Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions

Background

- Oral cancer is a significant global health problem
- Cancer of the lip and oral cavity is a relatively common cancer worldwide
    - 263,000 new cases yearly
    - 127,000 deaths in 2008
- Geographic variation on disease incidence and mortality
    - Incidence in developing countries is double that of developed countries
- Risk factors: alcohol consumption, tobacco use, betel quid chewing and low socioeconomic status
- Oral squamous cell carcinoma is the most common forms of cancer found in the oral cavity
    - Often preceded by premalignant disease
- Premalignant disease includes a heterogeneous group of conditions including erythroplakia, non-homogenous leukoplakia, erosive lichen planus, oral submucous fibrosis and actinic keratosis
- Progression of oral squamous cell carcinoma not fully understood
- Erythroplakia, erythro-leukoplakia have the highest malignant transformation rates
- Leukoplakia is the most common premalignant disease
    - Global malignant transformation rate 1.36% per year
- Early detection and excision of premalignant disease can prevent malignant transformation
- Evidence for treatment of premalignant disease effectiveness is limited
- Technology to treat and manage oral cancer have progress but mortality rates remain high
    - Late presentation by the patient
    - Early cancers are asymptomatic
- Oral cancer mortality can be reduced by:
    - Primary prevention
    - Secondary prevention (screening early detection)
    - Improved treatment
- No national population-based screening programs have been implemented

Index Tests

- Adjuncts to conventional oral exam to improve diagnostic accuracy
    - Vital staining (toluidine blue, tolonium chloride)
    - Oral cytology (OralCDx brush biopsy)

    - Light based detection (VELscope, Orascoptic DK, Identafi 3000) and oral spectroscopy
    - Blood and saliva analysis
- Gold standard for diagnostics is biopsy and histological examination

Clinical Pathway

- No standardized clinical pathway for individuals with premalignant disease
- Patient with identified lesions receive a conventional oral examination
    - Visual and tactile exam
- Subjective assessment is made based on clinical presentation
    - Referral to specialist for definitive diagnosis and biopsy as appropriate
- Supplementing the conventional oral exam could aid in the identification of oral lesions
    - Tests could have a triage role in assisting general dentists and specialists
    - Reduce the number of benign referrals
- Sample site selection for biopsy may be facilitated by use of diagnostic adjuncts
- Adjunctive tests can help to monitor a patient with history of cancer or premalignant disease

Review Objective

- Identify objective tests for oral squamous cell carcinoma and premalignant disease and evaluate their diagnostic accuracy

Methods

- Included studies evaluating index tests that reported on diagnostic accuracy
- Participants aged 16 years or older with clinically evident oral lesions
- Target conditions considered in review
    - Carcinoma
        - Oral squamous cell carcinoma
    - Potentially malignant disorders
        - Leukoplakia
        - Erythroplakia
        - Lichen planus
        - Lupus erythematous
        - Submucous fibrosis
        - Actinic keratosis
        - Hereditary disorders (dyskeratosis congenital, epidermolysis bullose)
        - Dysplasia (mild moderate, severe)
- Reference standard: scalpel, punch or fine needle aspiration biopsy with histological diagnosis
- 42 studies were included

    - Data from 4002 patients and 4337 lesions
    - Studies conducted between 1980 – 2012
    - Broad geographical spread
- No study assessed the diagnostic accuracy of blood and saliva analysis
- Studies were excluded for inappropriate patient selection or reference standard not being applied to all patients

Results

- Vital staining
    - 14 studies evaluated vital staining
    - Included 1248 individuals and 1338 lesions
    - Definition of target conditions varied between studies
    - Sensitivity 0.84
    - Specificity 0.7
    - Variation in range for sensitivity and specificity
- Oral cytology
    - 13 studies that evaluated oral cytology
    - 1554 participants and 1622 lesions were examined
    - Sensitivity 0.91
    - Specificity 0.91
- Light-based detection and/or oral spectroscopy
    - 13 studies were evaluated
    - 1253 patients 1397 lesions
    - Autofluorescence (VELscope)
        - Sensitivity 0.84
        - Specificity 0.15
    - Chemiluminescence (Vizilite)
        - Sensitivity 0.77
        - Specificity 0.28

What is the most accurate health technology for diagnosing oral cancer and potentially malignant disorders?					
Patient population	Patients referred to a secondary care facility for further investigation of a clinically evident lesion				
Index test	Conventional oral examination and adjunctive test (Vital Stain, Oral Cytology, Light-based)				
Reference test	Scalpel biopsy and histological assessment by experienced oral pathologist				
Target condition	Oral cavity cancer or potentially malignant disorder				
Included Studies	41 cross-sectional studies				
Test/Subgroup	**Summary accuracy: Sensitivity (95% CI)**	**Summary accuracy: Specificity (95% CI)**	**No. of participants/ lesions/studies**	**Prevalence Median (range)**	**Quality and Comments**
Vital Staining	0.84 (0.74 to 0.90)	0.70 (0.59 to 0.79)	1248 / 1338 / 14	0.50 (0.17 to 0.97)	High risk of bias [4]
Oral Cytology	0.91 (0.81 to 0.96)	0.91 (0.81 to 0.95)	1507 / 1575 / 12 [1]	0.43 (0.27 to 0.69)	High risk of bias [5]
Light-based	0.91 (0.77 to 0.97)	0.58 (0.22 to 0.87)	1021 / 1165 / 11 [2]	0.21 (0.04 to 0.73)	High risk of bias [6]
Vital Stain plus adjunct	Not possible [3]	Not possible [3]	402 / 478 / 6 [3]	0.27 (0.04 to 0.48)	High risk of bias [7]

Discussion

- Sensitivity and specificity were highest for cytology
- Cannot differentiate between dysplasia and oral squamous cell carcinoma necessitating tissue biopsy
- Cytology cannot be used as a replacement for biopsy
- Cytology may be useful as an additional test for frontline clinicians to triage low-risk lesions
- Cytology tests are not indicated for:
    - Persistent epithelial lesions without a clear etiology
    - Display high-risk features
        - Induration
        - Pain
        - Ulceration
        - Heterogeneous white, red or mixed lesions
    - Suggestive of variable histopathology within the lesion increasing the risk of sampling errors
- Cytology may report false positives or false negatives so surveillance and repeat sampling will be necessary
- No studies investigate cost-effectiveness of cytology compared to referral
- Beneficial for resource-poor countries where access to specialists is more limited
- Light-based technologies are limited by their low specificity
    - Use of this technology would result in unnecessary referrals/treatment
- Vital staining technology has suboptimal sensitivity and specificity
    - Should be used by expert clinicians to facilitate biopsy site selection or as a surveillance tool
- Not enough evidence to support combining technologies

Implications for practice

- None of the adjunctive tests are recommended to replace the current standard of biopsy and histological assessment
- Cytology shows promise as an adjunctive procedure to compliment conventional oral examination
    - Requires adequate training to correctly harvest cells
- Patients should be referred to specialists in the management of premalignant disease appropriately
- No evidence exists for use of adjunctive tests in primary care
    - All studies were conducted in a secondary care facility

Implications for research

- Quality of studies included were poor
- Need for further standardization of research to reduce bias
- Diagnostic potential of blood and saliva needs to be investigated
- Better understanding of genetics and epigenetic alterations in premalignant diseases would allow for the employment of real-time cytology
    - Identify early lesions with high risk for malignant transformation

Reference

Macey R, Walsh T, Brocklehurst P, Kerr AR, Liu JLY, Lingen MW, Ogden GR, Warnakulasuriya S, Scully C. Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD010276. DOI: 10.1002/14651858.CD010276.pub2