NARRATIVE REVIEW

Determinants Of Malignant Transformation Of Oral Potentially Malignant Disorders – Covering The Gaps

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ABSTRACT: Oral potentially malignant disorders (PMDs) are heterogonous group of lesions and conditions which are warned for future occurrence of oral cancer (mostly oral squamous cell carcinoma OSCC). Habits like tobacco or beetle quid chewing, smoking were considered to be the only important aetiologies of PMDs and OSCC. However, considering the updated reports of oral cancers, evidence exits on its occurrence in absence of any habit history or in normal sites as explained by concepts of field cancerization. This alarms for understanding all possible reasons which may determine the nature of a lesion or factors that are associated with malignant transformation to oral cancer. This review shall cover all possible factors that determine the malignant transformation of oral potentially malignant disorders so that a clinician can understand and judge upon on the progress of potentially malignant conditions to oral cancer just by examining the lesion and co-relating with the listed "Determinants of malignant transformation" for PMDs and OSCC.

KEYWORDS: *Potentially malignant disorders (PMDs), Malignant Transformation (MT), Oral epithelial dysplasia (OED), Oral squamous cell carcinoma (OSCC).*

Introduction:

Oral cancer is one of the most common cancers in Indian men while it is only the sixth most common cancer worldwide [1].It is estimated that more than one million new cases are being detected annually in the Indian subcontinent. Among the various oral malignancies, 90-95% are Squamous Cell Carcinomas (OSCC). [2] Treatment of oral cancer i.e. Radiotherapy and surgery have many long-term effects like permanent dysfunction (speech, mastication, loss of salivation, swallowing) and disfigurement of Oro-facial structures effecting patient physically, mentally and socially [3] It is to be known that many oral cancers develop from a pre-existing potentially malignant Disorders (PMDs).[4] Correct diagnosis of PMDs may help prevent malignant transformation in oral lesions and thus occurrence of OSCC.In early literature, the reasons for high prevalence of oral cancer and rates of malignant transformation of PMDs in Indian scenario were reported due to habits. [4-6] However, recent reports of oral cancer occurring in people with no habits or in normal mucosal sites are present.Occurrence of second primary tumours and recurrence of PMD is also reported which are explained by concepts of field cancerization. This

alarms for understanding all possible reasons which may determine the nature of a lesion or factors that predispose to oral cancer. This review shall cover all possible factors that determine the malignant transformation of PMDs so that a clinician can understand,judge and prevent progress of PMDs to oral cancer.

Understanding about the determinants of malignant transformation:

Sir James Paget (1870)[7] first described malignant transformation (MT) of an oral lesion into tongue carcinoma .Schwimmer (1877) [8] also reported the same findings. After WHO (2005) coined the term "potentially malignant disorders" the risk of malignancy is to be noted, in any condition or lesion having potential to undergo malignant transformation. [6]

There are certain factors like age, sex, location of the lesion, the systemic/immune status of the patient and stage/ type of the lesion with which the patient reports to clinician that reflect the ability of a PMD to transform into OSCC. These can be considered as 'clinical determinants' in malignant transformation. Oral epithelial dysplasia (OED) an important sign

to assess prognosis (MT) has be considered in this review as 'histological determinant' of malignant transformation. Categorization of these features that determine the MT of PMDs was roughly given by Silverman *et al* (1984) [9]where in a few criteria like the age, gender, anatomical location, number of lessons and paradoxically non-smoking history were considered in his assessment on malignant transformation of PMDs. However, Ho*et al* (2012) [10] have proposed histological determinants or oral epithelial dysplasia (OED) in important PMDs like leukoplakia and erythroplakia. The author considered size, site, and history of smoking, homogeneity of lesion and border significance. On the contrary, criteria like gender, age, alcohol consumption, and number of lesions were found insignificant in determining the malignant transformation. It is needless to mention that cancer risk is invariably increased in people with positive habit history compared to their habit less counterpart. However, OSCC arising in normal mucosa with no precancerous change or with negative habit history shows increased aggressive behaviour [11].

The determinants of malignant transformation of PMDs presented in this article (see table 1) is modified with reference to, Mortazavie*t al* [6],*sliverman et al*[9]. Scully *et al* [12]and George *et al* [13].Oral epithelia dysplasia (OED) is an important histo-pathological determinant, having a proportional relation (higher the grade, higher is chance of malignant transformation and vice versa) which is not discussed here.

