

## **ORAL CANCER**

### **Definition**

About 2% of all malignancies that can occur in the body arise in the oral cavity. In some areas of the world this percentage is higher. The majority of malignancies consist of squamous cell carcinomas of the covering oral mucosa, while the remaining include malignant tumours of salivary gland, lymphoreticular disorders, bone tumours, malignant melanomas, sarcomas, malignant odontogenic tumours, and metastases from tumours elsewhere in the body.

### **Epidemiology**

The incidence of squamous cell carcinomas of the oral cavity differs widely in various parts of the world and ranges from approximately 2 to 10 per 100,000 population per year. Such differences can to some extent be explained on the basis of environmental differences or life-style and habits among certain populations, such as betel-quid chewing, snuff dipping or the habit of reverse smoking. High incidence countries include those in south Asia such as Sri Lanka, India, Pakistan and Bangladesh; Bhas Rhin and Calvados regions in France; countries in central and eastern Europe; and Brazil. The incidence of oral carcinoma in Blacks is somewhat lower than in Whites, which is mainly due to the lower incidence of lower lip cancer in Blacks.

In most parts of the world the male-female ratio is approximately 2:1 for oral carcinomas, except for carcinomas of the vermilion border of the lower lip. In the latter site there is a strong male predominance. Oral squamous cell carcinomas are mainly found after the fourth decade.

### **Aetiology**

Use of tobacco in its various forms, including the use of smokeless tobacco, is regarded to be the main cause of oral cancer, particular when associated with the use of excess alcohol. High exposure to ultraviolet light increases the chance of developing cancer of the lower lip. Diets with low levels of vitamins A and C or inadequate consumption of vegetables and fruits may contribute to the risk of oral cancer.

Patients who are immunosuppressed, e.g. renal and homograft recipients and HIV-infected patients have a higher incidence of subsequent cancer development, particularly of the lower lip. Furthermore, a number of rare conditions predispose to the development of oral cancer, such as xeroderma pigmentosum, Fanconi's anaemia, and Bloom's syndrome.

In some patients with oral cancer, especially in females, none of the aforementioned factors or cofactors seem to be present, which makes the development of oral cancer all but completely understood.

Oral epithelial carcinogenesis seems to be a multistep process, also referred to as clonal evolution, that may be interrupted at various points. It has not been possible yet to identify chromosomal

regions containing specific genes that may play a specific role in the development of squamous cell carcinoma of the head and neck, but existence of allelic imbalance in gene loci at chromosomes 3p and 9p have been reported. Three sorts of genes have been implicated in the genesis of cancer: proto-oncogenes, that display dominant, gain of function mutations in cancer cells; tumour-suppressor genes, which are affected by recessive, loss of function mutations; aberrations in DNA repair genes. For a detailed account of molecular pathogenesis of oral cancer check references.

## **Clinical aspects**

### The primary

In European populations many oral cancers may arise *de novo*. In a high proportion of cases, however, oral cancer is preceded by clinically visible whitish (leukoplakia) or reddish (erythroplakia) changes in the oral mucosa. The most common locations of oral squamous cell carcinomas are the borders of the tongue, the floor of the mouth, and the vermilion border of the lower lip. In tobacco or betel quid chewers buccal groove and retromolar mucosa may be involved. A small percentage of patients with oral cancer have multiple primary squamous cell carcinomas, either elsewhere in the oral cavity or in the upper aero-digestive tract.

The average duration of symptoms is usually around four to five months, ranging from a few weeks up to one year. Part of the delay in diagnosis is due to the patient's lack of awareness of a serious condition ("Patient's delay") and as cancer in the mouth is not thought of as a likely event.

Relatively small carcinomas, measuring less than 1 cm, may be asymptomatic, being discovered as an incidental finding during routine dental examination. Patients with larger tumours may have varying complaints. In carcinomas of the tongue, pain is often the first symptom; this may be localised to the tongue or referred (e.g. to the ear). Some patients have noticed an ulcer or a growth of their oral mucous membrane, or just a whitish or reddish change that urges them to seek medical advice. Few patients with oral cancer will seek medical help because of an enlarged node in the neck as the first symptom.

