Review Article

Early Detection, Causes and Screening of Oral Cancer

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Abstract

Oral cavity Squamous Cell Carcinoma (SCC) is common, and despite its relative ease of detection, patients continue to present with late stage disease. The World Health Organisation (WHO) has urged member states to involve primary care givers (dentists and general practitioners) in increasing early referral for suspicious oral lesions.

Tobacco and alcohol consumption remain the two major risk factors for oral SCC. A brief screening history to identify high-risk individuals, followed bya simplebut thorough oral examination is the best tool available for screening for oral SCC. This is both cost effective and reduces mortality when applied to patients in high-risk groups.

ABBREVIATIONS

SCC: Squamous Cell Carcinoma

INTRODUCTION

Oral cavity Squamous Cell Carcinoma (SCC) is common. Whilstthe oral cavity is easily accessible for examination, and althoughtumors of this site cause symptoms at a relatively early stage, a large majority of patients continue to present with late stage disease. Despite readily and widely available treatment,oral cancer carries an overall disease specificrelative mortality of 49% [1].

In 2007 the World Health Assembly passed a resolution on oral health, urging all member states to "take steps to ensure that prevention of oral cancer is an integral part of national cancer control programs, and to involve oral health professionals or primary health care personnel with relevant training in oral health in detection, early diagnosis and treatment [2]." Despite the multitude of tools marketed to aid in the early diagnosis of oral cancer, there is no general population based screening method shown to reduce mortality associated with oral cancer [3]. Dentists examine their patient's oral cavity during almost every consultation and are in a unique position to both promote primary preventative measures to high risk groups, and aid in early diagnosis and referral of suspicious oral lesions.

Spectrum of disease

SCC's make up approximately 90% of tumors in the oral cavity, with adenocarcinoma/minor salivary tumors accounting for 5%, verrucous carcinoma and lymphoma 2% each and the remainder being uncommon sarcomas or odontogenic tumours. SCC will be discussed for the purposes of this review.

Epidemiology

Oral SCC is the 6th most common cancer globally and its incidence is increasing [4]. The burden of oral cavity SCC varies significantly with cultural risk-taking behaviors worldwide. India, Pakistan, Sri Lanka and Bangladesh have the highest incidence with up to 25% of all new cancers affecting the oral cavity [5], compared with 6% in France and 3% in the UK [6]. The age adjusted incidence is reported from approximately 3.4 to 13.8 per 100,000. Males are more often affected than females by a ratio of 1.5 : 1 [7]. A rising incidence has been noted in patients under 45yrs of age [8], with approximately 6% of oral cancers now occurring in this age group compared with 3% in 1973 [9]. The average period for which a patient is aware of an oral lesion prior to bringing it to the attention of their doctor is 3 months [10]. Unfortunately, over 60% of patients present with stage III or stage IV disease [11], and after treatment can expect only a 45% and 32% five-year survival respectively.

Risk factors

Smoking and alcohol consumption are powerful and synergistic risk factors for the development of oral SCC. Heavy drinkers and smokers have 38 times the risk of abstainers from both products [12]. 20pack-years seems to be the threshold at which a significantly increased risk of cancer is imparted [13,14], and the risk reduces back to baseline 10years after cessation [15]. Betel nut chewing and reverse smoking have a strong causal relationship particularly with buccal and hard palate subsites respectively - this accounts for the extremely high rates of oral SCC in countries where these behaviors are entrenched. UV sunlight is a clear aetiologic factor in lip SCC, which predominantly affects Caucasian males.

The role of Human Papilloma Virus (HPV) has been well

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established in SCC of the oropharynx [16], andwhile a link has been shown to exist with oral cancer also [17], further evidence is required to confirm it as a strong causal factor for the oral cavity. Immunocompromised individuals have a higher rate of nearly all malignancies and oral SCC is no exception. A number of genetic conditions carry an increased predisposition [18] – these are listed as part of Table 1. Chronic inflammation has long been purported to increase the risk of oral cancer – this may be the way in which candidiasis, syphilis, and chronic trauma from poor dentition contribute to a slight increase in risk of oral cancer. Poor oral hygiene has been linked to increased carcinogenesis, the exact mechanism is unclear but it may be related to carcinogenic effects from the high burden of polymicrobial oral flora [19].