1. Age:

The mean age at diagnosis of oral premalignancy is 50-69; less than 5% of diagnoses of OSCC are in patients under 30 years of age. [14,15] The prevalence of PMDs are also notable in young and old age groups, as the habit addition is reported at early ages[16] which is an aetiology of many PMDs.However, patients suffering from Xeroderma pigmentosa, Human Papilloma Virus (HPV) infections, Discoid lupus erythematosis (DLE), Xeroderma pigamenstosa, Blooms syndrome should be cautioned as there is increased chance of malignant transformation of these condition at younger age group. [17]

Older adults account for 60% of incidences of cancer and 70% of cancer related deaths.[18] The process of ageing favours two essential processes in cancer development. Firstly the acquisition of mutations and next the formation of a molecular and cellular environment which favours carcinogenesis [19].

As age advances, the processes like DNA repair become less active andefficient, allowing DNA adduct formation, hypo-methylation of DNA and more frequent mutations, chromosomal breaks and translocations. Mutations can inactivate anti-proliferative and apoptotic tumour suppressor genes, cause proto oncogenes to become oncogenes or hinder the function of DNA repair genes. The accumulation of such non- lethal genetic damage is the basis of cancer. [20].

The following geriatric factors may increase the risk of Pre-cancer and cancer :[20].

1. Co-morbidities: Old age is often associated with systemic diseases like Diabetes mellitus, Hypertension and other autoimmune disorders may predispose to cancer by rendering individual immune deficient.

2. Multisystem Functional loss: Reduction in number of nephrons and active liver cells due to ageing will compromise drug metabolism and concrete toxic agents (chemo-therapeutics) which in turn lead to adverse effects.

3. Maintaining hygiene and health: Difficult in old age individuals, predisposing to secondary infections. Recurrence of pre-existing or treated tumors could occur, owing to poor hygiene practices. Addiction to harmful habits over a long period of time also worsen the prognosis and favors recurrence.

4. Screening : often cancer screening is employed in young age groups, but participation of older groups is minimal, giving chance of existing tumor or pre-cancer to prevail for further progress. Only 9 - 15% of older adults participate in clinical trials even though over half of all new diagnoses are made in this population.[319]

5. Treatment outcome: Disease and disability, which may interfere with cancer treatment and recovery, are more likely to occur in older adults. Age is a predictor for increased surgical morbidity and mortality

6. Follow up: owing to difficulties in keeping follow up appointments, there could be recurrence of treated cancers.

7. Emotional concerns: Stress, social isolation and ability to cope up with treatment is comparatively low in older individuals than younger counterparts, which effects the treatment. Stress and DNA damage were shown with positive association by studies.

10. Anemia: Anemia is one common cause for failure and recurrence of tumors due to radio-resistivity it causes, making tissues hypoxic. Hemoglobin levels of 14.5 in men and 13 in women was associated with improved loco-regional and survival control. [3,19]

PMDs occurring at young ages can be attributed to following reasons:
Disorders with habit association, some infective causes (most common infection, candidiasis occurs in aged immune-compromised individuals) genetic disorders will occur at young age whilst, autoimmune disorders can occur in any given age.

However, some of the PMDs (OSMF and Reticular Lichen planus) at young age and most OSCC at old age are shown fatal. For instance,Ranganathan*et al* (2004)[21] showed in a case control study in Chennai, southern India, that the risk of developing OSMF was almost double for subjects below 21 years of age compared with that for the 21–40 year age group; the younger group developed features of OSMF in 3.5 years whilst the older group took 6.5 years from the start of the habit.

PMDs with genetic factors in aetiology and inherited disorders occur at an early age. Bloom syndrome shows its features by 26 years [22] (mean age) whilst Fanconi's anaemia can be diagnosed before child is born. [23]

Viral infections are often associated with young adult age group, often due to sexual transmission. Smith *et al* (2004) [24] showed the association of age and sex habits with HPV lesions and oral cancer. HPV infection was detected in 4.8% of 332 control patients from an outpatient clinic and in 2.9% of 210 college-aged men (age range, 18–23 years). Similarly, infections of Human immunodeficiency virus, Hepatitis (B and C), Herpes Simplex (1 and 2) occur in young adults. Thus, it can be inferred that viral infections like HPV, HSV, HCV and HIV occurring in adult age group is not uncommon.

