

Warning Signs and Symptoms of Oral Cancer and its Differential Diagnosis

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ABSTRACT

Oral Cancer (Oral Squamous Cell Carcinoma; OSCC) contributes to one of the important causes of mortality in human beings. These impending malignancies however may present clinically with warning signs and symptoms which is often neglected due to the lack of awareness in the population. Though there are developments in diagnosing early stage of oral cancer, the detection rate is continued to be minimal. Research proved a strong association between early diagnosis and better prognosis in these malignancies. Hence, knowledge regarding these warning indicators will certainly facilitate the clinicians to discover early cancer and provide an overall benefit pertaining to treatment in these patients. This review aims to highlight the early signs and symptoms of OSCC and their significance in improved prognosis of the patients. A Medline-PubMed search was conducted of the literature over the past years using the keywords: "oral squamous cell carcinoma", "warning signs", "Early symptom", "clinical presentation", "white lesion", "ulcer", "erythroplakia", and "abnormal growth". A total of 58 articles were reviewed, of which 11 were literature reviews, 15 were original studies and 32 were case reports. Appropriate Assessment

and analysis were performed to identify prompt warning signs and symptoms of OSCC. The key findings of all the early presentation were elaborated with its clinical significance. In addition, this paper also helps to identify particular type of oral malignancies with their common clinical presentation reaching its emphasis based on the warning signs and symptoms. The importance of re-evaluation and biopsy to diagnose/eliminate malignant lesion in doubtful clinical situation is also highlighted.

Key words: Oral cancer, Warning signs, Symptoms, Persistent ulcer, White/red patch.

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INTRODUCTION

Oral and maxillofacial cancer (malignancy) contribute to one of the primary reasons of mortality worldwide. According to histological data, oral squamous cell carcinoma accounts for majority of all oral cancer. Dentists add to the crucial group of health care professionals in diagnosing oral cancers by observing essential warning signs and symptoms on examination of the oral cavity and confirming with suitable diagnostic aids. Thus, pertaining to the oral region, a "sign" refers to an objective evidence of a oral condition detected by a dentist during the examination of the oral cavity while a "symptom" refers to a subjective evidence of disease or a patient's oral condition. Few signs may go unnoticed by the patient although they remain meaningful and significant to the health-care provider in assisting the diagnosis of medical condition(s) responsible for the patient's symptoms. Among all the dental signs and symptoms detected on regular history and examination of the patients, the warning sign points to the intimation, threat, or sign of an impending danger of the underlying disease. Usually, at the molecular level, the cells undergo multistep process which includes initiation, proliferation and progression to become cancer cells during the pathogenesis of oral cancer. The clinical features also depend upon the etiopathological behavior of the individual tumors.

In this article, warning signs and symptoms of oral cancer (Table 1,2) from the review of the available literature has been highlighted which might be first signal of undiscovered malignancies. These signs and

symptoms adds clue to the clinicians that aid in early diagnosis, timely evaluation and improved prognosis for the patients from an oncological perception. The other associated oral malignancies with the warning sign and symptoms are also highlighted (Table 3) which would be helpful for differential diagnosis in essential clinical situation.

WARNING SIGNS AND SYMPTOMS OF ORAL CANCER AND ASSOCIATED MAXILLOFACIAL MALIGNANCIES

Non Healing Ulcer [Figure 1]

Ulcerations in the mouth may exhibit from a simple to highly complex variations suggestive of oral malignancy. In other words, patients present with this chief complaint of "ulceration" depicting to the epithelium and connective tissue damage with the existence of an obvious central crater caused by oedema or proliferation in the surrounding tissue.¹ Health care professional must clearly grasp the distinction between malignant/premalignant lesions from the group of reactive lesions persisting for more than two weeks following the removal of etiological factors. These lesions become more suspicious when it increases in its intensity and turns non responsive to the ongoing treatment. Therefore, appropriate diagnostic procedures (i.e., gold standard biopsy in addition to other non-invasive chairside procedures of the lesion) are essential diagnostic

aids in the evaluation of any lesion that does not respond to usual therapy in 7 to 14 days.² Common oral and maxillofacial malignancies presented as persistent non healing oral ulcers are briefed in the following discussion.

