1.123–20.479) P = 0.034<br><br>Chi-square | BS= 0.756 $P < 0.001$<br><br>WHO= 0.644 $P < 0.001$ | Non-homogenous leukoplakia as a significant predictor of active disease (P=0.023)<br><br>Tongue lesions showed a 3.4 increased risk compared floor of mouth (P=0.013)<br><br>Major sized lesions displayed a 4.5 times increased risk compared to minor sized ones (P=0.045) | Severe dysplasia and carcinoma-in-situ showed a 4.6 and a 4.8 times increased risk, respectively.<br><br>High-grade dysplasia was also a significant predictor for disease active state, increasing the risk to approximately 3 times |
| Jayasooriya et al., 2020 Sri Lanka | 93 (73/20) | Incisional and excisional biopsy | N/A | 1 | Oral Pathologist | No | N/A | Mean: 30 Range: 10–72 | Low= 1<br>High=6<br><br>P= 0.07 Chi-square | No=0<br>Mild= 1<br>Moderate=1<br>Severe= 5<br>CIS= N/A<br><br>P= 0.02 Chi-square | BS= N/A<br>WHO= N/A | Eritroleukoplakia showed more increase risk compared with leukoplakia P=0.012<br><br>Site: buccal mucosa, tongue or Floor of mouth and other – no difference P=0.46<br><br>Chi-square test<br><br>Size: N/A | WHO 2005 dysplasia grading system predicted malignant transformation. Based on the data, validation of the two dysplasia grading systems using a larger sample is recommended for future studies. |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kujan et al., 2006 UK | 68 | Incisional and excisional biopsy | N/A | 4 | Oral Pathologist/General Pathologist | No | Yes | Mean: 22<br>Range 6 - 97 | Low=5 cases<br>High=28 cases<br><br>P<0.001 | No=1 case<br>Mild=2 cases<br>Moderate=14 cases<br>Severe=11 cases<br>CIS=5 cases | BS= 0.50 (95% CI: 0.35–0.67)<br><br>WHO= Weighted kappa = 0.63 (95% CI: 0.42–0.78)<br><br>Unweighted kappa = 0.22 (95% CI: 0.11–0.35) | | The new binary grading system proved to be a very good predictor for the malignant changes in oral epithelial dysplasia. |
| Nankivell et al., 2013 UK | 141 (71/54) | N/A | 62 (24-92) | 3 | Oral Pathologist/General Pathologist | N/A | Yes | Mean: 46<br>Range: 7-9 | Low=N/A<br>High=N/A<br><br>Overall=<br><br>OR 4.59, 95% CI 1.36-15.38<br><br>P = 0.014 | No=N/A<br>Mild=N/A<br>Moderate=N/A<br>Severe= N/A<br>CIS=N/A<br><br>Overall OR = 2.25 (95% CI 1.14-4.45)<br><br>P=0.02 | BS= 0.59<br><br>WHO= Weighted kappa = 0.49<br><br>P<0.001<br><br>Unweighted kappa = 0.31<br><br>P= 0.002<br><br>McNemar test | Size: N/A<br><br>Site: no difference<br><br>Smoking and alcohol P=0.012 OR 5.10 | There is less interrater variability when grading OED with the binary system compared with the WHO classification, but they do not support previously reported findings that the binary system improves prognostication compared to the WHO system. |

Abbreviations: BS: binary system; N/A: Not Applicable; OED: Oral epithelial dysplasia; WHO: World Health Organization

