

The Triad Approach in Oral Cancer- An Evidence Based Decision Analysis Update

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Abstract

Evidence based decision analysis involves the combination of critical thinking along with the usage of recent updated evidence from scientific literature. It plays a very essential role in improving the quality of health care by arriving at evidence based conclusions drawn from the clinician's expertise along with taking into consideration the patient's preferences and values. For making effective health care decision policies, there are certain external factors like National drug policies, regulations and standards, funding, local government bodies and internal factors such as human, financial resources, good leadership and support staff within the enterprise that play a pivotal role. Oral cancer is the 6th most common cancer in India that is most commonly associated with habits such as tobacco, alcohol and certain other etiological factors such as chronic irritation due to sharp tooth, spices, viruses such as Human papilloma virus, Epstein-Barr virus etc. Oral potentially malignant disorders (OPMD) include a group of precancerous lesions and conditions that have an increased tendency for malignant transformation. The triad approach in oral cancer involves the combination of timely diagnosis, proper treatment planning and estimation of prognosis for the long term survival of the patient. This article aims to explore this triad approach with highest levels of evidence in literature that include systematic reviews, meta analyses for the diagnosis and management of some common OPMDs along with personalized case scenarios highlighting how it was systematically adapted into the clinical practice.

Key words: Evidence, Decision analysis, Triad, Oral cancer, Oral potentially malignant disorders

How to cite this article: K.V.Swathi^{1*}. The Triad Approach in Oral Cancer- An Evidence Based Decision Analysis Update. Int J Drug Deliv Technol. 2026;16(84s):1009-1018. DOI: 10.25258/ijddt.16.84s.109.

1. Introduction

Evidence based decision making deals with a combination of critical thinking along with the exploration and use of the latest available evidence in the scientific literature for achieving the desired effect. (CIPD, 2023) In health care, it deals with the utility of the best available evidence along with the clinician's expertise taking into consideration the patient's values and preferences for making efficient health care evidences. (Gopalakrishnan, S., and Ganeshkumar, P., 2013) For making and adopting decisions on health care evidence based practices, systematic reviews and meta analyses being the highest literature evidence offer a pivotal role as they are a collection of data from recent literature. The formulation of systematic reviews and meta analyses require a team approach with proper methodological and sequential analysis. (Johnson, B.T. & Hennessy, E.A., 2019) There are various factors that have an influence on the adoption of health care decision making policies, they include external factors such as funding and regulatory mandates, National drug policies, guidelines and standards, existence of appropriate data such as evidence based models, local government bodies and internal factors such as a good leadership for taking forward the evidence based decision process, support staff within the enterprise (especially their skills and motivation), human and financial resources etc. Evidence based public health policies essentially involves three domains such as process, content and outcome. (Brownson, R.C., et al., 2009)

Evidence based management helps in the reduction of errors in judgment, potential sources of bias and promotes logical thinking and analysis as it is generally based on the recent trends in scientific research and development. It is essentially driven by facts and involves these evidence based principles into organizational practices. (Sohrabi, Z. & Zarghi, N., 2015) It involves systematic decision making by the critical appraisal of the evidence in the literature and the subsequent adaptation of the decisions by scientific methods with constant re-evaluation of the hypothesis to determine the effectiveness of the strategies. (Squara, P., 2013) In clinical practice, the ultimate goal of evidence based approach is achieving the desirable treatment outcome.

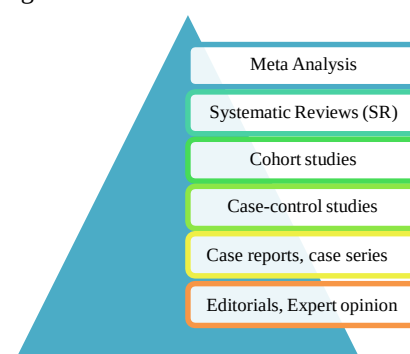


Fig 1: Levels of evidence in scientific literature
1.1 OPMDs and Oral Cancer

Oral potentially malignant disorders (OPMDs) include a group of precancerous lesions which are morphologically altered tissues where cancer is most

likely to occur than its apparently normal counterpart and precancerous conditions which are a generalized state associated with increased risk of cancer. (Warnakulasuriya, S., 2020) Most of these lesions generally have a tendency for transformation into oral cancer. Oral cancer is the 6th most common cancer in India most commonly associated with habits such as consumption of tobacco, alcohol but certain other etiological factors such as stress, presence of a chronic irritation such as sharp tooth, frequent intake of spicy food, syphilis and certain other viruses such as Human Papilloma Virus (HPV), Epstein Barr Virus (EBV) have also been associated with oral cancer. (Gupta, N. et al., 2016) The commonly occurring OPMDs include leukoplakia, erythroleukoplakia, lichen planus, oral sub mucous fibrosis (OSMF), lupus erythematosus, oral lichenoid lesions etc. It has been reported in literature that The International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) have stated that out of 15 million oral cancer cases, one third of it can be

