

REVIEW ARTICLE

Oral potentially malignant disorders: A proposal for terminology and definition with review of literature

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ABSTRACT

Several attempts to produce internationally accepted terminologies and definitions of 'oral precancer' have appeared in the literature. World Health Organizations (WHO) in 1972 subdivided 'precancer' into 'lesions' and 'conditions' with their definitions. Recent working group of WHO is not in favor of such subdivision and recommended the use of the term 'oral potentially malignant disorder (OPMD)'. This is mainly attributed to the recent advancement in molecular and genetic aspects of 'oral precancer'. But efforts to define OPMDs are few in the literature. 'Oral precancer' is ultimately colligated to oral squamous cell carcinoma (OSCC). With this semantics in mind, different OPMD and related terminologies in the literature used till date with their lexicographic analysis have been reviewed in the present paper. Attempt has also been made to propose desirable terminology and definition which suits to the current concept of OPMD. The proposed terminology and definition is based on the authors' opinions with a hope for further suggestions from readers.

Key words: Carcinoma prone, epithelial precursor, intra-epithelial neoplasia, oral squamous cell carcinoma, precancer, premalignant, preneoplastic

INTRODUCTION

Medical terminologies have always undergone refinement in the literature for the pursuance of correct, clear, uniform and unambiguous terminologies. This quest is necessary for standardization of the terminology, which must reflect the most advanced scientific understanding of the concept and adhere to the best available knowledge-representation principle. In parallel, progress in eHealth applications has led to increased use of electronic health records, which also require a standardized clinical terminology.

It has been well-established by researchers that virtually all oral cancers are preceded by visible clinical changes in the oral mucosa usually in the form of white or red patch (two-step process of cancer development). Prevention and early detection of such oral potentially malignant disorders (OPMDs) have the potential of not only decreasing the incidence but also

improving the survival of those who develop oral cancer.^[1] OPMD and related terminologies (precancer, premalignant, preneoplastic, carcinoma prone, epithelial precursor, intra-epithelial neoplasia, intra-epithelial carcinoma) are discussed widely in the literature. Several attempts to produce internationally accepted terminologies and definitions have appeared in the literature. OPMD and related terminologies are ultimately colligated to oral squamous cell carcinoma (OSCC). Hence, pathogenetically the terminology should reflect the ultimate meaning of OSCC. With this semantics in mind, different terminologies related to OPMD are reviewed and lexicographically analyzed in the present paper. Their closeness and deviation from association with OSCC is studied. The attempt has been made to propose a desirable terminology and definition so as to suit to the recent concept of OPMD.

Concept of OPMD

The terminologies and concepts discussed till date in the literature regarding OPMD are related to transformation of 'oral mucosa' to OSCC. To be more particular, OPMDs are directly or indirectly related to stratified squamous epithelium of lining, masticatory or specialized mucosa of the oral cavity. In another way, the OPMDs can be termed as 'oral mucosal potentially malignant disorders'.^[2] The concept of denoting

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some lesions or disorders of the oral mucosa as ‘precancerous’ is based on the evidence that:^[3]

1. In longitudinal studies, areas of tissue with certain alterations in clinical appearances identified at the first assessment as ‘precancerous’ have undergone malignant change during follow-up
2. Some of these alterations, particularly red and white patches, are seen to co-exist at the margins of overt OSCCs
3. A proportion of these may share morphological and cytological changes observed in epithelial malignancies, but without frank invasion
4. Some of the chromosomal, genomic and, molecular alterations found in clearly invasive oral cancers are detected in these presumptive ‘precancer’ or ‘pre-malignant’ phase.