**Figure 2 –** Results from Joanna Briggs Institute Critical Appraisal Checklist for studies reporting prevalence data.

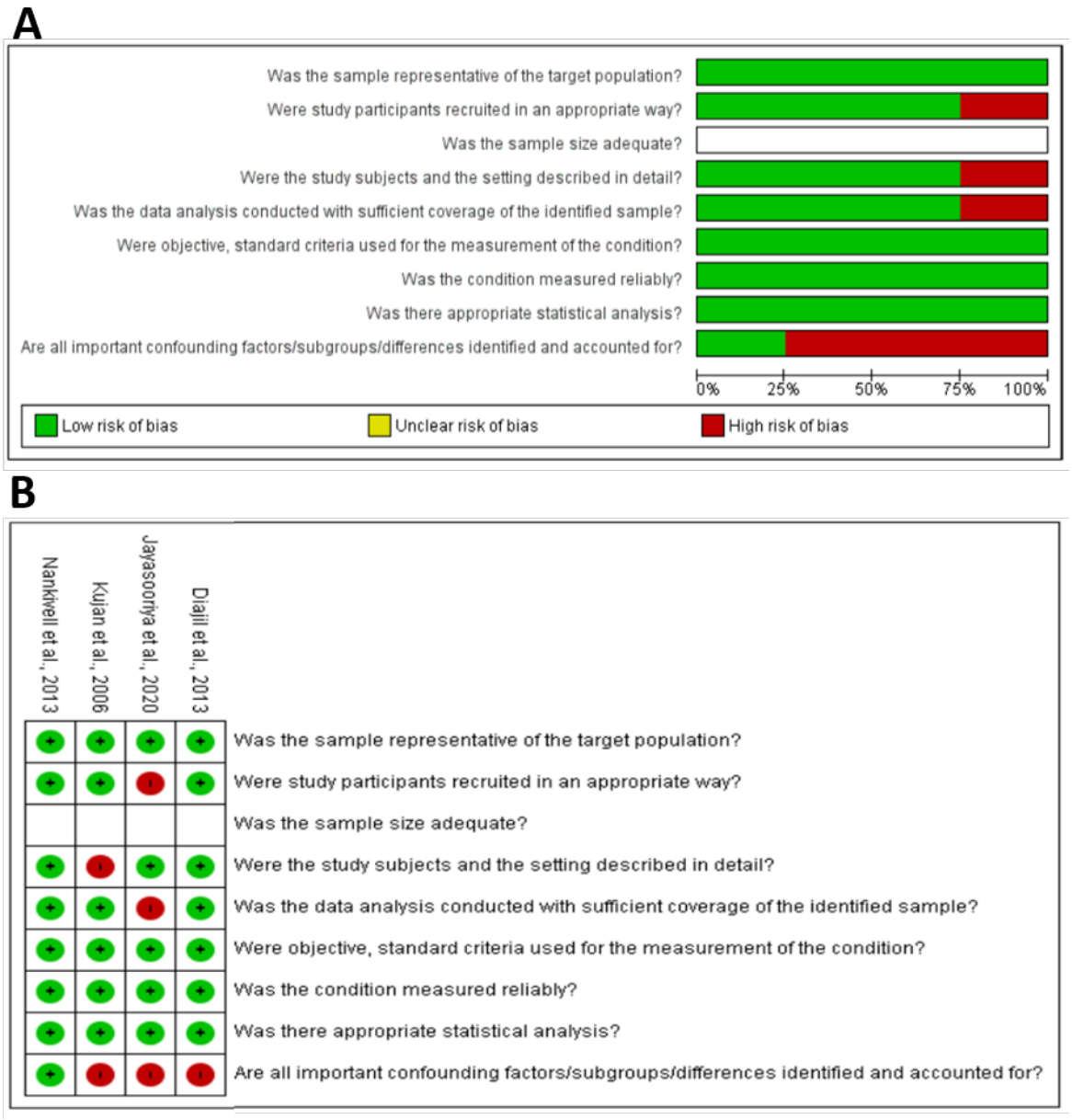
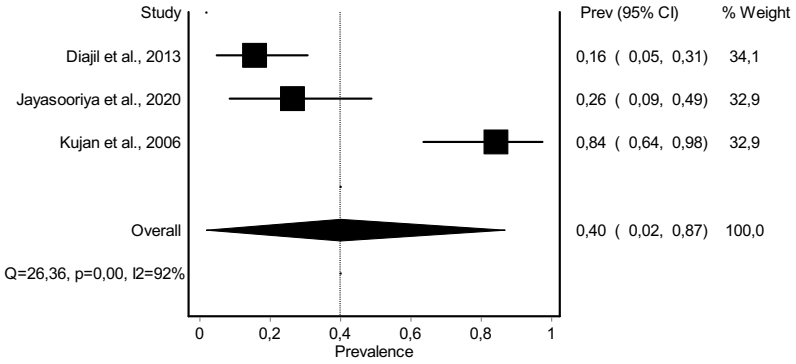


**Figure 3 - (**A) Forest plot of malignant transformation of severe dysplasia/carcinoma in situ (WHO grading). (B) Forest plot of malignant transformation of high-risk lesions (binary grading).