prevented by timely intervention with the help of appropriate screening strategies. (Johnson, D.E. et al., 2020) A combination of a proper diagnosis, appropriate treatment protocol leading to a favourable prognosis is very important for improving the overall quality of life in these patients. This article aims to explore the highest available evidence in literature that includes Systematic Reviews and Meta Analyses for the diagnosis and management of patients with some of the most common OPMDs and how it was adapted into the clinical practice with personalized case scenarios. It also throws light on the role of emerging field of molecular diagnostics in particular, genetic biomarkers that play a vital aspect in the prognosis of oral cancer in the recent trends.

Fig 2: The triad approach in evidence based decision analysis for OPMDs and oral cancer

2. Dealing with the Diagnosis

Generally, the initial diagnosis of oral cancer begins with a proper history taking and clinical examination of the patient. (Ratnawidya, W. et al., 2019) The important aspects in history taking in patients with suspicious oral mucosal lesions are directed towards the tobacco habit history, family history of previous cancers. This is followed by a thorough clinical oral evaluation along with palpation of the affected site and neck region. A radiographic assessment may also be indicated to know the extent of bone involvement. It is generally accepted that biopsy and subsequent histopathological examination is always the gold standard for the detection of malignant changes in patients with suspicious oral lesions. (Su, Y.-F. et al., 2021)

Since biopsy is an invasive procedure, the patient compliance is hindered in most situations during clinical practice. According to the latest evidence in literature, certain adjunctive diagnostic techniques

play a major role for the early detection of oral cancer.

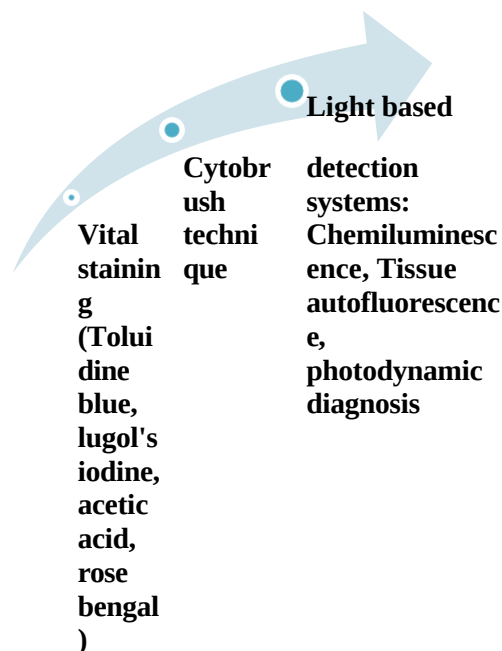


Fig 3: Some adjunctive diagnostic systems for early detection of oral cancer

2.1 Vital staining

Vital staining is also one of the most efficient chair side diagnostic aids for detecting dysplastic changes in various oral premalignant lesions. It can be done as supravital or intravital staining. In supravital staining living cells are stained and visualised under microscopy to examine whereas from intravital staining is done by introducing the stain into the body by injecting or other methods. There have been various stains used for vital staining which include toluidine blue, methylene blue, lugol's iodine, rose bengal, acetic acid etc. (Sudheendra, U.S., Sreeshyla, H.S. & Shashidara, R., 2014)

2.2 Cytobrush technique

It is a cytological technique which has a brush with bristles similar to a toothbrush which can penetrate into the mucosal tissues for the collect the cells in the region of suspicious oral lesions. (Bhatia, P.V. et al., 2020)

2.3 Light based optical devices

These optical devices are useful in the detection of changes in the optical properties of the surface epithelium and submucosa and are based on light absorption, scattering or fluorescence of the tissue. (Wilder-Smith, P. et al., 2010) Chemiluminescence is the process of emission of light as a result of chemical reaction with certain amount of heat production as well. (Shashidara, R., Sreeshyla, H.S. & Sudheendra, U.S., 2014) Chemiluminescent illumination produces a blue-white light of wavelength around 430-580 nm, this light is absorbed by the cells of the normal mucosa whereas it is reflected back as acetowhite hue in case of abnormal cells due to altered nuclear cytoplasmic ratio. The basis of tissue autofluorescence is endogenous fluorophores such as nicotinamide

adenine dinucleotide, flavin adenine dinucleotide in cells which produce a fluorescent emission when exposed to light of a specific wavelength. At these excitation wavelengths, normal cells show a pale green fluorescence whereas in case of abnormal mucosa, there is a loss of fluorescence and it remains dark. (Vashisht, N. et al., 2014) Literature evaluation for the highest levels of evidence for adjunctive techniques for oral cancer detection showed light based detection systems to have a major role in the early detection of dysplastic changes in patients with precancerous lesions due to their good diagnostic accuracy.