2. Sex:
With reference to high prevalence of oral habits in men compared to women, PMDs and OSCC prevalence is higher in men compared to women. As per Scully *et al* (2008) [12] studies have shown that epithelial dysplasia has a predilection for males, but the decrease in the male: female ratio for oral squamous cell carcinoma suggests the picture may be changing. [14, 15]

Although leukoplakia is more common in males than in females, the latter has a higher risk of developing oral cancer due to undetermined etiological facts. [25]
If men were predisposed to cancer due to smoking, women were predisposed due to other forms of tobacco i.e. snuff dipping, smokeless tobacco chewing and as an adjuvant material with beetle quid.

As per Mathew *et al* (2008) [26], prevalence of OSMF was more among men 3.07% compared to women 0.22% while, Sharan and co-workers (2012) [27] have reported a male predominance (73%) in their epidemiological study of OSMF among gutkha chewers of Patna, Bihar. The male to female ratio was 2.7:1.

Reasons for specific sex predilection of PMDs:
Males are commonly effected due to the prevalence of addiction to habits especially to Pan Masala, Betel quid and tobacco, causing OSMF. [27,28] Female predilection in cases of reverse smoking is noticed invariably in all parts of the world. [29-31] which is explained by reasons like, the fear of being spotted in society and to relive from tooth ache.

Some hereditary diseases like Fanconi's anemia, Xeroderma pigmentosum and Bloom's Syndromes have specific sex predilection owing to the pattern of disease inheritance. [6,13]

Actinic cheilitis being common in males is explained by the fact the lesions are observed with occupations of framers, construction workers and outdoor employees working under sun having fair complexion. [32]

Dyskeratosis Congenita (DC), an autoimmune disease associated with PMDs and OSCC affects men, and occurs inherited as X linked recessive disorder with male: female predilection of 13:1[33].

Thus, habit history, occupational exposure to radiation and inherited patterns (genetic factors) apart from the unexplained etiologies in case of some autoimmune diseases leading to OPMDs are responsible for sex predilection.

3. Size of the lesion:

It is a well-accepted fact that direct proportionate relation exists with size and prognosis. The larger area in the mouth OPMD occupies, the higher is that chance for malignant transformation to oral squamous cell carcinoma. [10] Diffused lesions spreading over large areas have been associated with high dysplastic changes. One good example of this is reverse palatal smoking, where diffused lesion is present.

Gómez *et al* (2008) [34] found epithelial dysplasia and OSCC in 83.3% and 12.5% of reverse smokers, respectively. The concept of field cancerization (Slaughter *et al* 1953) [35] considers whole mucosa exposed o carcinogen to be "preconditioned epithelium" from which a cancer can arise, tobacco followed by alcoholism are habits that precondition mucosa.

4. Location/ site of lesion:

It is fact that more than 70% of red lesions (erythroplakia), white lesions (leukoplakia, oral lichen planus) and conditions like OSMF affect buccal mucosa. The occurrence of lesion is very critical as a prognostic indicator, however the habit history (tobacco/ beetle quid chewing, pipe smoking, and reverse smoking) gives valuable clues to sites abused by the same. The sites commonly effected are buccal mucosa, lip vermilion, tongue and gingiva. [6]

The malignant transformation doesn't follow the same order. The floor of the mouth (42.9%), tongue (24.2%) and lip vermilion (24%) account for more than 90% of those with malignant changes. [6] Candidal lesions often affect the tongue primarily [36]. The dorsum of tongue has better prognosis while the ventral region of tongue is associated with high malignant transformation. The reason for susceptibility of lateral borders evident from repeated cytogenic damages in the region as per Fareed *et al* (2012) [37].

The sites most alarmed are floor of the mouth, ventrumand posterior 1/3rd of the tongue. The lesions unidentified in these sites if has a malignancy developed shall have worst prognosis. [36]

Iype*et al* (2001) [38] form an epidemiological study , on sites of involvement of OSCC, from Trivandrum, southern India, reported 52% of their patients had tongue involvement followed by 26% with lesions in the buccal mucosa.

As per review after a study on prevalence of oral lesions in Allahabad, India, by Ravi *et al* (2008) [38], the buccal mucosa (47.7%) was found to be most frequently involved site followed by tongue (27.6%).

