ORAL CANCER: A REVIEW

R.S Bedi, Gauri Pande, Jaipal Singh Patel, Zeeshan Khan and Nivedita Chauhan
Department of Oral & Maxillofacial Surgery,
Saraswati Dental College & Hospital, Lucknow (UP), India.

ABSTRACT
Oral cancer, undoubtedly, is among the most common malignancies worldwide, therefore early detection and treatment is imperative. The relatively poor prognosis associated with oral cancer highlights the importance of awareness towards the disease. New research is revealing trends that are changing the way we approach its screening, diagnosis and treatment. Limited access to cancer care, relative lack of trained healthcare providers and financial resources are some of the challenges to the management of oral cancer in India, despite improvements in diagnostic techniques and management strategies. The purpose of this article is to review the research relevant to this association, including epidemiologic studies, diagnostic screening procedures, prevention as well as treatment modalities.

Address for correspondence

Prof. (Dr.) R.S. Bedi
Principal & Head
Department of Oral & Maxillofacial Surgery,
Saraswati Dental College & Hospital,
Lucknow (UP), India.
Email: kingbedi99@gmail.com

Key words: Oral Cancer, Prognosis, awareness, epidemiologic, screening, Prevention.

INTRODUCTION

Epidemiology

Oral cancer is the sixth most common cancer globally. India has one of the highest incidences of oral cancer and accounts for about 30% of all new cases annually. In India, the gingival-buccal complex (alveolar ridge, gingival-buccal sulcus, buccal mucosa) forms the most common sub-site for cancer of the oral cavity, in contrast to cancer of the tongue that is more common in the western world(1). India has one of the highest incidences of oral cancer (age-standardized rate of 11.0 per 100,000 men and women per year) (2) making it the most common cancer among men (men:women ratio 2:1) (3). Around 90% of the oral cancer cases are diagnosed as oral squamous cell carcinoma, therefore oral cancer is also used as a synonym to oral squamous cell carcinoma.

A recent survey of cancer mortality in India shows cancer of the oral cavity as the leading cause of mortality in men and responsible for 22.9% of cancer-related deaths (4). There is a trend towards increasing incidence and delayed presentation of oral cancer (about

60% patients present at stage III or IV) (5). The Indian national cancer registry data show an increasing incidence as per age. However, the incidence among women is lower than the men. This can be related to differences in lifestyle and behavioural pattern between the two genders. The age group of 55-64 years has the highest incidence of oral cancer in the USA. In contrast, many patients were <40 years of age in high incidence countries such as India, Pakistan and Sri Lanka (6).

The incidence of oral cancer is higher in the lower socio-economic strata of society due to the higher prevalence of risk factors such as use of tobacco, exposure to sunlight, chronic irritation or trauma (Eduardo et. al.) and delay in the treatment for premalignant lesions. Also the burden of viral causes of cancer are quite high. According to International agency for cancer research estimates that one in five cancer cases are caused by viral infections. (Patric moore et. al.) The age-standardized mortality rates (India-5.2 per 100 000) have not improved despite improvements in diagnostic and management techniques (7). The overall 5-year survival rate for all stages of oral cancer is 60%. These rates are better for localized tumours (82.8%) as compared to tumours

with regional (51.8%) or distant metastases (27.8%).

Incidence and Trends of Oral Cancer in India

Oral cancer is a heterogeneous group of cancers arising from different parts of the oral cavity, with different predisposing factors, prevalence and treatment outcomes. There is a significant difference in the incidence of oral cancer in thedifferent regions of the world, with age-adjusted rates varying from over 20 per 100,000 population in India, to 10 per 100,000 in the U.S.A and less than 2 per 100,000 in the Middle East (8).

In comparison with the U.S. population, where oral cavity cancer represents only about 3% of malignancies, it accounts for over 30% of all cancers in India. The variation in incidence and pattern of oral cancer is due to regional differences in the prevalence of risk factors.

Aetiology

Tobacco is the single most important risk factor for oral cancer. In comparison to the people who never smoked, the relative risk of oral cancer is 5.3 times higher for people smoking <15 cigarettes per day, and 14.3 times higher for people who smoked >25 cigarettes per day (9). In India the use of smokeless tobacco is rampant in the form of betel quid (pan) that contains areca nut and lime with dried tobacco leaves; this form of tobacco has been shown to be highly carcinogenic (10).