A




B

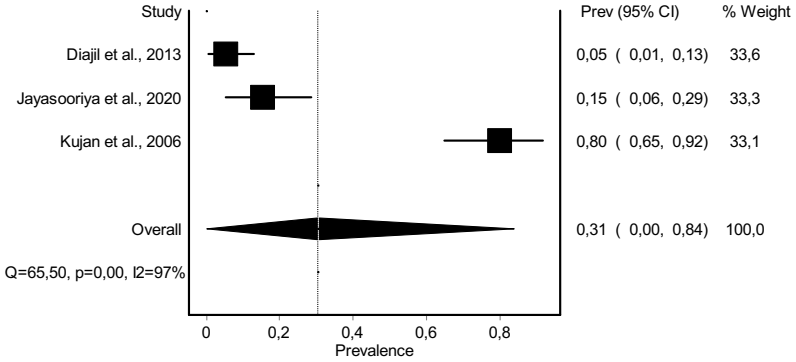
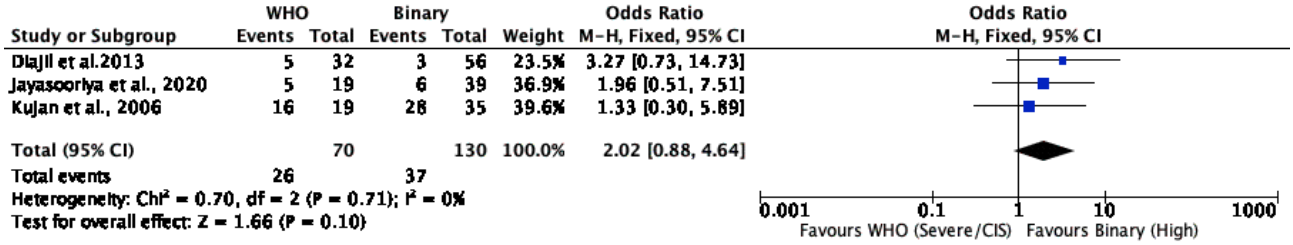


**Figure 4 -** Forest plot of malignant transformation of severe dysplasia/carcinoma in situ (WHO grading) and of high-risk lesions (binary grading).