OPMD related terminology: Literature review

The concept of ‘precancer’ begins in 1805 with a suggestion given by a European panel of physicians that there are benign diseases which will always develop into invasive malignancy if followed for a long time.^[4] The term ‘precancer’ was first coined in 1875 by Victor Babes, a Romanian physician. This concept later widened to include a number of diseases in various organ systems. Junctional nevi and xeroderma pigmentosa of the skin, leukoplakia and papillomas of the urinary bladder and larynx, polyps of the colon and solitary adenomas of the thyroid are some of the lesions thought to be precancerous.^[5]

Oral precancer, in particular, have a rich and fascinating literature extending as far back as 1870s, when Sir James

Paget, one of the England’s most renowned surgeon, proposed that ‘leukokeratosis’ or ‘smokers patch’ of the hard palate (nicotine palatinus) or the tongue in innervate pipe smokers carried an increased risk of eventual cancer transformation.^[6] Subsequently in the literature, various terminologies appeared in relation to the ‘precancer’ concept like ‘pre-malignant’, ‘preneoplastic’, ‘carcinoma prone’, ‘intra-epithelial neoplasia’ etc. But the information concerned the evolution of these terminologies is unavailable in the international literature. Because of the continuing challenge and confusion surrounding the oral cancer concept, the WHO has periodically convened International Workshops to redefine the term ‘precancer’ and various precancerous lesions. A much earlier working group of the WHO in 1978 used the term ‘precancer’ which was further classified into ‘lesions’ and ‘conditions’.^[7] The most recent workshop held in London 2005, recommended the use of the term OPMDs and elimination of the term ‘precancer’.^[3] However, the latest WHO monograph of Head and Neck Tumors (2005) uses the term ‘epithelial precursor lesions’.^[8] Recently, Manne RK proposed the term potentially malignant disorders/ individuals for the individuals with no known predisposing disorders or any clinically evident lesion but oral mucosa may be susceptible to cancer.^[9]

Lexical semantics of terminologies related to OPMD [Figure 1]

For lexicographic analysis of the terminologies, Dorland Illustrated Medical Dictionary (32nd ed.ition), Oxford Medical Dictionary (6th edition), Merriam-Webster Medical Dictionary (11th edition), Stedman’s Medical

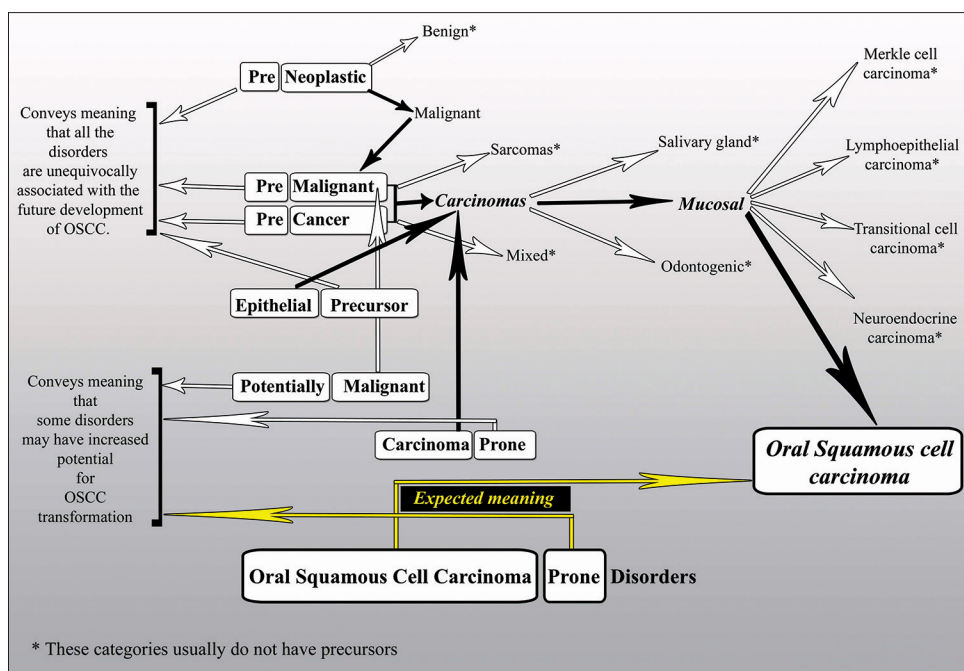


Figure 1: Diagram depicting the meaning of words associated with terminologies related to ‘oral precancer’. Black arrows depict the apartness and closeness of the terms to the expected meaning of oral squamous cell carcinoma

Dictionary (28th edition) and Mosby's Medical Dictionary (9th edition) have been used.