Evidence based on Systematic Reviews and Meta

Analyses in literature:

13 studies on chemiluminescence, 12 studies on tissue autofluorescence

• Rashid et al. 2015

Toluidine blue staining is effective in high risk populations and suspicious oral mucosal lesions

• Patton et al. 2008

2.4 Utilization in our clinical practice

A patient with OSMF subjected to a combination of toluidine blue staining and chemiluminescence. As seen in the picture below the site of biopsy taken was from the region showing positive for the index test (bluish acetowhite hue). The histopathology revealed hyperorthokeratosis with moderate epithelial dysplasia and advanced oral sub mucous fibrosis.

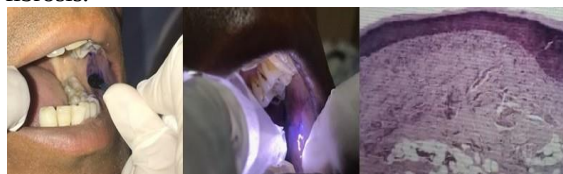


Fig 4: An OSMF patient subjected to toluidine blue staining and chemiluminescent examination followed by histopathology

This diagnostic accuracy study in a sample of 40 suspicious oral mucosal lesions revealed the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to be 100 %, 60 %, 93.3 %, 100 %, 0.800 respectively in comparison to the histopathology ($p=0.002$)

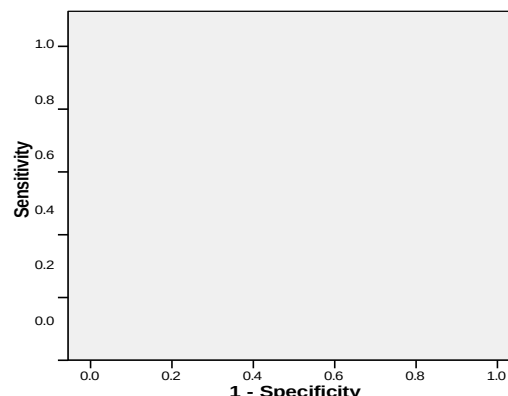


Fig 5: ROC curve of the diagnostic assay

Area	Standard Error ^a	Asymptotic Significance ^b	Asymptotic 95 % Confidence Interval	
			Lower bound	Upper bound
.800	.140	.035	.526	1.074

3. THERAPY OF SOME COMMON OPMDs-FROM EXISTING

STANDARDS TO RECENT ADVANCES

3.1 Oral leukoplakia

Leukoplakia is a white patch (or) plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk of cancer. It is the most commonly occurring precancerous lesion.

Key observations

Chemiluminescence showed good sensitivity in the detection of dysplasia in OPMDs and oral cancer particularly in case of white lesions such as leukoplakia. It was limited in detecting red lesions and the authors had suggested combining with toluidine blue. (Rashid et al.)

Tissue auto fluorescence had a good sensitivity and specificity in the detection of white, red lesions or a combination of both. (Patton et al.)