Many authors [6] [29] [39] demonstrated that lesions located on the lower lip had a higher risk of malignant transformation compared with upper for verrucous hyperplasia, [6] actinic cheilitis [41, 42] and cancer occurring due to solid organ transplants [39] [40].

In malignancy, the tongue (67.4%) was found to be the most frequent site, followed by buccal mucosa (7.75%).Ravi *et al* (2008) and Iype*et al* (2001) [38] had similarities in their interpretations that tongue is the common site for oral cancer to occur in patients with PMDs. Sites commonly affected by PMDs are listed in table according to study by Bokor*et al* (2004)

[43] while, Reibel*et al* (2003) [44] have reviewed and found relevant explanations with genetic basis for the reason for 'localization' (or site as a determinant). Authors have reported, that the concept of high-risk sites may gain support from genetic studies. In a recent study by Zhang *et al* (2001), it was found that epithelial dysplasia from high-risk sites had a higher frequency of loss of heterozygosity and a pattern of loss associated with an increased risk of progression to malignancy.

As per Lesch*et al* (1989) who have given explanations for a possible existence of a higher risk in the floor of the mouth and ventrolateral tongue could be that these areas are substantially more exposed to carcinogens pooled in saliva than other areas of the oral cavity, and a that a higher permeability of the epithelium exists, as indicated in experimental studies on human oral mucosa. This is an apt explanation why human micro nuclear assay showed more DNA damage from lateral borders of tongue [45]. The possible reasons poor prognosis in association to specific sites are given in table 2.

5. Duration of lesion:

Longer the duration of the lesion, higher the chance of malignant transformation. However studies showed that commonly OSCC occurred with duration of 5 years from PMD. [25] [46] Verrucous lesions (Proliferative verrucous leukoplakia and verrucous hyperplasia) show malignant aggressive behaviourin short duration.[25][36]

Ho*et al* (2009)[47] have done a study on prevalence of PMDs along with assessment of malignant transformation rates and the duration taken in months for the transformation to occur in PMD by following up the cohort. Likewise, Wang *et al* (2014) [48] have reported in a Prospective study in Taiwanese population, that the mean duration is a variable based on the type of PMD. Details in table 3, 4 respectively.

6. Type of lesion:

It is well accepted that nonhomogeneous leukoplakia is associated with a higher risk (4-7 fold) for MT compared to homogeneous lesions [11, 49] Thick leukoplakia undergoes malignant transformation in 1–7% of cases. The frequency of malignant changes in verruciform and speckled leukoplakia ranges from 4% to 15% and 18% to 47%, respectively. [25] Shafer *et al* [36] showed pure red lesion or erythroplakia to have a malignant transformation rate of 56.9% in examined 33 cases. However the red and white lesions follow the order pure red lesion (erythroplakia) followed by red and white lesion (erythroleukoplakia) and lastly the pure white lesion. [6, 36, 50] This shows that, considerable importance must be paid to pure red lesions.

Waal *et al* (2008) [51] mentioned that majority of erythroplakia will undergo malignant transformation. There are not enough documented series that would allow to calculate a reliable annual malignant transformation rate. There are no data from the literature about the recurrence rate after excision of erythroplakia.

As per villa *et al* (2014)[52] Erythroplakia was reviewed from studies worldwide, for 10 years and results showed sixty-two lesions developed oral cancer with a malignant transformation rate of 44.9%.

7. Diversity / heterogeneity of lesion:

Villa *et al* (2006) [52] have stated that there is a high malignant potential (55-65%) of pure red lesions (erythroplakia) despite its low prevalence ranging between 0.01% and 0.2% The presence of an erythematous component (erythroleukoplakia) seems to convey a greater risk for MT.

Ho*et al* (2009) [47] have done a retrospective analysis on MT rates of PMDs in males, and have concluded the importance of recognition of habit in males and site as tongue for lesions follow after diagnosis. Authors suggests that rigorous follow-up is advised in the first 2–3 years after the detection of PMDs. Finding a lesion located on the tongue appears to be the most important factor affecting malignant transformation of PMDs.

Bakri*et al* (2010) [53] have reported the presence of candida in leukoplakia (super infection). Similarly, Human papilloma virus (HPV 16, 18) has been associated with leukoplakia. Such infections have been associated with MT.

