

Oral Cancer – An Overview

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1. Introduction

Neoplasms of diverse cellular origin arise in the oral cavity and among these oral squamous cell carcinoma (OSCC) arising from the mucosa of the oral cavity constitutes to over 90%^{1,2}. Oral cancer encompasses all the malignancies originating in the oral tissues, including cancers of the lip, tongue, gingiva, floor of the mouth, buccal mucosa, palate and the retromolar trigone. It is the 6th most common cancer worldwide³. Oral squamous cell carcinoma is described as an invasive epithelial neoplasm with varying degrees of squamous differentiation and a propensity to early and extensive lymph node metastases, occurring predominantly in alcohol and tobacco using adults generally in the 5th and 6th decades of life.

Globally about 5,00,000 new cases of oral and oropharyngeal cancers are diagnosed and three quarters of these are from the developing world^{7,8,9}. Approximately 3,89,650 cases occurred in the year 2000 out of which 2,66,672 were in the oral cavity (ICD - 9 140 - 5) and 1,22,978 for the cancer of oropharynx (ICD - 9 146, 8-9). This represented about 5% of all cancers for men and 2% for women¹⁰. Oral and oropharyngeal cancers remain one of the more common cancers in the South and South East Asian countries, as opposed to Western society, where it accounts for only about 1 - 4% of the reported cancers incidence⁴. For example, the incidence of oral cancer in India is high, constituting about 12% of all cancer in men and 8% in women⁵; mortality rate is equally high in this population, ranking number one in men and number three in women⁶. Oral and oropharyngeal cancers therefore qualify as major public health problem, not only in India, but also globally.

Worldwide, oral cancer incidence rates appear to have been stabilizing over the last decade¹², but the greater frequency of oral cancer in certain regions and among specific populations is a cause for concern since their overall 5-year survival rate is 53% and it has not changed in the last two decades¹³. With this heightened awareness, research to further investigate the detection, diagnosis and prevention of oral cancer has recently been included as one of the targeted priorities supported by the National Institute of Dental and Craniofacial Research (NIDCR) in the United States¹⁴.

The overall 5 - year survival rate for patients without clinically evident cervical lymph node metastases is 85% . However, patients with microscopic lymph node metastases have a survival rate of 54%. It has been estimated that 20-50% of patients without clinically evident cervical lymph node metastases do in fact have microscopic metastases and therefore poorer

prognosis⁸⁷. Among the Indian population, the overall 5- year observed and relative survival rates were 30.5% and 39.7%, respectively. Survival steadily declined with advancing age and advanced clinical stages. 5-year observed survival was 59.1% for localized cancer, 15.7% for cancers with regional extension and 1.6% for those with distant metastasis. Those with tongue, buccal mucosa and retromolar trigone cancers had poor survival rates¹¹.

2. Risk factors for oral cancer

The cancer epidemic in developed countries, and increasingly in developing countries, is due to the combined effect of the ageing of populations, and the high or increasing levels of prevalence of cancer risk factors¹⁵. About 95% of patients with oral cancer are over 40 years of age at diagnosis, and the mean age at diagnosis is 60 years. The association of oral cancer with increasing age is consistent with the disease process being related to environmental risk factors. Risk rises dramatically among males from about 7/1, 00,000 at the age of 30 to approximately 80/1, 00,000 for the 60 year old¹⁵.

The development of oral cancer in many cases appears to be due to chronic exposure to topical carcinogens, notably tobacco and alcohol¹⁶ proposed to interact synergistically to increase cancer. However, there is a distinct geographical variation among the risk factors contributing to oral cancer. In the Western population exposure to sunlight (lip cancer), cigarette-smoking, and alcohol consumption are the frontline etiologic culprits compared with the use of smokeless tobacco and combustible tobacco more prevalent in the South East Asian countries¹⁷.

The concurrent use of tobacco and alcohol accounts for 75% of all oral cancers¹⁸. Other risk factors for oral cancers includes over exposure to sun rays, particularly the cancer of the lip, and malnutrition or poor dietary intake of essential minerals¹⁹. Currently the role of viruses such as human papillomavirus^{20, 21, 22, 23} is also implicated as a major risk factor. They are believed to induce cancers by altering the DNA and the chromosomal structures of the cells and by inducing proliferative changes of the cells they infect.

An increased consumption of fruits and vegetables is associated with lower risk of oral cancers²⁴. Thus, primary preventive measures in oral cancer includes, avoidance of tobacco and alcoholic intake, avoiding exposure to certain viruses and exposure to sunlight and consumption of fruits and vegetables.

