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*RESEARCH ARTICLE*

# ORAL SQUAMOUS CELL CARCINOMA: A OVERALL RETROSPECT

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*Abstract*

**Aim**: The aim of this article is to review the epidemiology, clinical features, and prognosis of oral scc.

**Purpose:** The intent of the present review was to present the histo-logical and molecular characteristics of the common type of oral cancer encountered by oral surgeons. Squamous cell carcinoma reports for 80% of all oral cancers. It might affect any anatomical site in the mouth, but most commonly the tongue and the floor of the mouth. It usually originate from a preexisting potentially malignant lesion, and occasionally de novo but in either case from within a field of precancerized epithelium. The role of tobacco and betel quid, heavy drinking of alcoholic beverages and a diet low in fresh fruits and vegetables are known risk factors for oral squamous cell carcinoma. Essential risk factors related to the carcinoma itself that are familiar with a poor prognosis include large size of the tumour at the time of diagnosis, the presence of metastases in regional lymphnodes, and a deep invasive front of the tumour. In oscc, associations have been identified between the proliferation, basal lamina degradation and connective tissue modulation. Therefore, the comparison of these factors with the survival time of oscc patients from the histopatho-logical diagnosis is of interest.



## Introduction:-

Head and neck cancer is one of the most mutual types of cancer worldwide, afflicting >500,000 individuals each year. Oral cancer is regared to be a preventable condition, due to the opening of early detection and treatment. Oral squamous cell carcinoma (oscc) represents 90% of all forms of head and neck cancer, and during the previous decade its incidence has increased by 50%.

Smoking and alcohol consumption are comrade with 90% of patients that exhibit oral cancer and the two factors appear to have a synergistic effect.

The majority of oscc are diagnosed at a late phase, in stages iii or iv, which markedly reduces the prospect of survival and leads to a significant deterioration in patient quality of life. Scorn the present available therapeutic strategies, which include the excision of malignant tissue and compounding of radiotherapy and chemotherapy, the 5 year survival rate is only 53%.

However, as not all persons who practice these high risk habits will develop oral scc, and as oral scc may be idiopathic, there must be person-specific genetic characteristics and environmental factors which may either afford protection against the development of oral scc, or may predispose to or even promote the development of oral scc.

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In the last 30 years, the 5-year survival rate of patients with oral scc has not improved despite advances in diagnostic techniques and improvements in treatment modalities. Indeed, the incidence and prevalence of oral scc are increasing, particularly in younger persons.

**Epidemiology of oral scc:**
Oral scc more frequently affects men than women (m:f = 1.5:1) most probably because more men than women indulge in high risk habits. The probability of developing oral scc increases with the period of exposure to risk factors, and increasing age adds the further dimension of age-related mutagenic and epigenetic changes. The reason for this is obscure.

A routine of conditions have been comraded with an elevated risk of developing oral scc including li fraumeni syndrome, plummer-vinson syndrome, fanconi anemia, chemotherapy induced immunosuppression of organ transplantation, dyskeratosis congenita, xeroderma pigmentosum and discoid lupus erythematosus.

In western countries oral scc involves the tongue in 30% - 50% of cases and the floor of the mouth in 25% - 30% of the cases, and together these sites account for about 50% of all cases of oral scc. The gingivae, palate, retromolar area and the buccal and labial mucosa are oral sites less frequently affected.

The ventral surface of the tongue and the floor of the mouth are the sites most commonly affected by scc because they are lined by thin nonkeratinised epithelium.

The mean 5-year survival rate of persons with oral scc is about 50% with no gender difference; but black persons have a lower five year survival rate than persons of other races. Other socio-demographic factors such as age, potentially carcinogenic habits (using alcohol, tobacco, betel quid) or socio-economic status are not consistently related to survival rates
.
The phase of advancement of oral scc at the time of diagnosis is the most imperative prognostic factor. Oral scc is most commonly diagnosed late in the course of the disease because affected persons fail to search professional advice timeously, either because they do not understand the importance of early signs and symptoms.

**Clinical features and course of oral scc:**
Oral scc may take numerous clinical forms. It may appear a leukoplakia, a verrucous leukoplakia, an erythro-leukoplakia, or an erythroplakia, any of which may eventually develop into a necrotic looking ulcer with irregular, raised indurated borders, or into a broad based exophytic mass with a surface texture which may be verrucous, pebbled or relatively smooth.

When traumatized, oral scc bleeds pronto and often becomes superficially secondarily infected. Oral scc is usually painless unless it is secondarily infected. Hugelesions may interfere with normal speech, mastication or swallowing.

The course of oral scc is unpredictable, but the tnm stage (t-tumour size, n-nodal metastasis, m-distant metastasis) of the primary tumour correlates well with the survival rate. The prognosis is best when the primary tumour is small and there is no evidence of regional lymphnode involvement or distant metastasis. In fact, the 5- year survival rate of persons with early-stage oral scc ac-cording to the tnm staging system may reach 70% - 80%, whereas the 5 year survival rate for ad-vanced-stage oral scc is about 50%.