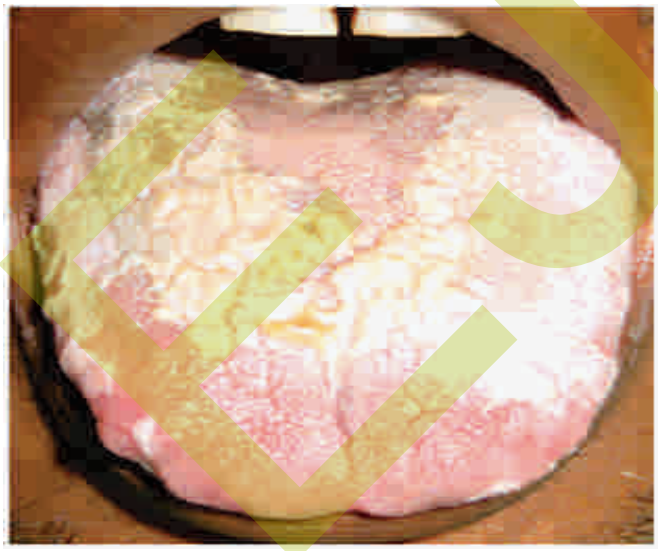


Figure: White lesion on tongue

Traditionally, the **betel quid** is placed in the gingival-buccal sulcus and often retained for prolonged durations, which is responsible for the high prevalence of gingivo-buccal cancer. Recently, there has been increasing popularity of dried tobacco and areca nut mixtures (pan masala, gutkha, zarda, khaini) especially among the youth, owing to their aggressive marketing in India.

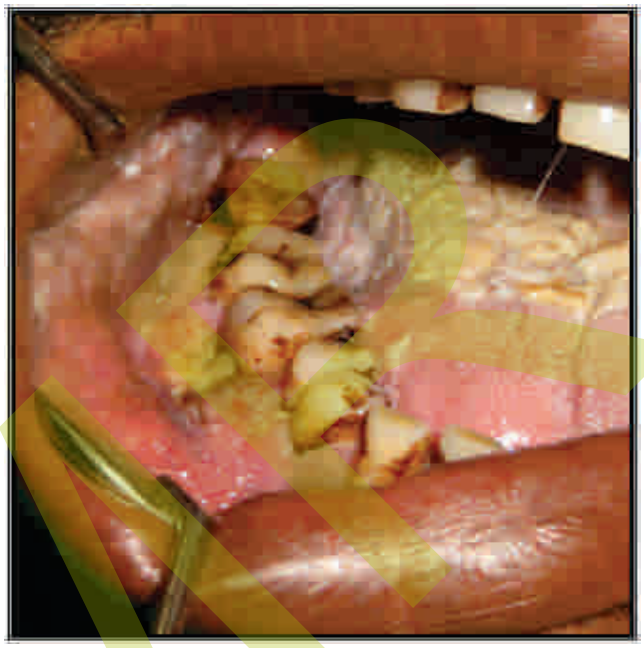


Figure: Lesion on the posterio-buccal surface of attached gingiva of mandible

Alcohol alone confers a 1.7-fold risk to men drinking 12 drinks per day as compared to non-drinkers. The consumption of 25, 50 and 100 g/day of pure alcohol was associated with a pooled relative risk of 1.75, 2.85 and 6.01, respectively, of oral and pharyngeal cancer (11). Tobacco and alcohol share a synergistic relationship, with alcohol promoting the carcinogenic effects of tobacco leading to a multifold increase in the risk of oral cancer with combined alcohol and tobacco exposure. Heavy drinkers and smokers have 38 times the risk of oral cancer compared with abstainers (12).

Viral Aetiology

Several viruses are linked with cancer in humans. Our growing knowledge of the role of viruses as a cause of cancer has led to the development of vaccines to help prevent certain human cancers. But these vaccines can only protect against infections, if given before the person is exposed to the cancer-promoting virus.

Human Papilloma Viruses are the leading cause of oropharyngeal cancers There are a group of more than 150 related viruses-. Called papilloma viruses because some of them cause papillomas, which are more

commonly known as warts. Some types of HPV only grow in skin, while others grow in mucous membranes such as the mouth, throat, or vagina. All types of HPV are spread by contact (touch).

The fastest growing segment of the oral and oropharyngeal cancer population are otherwise healthy, non-smokers in the 25-50 age range. In oral cancers, we are primarily concerned with number 16 which is also associated with cervical, anal and penile cancers. In the oral/oropharyngeal environment, HPV-16 manifests itself primarily in the posterior regions such as the base of the tongue, the back of the throat, the tonsils, the tonsillar crypts and tonsillar pillars.