Potentially malignant disorders

Use of the term 'Premalignant Lesion' is now discouraged in favour of the phrase "Potentially Malignant disorders [21]." The lesions of most relevance are erythroplakia, leukoplakia, oral lichen planus and submucous fibrosis.

Erythroplakia is defined as a "fiery red patch". These lesions are often symptomatic, have a degree of increased vascularity, and carry a high risk of harbouring dysplasia. All erythroplakic or leukoerythroplakic lesions should be referred for biopsy and or excision. Should mild or moderate dysplasia be confirmed on biopsy, its risk of malignant transformation is 10.3%, with high-grade dysplasia and carcinoma insitu carrying a 24.1% risk [22].

Leukoplakia is usually asymptomatic and is defined either as a "white plaque that will not rub off" or "a white plaque of questionable risk, having excluded other known diseases or disorders that carry no increased risk for cancer". Confounding benign causes of a white plaque include a frictional lesion from habitual trauma or cheek biting, linea alba (normal white streaks bilaterally along the occlusal line), and leukoedema amongst others [23]. The prevalence of Leukoplakia has been estimated at 2% [24], although the true rate when the latter of the two above definitions is applied is likely to be a little lower at a more modest 0.5%. The annual malignant transformation rate is estimated to be from 0.3% [25] to 1%. It is generally accepted that referral for biopsy or excision is warranted for these lesions.

Lichen Planus is an oral autoimmune condition with a number of morphological variants including reticular (fine white lacy lines), erosive (shallow ulcers), atrophic (thinned erythematous

mucosa), and bullous (fluid filled vesicles). It can be symptomatic typically with a burning feeling or hypersensitivity of the affected mucosa. There remains debate as to its status as a potentially malignant condition. It is generally accepted that its risk of malignant transformation is below 1% per year [26]. A patient with lesions such as these should be referred to a specialist for biopsy.

Submucous Fibrosis causes progressive trismus due to fibrosis of the connective tissues of the cheeks. It is strongly associated with betel nut/tobacco chewing and it is likely that the use of these carcinogens give it an association with oral cancer. The rate of malignant transformation is estimated at 0.5% per year [27].

Screening/early detection

Screening for a disease implies the application of a test to an asymptomatic population with the aim of detecting disease at an early stage. This disease must be a significant public health issue, and the natural history and management of the disease must be well understood such that improved outcomes can be expected when treated at an early stage. Furthermore the test itself and any morbidity associated with further investigation of false positives must be acceptable [28].

The established screening test for oral SCC is clinical examination - with biopsy and histopathological assessment being the gold standard to confirm the diagnosis. Oral cavity examination has been demonstrated in a meta-analysis by Downer et al [29] to have a sensitivity of 0.84 and a specificity of 0.97. For comparison they note that both mammography and cervical screening programmesshare an approximatesensitivity and specificity of 0.8 and 0.98 respectively. Oral examination is simple, takes only a few minutes, requires minimal equipment, is non-invasive and can be performed by a wide range of health professionals.

For widespread structured screening to be instituted it must be shown to not only be of value in reducing morbidity and mortality, but also to be cost effective. Sankaranarayanan et al [30] published a hallmark paper in the Lancet in 2005 in which they assessed their oral cancer screening programme when applied to a prospective cohort of over 87,000 individuals over the age of 35.They found no significant effect on the disease specific mortality when applied to the general population. However, subgroup analysis of smokers and/or drinkers showed a reduction in mortality of 43% and 22% in men and women respectively. A subsequent paper [31] found this approach to be cost effective - albeit in India where there is a high rate of oral cancer. There are no similar trials in a low prevalence society,howeversimulation modeling has shown that a screening oral examination in high-risk individuals in a western population may also be cost effective [32].