Near about two-thirds of oral scc are already of substantive size, and will have clinically detectable metastases to cervical lymphnodes at the time of diagnosis.

The impaced lymphnodes are firm and non-tender to pal- pation, and if extracapsular spread into the surrounding connective tissue has occurred, they will be fixed and matted. Significantly, in about 30% - 40% of cases with no clinical or imaging evidence of metastatic spread to lymphnodes at the time of diagnosis of oral scc, histopathological examination of the regional lymphnodes will show metastatic growth.

In addition, one study, 25% of cases of scc of the head and neck in which the regional lymphnodes appeared to be free of metastatic growth when examined microscopically, in fact, molecular analysis proved them to harbour

cancerous cells. The presence of extracapsular lymphnode spread is associated with a high-rate of local and regional recurrence, distant metastasis and mortality.

About 10% of patients with oral scc will have distant metastases at the time of diagnosis, most frequently to the lungs.

Critical factors at the time of diagnosis of oral scc- determining survival are the front of regional lymphnode metastases, the size (surface dimension) and depth (extent of local infiltration) of the carcinoma, the oral anatomical site affected and the histopathological grade of the carcinoma.

After treatment, factors correlating with survival will be whether or not the margins of the resected carcinoma were free of invading carcinomatous cells, because this will determine whether or not there will be local recurrence; and whether or not a second tumour will develop in the same or in a contiguous epithelialized precancerized field.

Squamous cell carcinoma of the lip, hard palate and maxillary gingiva infrequently metastasize to regional lymphnodes, usually run a relative indolent course and have a relatively favourable prognosis, while scc of the tongue, of the floor of the mouth and of the mandibular gingiva often metastasize to regional lymphnodes and are more aggressive with a less favourable prognosis.

In general, sccs of the posterior part of the oral cavity are much more likely to metastasize to regional lymphnodes than are comparable sccs of the anterior part of the oral cavity.

Tiny well-differentiated, low-grade oral sccs usually metastasize to regional lymphnodes only after invading connective tissue, muscle or bone. Likewise, poorly differentiated, high-grade oral sccs are biologically more aggressive and tend to metastasize to regional lymphnodes early in the course of the disease.

Although the grade of histological differentiation of oral scc reflects the aggressive capacity of the tumour, it appears that as an independent factor, it does not significantly influence the prognosis.

But then, the depth of the infiltration of the tumour as determined histopathologically correlates importantly with the prognosis. Oral sccs that have infiltrated more than 5 mm into the underlying tissues, are more likely to metastasize to lymphnodes with a poorer prognosis.

The peril of local recurrence is greatest when there are cancerous cells present in the surgical margins, but there is an increased risk of recurrence when the carcinoma- free margins are narrower than 5 mm or when there is still dysplastic though not frankly malignant epithelium at the margins.

Resection margins apparently free of malignant cells as determined by histopathological examination have been shown by molecular analysis to harbour transformed keratinocytes with a malignant profile.

Therefore, despite apparently successful treatment, persons who have had oral scc are at heightened risk of developing recurrence at the same site, from cancerous keratinocytes left behind at surgery. A carcinoma that subsequently develops within the field of precancerized epithelium from which the primary carcinoma had arisen is techni-cally a new carcinoma although it may be immediately contiguous to the site of the primary carcinoma.

The risk of developing multiple oral sccs within a cytogenetically altered precancerized field is higher in young persons, and in persons who continue to use tobacco, alcohol and betel quid after successful treatment of the primary carcinoma. It has been reported that about 30% of males and 20% of females who had a primary head and neck scc will develop a second field carcinoma within 10 years of the diagnosis of the primary carcinoma.

Oral scc can arise from pre-existing potentially malignant disorders including oral leukoplakia, erythroplakia, submucous fibrosis and lichenoid dysplastic lesions, or can arise de novo.

There is a debate in the literature with regard to the malignant potential of oral lichen planus, in particular the erosive form. While some researchers found an association between oral lichen planus and development of oral scc,

others did not. The view of authors of this article is that oral lichen planus does not pose an increased risk of oral scc.

It has been suggested that oral scc evolving from leukoplakic lesions have a better prognosis than those emerging de novo, but a recent study has shown that the prognosis is not significantly different in these two groups of oral scc.

**Ethnicity and socio-economic status as they relate to oral scc**

There is a different variation with regard to the incidence of and mortality from oral scc between different countries, between different locations and between groups. This may be attributed to exposure to different environmental factors and to ethnic-specific high-risk habits.

Oral scc is more prevalent in developing than developed countries. In israel, oral scc is more preva- lent among ashkenazi jews than among sephardic-jews probably because of their different geographic origins; [30] and in england it is more prevalent among indian people born in the indian subcontinent and migrated to england than among indians born in england or among white english people.