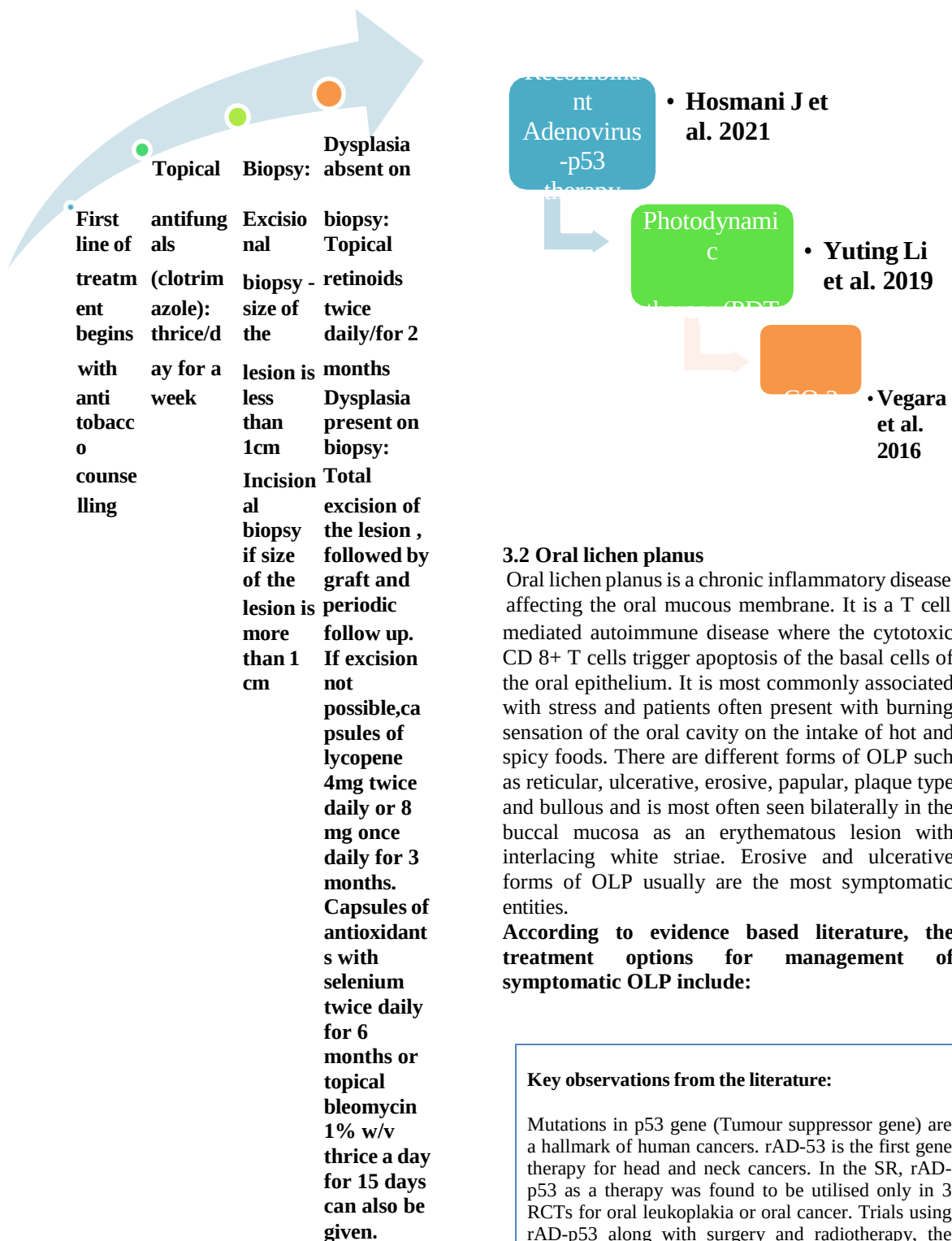


Fig 6: Treatment modalities for leukoplakia
Further analysis of literature for Systematic Reviews and Meta Analyses in the management of oral leukoplakia in recent 5 years:

3.2 Oral lichen planus

Oral lichen planus is a chronic inflammatory disease affecting the oral mucous membrane. It is a T cell mediated autoimmune disease where the cytotoxic CD 8+ T cells trigger apoptosis of the basal cells of the oral epithelium. It is most commonly associated with stress and patients often present with burning sensation of the oral cavity on the intake of hot and spicy foods. There are different forms of OLP such as reticular, ulcerative, erosive, papular, plaque type and bullous and is most often seen bilaterally in the buccal mucosa as an erythematous lesion with interlacing white striae. Erosive and ulcerative forms of OLP usually are the most symptomatic entities.