**Appendix 1** - Databases and search strategies.

| Database | Search strategy | Results Sep 3rd 2020 |
|---|---|---|
| **PubMed** | ("carcinoma in situ"[MeSH Terms] OR "carcinoma in situ" OR "Preinvasive Carcinoma" OR "Intraepithelial Carcinoma" OR "epithelial dysplasia" OR "intraepithelial carcinoma" OR "intraepithelial neoplasm" OR "intraepithelial neoplasms" OR "cytological changes" OR "architectural changes" OR "cellular atypia" OR "dysplastic changes") AND ("binary grading system" OR "scoring system" OR "histopathological grading" OR "histological diagnosis" OR "histologic grading" OR "WHO grading system" OR "World Health Organization grading system" OR "WHO classification") AND ("prognosis"[MeSH Terms] OR "prognosis" OR "prognostic factors" OR "prognostic factor" OR prognoses OR "assessment of risk" OR "malignant transformation" OR "Mouth Neoplasms"[Mesh] OR "Mouth Neoplasms" OR "mouth neoplasm" OR "oral neoplasm" OR "oral neoplasms" OR "cancer of mouth" OR "mouth cancers" OR "oral cancer" OR "oral cancers" OR "cancer of the mouth" OR "mouth cancer" OR "oral squamous cell carcinoma") | 262 |
| **Embase** | ('carcinoma in situ'/exp OR 'carcinoma in situ' OR 'preinvasive carcinoma'/exp OR 'preinvasive carcinoma' OR 'epithelial dysplasia'/exp OR 'epithelial dysplasia' OR 'intraepithelial carcinoma'/exp OR 'intraepithelial carcinoma' OR 'intraepithelial neoplasm' OR 'intraepithelial neoplasms' OR 'cytological changes' OR 'architectural changes' OR 'cellular atypia' OR 'dysplastic changes') AND ('binary grading system' OR 'scoring system'/exp OR 'scoring system' OR 'histopathological grading' OR 'histological diagnosis'/exp OR 'histological diagnosis' OR 'histologic grading' OR 'who grading system' OR 'world health organization grading system' OR 'who classification' OR 'binary histologic grading system' OR 'binary system of grading' OR 'who histologic grading system' OR 'world health organization histologic grading system' OR 'degree of dysplasia') AND ('prognosis'/exp OR 'prognosis' OR 'prognostic factors' OR 'prognostic factor'/exp OR 'prognostic factor' OR prognoses OR 'assessment of risk' OR 'malignant transformation'/exp OR 'malignant transformation' OR 'mouth neoplasms'/exp OR 'mouth neoplasms' OR 'mouth neoplasm'/exp OR 'mouth neoplasm' OR 'oral neoplasm' OR 'oral neoplasms' OR 'cancer of mouth' OR 'mouth cancers' OR 'oral cancer'/exp OR 'oral cancer' OR 'oral cancers' OR 'cancer of the mouth' OR 'mouth cancer'/exp OR 'mouth cancer' OR 'oral squamous cell carcinoma'/exp OR 'oral squamous cell carcinoma') | 3,557 |
| **Scopus** | TITLE-ABS-KEY("carcinoma in situ" OR "Preinvasive Carcinoma" OR "Intraepithelial Carcinoma" OR "epithelial dysplasia" OR "intraepithelial carcinoma" OR "intraepithelial neoplasm" OR "intraepithelial neoplasms" OR "cytological changes" OR "architectural changes" OR "cellular atypia" OR "dysplastic changes") AND TITLE-ABS-KEY("binary grading system" OR "scoring system" OR "histopathological grading" OR "histological diagnosis" OR "histologic grading" OR "WHO grading system" OR "World Health Organization grading system" OR "WHO classification" OR "binary histologic grading system" OR "binary system of grading" OR "WHO histologic grading system" OR "World Health Organization histologic grading system" OR "degree of dysplasia") AND TITLE-ABS-KEY("prognosis" OR "prognostic factors" OR "prognostic factor" OR prognoses OR "assessment of risk" OR "malignant transformation" OR "Mouth Neoplasms" OR "mouth neoplasm" OR "oral neoplasm" OR "oral | 386 |