Two vaccines known as Gardasil and Cervarix protect against the strains of HPV that cause cervical cancers (HPV-16 and 18), Garadsil also protects against two versions that cause genital warts (HPV-6 and 11). The vaccines can only be used to help prevent HPV infection they do not stop or help treat an existing infection (ORAL CANCER FOUNDATION) (AMERICAN CANCER SOCIETY).

Epstein-Barr Virus is a type of herpes virus. It is probably best known for causing infectious mononucleosis, often called “mono” or the “kissing disease.” In addition to kissing, EBV can be passed from person to person by coughing, sneezing, or by sharing drinking or eating utensils. EBV infection increases a person's risk of getting nasopharyngeal cancer (cancer of the area in the back of the nose) and certain types of fast-growing lymphomas such as Burkitt lymphoma. It may also be linked to Hodgkin's lymphoma and some cases of stomach cancer.

Other viruses affecting the oropharyngeal region are:

- **Human herpes virus-8 (HHV-8)** also known as Kaposi's sarcoma associated herpes virus (KSHV), has been found in nearly all tumors in patients with Kaposi's sarcoma (KS).
- **Human T-lymphotrophic virus-1 (HTLV-1)** has been linked with a type of lymphocytic leukemia and non-Hodgkin's lymphoma called adult T-cell leukemia/lymphoma (ATL). It belongs to class of retroviruses.
- **Human immunodeficiency virus (HIV)** Oral, oropharyngeal and pharyngeal cancer risk is around twice higher in people with HIV/AIDS, compared with the general population (13).
- **Hepatitis B virus (HBV) and hepatitis C virus (HCV)**

Low immunity
Research has established that people have an increased risk of mouth cancer if they are immuno-compromised such as patients infected with HIV, HBV; etc. Medications administered to suppress immunity after organ transplants also leads to higher risk of mouth cancer than in the general population.

Sunlight and Sunbeds
Skin cancers such as Basal Cell Carcinoma and Melanomas are relatively common on the face and neck regions, as these areas are often exposed to ultraviolet light (UV). Both the sun and tanning beds give off UV rays. These rays can cause skin cancers in unprotected skin. Some studies have shown an increase of skin cancer in people who regularly use sunbeds. Melanoma is the most serious type of skin cancer and can occur on the lips.

Family history and genetics also play an essential role in activation of oncogenes
Head and neck cancer risk is 70% higher in people with a family (particularly sibling) history of head and neck cancer, versus those without such history (14).

Occupational Hazarads
Formaldehyde and wood-dust are classified by the International Agency for Research on Cancer (IARC) as causes of nasopharyngeal cancer. Asbestos and exposure to printing processes (which may entail exposure to polycyclic aromatic hydrocarbons and mineral oils) have been classified by IARC as probable causes of pharynx cancer, based on limited evidence.

Oral and pharyngeal cancer risk is 25% higher in people exposed to asbestos and 14% higher in people exposed to polycyclic aromatic hydrocarbons compared with the general population (15).

Chronic trauma of the oral mucosa (CTOM) is the result of repeated mechanical irritative action of an intraoral injury agent. Defective teeth (malpositioned or with sharp or rough surfaces because of decay or

fractures), ill-fitting dentures (sharp or rough surfaces, lack of retention, stability or over extended flanges) and/or Para functional habits (e.g. oral mucosa biting or sucking, tongue interposition or thrusting), acting individually or together, could all be responsible of this mechanical irritation.CTOM could generate lesions on a healthy mucosa or intensify previous oral diseases (16).

SCC of the tongue is seen most frequently (27.6%), followed by cancer of the oropharynx (22.8%), lips (16.5%), floor of the mouth (14%), gingival (9.1%) hard-palate (4.1%) and buccal mucosa (3.5%) Oral cavity cancers occur predominantly at sites of potential dental and denture trauma, especially in non-smokers without other risk factors. Recognising teeth irritation as a potential carcinogen would have an impact on prevention and treatment strategies.