Asymptomatic squamous cell carcinomas often show erythroplastic changes, either smooth or granular in texture, without induration. In symptomatic tumours, usually measuring more than 1 to 2 cm, the most frequently encountered feature is an indurated area of ulceration. A squamous cell carcinoma may also manifest itself as an exophytic, papillary, or as a verrucous growth without much invasiveness, also referred to as verrucous carcinoma.

### Regional metastases; distant metastases

Attention must be paid to the potential spread of oral cancers to the cervical lymph nodes. In midline or near-midline cancers, contralateral and bilateral lymphatic spread may occur. The chance of lymphatic spread is mainly influenced by the site and size of the primary. Evidence of distant metastases of oral cancer at the time of admission is rare, but is seen frequently in late

stages of the disease.

## **Diagnosis**

The suspicion of malignancy is in most cases based on the clinical findings. The most significant feature noted in malignant disease is the presence of induration on palpating the margins or base of the lesion. The application of toluidine blue staining can be a useful additional tool in the diagnostic procedure of oral carcinoma. Exfoliative cytology and the more recently introduced brush biopsy assisted by computerised detection of abnormal cells can be other helpful diagnostic tools. It is, nevertheless, recognised that neither toluidine blue staining nor brush biopsy is a substitute for an adequate scalpel biopsy that allows for histopathologic examination.

The UICC (Union Internationale Contre Cancer) has developed a TNM (Tumour, Node, Metastasis) classification for 28 sites in the body, including the oral cavity (Table I) to grade the size and extent of tumour spread. New imaging techniques are also employed to assist the clinician in assessment of spread of disease. Examination under general anaesthesia is recommended to survey the upper respiratory and alimentary track for possible second primaries or precursor lesions.

## **Treatment, and follow-up**

### Dental and oral care

Dental caries and periodontal diseases have to be taken care of adequately before therapy, whether surgical or radiological, is instituted. Root remnants and impacted teeth should be removed as well, especially when radiotherapy is anticipated in the course of treatment as this will minimize the future risk of osteoradionecrosis of the jaw bones. If extractions or surgical removal of teeth are indeed necessary, a time interval of one to two weeks should be allowed before commencement of treatment by radiotherapy. In the presence of an ulcerative oral malignancy, extraction or surgical removal of teeth is a debatable procedure because of the risk of contamination of the wound with tumour cells.

When radiotherapy will be instituted, regular application of topical fluorides is strongly recommended for the protection of the teeth, not only during but also after radiotherapy, since irradiation damages the salivary glands. The resulting hyposalivation strongly predisposes to the development of (radiation) caries and, to a lesser degree, of periodontal disease. Furthermore, hyposalivation causes a very uncomfortable feeling of oral dryness (xerostomia). Apart from frequent mouth rinses and the use of artificial saliva, the use of parasympathomimetic drugs such as pilocarpine hydrochloride may be considered in the management of xerostomia.

In patients who have undergone irradiation of the head and neck region, and in which the jaw bones have been included in the field of irradiation, antibiotic prophylaxis is required for every tooth extraction, even when simple and undertaken many years after the irradiation, in order to avoid the

development of the severe form of osteomyelitis of the jaw bone, called osteoradionecrosis.

### Surgery

Most head-and-neck oncology centres prefer primary surgery and, in selected cases, postoperative radiation rather than preoperative radiation and then surgery. In general, the aim is to obtain a margin of at least one centimeter of clinically healthy tissue when excising a squamous cell carcinoma.

In the presence of lymph node metastases, a neck dissection may be carried out at the same time, either in continuity with the primary tumour ("en bloc" procedure) or as a separate, delayed procedure. For a number of reasons a prophylactic or elective neck dissection may be indicated in the absence of clinically detectable lymph node metastases. It is beyond the scope of this chapter to discuss in detail the various modifications in neck dissections.

### Radiotherapy

In several centres radiotherapy is given as the treatment of first choice, particularly in T1 and T2 oral squamous cell carcinomas, including those of the lower lip. The total dose is in the range of 60-70 Gy, given in multiple fractions, usually as 2 Gy per day. Dose fractionization regimes have been widely researched in many centres and can significantly improve the prognosis. After radical radiation, surgery may still be effective in case of residual or recurrent tumour growth ("Salvage surgery").