- *Squamous cell carcinoma* - Characteristically, squamous cell carcinoma appears as red or white, painless, indurated, non-healing ulcer with elevated and ill-defined margins. Most of the oral carcinomas may present with history of long standing non-healing ulcero-proliferative lesion with a rolled or indurated border. Common primary tumor sites of the oral cavity as reviewed in literature is attributed to buccal mucosa, tongue, lower alveolus, gingiva, floor of the mouth and palate.^{3,4}
- *Salivary gland tumor* - Salivary gland malignancies (muco-epidermoid carcinoma and adenoid cystic carcinomas) occur predominantly in the palate, cheek and gingival region of the jaws as a chronic ulcer.^{5,6}
- *Lymphomas*- Lymphomas may present as chronic ulcer covered with necrotic slough in the palatal region of the jaw in specific tumors of palate and paranasal sinus.^{7,8}
- *Leukemias*- Unlike, lymphatic tumours, leukemic tumours occur commonly in the gingival region of the mouth mimicking the clinical picture as lymphomas.^{9,10}
- *Basal cell carcinoma*¹¹ and *Metastatic tumors*^{12,13} may also present as ulcer.

White Patch With Firm Consistency [Figure 2]

Lesions appear “white” due to the reflection of the spectrum of light by abnormal keratin and constant bathing of the hyperkeratotic tissue in saliva, analogous to the appearance of palms and soles when immersed in water for long periods.¹⁴ These lesions predominantly are seen in the tongue, floor of the mouth and buccal mucosa.² Non-scrapable firm white lesions could be sub categorized as heterogenous or homogenous groups. White papillary lesions of heterogenous variant measuring more

Table 1: Potential warning signs/symptoms of the oral cancer.

<ul style="list-style-type: none"> • Non healing ulcer with or without induration / nonhealing socket • White patch with firm consistency • Red lesion or lesion with erythematous appearance (Erythroplasia) • Abnormal lump in the mouth with increase in size • Exophytic/ulceroproliferative growth • Mass or lump in the neck and neighbouring regions (Lymph node enlargement) • Mobility/ displacement/ non vital teeth/peri implantitis • Tooth pain and referral pain • Bleeding from the mouth (hemorrhage)
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than 1 cm usually denotes Verrucous carcinomas. Malignancies associated with these white patch includes *Squamous cell carcinoma* and its variants.^{15,16}

Red Patch (Erythroplasia) or Mixed White and Red Patch/ Lesions [Figure 3]

Red patches differ from early flat lesions to raised blotches or lumps complicating the clinical scenario and prognosis of the patient. These lesions appear true, velvety, red homogeneous to granular, velvety heterogeneous lesions in nature. They occur most commonly on the lateral surface of the tongue and floor of the mouth indicating the sites of poor prognosis.¹⁷ Areas of redness and inflammation as changes of mucosal abnormality, at high-risk sites persisting for more than 14 days without any obvious etiology or resolution should be biopsied and treated promptly. Unlike leukoplakia or other mixed lesions, persistent asymptomatic or symptomatic erythroplastic lesions at any site should be considered to be invasive carcinoma or at the very least carcinoma *in situ*. These lesions at high-risk sites also indicate the earliest and predominant sign of oral Squamous cell carcinoma. Common oral malignancies presented as red lesions includes *Invasive squamous cell carcinomas*,¹⁸ *Kaposi sarcoma*¹⁹ and *Basal cell carcinoma*.¹¹

Abnormal Lump in the Mouth with Increase in Size [Figure 4]

Many of the oral malignancies present as an abnormal lump which usually increase progressively in size. The surface would be smooth, erythematous, or ulcerated due to secondary trauma. The site occurrence would include either soft tissues or jaw bones. Common malignancy with this sign includes *Squamous cell carcinoma*,⁴ *Basal cell carcinoma*,¹¹ *Salivary gland malignancies*,²⁰ *Sarcoma*,²¹ *Melanoma*,²² *Lymphoma*,²³ *Intra osseous malignancies of maxilla and mandible*²⁴ and *Metastatic malignancies*.²⁵

Exophytic/ Ulceroproliferative Growth [Figure 5]

Exophytic lesions depicts an uncontrolled pathological growth of the oral mucosal surface with erythematous or mixed appearance. They usually occur in the buccal mucosa, alveolar ridge of maxilla and mandible, gingiva, floor of the mouth and the palate. Common malignant lesions with exophytic/ulceroproliferative nature of growth includes, *Squamous cell carcinoma and its variants*.^{15,26}

Verrucous carcinoma account for 4.5-9% of oral squamous-cell carcinomas which typically present as a slowly enlarging, gray or white, warty, exophytic growth on the buccal mucosa or gingiva of elderly men at the time of examination.¹⁶ Other tumors which may appear as exophytic include *Sarcomas*,²¹ *Salivary gland neoplasms*,²⁰ *Sialadenoma papilliferum* with malignant changes,²⁷ *Metastatic tumors*¹⁵ and *Multiple myeloma*.²⁸

Table 2: Warning Signs/symptoms according to the clinical presentation.