Tobacco: Overwhelming majority of carcinomas is closely linked to tobacco usage in various forms. Tobacco may be consumed as smoking tobacco or smokeless tobacco. It is used in various forms such as chewing tobacco, oral use of snuff, smoking of cigars, cigarettes, bidis, pipes, among others (Table – 1.1).

The smoking of tobacco is a widespread habit practiced by people from most cultures and societies throughout the world. While the custom of tobacco smoking is almost universal in its occurrence, there is considerable variation with respect to the amount of tobacco smoked and the form in which it is smoked. Smokeless tobacco is tobacco that is not burnt when it is used and is usually placed in the oral or nasal cavities against the mucosal sites that permit the absorption of nicotine into the human body. The two main types are the chewing tobacco and snuff. It may be used alone or in combination with other substances such as lime.

Smoking Tobacco	
Cigarette	Finely cured tobacco treated with sugars, flavoring agents wrapped in paper.
Bidi	Small quantity of shredded sun cured tobacco which is hand rolled into a piece of tendu (temburni tree leaf – Diospyrous melanoxylon).
Cigars	Made of cigar tobaccos, wrapped in a tobacco leaf, paper or reconstituted tobacco.
Chutta	Hand made cigar containing cured tobacco in a dried tobacco leaf wrapping.
Pipe – Briar Pipe, Meerschaum Pipe (England), Chillum (India)	Pipe tobaccos are of variable composition usually consist of blended tobaccos to which sugars and flavoring agents such as liquorices are added.
Smokeless tobacco	
Chewing tobacco	Plug tobacco, loose leaf tobacco and twist (roll) tobacco (Western World).
	Khaini, Pattiwala tobacco, Mainpuri tobacco, Mishri, Zarda, Kiwam, Gudakhu, Shammah, Nass, Naswar.
Snuff	A moist type, consisting of very finely cut tobacco which is used in the mouth and a dry type, which is finely pulverized tobacco and which is used orally or nasally.

Table 1.1. Different forms of tobacco and usage

Among the different smoking habits, the cigarette or cigar increased the risk of cancer by 6 times, hookah and pipe by 16 times and bidi smoking by 36 times²⁵ as compared to non smokers. In the largest population-based case-control study of oral cancer yet conducted¹⁶, strong positive trends in risk were observed according to amount and duration of each type of tobacco and amount of alcohol consumption. Relative to nonsmokers, heavy cigarette smokers (40+/day for 20+ years) experienced a four-fold risk (men) and ten-fold risk (women) after adjusting for alcohol intake. After controlling for smoking, moderate drinkers (15-29 alcoholic drinks/week) had a three-fold risk of oral cancer and heavy drinkers (> 30 drinks/week) experienced an eight- to nine-fold risk. Combined heavy smoking and drinking resulted in a greater than 35-fold excess risk.

The chewing of quid containing betel leaves, tobacco, and lime and the smoking of bidi contribute to the majority of cases in parts of India and Southeast Asia^{26, 27}. Among users of snuff, cancerous lesions typically arise at the site where smokeless tobacco or quid, is held in contact with the buccal mucosa or gingiva. Although not as prevalent as cigarette smoking, habitual use of pipes, cigars, and smokeless tobacco is associated with relative risks for cancers of the mouth as great as that for cigarette smoking²⁸. The site of origin of oral cancer usually corresponds to the placement of tobacco quid²⁹. The patients who chewed and smoked tobacco together had a tenfold higher risk of cancer of the oral cavity relative to the non-chewing, non-smokers, whereas the patients who only chewed tobacco had a six fold

higher risk of cancer and the patients who only smoked had a threefold increase in the same risk³⁰. It has also been demonstrated that the relative risk of chewing betel quid without tobacco for oral cancer was lowered compared to chewing betel quid with tobacco³¹. The role of areca nut in oral carcinogenesis is a matter of debate, however, areca nut and lime when used has had a definite carcinogenic effect, even when chewed without tobacco³².