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|---|---|---|
| | neoplasms" OR "cancer of mouth" OR "mouth cancers" OR "oral cancer" OR "oral cancers" OR "cancer of the mouth" OR "mouth cancer" OR "oral squamous cell carcinoma") | |
| **Web of Science** | TS=("carcinoma in situ" OR "Preinvasive Carcinoma" OR "Intraepithelial Carcinoma" OR "epithelial dysplasia" OR "intraepithelial carcinoma" OR "intraepithelial neoplasm" OR "intraepithelial neoplasms" OR "cytological changes" OR "architectural changes" OR "cellular atypia" OR "dysplastic changes") AND TS=("binary grading system" OR "scoring system" OR "histopathological grading" OR "histological diagnosis" OR "histologic grading" OR "WHO grading system" OR "World Health Organization grading system" OR "WHO classification" OR "binary histologic grading system" OR "binary system of grading" OR "WHO histologic grading system" OR "World Health Organization histologic grading system" OR "degree of dysplasia") AND TS=("prognosis" OR "prognostic factors" OR "prognostic factor" OR prognoses OR "assessment of risk" OR "malignant transformation" OR "Mouth Neoplasms" OR "mouth neoplasm" OR "oral neoplasm" OR "oral neoplasms" OR "cancer of mouth" OR "mouth cancers" OR "oral cancer" OR "oral cancers" OR "cancer of the mouth" OR "mouth cancer" OR "oral squamous cell carcinoma") | 132 |
| **LILACS** | tw:((tw:("carcinoma in situ" OR "Preinvasive Carcinoma" OR "Intraepithelial Carcinoma" OR "epithelial dysplasia" OR "intraepithelial carcinoma" OR "intraepithelial neoplasm" OR "intraepithelial neoplasms" OR "cytological changes" OR "architectural changes" OR "cellular atypia" OR "dysplastic changes" OR "Carcinoma Intraepitelial" OR "Carcinoma Pré-Infiltrante" OR "Carcinoma Preinfiltrante" OR "Carcinoma Pré-Invasivo" OR "Carcinoma Preinvasivo" OR "Carcinoma Preinvasor" OR "Carcinoma não Infiltrante" OR "Carcinoma no Infiltrante" OR "Carcinoma não Invasivo" OR "Carcinoma no Invasivo" OR "Carcinoma no Invasor" OR "Cancer Intraepitelial" OR "Neoplasia Intraepitelial" OR "Neoplasias Intraepiteliais" OR "Neoplasias Intraepitaliales")) AND (tw:("binary grading system" OR "scoring system" OR "histopathological grading" OR "histological diagnosis" OR "histologic grading" OR "WHO grading system" OR "World Health Organization grading system" OR "WHO classification" OR "binary histologic grading system" OR "binary system of grading" OR "WHO histologic grading system" OR "World Health Organization histologic grading system" OR "degree of dysplasia" OR "gradação histológica pelo sistema binário" OR "graduação histológica das displasias epiteliais" OR "Sistema binario de grado histologico" OR "sistema de gradação da Organização Mundial da Saúde" OR "sistema del gradación histológica de la organización mundial de la salud")) AND (tw:("prognosis" OR "prognostic factors" OR "prognostic factor" OR prognoses OR "assessment of risk" OR "malignant transformation" OR prognóstico OR prognósticos OR "transformação maligna" OR pronóstico OR pronosticos OR "transformacion maligna" OR "Mouth Neoplasms" OR "mouth neoplasm" OR "oral neoplasm" OR "oral neoplasms" OR "cancer of mouth" OR "mouth cancers" OR "oral cancer" OR "oral cancers" OR "cancer of the mouth" OR "mouth cancer" OR "oral squamous cell carcinoma" OR "Neoplasias Bucais" OR "Neoplasias de la Boca" OR "Cancer Bucal" OR "Cancer Oral" OR "Cancer da Boca" OR "Cancer de boca" OR "Câncer da Cavidade Bucal" OR "Cáncer de Cavidad Bucal" OR "Câncer da Cavidade Oral" OR "Cáncer de Cavidad Oral" OR "Câncer de Boca" OR "Cáncer de la Boca" OR "Câncer de Cavidade Bucal" OR "Cáncer de la Cavidad Bucal" OR "Câncer de Cavidade Oral" OR "Cáncer de la Cavidad Oral" OR "Neoplasia Bucal" OR "Neoplasia Oral" OR "Neoplasia da Boca" OR "Neoplasia da Cavidade Bucal" OR | 04 |

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|---|---|---|
| | "Neoplasia da Cavidade Oral" OR "Neoplasia de Boca" OR "Neoplasia de Cavidade Bucal" OR "Neoplasia de Cavidade Oral" OR "Neoplasias Orais" OR "Neoplasias da Boca" OR "Neoplasias da Cavidade Bucal" OR "Neoplasias da Cavidade Oral" OR "Neoplasias de Boca" OR "Neoplasias de Cavidade Bucal" OR "Neoplasias de Cavidade Oral" OR "Tumor da Boca" OR "Tumor da Cavidade Bucal" OR "Tumor da Cavidade Oral" OR "Tumor de Boca" OR "Tumor de Cavidade Bucal" OR "Tumor de Cavidade Oral" OR "Tumores Bucais" OR "Tumores Orais" OR "Tumores da Boca" OR "Tumores da Cavidade Bucal" OR "Tumores da Cavidade Oral" OR "Tumores de Boca" OR "Tumores de Cavidade Bucal" OR "Tumores de Cavidade Oral" OR "Tumor Bucal" OR "Tumor Oral" OR "Tumor de Boca" OR "Tumor de Cavidad Bucal" OR "Tumor de Cavidad Oral" OR "Tumor de la Boca" OR "Tumor de la Cavidad Bucal" OR "Tumor de la Cavidad Oral" OR "Tumores Bucales" OR "Tumores Orales" OR "Tumores de Boca" OR "Tumores de Cavidad Bucal" OR "Tumores de Cavidad Oral" OR "Tumores de la Boca" OR "Tumores de la Cavidad Bucal" OR "Tumores de la Cavidad Oral"))) AND ( db:("LILACS")) | |
| **Livivo** | ("carcinoma in situ" OR "Preinvasive Carcinoma" OR "Intraepithelial Carcinoma" OR "epithelial dysplasia" OR "intraepithelial carcinoma" OR "intraepithelial neoplasm" OR "intraepithelial neoplasms" OR "cytological changes" OR "architectural changes" OR "cellular atypia" OR "dysplastic changes") AND ("binary grading system" OR "scoring system" OR "histopathological grading" OR "histological diagnosis" OR "histologic grading" OR "WHO grading system" OR "World Health Organization grading system" OR "WHO classification" OR "binary histologic grading system" OR "binary system of grading" OR "WHO histologic grading system" OR "World Health Organization histologic grading system" OR "degree of dysplasia") AND ("prognosis" OR "prognostic factors" OR "prognostic factor" OR prognoses OR "assessment of risk" OR "malignant transformation" OR "Mouth Neoplasms" OR "mouth neoplasm" OR "oral neoplasm" OR "oral neoplasms" OR "cancer of mouth" OR "mouth cancers" OR "oral cancer" OR "oral cancers" OR "cancer of the mouth" OR "mouth cancer" OR "oral squamous cell carcinoma") | 212 |
| **OpenGrey** | ("carcinoma in situ" OR "epithelial dysplasia" OR "cellular atypia OR "dysplastic changes") AND ("binary grading system" OR "histologic grading" OR "WHO grading system") AND (prognosis OR prognoses OR "assessment of risk" OR "malignant transformation" OR "oral cancer" OR "oral squamous cell carcinoma") | 26 |