Preoperative radiotherapy is also sometimes used. In advanced squamous cell carcinomas preoperative chemo-radiotherapy may be administered. Radiotherapy is often applied postoperatively if the surgical margins have not been cleared, or because of the presence of multiple cervical lymph nodes, or when one or more lymph nodes show extracapsular spread.

### Chemotherapy

In general, chemotherapy is not currently being used as the treatment of first choice in oral squamous cell carcinoma. However, it may be useful in advanced oral cancer as a preoperative or preradiotherapeutic modality.

### Habit intervention

In all cases where there is a known risk habit suitable support must be provided to quit tobacco and to moderate alcohol use. Overall prognosis of patients continuing these habits is reportedly poor.

## **Prognosis**

The prognosis for a patient with oral carcinoma depends largely on the size, tumour thickness, pattern of invasion, perineural invasion, and site of the primary tumour as well as on the presence or absence of metastatic spread (Table II).

One should realize that survival figures are based on large series of patients and are of limited value for the individual patient. Indeed, some patients with large oral cancers do better than

expected, while others with very small oral cancers may do worse. There is clearly a biological variation of the tumour as well as the oral cancer patient that is not fully understood.

The cause of death in patients with squamous cell carcinoma of the head and neck is mainly due to recurrent locoregional disease and to a lesser extent to distant metastases.

Many patients with oral cancer have chronic heart, lung, and liver diseases and other problems related to alcohol ingestion or smoking; this co-morbidity is estimated to account for 30 per cent of deaths among patients with oral cancer.

Patients who have been treated for oral cancer are at risk of getting a second primary tumour either in the head and neck region or elsewhere in the body. Therefore, long term follow-up programmes including panendoscopy are important.

### **Prevention and screening**

Primary prevention of oral cancer mainly focuses on avoidance of the use of tobacco, alcohol and betel quid (areca nut). Secondary prevention is aimed at the early recognition of oral cancer, while tertiary prevention refers to the prevention of new cancer development after treatment of cancer.

Dentists and physicians can play a major part in preventing oral precancer and cancer by encouraging a healthy lifestyle, particularly with regard to quitting tobacco use and moderating alcohol consumption. Intake of 5 or 6 portions of fresh fruit and vegetables per day is recommended. Case evaluation should always include questions about numbers of cigarettes smoked each day (or other tobacco usage) and units of alcohol consumed per week. One of the problems encountered in programmes of behaviour modification is the distorted public perception of risk where rare risk factors are often given greater emphasis than the more important dangers such as alcohol and tobacco use.

Screening programmes are recommended for the detection of oral cancer in high-risk populations of the Third World and in high risk group patients in Western countries. Inspection of the oral cavity should also be part of every physical examination in the physician's and dentist's offices, particularly in patients older than 50 years who are heavy users of tobacco and alcohol. Optimal frequency for screening for oral cancer has not yet been determined but annual screening allows detection of new lesions.

**Table 1.** UICC TNM classification of malignant tumours (UICC, 2002)

<b>T Primary Tumour</b>			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
Tis	Carcinoma in situ		
T1	Tumour 2 cm or less in greatest dimension		
T2	Tumour more than 2 cm but not more than 4 cm in greatest dimension		
T3	Tumour more than 4 cm in greatest dimension		
T4a	<i>(lip)</i> Tumour invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (chin or nose) <i>(oral cavity)</i> Tumour invades through cortical bone, into deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face		
T4b	<i>(lip and oral cavity)</i> Tumour invades masticator space, pterygoid plates, or skull base, or encases internal carotid artery		
<b>N Regional Lymph Nodes</b>			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension		
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension		
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension		
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N3	Metastasis in a lymph node more than 6 cm in greatest dimension		
<b>M Distant Metastasis</b>			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
<b>Stage grouping</b>			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, N1	M0
Stage IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumour as T4.