The word 'pre' is used as a prefix in many OPMD related terminologies like precancer, premalignant, preneoplastic, etc., 'Pre' literally means (Latin *Prae-*) 'before', 'prior to', 'in advance of', 'early', 'before hand' and 'in front of'. Likewise the word 'precursor' (related terminology 'epithelial precursor'^[8] and 'precursor of OSCC'^[10]) is derived from Latin word *prae + currere*, 'to run'. It means something that precedes or coming before another (forerunners or predecessors). When 'pre' and 'precursor' is used in context to 'precancer' concept, it conveys that all the lesions are unequivocally associated with the future development of OSCC. According to the recent concepts, not all the disorders will transform into OSCC but there are disorders among which some may have an increased potential for malignant transformation. Hence, word 'potential' was recommended in the most recent workshop of WHO held in London in 2005.^[3] The word 'potential' literally means 'capable of being but not yet in existence', 'having possibility, capability or power', 'the inherent ability or capacity for growth, development or coming into being'.

The word 'prone' is derived from the Latin '*Pronus*' meaning 'naturally inclined to something', 'having tendency'. The terminology 'carcinoma prone' conveys the meaning that disorders included have a tendency or inclination or potential or likelihood of or a natural predisposition towards OSCC transformation. It also expresses the meaning that not all the lesions will undergo OSCC transformation but all are prone to and probably some may undergo OSCC transformation. We feel that the terms 'potential' and 'prone' are in agreement with the current concept of 'precancer'.

The word 'neoplasia' (related terminology 'preneoplastic' and 'intra-epithelial neoplasia') literally means 'a new growth' (Greek word *neos*, 'new', *plassein*, 'to mold'). Neoplasms can be benign or malignant. The word 'benign' is in no way related to OSCC. The word 'malignant' (related terminology 'pre-malignant' and 'potentially malignant') is derived from the Latin word *malignus*, meaning bad disposition. Malignant as applied to neoplasms, implies that the lesion can invade and destroy adjacent structures and spread to distant sites (metastasize) to cause death. Not all cancers pursue a deadly course. Some are less aggressive and are treated successfully, but the designation 'malignant' constitutes a red flag.^[11]

Malignant tumors are collectively referred to as 'cancers' derived from a Latin word, meaning 'crab'. The origin of the word 'cancer' is credited to the Greek physician Hippocrates (460-370 BC). The Roman physician, Celsus (28-50 BC) later translated the Greek term into 'cancer'. The term 'malignant neoplasm' or 'cancer' (related terminology 'precancerous') can be divided into sarcomas (arising from

mesenchymal tissue or its derivatives) and carcinomas (arising from epithelial cells). The word 'sarcoma' is unrelated to OSCC. The word 'carcinoma' (related terminology 'carcinoma prone' and 'intra-epithelial carcinoma') is derived from the Greek word *karkinos + oma* meaning a malignant epithelial neoplasm that tends to invade the surrounding tissues and metastasize to distant regions of the body. Carcinomas of the oral cavity can arise from the epithelia of salivary gland, odontogenic epithelia or mucosal epithelia. The salivary gland carcinomas and odontogenic carcinomas are not pertained to OSCC. In mucosal carcinomas, although OSCC is the most common one, the possibility of merkle cell carcinoma, transitional cell carcinoma, neuroendocrine carcinoma, lymphoepithelial carcinoma and basal cell carcinoma can not be brushed aside.

With the above discussion, it is realized that the terminologies 'precancer', 'pre-malignant', 'preneoplastic', 'carcinoma prone', 'epithelial precursor' and 'potentially malignant' 'intra-epithelial neoplasia' and 'intra-epithelial carcinoma', are far away from its expected meaning (of colligation to OSCC) [Figure 1]. As we are focusing on OSCC exclusively while defining the terminologies, the proposed terminologies in the literature till date appear quite vague. Semantically these terminologies may be correct but lexicographically they appear obscure. Hence we would like to propose a new modified terminology 'OSCC Prone Disorders' which is very close to the expected meaning and also bridges the undefined gap created by the previous terminologies. This terminology appears clear, precise and less ambiguous.