| | | |
|---|---|---|
| **ProQuest Dissertation and Thesis** | ("carcinoma in situ" OR "Preinvasive Carcinoma" OR "Intraepithelial Carcinoma" OR "epithelial dysplasia" OR "intraepithelial carcinoma" OR "intraepithelial neoplasm" OR "intraepithelial neoplasms" OR "cytological changes" OR "architectural changes" OR "cellular atypia" OR "dysplastic changes") AND ("binary grading system" OR "scoring system" OR "histopathological grading" OR "histological diagnosis" OR "histologic grading" OR "WHO grading system" OR "World Health Organization grading system" OR "WHO classification" OR "binary histologic grading system" OR "binary system of grading" OR "WHO histologic grading system" OR "World Health Organization histologic grading system" OR "degree of dysplasia") AND ("prognosis" OR "prognostic factors" OR "prognostic factor" OR prognoses OR "assessment of risk" OR "malignant transformation" OR "Mouth Neoplasms" OR "mouth neoplasm" OR "oral neoplasm" OR "oral neoplasms" OR "cancer of mouth" OR "mouth cancers" OR "oral cancer" OR "oral cancers" OR "cancer of the mouth" OR "mouth cancer" OR "oral squamous cell carcinoma") | 04 |
| **Google Scholar** | ("carcinoma in situ" OR "epithelial dysplasia" OR "cellular atypia OR "dysplastic changes") AND ("binary grading system" OR "histologic grading" OR "WHO grading system") AND (prognosis OR prognoses OR "assessment of risk" OR "malignant transformation" OR "oral cancer" OR "oral squamous cell carcinoma") | 100 |

Search strategies were performed for each database by using specifics words combinations and truncations with the support of a librarian.

**Appendix 2.** Results from Joanna Briggs Institute Critical Appraisal Checklist for studies reporting prevalence data (Munn et al. Int J Health Policy Manag. 3(3), 123–128, 2014).

| Author, year | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Total ΣY | Risk of Bias |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Diajil et al., 2013 | Y | Y | U | Y | Y | Y | Y | Y | N | 77,7% | Low |
| Jayasooriya et al., 2020 | Y | N | U | Y | N | Y | Y | Y | N | 55,5% | Mod |
| Kujan et al., 2006 | Y | Y | U | N | Y | Y | Y | Y | N | 66,6% | Mod |
| Nankivell et al., 2013 | Y | Y | U | Y | Y | Y | Y | Y | Y | 88,8% | Low |

*Y* yes, *N* no, *U* unclear, *NA* not applicable
Q1- Was the sample representative of the target population?
Q2- Were study participants recruited in an appropriate way?
Q3- Was the sample size adequate?
Q4- Were the study subjects and the setting described in detail?
Q5- Was the data analysis conducted with sufficient coverage of the identified sample?
Q6- Were objective, standard criteria used for the measurement of the condition?
Q7- Was the condition measured reliably?
Q8- Was there appropriate statistical analysis?
Q9- Are all important confounding factors/subgroups/differences identified and accounted for?