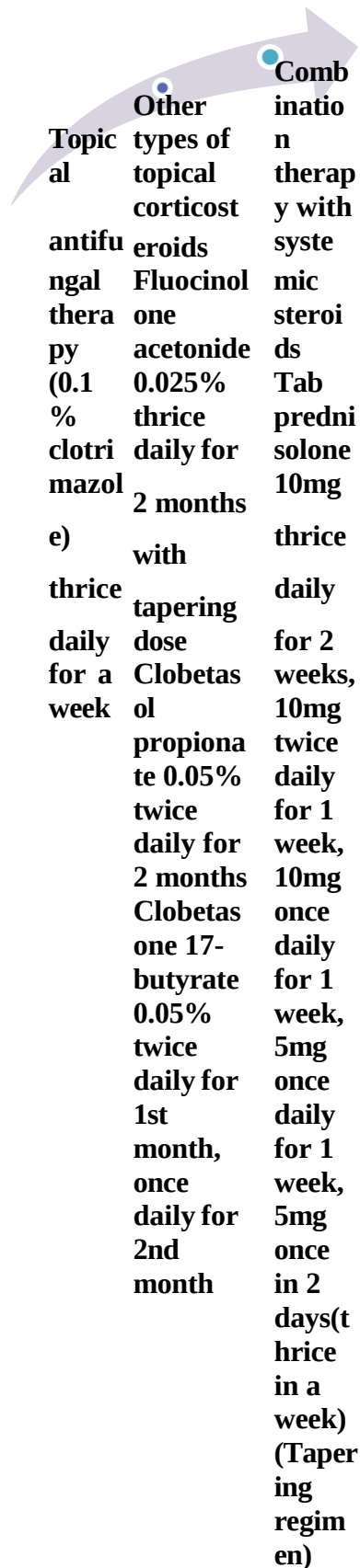
According to evidence based literature, the treatment options for management of symptomatic OLP include:

Key observations from the literature:

Mutations in p53 gene (Tumour suppressor gene) are a hallmark of human cancers. rAD-53 is the first gene therapy for head and neck cancers. In the SR, rAD-p53 as a therapy was found to be utilised only in 3 RCTs for oral leukoplakia or oral cancer. Trials using rAD-p53 along with surgery and radiotherapy, the survival rate was 100% for a follow up period of 3 years. (Hosmani et al.)

Photodynamic therapy: 16 studies were analysed in the SR, PDT resulted 76.1% good response in patients with leukoplakia. However, there was a wide recurrence range of 0-60% reported. (Yuting Li et al.)

CO2 laser is very effective in the management of leukoplakia and low associated morbidity. No conclusive evidence on its role in prevention to malignancy or low recurrence rates. There is lack of RCTs in comparison of CO2 laser with other lasers. (Vegara et al. 2016)



Key observations from the literature:

Pimecrolimus prevented better clinical relapse than tacrolimus. The SR had only one trial each that assessed thalidomide and retinoid but both had similar efficacy to tacrolimus. Increased side effects were reported in cyclosporine. (Silva et al.)

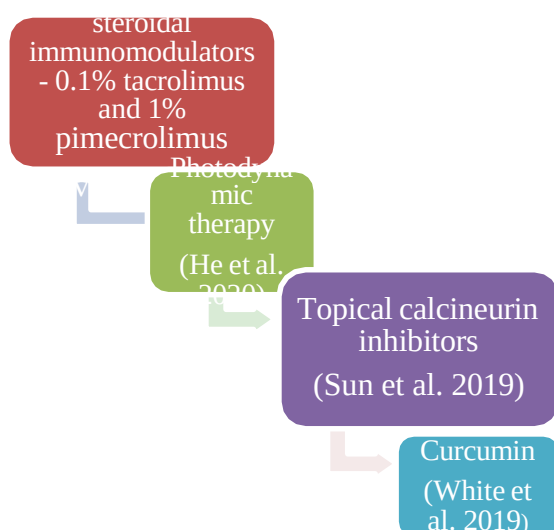
In this SR, pooled estimates of the studies of photodynamic therapy (PDT) in OLP patients revealed a reduction in the lesion size by 1.53 cm². The treatment had a partial response of 77%. The VAS score decreased by 3.82 and the Thongprasom sign score had also reduced by 1.33. (He et al.)

This was a large scale SR with 21 RCTS (965 patients). The effect of topical calcineurin inhibitors such as tacrolimus, pimecrolimus and cyclosporine were similar to topical corticosteroids for short term treatment of OLP. (Sun et al.)

Topical curcumin was effective in the reduction of pain, burning sensation and clinical manifestations of OLP but was not superior to topical corticosteroids. (White et al.)

Fig 7: Treatment modalities of OLP

The other type of treatment modalities for the management of OLP after the analysis of latest Systematic Reviews and Meta Analyses include:



3.3 Application in clinical practice

A patient with a severe erosive OLP presented with generalized desquamation of marginal and attached gingiva of both arches. Areas of erythema and extensive ulceration were also seen in the buccal mucosa. (Fig 8A). Patient was treated systematically with topical antifungal candid mouth paint (1% clotrimazole), Corticosteroid therapy : Tenovate (0.05% Clobetasol Propionate) topical application to the site of the lesion thrice daily, Betnesol 0.5 mg (crushed, powdered and mixed with water, used as mouth rinse twice daily), Cap. Doxycycline (Antibiotic) 100 mg once daily, Tab. Cetzine (Antihistamine) 10 mg once daily, Cap Evion

