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 erythematosus
    - 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

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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