Total = ΣY/applicable items (the not applicable (NA) items were excluded from the sum)
Risk of bias was categorized as high when the study reaches up to 49% score “yes”, moderate when the study reached 50 to 69% score “yes”, and low when the study reached more than 70% score “yes”

## **Appendix 3.** Results of The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) instrument

**Author(s)**:
**Question**: Binary System compared to WHO system for access Oral Epithelial Dysplasia Malignant transformation
**Setting**:
**Bibliography**:

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Binary System | WHO system | Relative (95% CI) | Absolute (95% CI) | | |
| **Malignant transformation** | | | | | | | | | | | | |
| 3 | observational studies | serious | not serious | not serious | not serious | strong association dose response gradient | 37/130 (28.5%) | 26/70 (37.1%) | **OR 2.02** (0.88 to 4.64) | **173 more per 1,000** (from 29 fewer to 361 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Interobserver agreement** | | | | | | | | | | | | |
| 2 | observational studies | serious | serious | serious | not serious | none | 209 | 209 | - | mean **0** (0.386 higher to 0.752 higher) | ⨁◯◯◯ VERY LOW | IMPORTANT |

**CI:** Confidence interval; **OR:** Odds ratio

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## ANEXOS

ELSEVIER

# ORAL ONCOLOGY

A Journal Related to Head & Neck Oncology

**AUTHOR INFORMATION PACK**

## TABLE OF CONTENTS




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## DESCRIPTION

*Oral Oncology* is an international interdisciplinary journal which publishes high quality original research, clinical trials and review articles, editorials, and commentaries relating to the etiopathogenesis, epidemiology, prevention, clinical features, diagnosis, treatment and management of patients with **neoplasms** in the **head** and **neck**.

*Oral Oncology* is of interest to head and neck surgeons, radiation and medical oncologists, maxillo-facial surgeons, oto-rhino-laryngologists, plastic surgeons, pathologists, scientists, oral medical specialists, special care dentists, dental care professionals, general dental practitioners, public health physicians, palliative care physicians, nurses, radiologists, radiographers, dieticians, occupational therapists, speech and language therapists, nutritionists, clinical and health psychologists and counselors, professionals in end of life care, as well as others interested in these fields.

Basic, translational, or clinical Research or Review papers of high quality and that make a contribution to new knowledge are invited on the following aspects of neoplasms arising in the head and neck (including lip, tongue, oral cavity, oropharynx, salivary glands, sinuses, nose, nasopharynx, larynx, skull base, thyroid, and craniofacial region, and the related hard and soft tissues and lymph nodes):

- **Etiopathogenesis**: natural history of cancer and pre-cancer; basic pathology, metastatic mechanisms; genetic changes; cellular and molecular changes; microorganisms; growth factors, adhesion and other molecules
- **Epidemiology**; risk factors; biomarkers; protective factors; geographic factors; prevention; screening and intervention
- Clinical features; **orofacial** effects of neoplasms at both local and distant sites; tumor staging and grading
- Diagnosis; **detection** of **cancer** and pre-cancer; cellular and molecular markers for diagnosis; advances in **imaging** and other functional diagnostic modalities for cancer and pre-cancer
- **Management** and **Prognosis**; clinical, cellular and molecular markers for prognosis; **treatment** options including surgical, lasers, photodynamic therapy, cryosurgery, micro- vascular and other forms of surgery, medical, radiotherapy, chemotherapy, immunotherapy, biological and gene therapy advances; molecular targets and new therapeutics (new cytotonics and molecular-targeted therapies); multimodality treatment; advances in reconstruction and rehabilitation, including flaps and grafts, alloplasty, bone and connective tissue biology; multidisciplinary teamwork in cancer care and **oral health care**.
- Quality of life issues; issues of consent; psychosocial aspects; patient and health professional information; patient involvement; psychological interventions, improving outcomes; the prevention,

diagnosis and management of complications, including, pain, hemorrhage, dysfunction, deformity, osteoradionecrosis, xerostomia, and others; rehabilitation; palliative and end of life care; and support teamwork.

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