The mechanism by which CTOM is thought to contribute to carcinogenesis is not clearly identified. It has been proposed that the wound of the oral mucosa may facilitate the absorption of other chemical carcinogens. Experimental studies of CTOM in animals together with evidence of inflammation related cancers, suggest that CTOM could work by at least other two mechanisms. One consists in the mitosis increase produced to repair tissue injury, which put cells at risk of DNA damage by other agents, initiating carcinogenesis. The other mechanism possibly involved could be because of the chronic inflammation, which happens in the site affected by CTOM, through release of chemical mediators and/or oxidative stress. This could induce genetic and epigenetic changes, damage DNA, inhibiting its repair, altering transcription factors, preventing apoptosis and stimulating angiogenesis; therefore, it could contribute in all stages of carcinogenesis.

DIAGNOSIS AND EVALUATION

The various diagnostic modalities for oral cancer detection are (17)

- Careful detailed history taking
- Visual examination and palpation
- Toluidine blue (Papanicolone Test)
- Excision biopsy and Histopathology
- Oral brush biopsy (OralCDx)
- Light-based detection systems
- Chemiluminescence (ViziLite Plus; Microlux/DL, Orascoptic-DK)
- Tissue fluorescence imaging (VELscope)
- Tissue fluorescence spectroscopy
- Biomarkers
- DNA-analysis
- Laser capture microdissection

A detailed history and physical examination are critical for the comprehensive evaluation of patients with oral cancer. In the early stages, oral cancer may have few symptoms which are often ignored. The most common presentation is a patch or a non-healing ulcer; such lesion particularly with a history of tobacco and alcohol consumption and which is persistent for over 6 weeks warrants a thorough investigation. Trismus, especially of recent onset, is an indication of infra-temporal fossa involvement, a sign of relative inoperability. Physical examination should allow for accurate mapping of the extent of contiguous involvement of surrounding structures such as the bone, deep musculature of the tongue, floor of the mouth, patient's functional ability, search for synchronous second primary, fixity to surrounding skin and soft tissue and regional lymph node status. This is done on the basis of TNM cancer staging given by AJCC.

Pathological diagnosis should be confirmed with tissue biopsy from the most representative non-necrotic area of the lesion. A fine-needle aspiration cytology (FNAC) of suspected region/cervical metastases for imaging is mandatory for locally advanced disease; CT scan has been shown to be better in demonstrating cortical bone involvement of the jaws and the status of cervical lymph nodes. MRI is preferred to assess the extent of involvement of soft tissue, skull base, infratemporal fossa, RT planning and medullary bone involvement. Hence, CT scan is preferred in buccal mucosa cancer while MRI is favoured for tongue cancer.

In early stage lesions amenable to trans-oral excision with a clinically node-negative neck, ultrasound with or without FNAC is the initial investigation. Ultrasound is also preferred for close observation and follow-up of the neck in patients who are lymph node negative. The role of newer imaging modalities such as SPECT (Single positron emission computed tomography) & PET-CT are being used to improve the information available from radio isotope imaging of the cancer patient .(Coleman et.al. 1991) But these modalities lack sufficient evidence in pre treatment assessment. However, it is useful in assessing post-treatment residual/recurrent disease.

BIOPSY

Oral tissue biopsy is the gold standard diagnostic procedure, necessary for lesions that cannot be diagnosed on the basis of the history and clinical findings alone. A thorough inspection of the oral cavity should be a part of any complete head and neck examination. A 0.5-mm margin should be maintained between the cut and the representative area to be

sampled. As a general principle, including tissue subjacent to the epithelium and removing a wedge of manageable size is desirable. Therefore, a minimal depth of 3 mm, minimal length of 3-6 mm, and minimal width of 1-2 mm Biopsy is often the definitive procedure that provides tissue for microscopic analysis.

New advances in oral cancer diagnosis

Because the scalpel biopsy for diagnosis is invasive and has potential morbidity, it is reserved for evaluating highly suspicious lesions and not for the majority of oral lesions which are clinically not suspicious. Furthermore, scalpel biopsy has significant interobserver and intraobserver variability in the histologic diagnosis of dysplasia (with only 56% agreement rate between them) (17).There is an urgent need to devise critical diagnostic tools for early detection of oral dysplasia and malignancy that are practical, non- invasive and can be easily performed in an out-patient set-up. Diagnostic tests for early detection include brush biopsy, toluidine blue staining, autofluorescence, salivary proteomics, DNA analysis, biomarkers and spectroscopy.

Laser Capture Microdissection

Laser capture microdissection (LCM) has made the study of cancer biology more precise and has greatly boosted the efforts in defining the molecular basis of malignancy. LCM may be also used to detect the biomarkers and establish protein fingerprint models for early detection of oral squamous cell carcinoma (OSCC). LCM combined with SELDITOF-MS technology and bioinformatics approaches may not only facilitate the discovery of better biomarkers but also provide a useful tool for molecular diagnosis (18).