(Vitamin E) once daily for a week. The patient showed remarkable improvement in signs and symptoms in the second week. (Fig 8B). The patient was also followed up subsequently. This case report has also been published in the literature to bring to the scientific forum. (Swathi, K.V. & Maragathavalli, G., 2019)



Fig 8A)



8B)

Fig 8: A) Pretreatment images of a patient with erosive OLP B) Post treatment images

4. PROGNOSIS – DETERMINING THE LONG TERM SURVIVAL

Prediction markers of OPMDs and oral cancer: Are genetic diagnostic markers gaining importance in the recent era?

Tumour markers are substances that are produced as a result of the body's response to a cancer cell or can also be elevated in certain non-cancerous (benign) lesions as well. These markers may also be produced by the tumour itself and they can be tumour specific marker (specific for the individual tumour) or can be tumour associated markers (associated with different tumours of the same type of tissue). These markers are very useful in the prediction and prognosis of

various cancers as they can be measured easily from body fluids such as saliva, blood, urine. With regards to the evidence based decision analysis for predicting the malignant transformation risk of OPMDs to oral cancer, current scientific literature supports the genetic markers to have an immense application. The evidence from systematic reviews on the scope of genetic markers for the prediction and prognosis of oral cancer include:

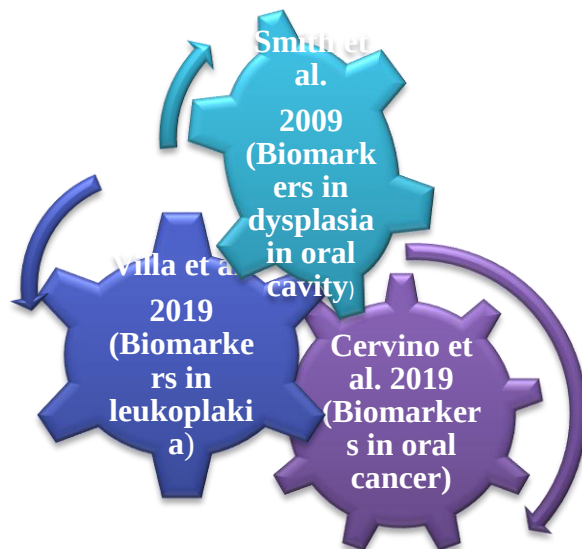


Fig 9: Genetic markers in OPMDs and oral cancer documented in literature

Some key observations from the literature evidence:

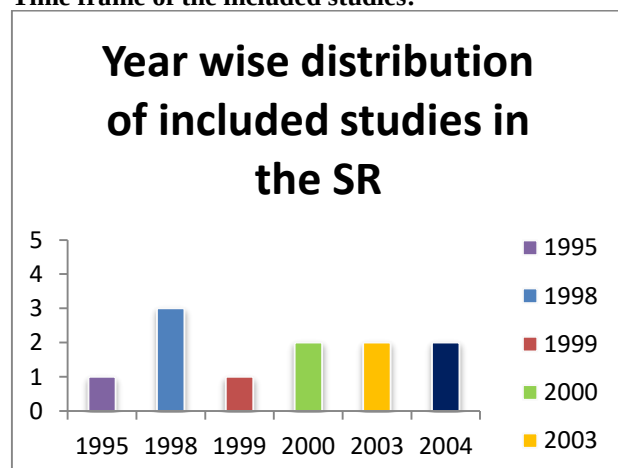
A decade back in **2009**, a systematic review by **Smith et al.** explored the role of certain biomarkers and genetic abnormalities for prediction of malignant transformation in patients with **oral dysplasia**.

Highlights of the Systematic Review:

In this systematic review, 13 studies were included describing oral dysplasia as common precursor to oral

Time frame of the included studies:

cancer with a prevalence range of 6-36%. The World Health Organization (WHO) classification of the histological grades of dysplasia as mild, moderate and severe dysplasia have been regarded to be more subjective and an emphasis for a better prediction model based on genetic biomarkers and certain genetic abnormalities for oral cancer has been elicited in this systematic review.



