

# Oral Cancer

## *epidemiology and aetiology*

### **Introduction**

Oral cancer is a relatively uncommon condition but when it does occur it can be devastating to the patient and their family. As with other malignant diseases the prognosis for cure improves the earlier the diagnosis is made and appropriate treatment started. Moreover, treatment for a small early lesion is likely to be less mutilating and have a lower morbidity than treatment for a large advanced lesion. Unlike many malignant lesions occurring elsewhere in the body oral scc can be readily observed in its' early stages. There are few places in the oral cavity that a lesion can genuinely progress unnoticed by patient and clinician. The fact that so many patients still continue to present late with advanced disease is a sad indictment of the state of dental care in the UK in the 1990's. While undoubtedly many patients hide their cancer for various reasons an unacceptably high number are either misdiagnosed or simply missed by their doctor or dentist. General dental practitioners are ideally placed to spot the early warning signs of oral scc in their patients'. You must be aware of the signs and symptoms of oral cancer and thoroughly examine your patients' mouths at every visit and take appropriate action if a suspicious lesion is found. This particularly applies to those in high risk groups. The problem is, like in so many other areas of health care those most in need and with most to benefit from early diagnosis are unlikely to take advantage of the facilities available. The other problem is that any one practitioner is only likely to see 1 or 2 patients in their practising lifetime with scc. Nevertheless, if we are to make any inroads in reducing the morbidity and mortality of this appalling disease we must strive for early diagnosis and the GDP and GMP are the clinicians best placed to achieve this.

### **Epidemiology**

#### **Incidence**

Squamous cell carcinoma (scc) accounts for about 90% of all oral malignancy the remainder include salivary gland neoplasms, lymphomas and sarcomas. These 2 tutorials are only concerned with oral squamous cell carcinoma.

In the UK the annual incidence of scc is 2.5 - 6.9 :100,000 population where it accounts for between 2 - 5% of all malignant lesions. In parts of India the rate is 19.6:100,000 and accounts for 40% of all malignancies. The rate of new oral cancers would appear to be falling from its' peak in 1920 to the present levels. However, there is disturbing evidence that cancers of all types including oral cancer are on the increase. This appears to be a real increase and not just due to improved diagnosis and an increase in the proportion of elderly people in the population. Moreover, there is a strong clinical impression as yet unsubstantiated that we are seeing a rise in incidence of aggressive oral scc in young patients with no accepted risk factors. The cause for this (if true) are unknown. Much of the geographical variation is due to the inclusion of lip cancer in the statistics. Lower lip

cancer is strongly related to the amount of sunlight and fishermen in Newfoundland have the highest incidence of scc at 29.9:100,000 because of their very high incidence of lower labial cancer. The variation in incidence between UK and India on the other hand is due to differences in tobacco usage.

### **Age & Sex**

Oral scc is predominantly a disease of the elderly with 72% occurring between 55 & 75 years of age with a mean age of 63 years.

The male:female ratio has fallen dramatically from 10:1 in the 1930's to 1.3:1 in the 1970's. This is due to a falling incidence for males while at the same time female scc on the increase.

### **Site**

Excluding scc of the lower lip the most frequent sites for oral scc in descending order are: tongue, floor of mouth and mandibular alveolus. The rest (buccal mucosa, hard & soft palate, maxillary alveolus and antrum) are of about equal frequency. It is postulated that the lateral borders and ventral surface of the tongue, the floor of mouth and the mandibular alveolus form a "sump" into which saliva containing carcinogens pools and can act over an extended period of time.

### **Aetiology**

Oral scc may arise in a previously normal area of mucosa or from within an area of abnormal mucosa. The abnormal mucosa may contain a precancerous lesion or be a premalignant condition

Oral precancer may be defined as a lesion consisting of morphologically altered tissue in which cancer is more likely to occur than in its' apparently normal counterpart. Oral premalignancy may be defined as a generalised state associated with a significantly increased risk of developing cancer. Some authors use the terms synonymously.

It is thought that cancer arises as a result of a carcinogenic agent initiating a change in a regulator or a suppresser oncogene that ultimately results in cellular atypia.

### **Premalignant cancerous and premalignant lesions**

There are 2 precancerous conditions in the mouth: leukoplakia and erythroplakia. The definition of both is unsatisfactory and is one of exclusion. Leukoplakia is a white patch that cannot be characterised clinically or pathologically as any other disease. The clinical appearance varies from smooth and white through wrinkled and grey. The patches may be small and discrete or cover a large area of the mouth. The lesion is white because of the presence of keratin as a result of irritation. The irritation may be

mechanical, thermal or chemical. Tobacco smoking and chewing are major causes of leukoplakia.

The incidence of malignant change increase with the age of the lesion from 2.4% at 10 years to 4% at 20 years. Older patients show a greater potential for malignant change. Leukoplakia of the floor of the mouth and ventral surface of the tongue show the greatest potential for malignant change. Some leukoplakia is non-homogenous in appearance (speckled leukoplakia).