DNA-Analysis

DNA image cytometry measures ploidy status to determine the malignant potential of cells. After staining with Feulgen dye, the cytological samples are compared with a reference group of cells. A computer-assisted analysis has been recently designed to identify deviations of cellular DNA content. Genomic instability contributes towards cancer development, and abnormal DNA content may distinguish the dysplastic lesions that might progress to cancer (19).

Lab-on-a-Chip

Broadly, microfluidics technology -also referred to as lab-on-a-chip or micro-total-analysis systems (TAS)-is the adaptation, miniaturization, integration, and automation of analytical laboratory procedures into a single device or “chip.” Microfluidics is often regarded as the chemistry or biotechnology equivalent of the silicon integrated circuit chip that has revolutionized electronics, computers, and communications (20).The detection of oral dysplastic and cancer cells within the chip utilizes membrane-associated cell proteins that are singularly expressed on the cell membranes of dysplastic and cancer cells as well as their unique gene transcription profiles.

MICROSCOPY

It is the technical field of using microscopes to view objects and areas of objects that cannot be seen with the naked eye (objects that are not within the resolution range of the normal eye). There are three well-known branches of microscopy: optical,electron, and scanning probe microscopy. Spectral cytopathology (SCP) is a recently developed technique for diagnostic differentiation of disease in individual exfoliated cells. SCP is carried out by collecting information on each cell's biochemical composition via an infrared micro spectral measurement, followed by multivariate data analysis. Deviations from a cell's natural composition produce specific spectral patterns that are exclusive to the cause of the deviation or disease. These unique spectral patterns are reproducible and can be identified and employed via multivariate statistical methods to detect cells compromised at the molecular level by dysplasia, neoplasia, or viral infection (21).

Saliva-Based Oral Cancer Diagnosis

Using saliva for disease diagnostics and health surveillance is a promising modality in the detection of cancer, (Cheng et.al. 2014). Salivary genomic and proteomic biomarkers represent a non-invasive and easy approach. (Bano et.al.) Extensive research has yielded 100 biomarkers reported in literature. (Cheng et.al. 2014). However more extensive research is required to find reliable salivary markers as the ones reported are less sensitive and specific prognostic markers.

At present, the diagnosis of OSCC is based on comprehensive clinical examination and histological analysis of suspicious areas, but it may remain undetected in hidden sites. A new area of strong research interest is the use of saliva as a diagnostic aid for early detection of OSCC, which has the advantage of being noninvasive, safe and patient compliant. Proteins, mRNA, enzymes, and chemicals extorted from saliva have been found at sufficiently distinct levels between OSCC and control samples to be considered as potential biomarkers. These biomarkers may perhaps be important indicators of physiological or pathological conditions and provide information for the detection of early and differential markers for disease. They could be a prospect to serve as a widely

available screening tool that is independent of the localization of a lesion for diagnosis. This, being an added advantage over other detection methods gives salivary biomarker screening the potential to categorize patients with malignant and potentially malignant lesions (22,23).

Tumour markers

With the evolving understanding of the genetics and molecular basis of human malignancies, there has been much interest in determining whether specific molecular changes in different premalignant and malignant tumours might guide treatment decisions. Tumour markers cannot be construed as primary modalities for the diagnosis of cancer. Their main utility in clinical medicine has been a laboratory test to support the diagnosis. Only a few have stood the test of time and proved to have clinical usefulness. New investigative techniques at the cellular and molecular level show great promise at defining potentially malignant lesions but further prospective, in depth studies are required to determine their practical usefulness.

Potential uses of tumor markers

- Screening in general population
- Differential diagnosis in symptomatic patients
- Clinical staging of cancer
- Estimating tumour volume
- Prognostic indicator for disease progression
- Evaluating the success of treatment
- Detecting the recurrence of cancer
- Monitoring responses to therapy
- Radioimmuno localization of tumour masses
- Determining direction for immunotherapy

Specific tumor markers implicated in oral neoplasms

Alpha-1-antichymotrypsin (1-ACT) & factor XIIIa antibodies:

Study on peripheral giant cell lesions and central giant cell lesions for characteristics of both cell types by evaluating for Alpha-1-Antichymotrypsin (1-ACT) & Factor XIIIa antibodies (markers specific for histiocyte/macrophage) concluded that giant cell lesions of the oral cavity may arise from precursor cells that express markers for both macrophages and osteoclasts (24).

