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Letter to the Editor

The need to reassess studies on detection of potentially premalignant and malignant oral lesions

Identification of oral mucosal lesions with the potential for malignant transformation is critical in order to provide the appropriate treatment with the goal of preventing cancer or early detection of cancer in order to lead to diagnosis and treatment of early stage disease. Classification of the histologic grade of dysplasia is variable[1–5] and furthermore, the risk of progression of low-grade dysplastic lesion to cancer is not predictable based upon phenotypic change on biopsy, although more advanced dysplasia has a higher risk of progression.[2,4] Mild dysplasia (low-grade squamous epithelial lesion) may be classified as "non-serious pathology" because of the potential reversible nature of the lesion.[2,4,6] In addition, pathologic diagnosis particularly of dysplasia, is subject to intra- and inter-examiner variability.[5,7,8] In the study of Fischer et al. a total of 21 local and 3 central pathologists in 10 medical centers examined 75 histology specimens.[1] All pathologists evaluated the same biopsy slides independently of one another and they were blind to the clinical features of the lesions. The agreement between the pathologists was good when carcinoma-in situ and carcinoma were grouped together [(kappa: 0.90 (95% CI:0.79, 1.00)]; however, the agreement was fair for dysplastic lesions [kappa: 0.47 (95% CI:0.18, 0.76)]. Of importance, it was observed that the presence of inflammatory changes within the tissue reduced the ability of the pathologists to identify dysplastic or malignant changes.[2] This study confirmed the results of a previous study performed by the same research team,[7] where kappa for lesion diagnosis was 0.59 (95% CI:0.45, 0.72) for the entire study population. With recategorization of the lesions into three groups as "no abnormality/hyperkeratosis", "mild, moderate or severe dysplasia" and "carcinoma-in situ and carcinoma", the agreement between the pathologists increased to 0.70 (95% CI:0.56, 0.84). Lesions without inflammation had higher kappa values when compared to that of the lesions with inflammation (kappa values 0.67 (95% CI:0.53, 0.80) and −0.10 (95% CI:0.27, 0.07), respectively).[7] Thus, the reliability of histopathology to estimate the risk of progression of a potentially malignant lesion continues to be of concern, because variability in interpretation creates limitation in assessing the true nature of a lesion and complicates assessment of studies of diagnosis and the outcomes of interventional studies.

Even though histopathology represents the current "gold standard" in diagnosis, molecular abnormalities precede phenotypic change and may be present at margins of lesions that are clinically and histologically benign. Residual disease may remain at sites of excised lesion due to inability to determine the extent of molecular change by clinical and even histological examination, condemning the patient to recurrence of clinical disease.[7,9–12] Several studies suggest that toluidine blue stained lesions present LOH (loss of heterozygosity, allelic loss).[13–15] Guo et al. reported that in addition to all SCC cases, 82% of carcinoma-in situ or dysplasia and 59% of cases without dysplasia showed LOH in at least one marker.[13] Three-quarters of the lesions identified by toluidine blue were clonal and therefore had the potential to progress to malignancy.[13] Zhang et al. in a prospective study showed that progression of OPLs to SCC was significantly higher in stain positive areas, with a four-fold higher risk of progression to SCC even in lesions with benign histopathology or mild dysplasia.[15] After 44 months, 33% of the toluidine blue positive OPLs with or without dysplasia progressed to SCC, but this was observed only in 5% of the toluidine blue negative mucosal lesions ($p = 0.0002$).[15] Zhang et al. suggested that due to its potential to identify molecular changes that may be associated with progression to malignancy, toluidine blue staining intensity may provide important guidance for further study and followup.[15] These findings indicate that toluidine blue positivity may represent risk of molecular change even in lesions with benign histopathology and suggest that "false positive" toluidine blue results based upon histomorphology may represent molecularly true positive lesions with risk of progression to OSCC.[13] Phenotypic change is expected to occur following sufficient molecular change, and it appears that at least a portion of the cases identified as "false positive" toluidine blue staining reported in the literature may represent benign histopathology or lesions with mild dysplasia that harbor molecular change and are at risk for progression.

Since these findings complicate past, current and future clinical studies and patient care, we suggest that investigations examining the utility of detection and adjuncts to diagnosis, natural history studies and interventional studies require caution in interpretation. Clinical care and studies of potentially malignant and premalignant lesions and margin delineation in known cancer cases must recognize the limitations of current diagnostic procedures including biopsy. Furthermore, future studies should include a panel of blinded pathologists to assess phenotypic change, and various molecular measures should be employed when available to predict the behavior of potentially malignant lesions. Advances in molecular measures will greatly assist studies assessing diagnostic utility, clinical care and interventions for management of potentially malignant oral lesions.

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1368-8375/$ - see front matter
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Pelin Güneri
Ege University, School of Dentistry,
Department of Oral Diagnosis and Radiology,
35100 İzmir, Turkey
Tel.: +90 2323881081; fax: +90 2323880325
E-mail address: peleen_2000@yahoo.com

Joel B. Epstein
Department of Oral Medicine and Diagnostic Sciences,
College of Dentistry, University of Illinois,
Chicago, Illinois, USA
Department of Otolaryngology/Head and Neck Surgery,
Chicago Cancer Center,
College of Medicine,
University of Illinois,
Chicago, Illinois, USA

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