**Table 2.** 5-year survival in oral cancer

<b>Subsite</b>	<b>Overall</b>	<b>According to stage</b>			
		<b>I</b>	<b>II</b>	<b>III</b>	<b>IV</b>
Mobile tongue	45%	80%	60%	30%	15%
Floor of mouth	50%	80%	70%	60%	30%
Buccal mucosa	45%	75%	65%	30%	15%
Retromolar trigone	60%	75%	70%	60%	30%
Lower gingiva	65%	75%	60%	50%	60%
Lip	85%	90%	85%	70%	60%

Ph. Rubin. Clinical oncology. A multidisciplinary approach for physicians and students. 7th edition, 1993. W.B. Saunders Company, Philadelphia London Toronto Montreal Sydney Tokyo. ISBN 0-7216-3761-2



**Figure 1.** Ulcerative lesion of lateral tongue with a keratotic border raising the suspicion of a carcinoma in a young adult male smoker

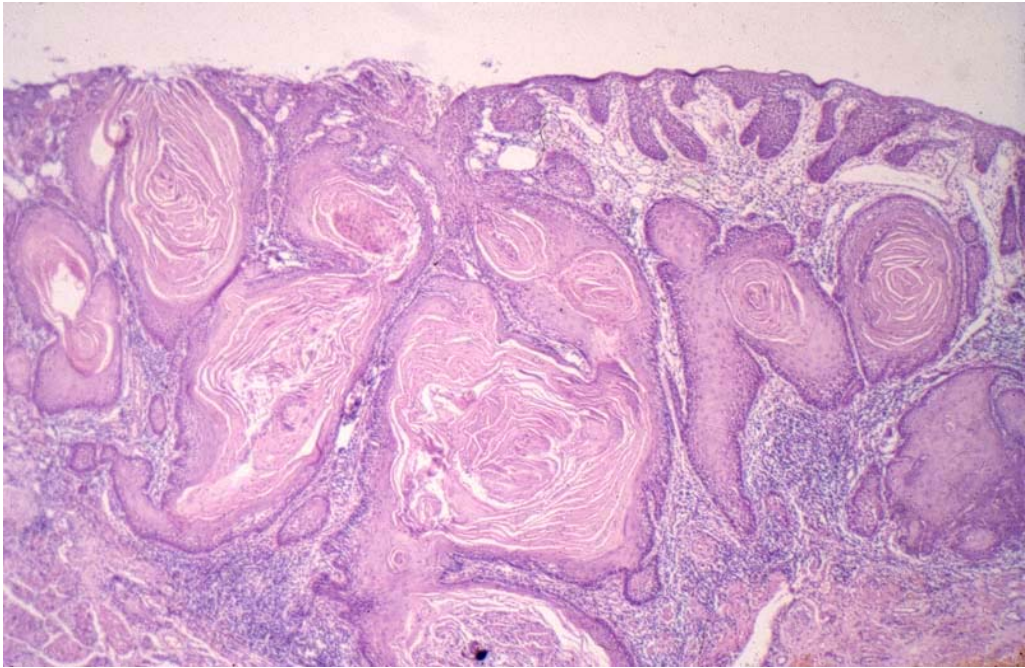


**Figure 2.** A non-healing ulcer of soft palate extending to oro-pharynx in an elderly male





**Figure 3.** A verrucous carcinoma of commissure and cheek in an Asian areca/betel quid chewer



**Figure 4.** Well-differentiated squamous cell carcinoma of the oral mucosa

### Further reading

- 1 Leethanakul C, Knezevic V, Patel V, et al. Gene discovery in oral squamous cell carcinoma through the Head and Neck Cancer Genome Anatomy Project: confirmation by microarray analysis. *Oral Oncol* 2003; 39:248-258
- 2 Warnakulasuriya S. Cancers of the oral cavity and pharynx. In: Vogelstein B & Kinzler KW. *The Genetic Basis of Human Cancer*. New York: McGraw Hill. 2002; 773-784.
- 3 Warnakulasuriya KAAS, Johnson NW. Sensitivity and specificity of OraScan toluidine blue mouthrinse in the detection of oral cancer and precancer. *J Oral Pathol Med* 1996; 25:97-103.
- 4 Sciubba JJ. Improving detection of precancerous and cancerous oral lesions. *J Amer Dent Association* 1999; 130: 1445-1457.
- 5 Ferlay J, Bray F, Pisani P and Parkin DM. *GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0*. IARC CancerBase No. 5. Lyon, IARC Press, 2001.
- 6 Nagao T, Warnakulasuriya S. Annual screening for oral cancer detection. *Cancer Detection and Prevention* 2003; 27: 33-337.