While about 3% of homogenous leukoplakias undergo malignant change this rises to about 11% for the nodular speckled variety and as high as 38% if erosions are present.

Erythroplakia may be defined as is a red velvety patch that cannot be characterised clinically or pathologically as any other disease. They are usually irregular in outline although clearly demarcated from the surrounding normal tissue. The incidence of malignant change is 17 times that of leukoplakia. The majority of erythroplakias are areas of severe epithelial dysplasias or carcinoma *in situ*.

Several mucosal conditions are associated with an increased propensity for developing oral scc.

1. Chronic hyperplastic candidiasis thick white plaques are formed. Candida is also often found in the speckled areas of speckled leukoplakia. There may be an associated immunodeficiency state.
2. Lichen planus is usually a benign mucosal condition resulting in mild soreness of buccal mucosa and gingivae. In a small number of cases an aggressive erosive form occurs which appears to be associated with a slightly increased risk of malignant transformation.
3. Sideropenic dysphagia [Plummer-Vinson syndrome] (iron deficiency anaemia, gastric achlorhydria, oesophageal web, dysphagia & post cricoid carcinoma) is particularly common in Swedish women where it accounts for the high incidence of cancer of the upper GI tract. Among women in Sweden with oral scc 25% were sideropenic. The likely pathogenesis is one of epithelial atrophy resulting in an increased uptake through the oral mucosa of any carcinogens present. While the anaemia responds to iron supplementation it is not known whether this also reduces the risk of developing scc.
4. Submucous fibrosis is virtually confined to the Indian subcontinent and its' people although cases have been reported in Bengali immigrants in UK. It results from irreversible cross linkage of collagen fibres resulting from the chemical released from the Betel quid by Betel nut chewers. The resulting epithelial atrophy is thought to allow carcinogens to enter the mucosa more readily.

The common factor with the premalignant lesions is their ability to damage normal mucosa leading to epithelial atrophy.

**Aetiological factors thought to be significant in a series of 194 patients.** From Henk JM & Langdon JD. 1985 Malignant tumours of the oral cavity. p4 Edward Arnold.

<i>aetiology</i>	<i>number</i>	<i>percentage</i>
none	108	55.7
leukoplakia	39	20.1
cigarette smoking	22	11.3
mechanical irritation	14	7.2
excessive alcohol	3	1.5
syphilis	3	1.5
chronic hyperplastic candidiasis	2	1.0
betel nut chewing	1	0.5
pipe smoking	1	0.5
other	1	0.5

Tobacco and alcohol are held to be the 2 commonest causes of oral scc at the present time and their effects are likely to be synergistic. It is difficult to evaluate the role of each individually as heavy smokers tend to be heavy drinkers (and have poor dental health).

### **Tobacco**

Historically clay pipe smoking was responsible for much scc especially of the lip but this is a very uncommon habit nowadays in the UK but occurs in India where 7% of hookli (short clay pipe) smokers develop leukoplakia. Reverse smoking, common in South and Central America, the Caribbean and India is associated with scc of the hard palate.

Cigarette smoke contains over 30 tumorigenic agents including Benzanthracene and Benzopyrene. Heavy smokers (>20 cigarettes or >5 cigars per day) are 6 times more likely to develop oral cancer than non-smokers. Even light smokers have an increased risk of life time non-smokers. In a study of 945 patients with oral scc only 3.4% had never smoked. However, while cigarette smoking undoubtedly has an aetiological role it must be limited as while the incidence of oral scc has been falling cigarette smoking has been rising in the developed countries. Pipe and cigar smoking are certainly important in causing oral cancer. Marijuana smoke contains greatly increased levels of Benzanthracene and Benzopyrene and oral scc has been reported in young patients (average age 27 yrs) who use Marijuana regularly.

Chewing tobacco (Skoal Bandits) and snuff dipping are potent causes of oral scc in the area where the tobacco is held. N-Nitrosamines are the most important carcinogenic agents in chewing tobacco. In south east USA scc of the mandibular alveolus is common. The majority are verrucous carcinomas. This has been linked to the wide spread habit of snuff dipping especially among women who account for 45% of cases. Of women with oral scc 90% were habitual snuff dippers.

The prevalence of oral cancer is highest in Asia. This has been linked to the widespread habit of betel nut chewing. Betel nut is taken in the form of a betel quid. The quid consists of tobacco, slaked lime and betel nut wrapped in a betel leaf. Traditionally, differing geographical areas hold the betel quid in different parts of the mouth: cheek, labial sulcus or floor of mouth. The variation in site of oral cancer coincides with the variation in the betel quid position.

### **Alcohol**

Various studies have shown an increased risk of developing oral scc of between 2 and 20 times normal for heavy drinkers. The nature of the effect is unknown but is likely to be due to contaminants or congeners in the alcohol. Hence the increased incidence with the use of home produced spirit and rough wine. Northern France has particularly high incidence of scc (14%) widely thought to be due to the rough local wine consumed in large quantities. There is some evidence that there is a systemic effect and that alcoholic cirrhosis accelerates malignant change and also potentiates other agents acting on the oral mucosa.