Tobacco consumption is positively correlated with accumulation of DNA damage, and exposure to tobacco related chemical carcinogens could provide direct damaging effects on the cellular DNA in the human oral cavity^{33, 34}. DNA damaging agents found in tobacco include benzo(a)pyrene (B(a)P) and tobacco specific N'-nitrosamines (TSNAs). Examples of TSNAs are N-nitrosornicotine (NNN) and 4-[methylnitrosoamino]-1-[3-pyridyl]-1-butanone (NNK) and these chemicals exhibit carcinogenicity in animals^{33, 35}. In fact, damaged genomic DNA has been detected as DNA adducts in various tissues of cigarette smokers^{36, 37}. Nitrosamines contain the organic functional group N-N=O, and are formed by the nitrosation (addition of an N=O group) of secondary and tertiary amines. Another chemical term for these tobacco amines is an "alkaloid", an organic base that contains nitrogen and is located in a seed plant. TSNAs are created during fermentation, curing and burning of the tobacco leaf. These findings strongly suggest a causal role of tobacco use in oral carcinogenesis³⁸.

Alcohol: The independent risk of alcohol in oral cancer etiopathogenesis is uncertain as most of the alcohol users are smokers as well. Alcohol is thought to be associated with carcinogens through several mechanisms in that it may damage the oral mucosa through a direct effect on cell membranes, removing lipids and increasing the permeability of the oral mucosa to noxious carcinogenic substances. It also has systemic effects and alcohol related liver damage may potentiate the action of carcinogens in the oral mucosa by reducing the body's ability to detoxify harmful compounds. Alcohol also has immunosuppressive effect and this together with a degree of nutritional deficiency may also contribute to the carcinogenic process. In addition, acetaldehyde a direct metabolite of alcohol is a carcinogen and may be produced both systemically and by the oral micro flora.

Viruses: Both RNA-containing and DNA-containing viruses have been identified as carcinogenic. These viruses may incorporate one or more of the functional genes into the host DNA and secondly the persistent expression of this viral genome may maintain the host cell in the transformed state. Although Epstein - Barr virus (EBV), Herpes Simplex viruses (HSV), Retroviruses and Human papillomaviruses (HPVs) have all been implicated to play a role in the development of oral carcinoma, HPV is increasingly highlighted as a risk factor in oral carcinogenesis^{39, 40, 41, 42}.

HPVs, especially those genotypes of known high oncogenic potential in uterine cervix and skin such as HPV 16 and 18, are found in a variable but small proportion of oral cancers. This has led to the speculation that HPV infection, perhaps arising from oral/ genital contact, might be important in some cases. Of interest is the observation that HPV containing cancers at these sites do not generally show TP53 mutations, contrary to HPV DNA negative cancers⁴³.

It is well known that E6 protein from "high risk" HPV interact with E6 associated protein (E6/E6-AP) complex, which binds to and induces degradation of p53 protein^{44, 45}. "High risk" HPV infection, however, directly abrogates the innate check point mechanisms against

such environmental challenge, resulting in the accumulation and propagations of mutations. Hence, the viral infection in combination with existing chemical carcinogens may be the paramount causative agents for the development of oral cancer⁴⁶.

Diet and deficiency states: Recent epidemiologic studies have indicated that diet may play an important role in the origin of these cancers. Findings have pointed to the protective effects of a diet consistently high in fresh fruits; vegetables; vitamins A, C, and E; and carotenoids, even with adjustment for alcohol intake and smoking^{47, 48, 49, 50, 51}. A reduced risk of oral cancer associated with vitamin E supplementation has been shown in one study⁵². Certain deficiency states may cause epithelial atrophy, which renders the epithelium vulnerable to action of carcinogens. Vegetarianism versus non vegetarianism has failed to show any role in oral cancer development⁵³. High levels of carotenoids have been shown to be strongly related to lower risk of oral cancer development. The possible role of micronutrient ingestion with an associated antioxidant effect has been emphasized. Natural carotenoid compounds, dietary selenium, folate and vitamin A, C and E have been stated to offer protective effects regarding cancer development⁵⁴. Iron deficiency anemia, a relatively common disorder, may produce atrophic oral changes (as seen in patients with Plummer-Vinson syndrome) that may predispose to malignant transformation⁵⁵.

Oral cancer affects men more often than women because of heavier indulgence in both tobacco and alcohol habits in most countries^{58, 59}. However, in India the oral cancers are also common among women due to tobacco chewing habits. The male to female ratios, globally, however, is lower for cancer of the oral cavity than for cancer of the oropharynx, perhaps suggesting that higher exposure to tobacco smoking and alcohol drinking are required to induce oropharyngeal than oral cancer⁶⁰. An epidemiological review on oral cancer in India showed that the mean age was 57.1 years for males and 58.6 years for female patients with peak age frequency in the sixth decade for men and seventh decade for women⁵.