In the united states, the average 5-year survival rate for black people is lower than for white people with oral scc and in general, oral scc is at a significantly more advanced stage in black people than in white people at the time of diagnosis.

The racial disparity with regard to the stage of oral scc, and with regard to the outcome of treatment is brought about by a complex interaction of factors. It is possible that pathobiologically oral scc is more aggressive in blacks than in whites, or that for cultural, educa- tional and socioeconomic reasons blacks delay longer before seeking medical advice than do whites.

Thus while socioeconomic status, educational level, cultural influences and limited access to health care services do not play any direct role in the development of oral scc, they do indirectly influence the higher morbidity and mortality from oral scc in persons from disadvantaged backgrounds.

**Prevention and control of oral scc**

The overall aim of cancer prevention is to reduce the incidence of the disease; and of cancer control is to detect the disease in its initial stages and to promptly institute effective and efficient treatment.

Measures directed at the public to reduce the incidence of oral scc and to alert those at risk to the benefits of early detection should include education about the risk- factors associated with the disease, about the early signs and symptoms of the disease, and about the hazards of delaying seeking professional advice.

Professional measures should include the making available of immediate effective and efficient medical treatment, and of screening programmes for high-risk populations with a view of identifying potentially malignant oral disorders, or early scc.

This is of paramount importance because in general, abstinence from the use of tobacco and betel quid, and moderation in the consumption of alcoholic beverages, together with an increase in fresh fruits and vegetables in the diet, may reduce the incidence of oral scc by almost 80%.

Many healthcare practitioners do not routinely perform oral soft tissue examinations for those patients who are known to practice habits associated with increased risk of oral cancer. However, in order to increase the rate of early diagnosis of oral scc, healthcare practitioners should make a point, whenever possible, of examining the mouth as part of a general examination.

If any suspicious lesions of the oral soft tissues are detected the patient should be referred to an appropriately qualified practitioner for further investigation.

There can be little doubt that careful annual examination of the mouth in all persons above the age of 40 years will result in a significant improvement in the rate of early detection of oral cancer with all the therapeutic advantages.

A very obvious shortcoming of such an idealised plan is that a great proportion, if not the majority of those at risk of oral scc do not attend annually for any healthcare.

**Treatment:**

The treatment of oral scc generally requires the services of a multidisciplinary team, the primary purpose of treatment always being to eradicate the cancer, to prevent recurrence, and insofar as is possible to restore the form and function of the affected parts.

The choice of a specific treatment modality is dictated by the nature of the carcinoma and by the general condition of the patient. Various factors related to the carcinoma include the specific site affected, the clinical size, the extent of local invasion, histopathological features, regional lymphnode involvement and distant metastasis. Patient factors include age, general health status, a history of previously treated oral scc and high-risk habits.

A mixture of modalities are available for the treatment of oral scc. These include excision/resection, radio-therapy, systemic cytotoxic chemotherapy and blocking of epithelial growth factor receptor (egf-r), or a combination of these, either concurrently or in an orderly sequence.

Surgery is the preferred first line treatment of small, accessible oral sccs. However, advanced-stage oral scc is usually treated by a combined treatment program of surgery, chemotherapy, and radiotherapy.

In cases of recurrent oral scc, egf-r inhibitor coupled with chemoradiotherapy, is the first line of treatment.

Surgical resection of oral carcinoma with tumour free margins of less than 5 mm may be followed by local recurrence and possibly by distant metastasis, and usually necessitates the administration of post-surgery chemo-radiotherapy. The presence of dysplastic epithelium in post-resection carcinoma free margins is of debatable importance, but it is not usually considered to be a strong indication for treatment .

There are two possible explanations for this high rate of recurrence.

Firstly, few carcinomatous keratinocytes may have persist in the margins of the surgical wound, but because there were so few, they were not detected by histopathological examination; secondly, the enormous field of precancerized epithelium comprising precancerous keratinocytes at different stages of transformation from which the primary carcinoma developed, was not removed at the surgical procedure.

It may also look ordinary microscopically, but nevertheless may harbour keratinocytes with cytogenetic alterations including loss of heterozygosity and p53 mutations, or epigenetic changes in methylations of certain promoters of tumour suppressor genes and dna repair genes.

Following acquisition of additional genetic alterations, either keratinocytes in the dysplastic epithelium or the genetically transformed keratinocytes may become cancerous giving rise to a new field carcinoma close to where the primary carcinoma had been excised, creating an impression of recurrence.

Thus, the reappearance of scc in the immediate or general vicinity of the primary oral scc, may be a recurrence if the two carcinomata exhibit identical genetic profiles; may be a new field carcinoma from a subclone of cells within the field if the genetic profiles of the two cancers are similar, but not identical; or may be another primary carcinoma from a different clone within the same field of precancerization if the genetic profile of the two tumours are dissimilar.

It would be significantly advantageous if it were possible to treat a field of precancerized oral epithelium.

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