The question still remains as to which group of health professionals should be undertaking oral cancer screens? An interesting paper by MacPherson et al [33] surveyed 357 general medical practitioners (GP's) and 331 general dental practitioners to assess their knowledge of, and their self-perceived ability to diagnose oral cancer or precancerous lesions. 58% of Dentists claimed to examine opportunistically for signs of oral cancer

Table 1: Risk Factors for Oral SCC.

Major Risk Factors:	
Smoking	
Alcohol	
Betel Nut (buccal/retromolar trigone)	
UV light (lip)	
Reverse smoking (hard palate)	
Minor Risk Factors:	
HPV	
Immune deficiency	Genetic: Fanconi's anaemia, dyskeratosis congenita, xeroderma pigmentosa, plummer-vinson syndrome, patterson-kelly brown syndrome, scleroderma, diabetes.
Micronutrient deficiency (low fruit and vegetable intake)	
Syphilis, Chronic candidiasis	
Prior radiation exposure	
Periodontal disease	
Poor oral hygiene [20]	

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compared with GP's who overwhelmingly only examined if a symptom was raised. 37% of dentists felt confident in their ability to diagnose these lesions, compared to only 15% of GP's. A lack of specific education was cited as an important barrier to improving performance. Unfortunately while dentists are both more confident and more likely to examine the oral cavity of their patients, the high risk population are infrequent attenders to general dental practices [34]. Heavy smokers and drinkers from low socio-economic backgrounds tend to only present for dental care in the context of a dental abscess or severely carious teeth often with a corresponding florid gingivitis, whichmay impede or confound lesion detection. Furthermore, older patients who have a higher risk of cancer are frequently edentulous and have no cause to see a dentist. Another major barrier for these patients is the cost of dental care, which is self-funded by patients in many countries.

How to perform a screening oral examination

Oncological examination of the oral cavity is simple, cost free, non-invasive and should be within the skill set of all GP's and dentists. Table 2 gives a brief account of equipment required and areas to examine.Palpation is of particular relevance- with bulky/firm lesions being of much higher concern than a soft lesion with identical texture to the adjacent tissues.

The areas easily overlooked are the lateral tongue, glossotonsillar sulcus and the floor of mouth as these areas require the patient to actively move their tongue to the contralateral cheek and also require active retraction of the tongue with a depressor to allow visualization.Table 3 lists the key red flag clinical features on history and Table 4 highlightssuspicious signs that should trigger referral Figures 1, 2 and 3.

Adjuncts

Many adjuncts to clinical examination for oral SCC exist. However as eluded to by Lingen et alxi in their excellent position paper of the American Academy of Oral and Maxillofacial Pathology, despite the "tantalizing implication that such technologies may improve detection of oral cancers and pre-cancers beyond conventional oral examination alone" none have been proven to do so.

Table 2: Oncological Oral cavity Examination. *areas easily overlooked.

Equipment required:
Good lighting (ideally a head light)
Tongue depressor +/- dental mirror
Gloves to allow palpation of lesions
Assess the oral cavity subsites systematically:
Both lips from vermilion to gingivo-labial sulcus
Buccal mucosa
Gingiva
Retromolar Trigone
Hard Palate
Floor of Mouth and glossotonsillar sulcus*
Tongue
- Dorsum (opposed to hard palate)
- Ventral surface* (opposed to floor of mouth)
- Lateral tongue*
Soft Palate and Tonsil fossae (strictly speaking these are oropharynx sites but should be
included in a screening oncological oral examination)

Table 3: High risk patient factors.

The high risk patient for Oral SCC
Male in 50's to 60s
Exposure to tobacco, alcohol, betel nut.
Low socioeconomic group
History of prior oral SCC (3-7% incidence per annum of 2nd primary)
Immunocompromised

Table 4: ExaminationRed Flags.