Other factors: Carcinoma of the vermilion border of the lip is more often linked to working outdoors in fair skinned individuals regularly exposed to sun light. This has been attributable to the effect of UV radiation^{26, 56}. Oro-dental factors like poor oral hygiene, faulty restorations, sharp teeth and ill-fitting dentures may also play a role in the etiology of oral cancers⁵⁷.

3. Clinical features

The clinical features of oral cancer differ considerably for different intraoral locations. Patients with small oral and oropharyngeal SCC are often asymptomatic or may present with vague symptoms and minimal physical findings. Hence, a high index of clinical suspicion is needed to diagnose small lesions, especially if the patients have tobacco and alcohol habits. Patients may present with red lesions, mixed red and white lesions or white plaques. Co existing white plaques may be observed adjacent to carcinomas and this implies an origin in a pre existing white lesion though the prevalence of this association varies considerably. However, most patients present with signs and symptoms of locally advanced disease. The clinical features may vary according to the affected intra oral site. Mucosal growth and ulceration, pain from the lesion, referred pain to the ear, malodor from the mouth, difficulty with speaking, discomfort while chewing, pain with swallowing, weight loss, swelling in the neck are the common presenting symptoms of locally advanced oral

cancers. Occasionally patients present with enlarged neck nodes without any symptoms from oral or oropharyngeal lesions. Extremely advanced cancers present as ulceroproliferative growths with areas of necrosis and extension into the surrounding structures. In the advanced stages patients may present with orocutaneous fistula, intractable bleeding, severe anaemia and cachexia.

Tumors may arise in any part of the oral cavity and its preferential occurrence varies with the geographical domain reflecting different risk factors. Within the oral cavity, oral cancer may be localized to buccal mucosa, upper and lower gingiva, hard palate, anterior two thirds of the tongue, including the dorsal, ventral and lateral surfaces, and floor of the mouth. The most common oropharyngeal site of involvement for SCC is the base of tongue.

Oral cancers have a varied clinical presentation in that they may be exophytic or endophytic. Exophytic lesions typically have surfaces that are irregular, fungating, papillary or verruciform and its color may vary from normal to red to white, depending on the degree of vascularity and the amount of surface keratin. The surface is often ulcerated, and the tumor feels indurated on palpation. The endophytic growth pattern is characterized by a depressed, irregularly shaped, ulcerated central area with a surrounding "rolled" border of normal, red or white mucosa. The rolled border results from invasion of the tumor downward and laterally under adjacent epithelium.

Carcinoma of the lip is typically found in light skinned persons with either long term exposure to ultraviolet radiation from sunlight or a history of sunburn early in life. It also may arise at the site where a cigarette, cigar or pipe stem is held by the patient. Almost 90% of lesions are located on the lower lip. The typical vermilion carcinoma is a crusted, oozing, non tender, indurated ulceration that is usually less than 1cm in its greatest diameter. The tumor is characterized by a slow growth rate and metastasis is a late event^{61, 62}.

The most common intraoral carcinoma is the tongue, usually the posterior-lateral and ventral surfaces. Cancer of the tongue may appear as a red area interspersed with nodules or as an ulcer infiltrating deeply, leading to reduced mobility of the tongue. These tumors are painful. Advanced stages are associated with drooling. Lesions near the base of the tongue are particularly insidious, since they may be asymptomatic until they attain advanced stage. Even then the only manifestation may be a sore throat and dysphagia. The specific site of development of these tumors is of great significance, since the lesions on the posterior portion of the tongue are usually of a higher grade of malignancy, metastasize earlier and offer a poorer prognosis, especially because of their inaccessibility for early diagnosis and treatment. Metastasis occurs with greater frequency in cases of tongue cancer. In India, the cancers over the anterior 2/3 of tongue are related to the tobacco chewing habit and posterior 1/3 lesions are related to bidi smoking^{63, 64}.

Carcinoma of the floor represents 15 - 30% of all intra oral cancers. Cancers of the floor of the mouth may arise as a red area, a small ulcer or as a papillary lesion. Most patients present with discomfort or irritation at the site of the tumor. This type of cancer affecting predominantly the males of the higher age group has shown to be associated with tobacco usage and alcohol drinking⁶⁵. The typical carcinoma in the floor of the mouth is an indurated ulcer of varying size situated on one side of the midline. Because of its location, early extension into the lingual mucosa of the mandible and into the mandible proper as well as into the tongue occurs with considerable frequency. Of all intra oral carcinomas, oral

floor lesions are the most likely to arise from a preexisting leukoplakia or erythroplakia. It is also the oral cancer site most often associated with the development of a second primary malignancy of another aerodigestive tract location or a distant organ. Metastasis from the floor of the mouth are found most commonly in the submandibular group of lymph nodes and since the primary lesion frequently occurs near the midline where a lymphatic drainage occurs contra lateral metastases are often present⁶⁶.