Definition: Review and proposal

In 1978, working group of WHO classified 'precancer' into 'lesions' and 'conditions' with following definitions^[7]

- A precancerous lesion is 'a morphologically altered tissue in which oral cancer is more likely to occur than in its apparently normal counterpart'
- A precancerous condition is 'a generalized state associated with a significantly increased risk of cancer'.

At the time these terms were coined, it was considered that the origin of a malignancy in the oral cavity of a patient known to have a precancerous lesion would correspond with the site of precancer. On the other hand, in precancerous condition, cancer may arise in any anatomical site of the mouth or pharynx. It is now known that even the clinically 'normal' appearing mucosa in a patient harboring a precancerous lesion may have dysplasia on the contralateral anatomic site^[12] or molecular aberrations in other oral mucosal sites suggestive of a pathway to malignant transformation and that cancer could subsequently arise in apparently normal tissue^[13] Moreover, the concept of field cancerization and relatively high rate of second primaries seen in the oral cavity further weaken these definitions. Later in 2002, Küffer *et al.*,^[10] proposed a unified classification of oral 'precancerous lesions' partly based on

the gynecological model, taking into account the histological patterns and clinical correlations. One of the central features of their proposal is the classification of all cases without dysplasia as risk lesions and of all cases with dysplasia as precursor lesions of OSCC. The current Working Group of WHO (2005) did not favor subdividing precancer to lesions and conditions and the consensus view was to refer to all clinical presentations that carry a risk of cancer under the term ‘potentially malignant disorders’ to reflect their widespread anatomical distribution.^[3] However they have not proposed a definition for OPMD.

The latest WHO monograph on head and neck tumors (2005) uses the term ‘epithelial precursor lesions’^[8] and defined it as ‘altered epithelium with an increased likelihood for progression to squamous cell carcinoma’. It is also mentioned that word ‘altered’ in the definition means epithelial dysplasia. Rarely malignant changes can develop even in clinically and histomorphologically normal epithelium (non-dysplastic) which makes the given definition somewhat incomplete. Development of second primary tumor at clinically normal mucosa supports the contention.^[14] Moreover, we feel that alterations and mutations in the genetic material of oral epithelia are an integral part of ‘pre-malignancy’ and should be reflected in the definition. Various etiological factors are associated with OPMD suggesting different pathogenesis. But the fact, which can not be ignored, is that predominantly tobacco is responsible for OSCC transformation. We feel that this should be included as a part of definition. In support of varied pathogenesis, Sarode *et al.*,^[15] proposed a novel pathogenesis based classification of OPMDs in which all the disorders either carry some risk and/or predispose the oral mucosa to OSCC transformation.

With all this discussion in mind, attempt has been made to propose a definition for OSCC prone disorders which is as follows:^[16]

‘It is a group of disorders of varying etiologies, usually tobacco; characterized by mutagen-associated, spontaneous or hereditary alterations or mutations in the genetic material of oral epithelial cells with or without clinical and histomorphological alterations that may lead to oral squamous cell carcinoma transformation.’^[16]

The word ‘disorders’ used in the proposed definition is more apt over the words ‘lesions’ and ‘conditions’. The word ‘disease’ is not used because patient having ‘precancer’ may not necessarily be diseased. The suggested definition depicts the molecular nature of the OPMD along with the possible presence and absence of clinical and histomorphological alterations. The rationale behind including the “with or without clinical or histomorphological changes” statement is that there could be genomic alterations in normal (clinically and histopathologically) appearing mucosa that makes oral cavity susceptible for OSCC transformation. Such disorders are mentioned in our proposed classification of oral potentially

malignant disorders as group III and IV category.^[15] Although each such disorders have their own diagnostic workups, genomic alterations of the oral epithelium would be the best method to identify such individuals/disorders.

The suggested terminology is not a consensus based of any organization or conference. Hence, we would like to declare that the proposed terminology and definition is based on the authors’ opinions with the hope of further suggestions from readers.

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