Soft tissue associated	Hard tissue associated	Generalised
<ul style="list-style-type: none"> • Non healing ulcer with or without induration / nonhealing socket • White patch with firm consistency • Red patch (Erythroplasia) or mixed white and red patch/ lesions. • Abnormal lump in the mouth with increase in size. • Exophytic/ulceroproliferative growth • Mass or lump in the neck (Lymph node enlargement) • Bleeding from the mouth (hemorrhage) 	<ul style="list-style-type: none"> • Tooth pain • Mobility /displacement /non vital teeth • Peri implantitis 	<ul style="list-style-type: none"> • Referral pain.

Table 3: Warning signs and symptoms and their commonly associated oral malignancies.

Non healing ulcer with or without induration / nonhealing socket	Squamous cell carcinoma ^{3,4} Salivary gland tumors ^{5,6} Lymphomas ^{7,8} Leukemias ^{9,10} Intra oral basal cell carcinoma ¹¹ Metastatic tumors ^{12,13}
White patch with firm consistency	Squamous cell carcinoma and its variants ^{15,16} (Verrucous carcinoma, papillary carcinoma)
Red patch (Erythroplasia) or mixed white and red patch/ lesions	Invasive squamous cell carcinoma ¹⁸ Kaposi sarcoma ¹⁹ Basal cell carcinoma ¹¹
Abnormal lump in the mouth with increase in size	Squamous cell carcinoma ⁵ Intra oral basal cell carcinoma ¹¹ Salivary gland malignancies ²⁰ Sarcoma ²¹ Melanoma ²² Lymphoma ²³ Intra osseous malignancies of maxilla and mandible ²⁴ Metastatic malignancies ²⁵
Exophytic/ulceroproliferative growth	Squamous cell carcinoma ^{15,26} Verrucous carcinoma ¹⁶ Salivary gland neoplasm ²⁰ Sarcoma ²¹ Sialadenoma papilliferum with malignant changes ²⁷ Metastatic tumors ¹³ Multiple myeloma ²⁸
Mass or lump in the neck and neighbouring regions (Lymph node enlargement)	Squamous cell carcinoma ^{29,32} Metastatic tumors ^{33,35} Melanoma ²² Lymphoma ³⁴ Salivary gland neoplasms ⁶
Mobility/ displacement/ non vital teeth	Squamous cell carcinoma ^{36,37} CENTRAL TUMORS Malignant odontogenic tumor ^{24,38} Sarcomas ⁴¹ Salivary gland malignancies ⁴² Burkitts Lymphoma ⁴³ Multiple myeloma ²⁸
Periimplantitis Tooth pain/referral pain	Squamous cell carcinoma, B cell lymphoma ⁴⁴ Squamous cell carcinoma ⁴⁶⁻⁴⁸ lymphoma ⁵⁰ Osteosarcoma ⁴⁰ Metastatic malignancies ²⁵ Tumors of maxillary antrum ⁴⁹ Burkitts lymphoma ⁴³ Central salivary gland tumors ⁵¹ Multiple myeloma ⁵² Malignant melanoma ⁵³
Bleeding from the mouth (hemorrhage)	Squamous cell carcinoma ³ Multiple myeloma ^{28,54} Leukemias ⁹ Lymphoma ⁵⁵ Sarcoma ⁵⁶ Mucoepidermoid carcinoma ⁵⁷ Metastatic tumors ⁵⁸ Malignant melanoma ⁵³



Figure 1: Non-healing ulcer.



Figure 4: Exophytic growth.

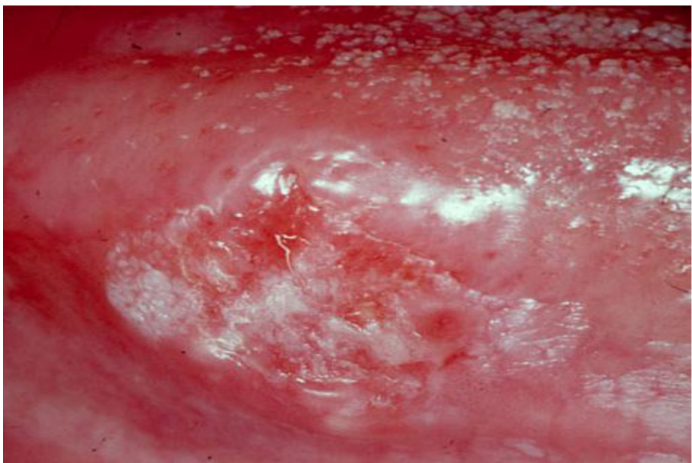


Figure 2: Firm white patch.



Figure 5: A Mass/lump appearance.



Figure 3: Red patch.