Red Flags – trigger for referral
Non healing lesion >2 weeks
Ulcer or mass with raised heaped up margins, puckering/tethering of surrounding tissues
Pain or numbness/tingling associated with a persistent lesion
Red lesion(erythroplasia) or Red-White lesion (leuko-erythroplakia)
Unexplained loose tooth or non-healing extraction socket.
Neck mass

Figure 1 An early (T1) lateral tongue SCC. Firm to palpation, central ulceration, heaped edge.

Figure 2 An early (T1) lateral tongue SCC. Firm to palpation, central leukoplakia andsurrounding tethering.

Figure 3 T2 Lateral tongue SCC. Firm and tender to palpation, exophytic, contact bleeding, ulcerated with a heaped edge.

Toludine Blue is a topical dye, which is concentrated in cells with abundant nucleic acids, and has been used for decades on the cervix to aid in identification and demarcation of mucosal abnormalities. There is a large volume of literature assessing its role in the oral cavity, with mixed results. While it is generally accepted that Toludine Blue staining has a high sensitivity for detecting carcinoma, its sensitivity for identifying dysplasia is poor (sensitivity approximately 50% [11]) and has a low specificity with most oral lesions benign or otherwise taking up the dye to some degree. As a somewhat subjective guide to clinicians it is felt that carcinomas are likely to stain a deep royal blue, whereas benign lesions (leukoplakia's, leukodema, lichen planus etc) are more often a pale blue [35]. In their systematic review, Gray et al [36] concluded that "the high rate of false positive stains and the low specificity in staining dysplasia likely outweigh the potential benefits of any additional cancers detected".On balance this adjunctive measure offers benefits in targeting lesions to biopsy. However, it has only thoroughly been assessed for use in the hands of oral specialists, and only on lesions already identified by a clinical examination.

Brush Biopsy(OralCDx) utilises a stiff cytology brush to sample cells from the surface and basal layer of a lesion. When sent back to the provider's laboratory it will yield either a positive, atypical or negative result.Its main role is in sampling lesions that on clinical grounds are felt likely to be innocuous [37,38]. Lingen concludes that "this tool may be beneficial in the patient with multiple lesions throughout their oral cavity" who is unlikely to accept a scalpel biopsy of them all, or "in the non-compliant patient who is unlikely to come back for a follow-up exam or accept an immediate referral to an oral surgeon".

Multiple optical detection systems have been developed and marketed for the detection of oral premalignant lesions and oral cancers. These include tissue reflectance tools such as the ViziLite [39] which prepare the mucosa with an acetic acid mouthwash, tissue auto fluorescence technologies such as the VELscope [40], and Narrow Band Imaging [41] to name but a few. On the whole in comparison to standard oral examination, these technologies are expensive to set up, have a significant learning curve,and can betime consuming and labour intensive to use. While these techniques often have a high sensitivity for detecting premalignant and malignant oral lesions, their specificity is typically poor and again these systems should be reserved for the oral specialist with little or no role in the primary care setting.

CONCLUSION

Oral SCC occurs typically in males from a low socioeconomic background who smoke and consume alcohol. Patients unfortunately continue to present with late stage disease. An oral screening examination is a simple non-invasive test to apply, has a comparable sensitivity and specificity to that of the well established cervical and breast cancer screening programs, and is felt to probably be cost effective when applied to high-risk individuals in western society.

In the absence of any formal screening program being introduced, dentists and GP's can best serve these high-risk patients by performing regular opportunistic oral examination and educating these patients to increase their awareness of the early signs and symptoms of oral cancer. Oral medicine specialists, Otorhinolaryngologists and Oral maxillofacial surgeons must improve efforts to educate Dentists and GP's to ensure they feel adequately equipped and supported to perform this role.If a suspicious lesion is found, immediate referral for further investigation and subsequent treatment is warranted.

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