Cancer of the buccal mucosa may present as an ulcer with indurated raised margin, exophytic or verrucous on the side with the placement of betel quid. In advanced stages these lesions infiltrate into the adjacent bone and overlying skin. Leukoplakia is a common predecessor of carcinoma of buccal mucosa and they originate in the commissural areas and spreads posteriorly. The most common sites of metastases are the sub maxillary lymphnodes^{67, 68}.

Carcinomas from gingiva and alveolar ridge are usually painless and most frequently arise from keratinized mucosa. It is generally agreed that carcinoma of the mandibular gingiva is more common than the involvement of maxillary gingiva. Carcinoma of the gingiva usually manifested initially as an area of ulceration which may be purely erosive or may exhibit an exophytic granular or verrucous type of growth. The tumor arises more commonly in edentulous areas, although it may develop in a site in which teeth are present. The attached gingiva is more frequently involved than the free gingiva. The proximity of the underlying periosteum and bone usually invites early invasion of these structures. In maxilla, gingiva carcinomas often invade into the maxillary sinus, or it may extend onto the palate or into the tonsillar pillar. In the mandible, extension into the floor of the mouth or laterally into the cheek as well as deep into the bone is rather common. Of all the intra oral carcinomas, this one is least associated with tobacco smoking and has the greatest predilection for females⁶⁹.

Tumors of the alveolar ridge may occasionally present difficulty in wearing dentures or may present loose teeth associated with pain and bleeding during brushing of teeth. Tumors of the hard palate are not particularly common lesions and palatal carcinomas usually manifests itself as a poorly defined, ulcerated, painful lesion on one side of the midline. It crosses the midline, and may extend laterally to include the lingual gingiva or may posteriorly extend to involve the tonsillar pillar or uvula. Tumors of the hard palate often presents as papillary or exophytic growths, rather than a flat or ulcerated lesion.

Cancers of the soft palate and oropharyngeal mucosa has the same basic clinical appearance as more anterior carcinomas, except that in this posterior location the patient often is unaware of its presence and the diagnosis may be delayed. The tumor site is greater than that of more anterior carcinomas and the proportion of cases with cervical and distant metastasis at diagnosis is higher⁷⁰.

4. Relevant diagnostic procedures

Early detection of cancer is the most effective means of reducing mortality. Accurately identifiable biomarkers for early detection may provide newer avenues and constitute potential targets of cancer and its risk assessment. Screening for oral cancer should include a thorough history and physical examination. The clinician should visually inspect and palpate the head, neck, oral and pharyngeal regions. This procedure involves digital

palpation of neck node regions, bimanual palpation of the floor of mouth and tongue. Protraction of the tongue with gauze is necessary to visualize fully the posterior lateral tongue and tongue base. The clinician should review the social, familial and medical history and should document risk habits, a history of head and neck radiotherapy, familial history of head and neck cancer and a personal history of cancer.

The diagnosis is confirmed by biopsy. The specimen is taken from the clinically most suspicious area, avoiding necrotic or grossly ulcerated areas and biopsy specimens from more than one biopsy site may need. In patients with enlarged cervical lymph nodes and an obvious primary in the oral cavity, the biopsy is always taken from the primary site and not from the lymph node. In such situations, fine needle aspiration cytology may be carried out to verify the involvement of the node. If no obvious primary site is found in patients presenting with neck nodes, fine needle aspiration of the lymph node can be performed to help establish the diagnosis. In patients for whom fine needle aspiration is non diagnostic, excisional lymph node biopsy is required. Patients with SCC of the oral cavity or oropharynx have a risk of multiple primary tumors in the pharynx or larynx, as well as in the tracheobronchial region and oesophagus so routine panendoscopy is often performed to evaluate these sites.

Imaging: Intra oral and dental radiographs, in combination with orthopantomography, may help in identifying involvement of the underlying bone. Three dimensional imaging with computed tomography (CT) and magnetic resonance imaging (MRI) is frequently used to supplement the clinical evaluation and staging of the primary tumor and regional lymph nodes. CT scan or MRI gives more information about the local extent of the disease and also help to identify lymph node metastases. MRI is more informative when evaluating the extent of soft tissue and neurovascular bundle involvement. The combination of soft tissue characterization and anatomical localization afforded by CT and MRI make them valuable tools in the preoperative assessment of patients. Distant metastasis from oral cancer is uncommon at presentation. At minimum, a routine radiograph of the chest is performed to rule out lung metastases.