Began *et al* (2012)[50] have stated ,proliferative verrucous leukoplakia (PVL) occurs more in non-smokers, elderly women having high MT ranging from 65 % (in women) to almost 100% when in case of non-smoking women at extreme ages. Waal *et al* 2008[51] have listed criteria for the same (see table 5).

Bouquot*et al* (2006) [54] in a review on PMDs have given a comparative risk of MT rates. The order is *Proliferative verrucous leukoplakia, Erythroplakia, Nicotinepalatinusinreversesmokers,OralSubmucous fibrosis, Speckled, granular(non-homogeneous) leukoplakia, Laryngeal keratosis/leukoplakia, Actinic cheilitis, Smooth, thick (homogeneous) leukoplakia, Smokeless tobacco keratosis and Lichen planus.*

CONCLUSION:

Understanding the 'determinants of malignant transformation' of PMDs will guide a clinician on the risk of malignant transformation and to assess the prognosis as per the lesion's demographic, clinical and histo-pathological factors. The'determinants of malignant transformation' discussed here will guide a clinician to various aspects to be checked upon, while examining a PMD prior to a biopsy. It is recommended to evaluate grades of dysplasia, (Histo-pathological determinant) following a biopsy for suspected site and for reporting a final diagnosis. Knowing, that many OSCC develop from PMDs, early diagnosis of these lesions and understanding the ability of these lesions to undergo malignant transformation and associated risk factors can help save many lives form claws of cancer.

Table 1: A Modified Classification for Determinants Of Malignant Transformation Of Oral Potentially Malignant Disorders:
I Demographic determinants:
1. Age   2. Sex
II Clinical determinants
1. Association with habit.
2. Site of occurrence of lesion.
4. Size of the lesion
4. Duration of lesion.
5. Diversity/ Clinical sub type
6. Heterogenicity of lesion
III Histological Determinants: 1. Oral epithelial Dysplasia (OED)

Table 2: Reasons for worst prognosis in floor of the mouth and tongue [25,44,45]	
1	Initial lesion grows often unnoticed.
2	Growing lesion has chance to spread or invade into surrounding vital structures.
3	Surgical therapy in these region is destructive causing functional loss and these are often sites of recurrence.
4	The tongue has rich lymphatic drainage, into submandibular or directly into deep cervical nodes, favouring skip metastasis.
5	Salivary pooling action, precipitating carcinogens in floor of mouth.
6	Genetic factors – loss of heterozygosity noted from evidence of damaged DNA form these sites.

Table 3 : Malignant transformation of PMDs considering age, duration, And transformation rates from a retrospective study [47]					
PMD	**Age (years)**	**Mean Duration (months)**	**Duration Range**	**Malignancy (%)**	**Transformation rate (MT)**
Epithelial dysplasia	46.70(11.51)	38.18(27.90)	6.53–101.2 8	24.24) 7.62	(2.34–12.90)
Verrucous hyperpla-sia	46.66(11.11)	41.87(42.47)	6.07–185.5 9	(20.00) 5.21	(1.60–8.82)
Hyperkeratosis or epithelial hyperplasia	42.51 (12.98)	32.94 (32.81)	6.13–135.23 6	(8.57) 3.26	(0.65–5.87)

Table 4 :Number, percentage and mean duration of the malignant transformation of PMDs with different histological diagnoses, in Taiwanese patients with high habit history

Histological Diagnosis	Number (duration)	MT rate
Epithelial dysplasia with oral Submucous fibrosis	9/186 (4.84)	42.47
Epithelial dysplasia with hyperkeratosis or or epithelial hyperplasia	63/957 (6.58)	27.86
Oral Submucous fibrosis	37/994 (3.72)	37.42
Lichen planus	2/381 (0.52)	8.07
Verrucous hyperplasia	59/869 (6.79)	33.49
Hyperkeratosis or epithelial hyperplasia	49/1684 (2.91)	36.55
TOTAL	219/5071 (4.32)	33.56

Table 5: Factors to be considered in overall risk assessment of leukoplakia.[51]

1	Female gender
2	Long duration of leukoplakia
3	Leukoplakia in non-smokers (idiopathic leukoplakia)
4	Location on the tongue and/or floor of the mouth
5	Size > 200 mm2
6	Non-homogeneous type
7	Presence of C. *albicans*

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