Mass or Lump in the Neck and Neighbouring Regions

Oral cancer has an abundant potential for metastasis to head and neck lymph nodes with 34% to 50% of reported incidence. Metastatic spread

to cervical lymph nodes result in decreased survival rate in Oral Squamous Cell Carcinoma (OSCC) patients. Lymphedema is a common late effect in patients with head and neck cancer, and it develops either as a secondary deposit or metastatic spread via multiple external and internal anatomical locations. Oral malignancies associated with neck mass includes *Squamous cell carcinoma*,²⁹⁻³² *Metastatic tumors*,^{33,35} *Melanomas*,²² *Lymphomas*³⁴ and *Salivary gland neoplasms*.⁶

Mobility /Displacement/Non Vital Teeth/Peri Implantitis

Primary squamous cell carcinoma which occurs in the gingival region frequently gives these types of tooth related clinical features as an early sign. These are mainly due to involvement of periodontium with cancerous lesion.^{36,37} However, tooth mobility, displacement and nonvital teeth are most common signs present in *central tumors of the jaws*.^{23,24} They include *Malignant odontogenic tumors*,^{24,38} *Osteosarcomas*,⁴⁰ *Ewings sarcoma*,⁴¹ *Intraosseous muco epidermoid carcinomas*,⁴² *Burkitts lymphoma*,⁴³ *Multiple myelomas*.²⁸ Primary malignancies such as *Squamous cell carcinoma* and *Large B cell lymphoma* may also clinically present as peri implantitis.⁴⁴

Tooth Pain and Referral Pain

Orofacial pain may be a presenting symptom of primary tumors, metastatic disease, or distant non-metastasized cancer. Mechanisms under-

lying cancer-associated pain are very complex.⁴⁵ Oral squamous cell carcinoma could also present as tooth pain as a symptom. The histological endophytic growth patterns of OSCC might be significant risk factors for the presence of spontaneous pain before treatment resulting in poor prognosis.^{46,47} Sound painful tooth/teeth were the most common symptom in OSCC patients (27.5%)⁴⁷ and the initial clinical presentation could be a tooth pain.⁴⁸ Most frequent initial symptom was toothache (36.2%) in malignant neoplasm of maxillary antrum.⁴⁹ Radiating ear pain in lymphoma of the tongue is also reported.⁵⁰ Tumors presented with tooth pain includes *Squamous cell carcinomas*,^{46,47,48} *Malignant tumors of the jaw commonly osteosarcoma*,^{24,40} *Metastatic malignancies*,²⁵ *Tumors of maxillary antrum*,⁴⁹ *Burkitts lymphoma*,⁴³ *Salivary gland tumors*,⁵¹ *Multiple myeloma*,⁵² and *Malignant melanomas*.⁵³

Haemorrhage – Oral Cavity

Spontaneous bleeding from mouth is a common symptom in several oral malignancies. Often, it is observed in tongue and gingival region of the mouth. It could be due to primary cancer or secondary to trauma to the malignant lesion. Malignancies commonly presenting with this symptom are *Squamous cell carcinoma*,³ *Leukemias*,⁹ *Malignant melanomas*,⁵³ *Multiple myeloma*,⁵⁴ *Lymphoma*,⁵⁵ *Sarcoma*,⁵⁶ *Muco epidermoid carcinoma*,⁵⁷ and *Metastatic tumors*.⁵⁸

CONCLUSION

Health care practitioners should remain alert for signs and symptoms of oral malignant and premalignant lesions while performing routine examinations. Recent studies showed alterations in the incidence of oral cancer regarding to age, gender, etiologic factors and the anatomical areas of occurrence. These factors insisted the significance of prompt clinical evaluation while examining suspicious oral lesions. Awareness regarding the early signs and symptoms of malignancies would certainly increase the overall survival rate of the cancer patients. In addition, informed discussions regarding warning signs and symptoms could be beneficial while 'observe and treat' cases of high risk potentially malignant disorders. It is mandatory for the physician to re-evaluate and perform gold standard biopsy procedure that would aid in appropriate diagnosis and facilitate the treatment with better prognosis in suspicious lesions. Biopsy might also avoid either over diagnosis nor over treatments. In oral cancer patients, evaluations of the other potential areas like esophagus, larynx, hypopharynx, and lungs should be accomplished in addition to the routine clinical and laboratory investigations to rule out another primary cancers. Though biopsy is considered as confirmatory diagnosis it is emphasized to validate and expanding the utility of auxiliary advanced diagnostic procedures clinically to identify early cancerous lesions.

Physicians decision would depend on further advanced diagnostic procedures or specialist referral without any additional delay. This article has focused primarily to shed light on the "Warning signs and symptoms" – oral cancer" as a tool for alerting clinicians for early diagnosis, effective treatment and better prognosis of patient.

"Caution, Care and Attention – Basic tool in eradication of oral cancer".

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ABBREVIATIONS

OSCC: Oral squamous cell carcinoma.

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