5. Tumor spread

Local spread of oral SCC, in the early stages, is relatively predictable in tissues that have not been previously irradiated. It is influenced by local anatomical features. Lip SCC spreads superficially and then into deeper tissues. Floor of mouth SCC spreads superficially rather than in depth, invading into the myelohyoid muscle or the sublingual gland only at late stage. Tumor involving the lateral margin of tongue, whether arising there directly or by superficial spread from the floor of mouth, tends to spread deep within the tissue. The intrinsic muscles of tongue run in small bundles in all directions such that invading tumor encounters some muscle running at right angles to the surface. Tumors of palate spread superficially rather than deep and this is also true for more posterior tumors of the oropharynx.

Spread of SCC into bone is a frequent problem. The mandible is involved much more frequently than the maxilla. Tumors in the mandible can involve the inferior alveolar nerve with a particular likelihood of spread posteriorly along the nerve. Cancers arising in gingiva

or alveolus and those involving these sites by extension from adjacent sites are unlikely to invade into the mandible⁷¹.

Tumor spread in previously irradiated soft tissues tends to be more extensive and less predictable than in normal tissues and as a consequence requires more extensive surgery if excision is attempted. Spread to local lymph nodes worsens the prognosis in oral and oropharyngeal cancer. The mechanism of spread from primary site to lymph nodes is almost always by dissemination. The lymph nodes in the neck are divided into levels. The lymphatic drainage from the head and neck sites is relatively predictable⁷².

Levels at high risk for metastasis from OSCC are level I, II and III and to a lesser extent level IV. Although Level II is the most frequently involved, some tumors spread to Level III or IV, with or without involvement of Level I. This has given rise to the concept of skip metastasis. Bilateral spread to the neck is likely to occur from tumors involving the midline, especially tumors of the posterior tongue or soft palate. Extra capsular spread of tumor involving lymph nodes is associated with a poor prognosis. There have been many studies attempting to predict the presence of lymphatic spread from features of the primary tumor^{66, 73}. While the implementation of multi-modality neoadjuvant therapy for the treatment of head and neck cancer has resulted in an improvement in local regional control, there has been a resultant increase in the reported incidence of distant metastasis. This shift in the pattern of patient treatment failure highlights the importance of identifying patients at high risk of developing metastasis, accurately detecting metastasis, and improving treatment strategies for advanced disease. Currently, metastatic lesions from head and neck primaries portend a poor prognosis⁷³.

Pattern of the invasive front is a useful predictor in that a non cohesive front is associated with increased likelihood of metastases. Other factors associated with increased risk of metastases are perineural spread at the invasive front, lymphovascular invasion and tumor thickness. For diagnostic purposes, a thickness of 5mm or greater is used as indicating increased risk of nodal spread⁷⁴. Until recently hematogenous spread of oral cancer had been regarded as less important than local and lymphatic spread. However, its importance is increasing as loco-regional control improves. Blood borne spread most often involves lung^{75, 76}. The best predictor of the likelihood of spread is involvement of the neck at multiple levels. This suggests that the route of entry of tumors into the circulation is most often via the large veins in the neck and that haematogenous spread is in effect tertiary spread following extracapsular spread from neck nodes.

6. Staging

Clinical staging refers to an assessment of the extent of the disease before undertaking treatment. The purpose of staging is for the selection of the most appropriate treatment plan, for meaningful comparison of the end results reported from different sources and for determining tumor size, extent of metastasis, and other indicators of patient prognosis.

TNM clinical classification of carcinomas of the lip and oral cavity^{77, 78}

- T - Primary tumor
- TX - Primary tumor cannot be assessed
- T0 - No evidence of primary tumor

- Tis - Carcinoma in situ
- T1 - Tumor 2cm or less in its greatest dimension
- T2 - Tumor more than 2cm but not more than 4cm in greatest dimension
- T3 - Tumor more than 4cm in greatest dimension
- T4a (Lip)
- Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth or skin (Chin or nose)
- T4b (Oral cavity)
- Tumor invades through cortical bone, into deep / extrinsic muscles of the tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), maxillary sinus or skin of face
- T4b (Lip and oral cavity)
- Tumor invades through masticator space, pterygoid plates, or skull base or encases internal carotid artery
- NOTE - Superficial erosion alone of bone/ tooth socket by gingival primary is not sufficient to classify tumor as T4
- N - Regional Lymph nodes (Cervical nodes)
- NX - Regional lymph nodes cannot be assessed
- N0 - No regional lymph node metastasis
- N1 - Metastasis in a single ipsilateral lymph node, 3cm or less in greatest dimension.
- N2 -
- N2a - Metastasis in a single ipsilateral lymph node, more than 3cm but not more than 6 cm or less 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
- Note - Midline nodes are considered ipsilateral nodes.
- (M) - Distant metastasis
- MX - Distant metastasis cannot assessed
- M0 - No evidence of distant metastasis
- M1 - Distant metastasis is present

7. Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1,2,3	N1	M0
Stage IVA	T1,2,3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

8. Grading

Squamous differentiation, often seen as keratinization with variable “pearl” formation and invasive growth are the prerequisite features of SCC. Invasion is manifested by the disruption of basement membrane and extension into the underlying tissue, often accompanied by stromal reaction. Angiolymphatic and perineural invasion are additional signs of malignancy.

The tumors are traditionally graded into well - moderately - , and poorly differentiated SCC. Well differentiated SCC resembles closely normal squamous epithelium. Moderately differentiated SC contains distinct nuclear pleomorphism and mitotic activity, including abnormal mitoses; there is usually less keratinization. In poorly differentiated SCC, immature cells predominate, with numerous typical and atypical mitoses and minimal keratinization. Most SCC is moderately differentiated, so grading by differentiation is really of limited prognostic value, as compared to pattern of invasion. Broder’s⁸² grading was the first of the systems which initiated quantitative grading of cancer. This classification system was based on the estimated ratio of differentiated to undifferentiated elements in the tumor. The author suggested a grading system in which a grade I lesion was highly differentiated (its cells were producing much keratin), while grade IV were poorly differentiated (cells were anaplastic and showed no keratin formation) (Tab 1.2).

	<ul style="list-style-type: none"> Numerous epithelial pearls, considerable cellular keratinization with inter cellular bridges;
Grade I:	<ul style="list-style-type: none"> Less than 2 mitoses per high power field, Atypical mitosis and multinucleated giant cells rarely present, minimal nuclear and cellular pleomorphism.
Grade II:	<ul style="list-style-type: none"> Epithelial pearls infrequent or even absent; neither keratinization of individual cells nor the presence of intercellular bridges; 2-4 mitoses per high power field with occasional atypical mitosis; Moderate pleomorphism of cells and nuclei.
Grade III:	<ul style="list-style-type: none"> Epithelial pearls rarely seen; negligible cellular keratinization and no inter cellular bridges; More than 4 mitoses per high power field with frequent atypical mitoses, cellular and nuclear pleomorphism marked.
Grade IV:	<ul style="list-style-type: none"> Highly anaplastic, practically no keratin formation

Table 1.2. Histologic Grading of Oral Cancer⁸²

Later Anneroth et al developed a much better classification system in 1987⁷⁹ (Tab 1.3)

Morphologic parameters	1	2	3	4
Degree of keratinization	Highly keratinized (50% of cells)	Moderately keratinized (20-50% of cells)	Minimal keratinization (5-20% of cells)	No Keratinization (0-5% of cells)
Nuclear Polymorphism	Little nuclear polymorphism (>75% mature cells)	Moderate to abundant nuclear polymorphism (50-70% mature cells)	Abundant nuclear polymorphism (25-50% mature cells)	Extreme polymorphism (0-25% mature cells)
Number of mitosis/high power field	0-1	2-3	4-5	>5
Pattern of invasion	Pushing, well delineated infiltrating border	Infiltrating solid cords, bands of strands	Small groups of cords of infiltrating cells	Marked and wide spread cellular dissociation in small groups
Stage of invasion	Carcinoma in situ or questionable invasion	Direct invasion but involving lamina propria only	Invasion below lamina propria adjacent to muscle, salivary gland and periosteum	Extension and deep invasion replacing most of the stromal tissue and infiltrating jaw bones
Lymphoplasmocytic invasion	Marked	Moderate	Slight	None

Table 1.3. Histologic Grading of Malignancy of tumor cell population (points)

All the above features are graded in the most poorly differentiated parts of the tumors. Each morphologic feature is graded from 1 to 4, and a total malignancy score is the sum of scores. A high total score indicates a poor prognosis. However this system had a few drawbacks as it was complicated and time consuming. Besides which the evaluations of features were dependent on a large and representative biopsy.

