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A treatment for oral precancerous lesions: Why do we not yet have a treatment?

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I was asked to lecture on the management of oral precancerous lesions, and to specifically focus on my personal approach to these lesions given 33-year's of experience working with this particular population.

One thought kept coming back as I was preparing this presentation: "How is it possible that despite our having an early marker for oral cancer - namely, oral dysplasias we are no more effective today than we were 50 years ago in the fight against oral cancer? By this I mean that the mortality rates for oral cancer have not changed in spite of the professional awareness of precancerous lesions, and their potential risk of becoming malignant. Moreover, these lesions present to us the possibility of observable changes in the oral mucosa weeks and months prior to the onset of cancer.

We could all agree that this is a unique and rare opportunity because few cancers, with the exception of perhaps skin cancer and melanomas, allow such easy access to them. Oral cancer and pre-cancerous lesions are so visible to the eyes that it is perplexing why we have failed so badly in defeating or even eradicating oral cancer through early diagnosis and treatment. One counter example to illustrate my point is the case of lip cancer, the only oral site where we have made major improvements both by significantly reducing its occurrence, and by increasing the cure rates. This success has been the result of extensive public campaigns reporting the effect of solar radiation on the lips, the ensuing recommendations for wearing sun block and hats, and early detection with timely treatment.

Several points must be addressed to understand the most conceivable reasons we have failed to do the same in the case of oral cancer. For instance, given the easy access to these pre-cancerous oral changes, and the relatively consistent oral appearance and sites predilection, we should have been empowering patients and other health care providers to look for these oral markers instead of having handed all the responsibility to the dental profession, namely the specialists in oral medicine, oral pathologist and oral surgery (1,2). Secondly, we have neglected to educate the public in regard to risk factors for oral cancer other than tobacco and alcohol abuse, such as oral sex (3), poor diet (4), and oral candidiasis (5,6), to list the most plausible risk factors.

In addition, another relevant question to us dental professionals is whether we haven't somehow neglected to

further scrutinize the natural course and/or behavior of this condition. Indeed, one of the most important aspects in fully understanding, and describing a disease, including its prognosis, and developing effective treatment modalities is knowing their natural history.

Perhaps influenced or biased by the early connotations associated with pre-cancerous lesions, specifically oral leukoplakia, we have recklessly chosen to treat, at all cost, instead of trying to learn more about the behavior of precancerous lesions, in particular erythroplakias and erythroplasias, even when we know that the risk of transformation is higher than for oral leukoplakia (7,8). The fact is that by doing so, we have made no progress in preventing oral cancer, and/or improve prognosis. Instead, we have continued to witness these lesions becoming cancerous before our eyes as we over-treat them. At present, there is no one test that can predict if a precancerous oral lesion will become full-blown cancer (9-12).

Indeed, the most serious problem in my view are (1) the insufficient understanding of the long-term behavior of these lesions, for instance which lesion will become malignant and/or when, and (2) the fact that we lack effective treatments.

Some colleagues often claimed that it is unethical to carry out double-blind controlled clinical studies on patients with precancerous oral lesions, yet by continuing to do what we are now doing is equally unethical, in my view. In fact, we are not really improving the patient's prognosis and it is unclear whether what we are doing is making the situation even worse. I must admit that in some cases we may postpone the development of cancer by few years. But even then we don't know if it is because of our treatment or if this was going to be the case regardless of treatment (9,12).

Actually, one factor, which could explain our inability to determine which dysplasias, will become malignant and in need of treatment is the lack of a reliable molecular marker(s) (11,13,14). Moreover, an apparent reluctance to use a uniform reporting system has precluded the universal standardization of our reporting (15,16) for multi-center epidemiologic and clinical studies.
Also, identifying key cellular/ molecular marker(s) will not only solve our diagnostic dilemmas but will lead into the development of new screening tools and therapies.

What we need to do next, I believe, is to pause and refocus our research objectives in order to gain a better understanding of what happens to these lesions when followed carefully, coupled with an evaluation of the presence and role played by local factors. Furthermore, we may have to revisit our nomenclature and classification, and radically simplify it. We should ask ourselves " Why don't clinicians want to use it". For example, the term "non-homogenous and homogenous leukoplakia" should be streamlined to "idiopathic leukoplakia" for white lesions, "idiopathic erythroplakia" for white and red lesions, and "idiopathic erythroplasia" for red lesions. Or perhaps we should limit it even further to white lesions (for idiopathic leukoplakia) and red lesions (for idiopathic erythroplasia and erythroplakia).

This will imply, to the reader, that clinicians have examined all plausible association, and that their presence is not accounted for by any local and/or systemic factor such as tobacco, trauma, alcohol, contact allergy, etc. stressing their seriousness. Also, this will facilitate or simplify the way in which clinicians select patients for their studies and how they report their findings.

At present there is no Gold Standard treatment for precancerous lesions that has been clinically proven to be effective (11). Most treatments have been hampered by the absence of a uniform reporting system for classification and staging of the disease, as previously emphasized by van der Waal (15) without which it will be almost impossible to objectively monitor any treatment outcome. Likewise, any molecular or genetic research will be meaningless without proper classification of the oral lesion (13).