However, like cigarette smoking the consumption of alcohol has risen in the UK in the last 40 years while the incidence of oral scc has been falling.

### **Syphilis**

For many years syphilis was regarded as a major aetiological factor in oral scc. In 1958 one study found 19% of patients with lingual cancer to be seropositive for syphilis. Some argued it was the heavy metals and arsenicals used to treat syphilis that cause the scc. Tertiary syphilis is now uncommon with very few cases being seropositive (about 1.5%). Langdon postulates that the reduction in syphilis and clay pipe smoking together may explain the reduction in the incidence of oral scc over the last few decades.

### **Dental Factors**

A poor dental state with sharp teeth, poor restorations, sepsis and ill fitting dentures have often been incriminated in the aetiology of scc. More often than not patients with these problems also have scc. So, as alluded to in the introduction, the patients most likely to get scc are least likely to visit a dentist and get an early diagnosis and treatment.

Frequent mouthwash users, especially of the alcoholic type appear to be more at risk than the general population of getting scc. 5% of one study who neither drank nor smoked used mouthwash with between 14 and 28% alcohol twice a day for 20 years.

## Viruses

Herpes simplex viruses (HSV) and human papilloma viruses (HPV) have been implicated in the aetiology of premalignant epithelial lesions and carcinoma of the skin and mucosa of the cervix, larynx, oesophagus and oral cavity. Raised antibody titres to HSV-1 are often found in patients with oral scc although similar results can be found in patients with benign mucosal disease. RNA complementary to HSV-DNA has been found in human oral scc cells indicating the presence of the viral genome in tumour tissue.

HPV antigens have been found in between 11% and 80 % of oral epithelial dysplasias and scc. HPV 16 & 18 are often associated with oral scc.

The problem with viruses and scc is that they are also found in normal tissues and if there is a viral role for oral scc why are such common and ubiquitous viruses not associated with more cases of scc. While it is likely that viruses especially HSV have a role in carcinogenesis (synergistically with smoking and alcohol) they may also just be passengers and contaminants in altered tissue. i.e. is it a casual or causal relationship?

## Classification & Staging

### TNM classification for oral squamous cell carcinoma

#### Tumour - T

- TIS Carcinoma in situ
- T1 Tumour 2cm or less in greatest dimension
- T2 Tumour > 2cm but no more than 4cm in greatest dimension
- T3 Tumour > 4cm in greatest dimension
- T4 Tumour with direct extension to bone, muscle, skin antrum, neck etc.

#### Nodes - N

- N0 No evidence of regional lymph node involvement
- N1 Metastasis to ipsilateral lymph node no more than 3cm diameter
- N2a Metastasis to single ipsilateral lymph node >3 cm & < 6 cm diameter
- N2b Metastases in multiple ipsilateral lymph nodes, none > 6 cm diameter
- N2c Metastases in bilateral or contralateral lymph nodes, none > 6 cm diameter
- N3 Metastases in lymph nodes > 6 cm diameter

#### Staging

Tumour	Nodes	Metastases	Stage
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T1	N0	M0	1
T2	N0	M0	2
T3	N0	M0	3
T1-3	N1	M0	3
T4	N0	M0	4
T(any)	N2	M0	4
T(any)	N3	M0	4
T(any)	N(any)	M1	4

### Prognosis

Stage	Incidence (%)	5 year survival (%)
1	17.7	77
2	12.9	76
3	61.3	44
4	8.1	20

## **Treatment**

3 basic modalities: Surgery, radiotherapy (implants and external beam) & chemotherapy. Each may be used alone or together as adjuvant treatment. Choice of modality depends on tumour stage, tumour type, bone involvement, medical health of patient and local availability of expertise.

**Stage 1** Both surgery and radiotherapy produce equally good results.

**Stage 2** Both surgery and radiotherapy probably produce equally good results but most would have primary surgery.

**Stage 3** Primary surgery and postoperative radiotherapy.

**Stage 4** Primary surgery and postoperative radiotherapy.

Postoperative radiotherapy if N0 cases found to have involved nodes at operation (about 30%) and/or resection margins not clear. For recurrences salvage surgery may be used if radiotherapy already given to maximum dose.

Some centres use preoperative radiotherapy. No survival advantage but can make subsequent surgery more difficult if takes place before or after 6 weeks post radiotherapy.

Chemotherapy has unpredictable results. In UK only used for inoperable or recurrent stage 4 disease either with or without radiotherapy.

## **Controversies**

How to treat the N0 (clinically node-negative neck). Watch & wait or elective surgery or radiotherapy. Clinical staging of lymph node status is only 70 - 80% accurate. Neck dissection and radiotherapy have associated morbidity and mortality thus must be able to demonstrate a survival advantage if used in N0 cases. Although survival drops by about 50% with subsequent lymph node involvement evidence suggests that no advantage in elective treatment of N0 neck over watch & wait and treat as necessary protocol.

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T(any)	N2	M0	4
T(any)	N3	M0	4
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