Invasive front

Tumor growth at the invasive front can show an expansive pattern, an infiltrative pattern or both. Expansive growth pattern is characterized by large tumor islands with well defined pushing margins and is associated with a better prognosis. Infiltrative growth pattern is characterized by scattered small irregular cords or single tumor cells, with poorly defined infiltrating margins and is associated with a more aggressive course⁸⁰.

Bryne et al⁸¹ modified this system as they found that deep, invasive cells of the tumor appears to be histologically less differentiated than cells in the more superficial parts. They included a new parameter “invasive cell grading” into the system proposed by Anneroth et al.⁷⁹ The grading system described by Bryne et al⁸¹ consists of five morphological features namely degree of keratinization, nuclear polymorphism, number of mitoses, mode of invasion and plasma-lymphocytic infiltration. Each of these features was scored from 1 to 4 according to the definitions given by Anneroth et al⁷⁹. Only the cells at the deep, invasive margins of the tumor were graded. The scores for each morphological feature were summed into a total malignancy score.

9. Prognosis and predictive factors

Tumor size and nodal status are the most significant prognostic factors. Histological grade correlates poorly with patient outcome. The value of grading improves when only the deeply invasive margins of the tumor are evaluated. Tumors invading with pushing borders are less aggressive than tumors showing a non cohesive front showing diffuse spread with tiny strands or single cells. Major risk factors that adversely influence prognosis are two or more positive regional nodes, extra capsular extension of nodal disease or positive margins of resection. The other important histologic features associated with poor prognosis are tumor thickness and vascular invasion^{83, 84, 85, 86, 87}.

Second Primary Tumors: It has been recognized that patients with oral cancer are at a risk of second tumors in the upper aero digestive tract. This has been reported to occur in 10 – 35% of cases^{88, 89}. These may be synchronous with the index tumor or, if occurring after intervals of longer than months are described as metachronous. Recurrence of the index tumor after treatment can be diagnosed by the pathologist where the tumor is in deeper tissue and not associated with epithelial surface. However, the most frequent situation of the second tumors is when they arise from surface epithelium adjacent to the treated index tumor. On morphological grounds these are diagnosed as second primary tumors. The increasing use of molecular biological techniques has allowed distinction to be made between molecularly distinct second primary tumors and second field tumors derived from the same genetically altered field as the index tumor.

10. Glossary

Oral cancer: Cancer of the lip, tongue, salivary glands, and other sites in the mouth

Oral Leukoplakia: A predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion; some oral leukoplakias will transform into cancer.

Precancerous lesion: A morphologically altered tissue in which cancer is more likely to occur than its apparently normal counter part.

Quid: Defined as “a substance or mixture of substances placed in the mouth or chewed and remaining in contact with the mucosa, in raw or any manufactured or processed form.” Clear delineation on contents of the quid (areca quid, tobacco quid and areca and tobacco quid) are recommended as absolute criteria for finer sub divisions to be added if necessary.

Betel quid: The betel quid refers to any quid wrapped in betel leaf and is therefore a specific variety of quid

Nass - a preparation of local tobacco, ash and cotton or sesame oil

Naswar - a mixture of powdered tobacco, slaked lime, cardamom oil

Betel quid - fresh betel leaf, fresh areca nut, slaked lime, catechu and tobacco

Pan masala - areca nut, slaked lime, catechu, condiments and tobacco

Mainpuri - Tobacco, slaked lime, arecanut, camphor and cloves

Mawa - Areca nut, tobacco and slaked lime

Khainin - Tobacco and slaked lime

Gutka - An industrially manufactured tobacco and areca product

11. References

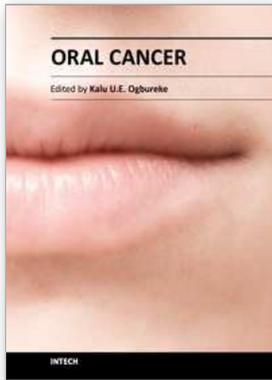
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Oral cancer is a significant public health challenge globally. Although the oral cavity is easily accessible, early diagnosis remains slow compared to the enhanced detection of cancers of the breast, colon, prostate, and melanoma. As a result, the mortality rate from oral cancer for the past four decades has remained high at over 50% in spite of advances in treatment modalities. This contrasts with considerable decrease in mortality rates for cancers of the breast, colon, prostate, and melanoma during the same period. This book attempts to provide a reference-friendly update on the etiologic/risk factors, current clinical diagnostic tools, management philosophies, molecular biomarkers, and progression indicators of oral cancer.

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