From reviewing the literature my personal thought is that subjective criteria have largely been used to diagnose precancerous lesions, clinically and histologically. Clinicians as well as oral pathologists cannot agree on any specific pattern of histological findings to establish a consistent and reproducible diagnosis (16-19). We presently use the terms "mild", "moderate", "severe" dysplasia, which does not help the clinician in making an intelligent decision on when and how aggressively to treat.
Pathologist like clinicians will have to simplify their classification system for it to be used (20). Clinicians likewise have not been able to agree on what is to be identified as "erythroplakia", "lichenoid changes", "lichen planus", " candidiasis" lichenoid-dysplasia" (11,21,22). To compound the problem, all molecular markers thus far have been inconclusive (10, 13,14), and/or too expensive to be used routinely in any clinical setting.

With the exception of a few clinical and intervention studies (11) the majority of publications on the treatment of precancerous lesions comprise pilot studies, case-series, reporting, reviews and letters (11). In other words, there are no well-designed clinical trials, sys-

tematically tested and proven to be effective for precancerous lesions.

All treatments seem to help one way or another depending on who conducted the study. So far the most popular seem to be the use of CO_2 laser (23-25).

Clearly attested for in the literature, and confirmed by my own personal experience, CO2 laser provides the easiest, cleanest and most convenient approach to patients and clinicians. Yet, we need to be aware of the fact that even this procedure has not been universally standardized. Further studies should at least consider randomizing patient selection to avoid clinician's selection bias, and should adhere to strict disease classification guidelines (11).

In CO2 laser protocols, the only constant variable is that we use CO2 laser; any other aspect of the treatment is solely a decision made by the clinician. Issues regarding patient selection, surgical margins, required to guarantee disease control, the depth of the surgical sample, etc, are all arbitrarily determined by the clinician, and/or surgeon. So, whether or not you have a positive outcome depends primarily on the clinician's experience in selecting the right lesion, and properly mapping it at the time of the surgery, as well as having a skilled and experienced surgeon performing the procedure. This could explain the discrepancy in outcomes from different case-series published in the literature (24,25).

As I mentioned earlier, we need to systematically collect information on other, local factors such as candidiasis, HPV associated lesions (3,26), nutrition, and xerostomia (27).

Until we have a better understanding of the course of precancerous lesions, specifically erythroplakias and erythroplasias, and can develop a reliable diagnostic instrument, we will not be able to accurately evaluate treatment outcome. Any outcome whether favorable or not could be the result of chance, misdiagnosis, over -diagnosis, or under-diagnosis, and not necessarily the effectiveness of a treatment approach.

In summary, we need to work toward the identification of cellular/molecular makers to help in diagnosis (28,29), and therapies.

In parallel, we must try to educate the population not only about the risk factors associated with oral cancer but also the most common clinical sites, and appearance of oral pre-cancerous lesions and oral cancer. Preliminary data indicates (1,2) that there is a period of approximately 7-month from the time a patient becomes aware of a problem in their mouth to the time of treatment. Given the success Dermatologists have had in educating health care providers and the public on the risk factors and clinical appearance of skin cancer including melanoma, there is all reasons to believe that we the oral health care providers could achieve the same success.

The management approach to precancerous lesions which I have developed consist of the following steps and/or guidelines: Obtain detail information on the family history of cancer, medical history (of any HPV-associated lesions), and thorough social history (use of tobacco, alcohol, and/or recreational drugs)

1. Perform a careful oral examination and do record by photos any oral changes.
2. Work out a provisional diagnosis, which will help in determining biopsy site (s). Use toloudine blue to map and/or help in selecting the most appropriate biopsy site. Consider all high risk sites (lateral tongue, floor of the mouth, soft palate) for biopsy.
3. When candida is suspected, treat prior to biopsy. For patients with a positive history of oral candidiasis at baseline, identify any underlying medical problems (diabetes), and referred for treatment. In patients otherwise healthy look for local factors (xerostomia).
4. Always compare patient's history with clinical findings and evaluate the significance of such findings (erythroplakia in a young woman, with unknown risk factors on lateral tongue). Some findings should alert the clinician as to the severity of the situation, and will help in determining treatment protocol, frequency of clinical visits and biopsies.
5. Evaluate every lesion in the mouth, and re-access on each follow up visit. Patient can develop new lesions. I always keep in mind that a patient may have different type of lesions at the same time.
6. First order of treatment must include stabilization of the mouth (treat for dryness, and fungal infection). Insist on the importance of good oral hygiene, and good nutrition.
7. Use toloudine blue to monitor disease instead of performing un-necessary biopsies.
8. Use CO2 laser in cases involving severe dysplasia where significant changes are seen over time, and the patient is symptomatic. Prior to laser take a biopsy, and properly orient sample for further evaluation of the lesion. When thinking of margins use same principles as for cancer removal.

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