Adjunctive techniques for oral cancer examination and lesion diagnosis: a systematic review of the literature

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CRD summary
This review of adjunctive techniques for detecting oral malignant/premalignant cancer lesions found: toluidine blue staining effective in high-risk populations; OralCDx brush biopsy useful for assessing suspicious lesion dysplastic changes; and insufficient evidence on visually-based adjuncts. Positive conclusions on toluidine blue and OralCDx were not adequately supported. Limited, widely-varied data and review weaknesses mean the accuracy of adjunctive techniques is uncertain.

Authors' objectives
To assess the effectiveness of adjunctive techniques (additional to oral mucosal visual and tactile examination under incandescent light) in detecting oral premalignant and malignant lesions.

Searching
PubMed, Web of Science and the Cochrane Library were searched to February 2008, for English language publications. Search terms and search strategy were reported in an online supplement (see URL for Additional Data). Bibliographies of review articles were screened for additional studies.

Study selection
Studies that assessed the diagnostic accuracy of vital tissue staining with toluidine blue, visualisation adjuncts (ViziLite, Microlux DL, Orascoptic DK, VELscope), toluidine blue staining and ViziLite (chemoluminescent light detection system) in combination, or cytopathology (OralCDx brush test system) for the detection of oral premalignant and malignant lesions were eligible for inclusion. Included studies were required to use histological confirmation of tissue biopsy as the reference standard and to report sufficient data to calculate measures of diagnostic accuracy (e.g. sensitivity, specificity, positive and negative predictive values).

In most included studies, patients had suspicious oral lesions or a history of oral cancer, but some had known current oral cancer. Limited study details and results were reported in an online supplement, including details of adjunctive tests used, and in the case of visualisation adjuncts, operator details.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
The methodological quality of included studies was assessed using an 11 item checklist to assess research design (details provided in the on-line supplement), study protocol, data analysis, measurement and validity. Studies were assigned an overall quality score from zero to 20 and this was then re-scaled to give a zero to 100 score.

Two authors rated each study and combined their results to give a final score with standard deviation.

Data extraction
Data were extracted to calculate sensitivity, specificity, positive and negative predictive values. Equivocal results were classified as positive for the calculation of accuracy measures.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Studies were combined in a narrative synthesis, grouped by adjunctive technique.
Results of the review

Twenty-three studies were included in the review. The figures cited below were given in online supplementary tables (see URL for Additional Data).

**Vital staining with toluidine blue** (14 studies, 17 data sets, 2,285 participants and 2,309 lesions): The quality scores for studies that assessed the accuracy of vital tissue staining with toluidine blue ranged from 15±5 to 77.5±2.5. Biopsy was not performed in all positive lesions in all studies. The prevalence of oral premalignant and malignant lesions ranged from 26 to 81%. Diagnostic sensitivities ranged from 38 to 100%; specificities ranged from 9 to 100%.

**Visualization using ViziLite** (three studies, 179 participants, 183 lesions): All studies included only patients with previously visualised mucosal lesions. The quality scores for studies that assessed the accuracy of ViziLite ranged from 32.5±2.5 to 55±5. Diagnostic sensitivity was 100% in all cases; specificity ranged from 0 to 14%. One study (n=84 participants, 97 lesions) assessed the accuracy of ViziLite in combination with toluidine blue staining. The quality score for this study was 55.5 ± 5. Diagnostic sensitivity was 100% and specificity was 55%.

**Visualization using VELscope**: No studies were identified that assessed the current VELscope, but two studies (three data sets) assessed the accuracy of the underlying technology. The quality scores of these studies were 42.5±2.5 and 60±0. Diagnostic sensitivity ranged from 98 to 100%; specificity ranged from 78 to 100%.

**Cytopathology using the brush biopsy OralCDx** (four studies, 1,435 participants, 749 lesions): The quality scores for studies that assessed the accuracy of cytopathology using the brush biopsy OralCDx ranged from 37.5±2.5 to 50±0. The prevalence of oral premalignant and malignant lesions ranged from 19 to 38%. Diagnostic sensitivities ranged from 71 to 100%; specificities ranged from 25 to 94%.

No studies of Microlux DL (low-energy blue light system) or Orascoptic DK (hand-held LED instrument with an oral lesion screening attachment) met the inclusion criteria.

Authors’ conclusions

There was evidence that toluidine blue was effective as a diagnostic adjunct for use in high risk populations with suspicious mucosal lesions. OralCDx was useful in assessment of dysplastic changes in clinically suspicious lesions, but there were insufficient data to assess usefulness in innocuous mucosal lesions. There was insufficient evidence to support or refute the use of visually based examination adjuncts.

CRD commentary

The review provided a clearly stated research question and defined inclusion criteria for the index test, reference standard for confirmation of positive lesions and outcome measures. However, no inclusion criteria were defined for participants and it was unclear how negative test results were confirmed. A number of sources were searched for relevant studies, but the restriction to published English language studies introduced the possibility of language and publication biases and omission of relevant studies. Measures to minimise reviewer error and/or bias were applied to the quality assessment, but it was unclear whether similar measures were applied throughout the review process.

The methodological quality of included studies was assessed, but results were reported as summary scores (generally not recommended as a practice). In addition, studies with 'low quality' scores were excluded from the authors' reporting of results for one of the index tests; it was unclear how this quality threshold was set and whether it was applied elsewhere in the review. The results of individual studies and study details were only reported in an online appendix, which was (in places) inconsistent with the main body of the article. Accuracy measures varied widely across studies for each index test assessed and insufficient detail of included study participants was reported to facilitate interpretation.

Overall, the authors’ positive conclusions on the usefulness of vital tissue staining with toluidine blue and cytopathology using the brush biopsy OralCDx were not adequately supported by the data presented. Limited, heterogeneous data and weaknesses in the review process mean that the accuracy of adjunctive cancer detection techniques is uncertain.

Implications of the review for practice and research

**Practice**: The authors stated that, given the lack of data on the effectiveness of adjunctive cancer detection techniques...
in general dental practice settings, clinicians must rely on a thorough oral mucosa examination supported by speciality referral and/or tissue biopsy for diagnosis of oral premalignant and malignant lesions.

Research: The authors stated that further studies are needed to assess the accuracy of adjunctive techniques in general practice settings and in low risk patients. They also provided detailed recommendations for the design of future studies, including direct comparisons of different adjunctive techniques, standardization of diagnostic techniques, consecutive recruitment of participants, duplicate assessment of examinations, and intention-to-diagnose analysis. Future studies should assess the effectiveness of adjunctive techniques for early identification of dysplastic lesions that later undergo malignant transformation.

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