Genetic biomarkers and gene abnormalities implicated in oral cancer

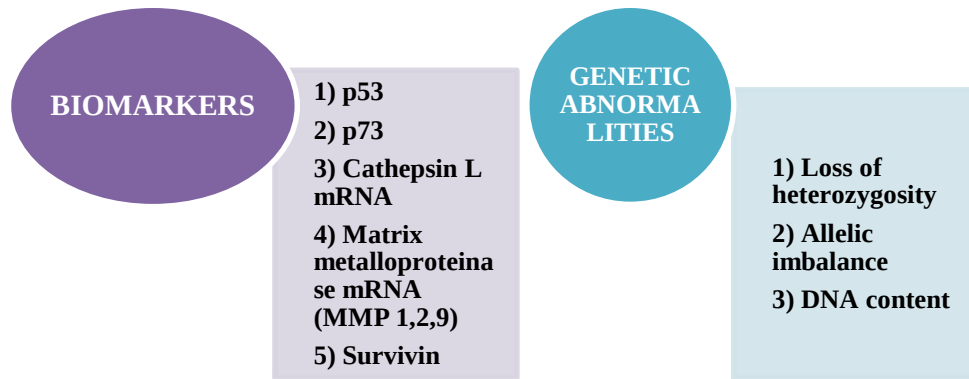
Observations:

Distribution of studies from 1995-2006 in this SR

Study design was heterogeneous and included retrospective case-control, retrospective cohort, retrospective case series and prospective cohort.

Consistency of studies in literature evident from 2000-2004.

Growing evidence for molecular markers in prediction for oral cancer



Lacunae in this literature

- ❖ More detailed assessment of the effect size has not been mentioned with a possible risk of publication bias.
- ❖ Data for the relative risk analysis were taken from pooled analysis and not from original publications questions the methodological quality.
- ❖ The criteria for clinical and histological definitions need more standardization.
- ❖ Lack of adequate clinical data as this systematic review has included mostly

retrospective studies, the clinical use of markers in risk stratification as in the for the practice guidelines for proper treatment planning and favourable prognostic outcomes.

A more recent systematic review by **Villa et al. in 2019** on longitudinal studies based on the evidence from **World Workshop on Oral Medicine VII** explored the utility of prognostic biomarkers in **oral leukoplakia** which is the most common OPMD.

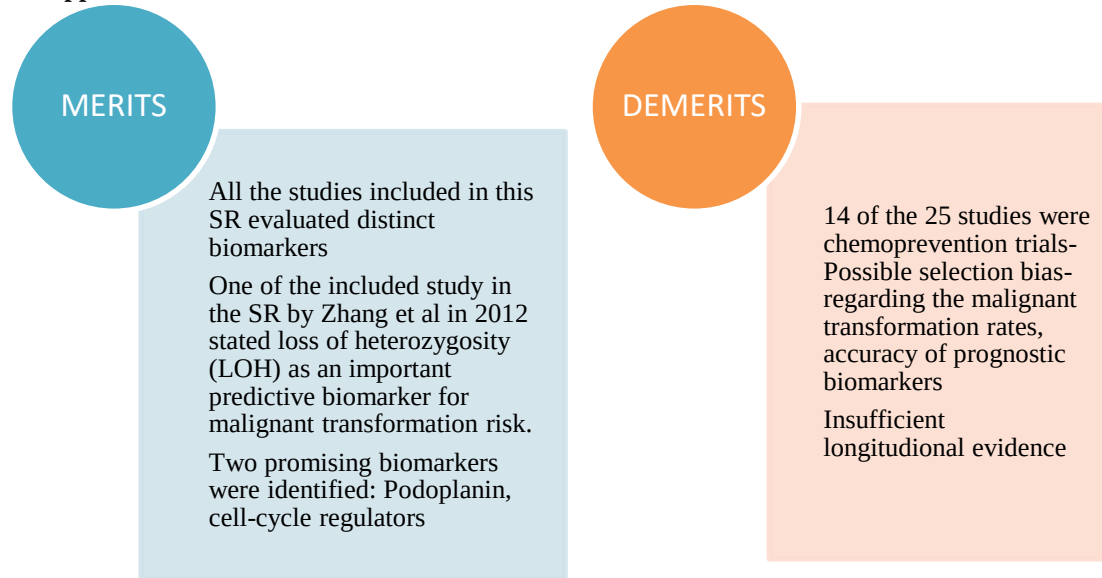
Highlights of the Systematic Review:

- 1 • Assess whether prognostic biomarkers could stratify the risk of malignancy in leukoplakia
- 2 • Relationship between prognostic markers, clinicopathological and risk factors
- 3 • If biomarkers could independently predict the malignant transformation of leukoplakia
- 4 • Minimising follow-up intervals
- 5 • Efficacy of investigated biomarkers and management protocol
- 6 • Formulation of ALGORITHM- Evidenced based management for leukoplakia

