Editorial

Why are we still unable to accurately determine the malignant potential or the behavior of oral mucosal lesions?

Despite technological advances in medicine, health care providers struggle with the inability to determine the malignant potential of oral mucosal lesions and consequently, the insufficiency in early diagnosis of oral mucosal malignancies. Due to the relatively rare occurrence of oral malignant disease, differentiating ominous lesions of the oral mucosa from much more common benign lesions is challenging since these lesions may have similar appearances and they may not cause clinical complaints of malignant lesions until reaching an advanced stage [1,2].

Among the oral mucosal lesions that have a risk of malignant transformation, oral leukoplakia, erythroplakia and irregular lesions deserve the attention of clinicians [3,4]. Leukoplakia is a common lesion and is observed clinically up to 4.9% of the world population [5–9]. While the vast majority of oral leukoplakia represents benign conditions, some have suggested that long-standing oral leukoplakia should be considered as a potential precursor of oral cancer [3,4], however given that only a small percent harbor oral cancer [3,4], the concern of over treatment and increased cost of care is significant [10,11]. The variability in reported progression to cancer is enormous and depends on variability in study design. The reported malignant transformation rate ranges from 0.13 to 36.4% [4,7–9,12,13] within a period of 1–30 years [3,4,9]. Given these data, clinical care and clinical trials are complicated. These challenges are highlighted by considering the potential rare event of progression to cancer, and studies of even hundreds of patients may have few events leading to limited value of outcomes in even the largest studies performed to date. Furthermore, only controlled, randomized trials with sufficient time of follow-up can provide any guidance in future care.

Since 1953, the “field of cancerization” concept which hypothesizes that patients with OSCC frequently presented with regional potentially premalignant changes and may have multiple primary tumors in the upper aerodigestive tract since the entire epithelium presents a higher proportion of potentially premalignant changes in the oropharynx [14,15] has been discussed. These areas with potentially malignant molecular changes may lead to new primary cancers over time [8,16,17]. In addition to molecular epithelial change, the microenvironment including connective tissue signaling is considered critical in potential progression or regression of mucosal lesions. Additionally, new oral leukoplakia in older patients is considered at potentially higher risk than those of the younger individuals, probably due to decreasing immune function and cumulative effect of associated risk factors, unless local factors are identified as risk factors, such as local trauma [18,19]. Female gender is also suggested as a risk factor although the mechanisms of this potentially increased risk are not known [9].

It is well known that as in other potentially malignant conditions involving other tissues and body sites, oral leukoplakia may either regress or disappear in time in patients even those who received no treatment [20–22]. Oral dysplastic lesions “Risk of Regression” [reversal of dysplasia to benign] is greater than the “Risk of Progression” and any interventional therapy with significant side effects and morbidity should be exercised cautiously and only in selected cases [22]. Although it is generally thought that the prognosis of transformation potential are based on the histologic grade by evaluating the degree of cellular and architectural aberration above the epithelial basement membrane [23,24], we still require reliable histopathological parameters that predict the potential for successive transformation of oral leukoplakia lesions to malignancy, including severity of dysplasia [25,26]. Briefly, classical histopathological examination of precursor lesions has been presented as an insufficient method to predict their malignant potential [27], and molecular markers have been introduced to determine the malignant transformation potential of oral mucosal lesions [28,28,30]. Chromosome instability assessment by DNA image cytometry (ICM) and dual target FISH for chromosomes 1 and 7 on paraffin-embedded tissue sections predicts the progression of premalignant oral lesions [28]. High expression of hypoxia-inducible factor-1α or carbonic anhydrase 9 [29] and adjunctive markers for demonstrating topoisomerase 2A and MCM2 upregulation [30] have been reported as useful indicators of lesion prognosis. On the other hand, there are also reports showing contrasting results regarding the use of individual molecular markers, due to heterogeneity of series, different anatomic locations, other differences in methodology, and intratumoral heterogeneity of the marker [31]. In conclusion, despite advances in molecular biology, there are still currently no markers available in clinical practice to accurately predict the malignant transformation of oral leukoplakia [8,15,24].

Some authors recommend excision of any leukoplakia whether or not dysplasia is present [8,24], however, the vast majority are benign and excision does not show benefit with respect to progression to cancer [6,22,26,32,33]. The lack of benefit of excision may relate to surface area and margins as well as depth of excision that includes regional connective tissue. Thus, the effect of excision margin width on the recurrence of the malignant lesions is still obscure [6,15,24].

In addition, time to malignant transformation duration is not known [25,26,34] and therefore, long-term surveillance is needed since progression to cancer is thought to be a slowly progressive process with malignant transformation potentially occurring in a 10 year time frame [34,35]. Because of the recurrence rate and
malignant transformation potential of oral leukoplakia lesions, follow-up every 3 months in the first year, every 6 months in the second year [13,24], and annually for life thereafter has been discussed [24,32]. The reason for life-long follow-up is the wide variation among the incidence of oral leukoplakia lesions that will progress to malignancy due to the influence of environmental factors, sustained use of tobacco, alcohol abuse, and viral infections [36]. However, these recommendations represent expert opinions drawn from the literature and studies to guide the duration and frequency of follow-up of treated or untreated patients with oral mucosal lesions are still needed.

As we are currently unable to accurately identify lesions at risk of progression to cancer, clinicians shall also consider the efficacy of different treatment methods including topical/systemic interventions, surgical removal (scalpel surgery, laser, cryotherapy), and photodynamic therapy [7,12,15,17,33,37,38], side effects of the treatment provided prior to removal of mucosal lesions with severe dysplasia or carcinoma-in-situ. While small lesions may have lower risk with surgery, excision of larger lesions carries greater risk of significant effect upon symptoms and function, and may be closely followed rather than attempting excision. Regardless of whether small isolated lesions are excised, regularly scheduled follow up of the patient is still needed. Counter intuitively, larger dysplastic lesions should be followed for active surveillance as excision does not have predictive benefit and because surgery for wider spread areas of change have greater risk for negative symptomatic and functional outcomes. Therefore, for all lesions active surveillance is recommended.

Other parameters that contribute to the difficulty of early diagnosis of malignant transformation should be thoroughly addressed. Among these, the lack of accurate knowledge regarding the process of carcinogenesis [why and how it happens?] what is the natural history? what features determine the prognosis of the lesion? why do some lesions regress but others progress?] are as important as the limitations of the observer [physical, vision, cognition, etc., educational], facility [lack of specialists and special centers] and detection methods [pitfalls of clinical exam, vital staining, brush cytology, optical devices, etc] to identify the changes in oral mucosa which requires further examination due to the suspicious nature of the area (including molecular analysis of the biopsy specimen). In addition, variability in histologic interpretation and lack of predictive value of dysplasia complicate the pathologic assessment. Thus, development of new approaches both for clinical, histological and molecular evaluation are clearly required and must be studied in controlled, randomized multicenter well-designed natural history trials with sufficient power in order to deliver individualized cancer therapy and follow-up to provide guidance in the future. While observational studies provide the prospect for discovery and validation of predictors of progression as well as evidence-based recommendations for follow-up of patients regarding the time-course of malignant transformation, randomized studies of various treatment methods could offer data about the preferred treatment protocols of high-risk lesions.

Conflict of interest
None declared.

References