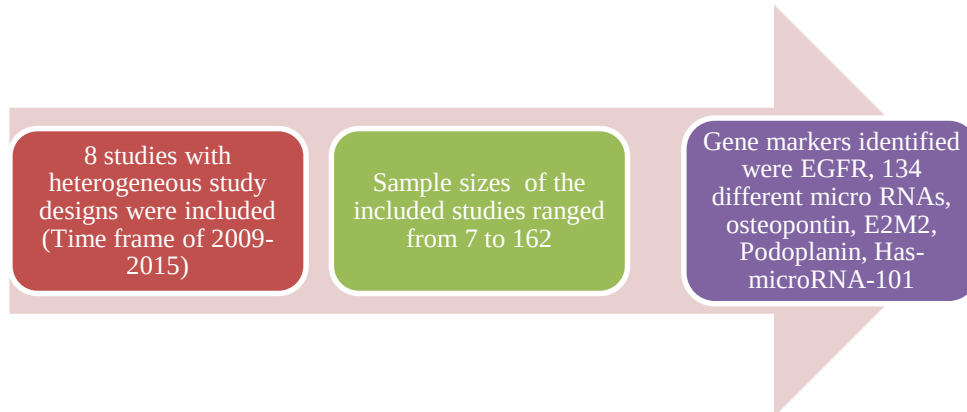
Types of biomarkers analysed in the included studies in the SR:

- ✚ Inflammatory or oxidative biomarkers
- ✚ Growth factors
- ✚ Cell signaling biomarkers
- ✚ Genetic and cellular regulatory factors
- ✚ Ion channels
- ✚ Sustained angiogenesis factors
- ✚ Epigenetic biomarkers

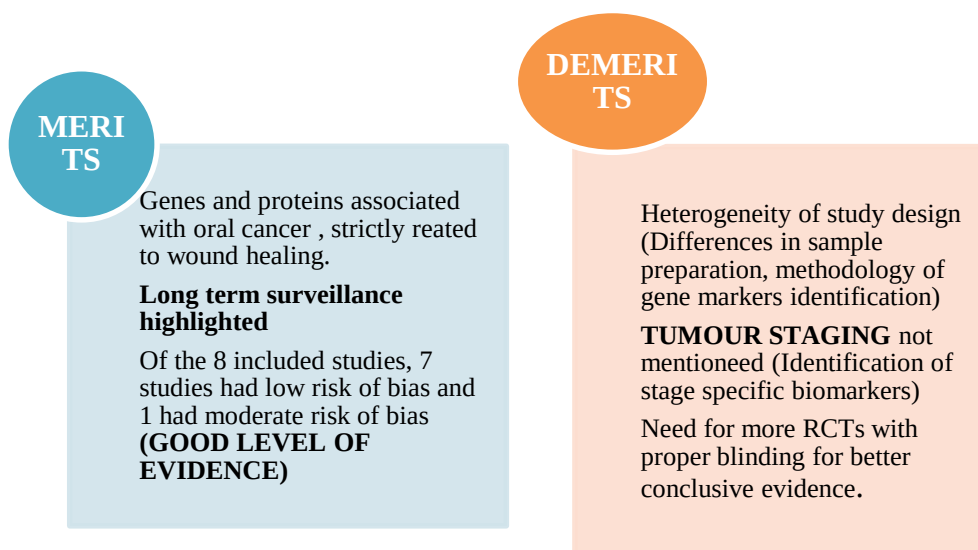
Critical appraisal of the literature:



With regards to a recent evidence on biomarkers in **oral cancer**, a systematic review by **Cervino et al. in 2019** evaluated molecular biomarkers related to oral cancer based on clinical trial outcome evaluation.



Critical analysis of this literature evidence:



5. CONCLUSION

As health is a state of complete physical, mental and social wellbeing, a proper

diagnosis and treatment planning of the disease based on the latest evidence from literature is very important for improving the

overall quality of life of the patient. Evidence based decision making will help in the formulation of clinical practice guidelines as it is backed with up to date data from scientific research and clinical trials. Future scope holds for conducting more continuing development education programs on evidence based research practices right from the institutional level to train the health care professionals when they start their journey of clinical practice.

Conflicts of interest: Nil

Funding: Nil

Ethical approval: Not applicable as this is a decision analysis review

Data availability: Not applicable as this is a decision analysis review, however the in text citation of the references of the study/case report analysed in this review has been provided.

Author contribution statement: Only one author is involved in this manuscript: K.V.Swathi: Manuscript design, analysis, drafting, analysis and review

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