BCL-2:

Bcl-2 has been suggested as a significant prognostic indicator in early Squamous Cell Carcinoma of head and neck.

Beta 2-Microglobulin:

A definite increase in the level of beta 2- microglobulin has been observed in patients with oral submucous fibrosis and oral cancer (25).

CD44, CD80, CD105 (ENDOGLIN):

Differences in the expression of HA and CD44 among different types of salivary gland tumours has been noted, but are not correlated with biologic behavior. In oral SCC's decreased expression of CD80 may serve as a marker for increased tumourigenicity during early development, and decreased expression of CD44 correlated with decreased survival rate. Increasing evidence suggest that endoglin (CD105) is a new powerful marker of neovascularization in solid malignancies and positive CD105 vessels in Adenoid cystic carcinomas increases risk of metastasis (26).

Cytokeratins:

Monospecific keratin antibodies are useful for evaluation of epithelial differentiation changes in oral dysplasia's and oral SCC. CK19 and CK8 are markers of sequential premalignant changes in head and neck carcinogenesis. Non-expression of CK5 may be an early event occurring in tobacco-associated pathological changes in the buccal mucosa (27).

Cathepsin-D:

Cathepsin D is postulated to promote tumour invasion and metastasis. It is a potential independent predictor of cervical lymph node metastasis in Head and Neck SCC.

SPECTROSCOPY

Optical spectroscopy explores the optical phenomena resulting from the interaction of light with biological tissue. It may be particularly useful for the analysis of differences in-between normal and cancerous tissue because of major scattering, absorption and fluorescence changes which are known to occur during the development of cancer. Optical spectroscopy has the potential to detect malignant lesions earlier, before they become macroscopically visible, by probing tissue biochemistry and morphology in vivo in real time. Three optical techniques that are currently utilized in the detection of PMOL and oral malignancies are; Fluorescence, Elastic scattering and Raman spectroscopy. Autofluorescence and

Table : Broad classification of tumour markers[3]

I.	PROLIFERATION MARKERS	Ki-67, PCNA, p27 Kip/gene, DNA polymerase alpha, p 105, p120, Statin
II.	ONCOGENES	c-erbB-2 gene, ras gene, myc gene, bd-2 gene
III.	GROWTH FACTORS AND RECEPTORS	EGFR (Epidermal growth factor receptor) Transforming growth factor B-HCC Fibroblast growth factor receptor insulin and insulin like growth factor receptor,
IV.	TUMOUR SUPPRESSOR GENES	53 Retinoblastoma susceptibility suppressor gene.
V.	SEROLOGICAL TUMOUR MARKERS	a. Markers associated with cell proliferation b. Markers related to cell differentiation: (Carcinoembryonic proteins like Carcinoembryonic Ag, a-Feto protein) c. Markers related to metastasis: d. Related to other tumour-associated events. e. Related to malignant transformation. f. Inherited mutations. g. Monocional Ab-defined tumour markers

[3]

chemiluminescence have been studied as non-invasive in-vivo tools for the detection of (pre-)malignant tissue alterations (17,27).

TOMOGRAPHY

Optical coherence tomography (OCT) is a non-invasive tomographic imaging modality to detect areas of inflammation, dysplasia and cancer. OCT is a relatively new high-resolution optical technique that permits direct immediate imaging of the oral epithelium on the surface and at depths exceeding 2mm. It has been compared to ultrasound scanning conceptually. Both ultrasound and OCT provide real time structural imaging, but unlike ultrasound, OCT uses light to provide cross-sectional, high-resolution sub-surface tissue images. Because image resolution can be as good as 5 µm, these images provide an excellent indication of the most important sites for surgical biopsy. With the advent of ever faster and higher-resolution OCT systems, this imaging data may well replace the need for biopsies in many situations in the foreseeable future (28).

STAGING

Staging of the malignancy enables to device an individualised treatment plan for patients with better understanding of prognosis and outcome. The stage of cancers of the oral cavity is based on the size of the primary tumour along with involvement of surrounding structures, cervical lymph node status and distant metastases (2009 American Joint Committee for Cancer revised cancer stage groupings for oral cavity SCC) (29).

TREATMENT

Surgery and neck dissection

Surgery is the most common treatment for oral cancer. For more advanced tumours surgery is combined with local RT and/or systemic CT (29,30,31). The intent of surgery is to completely remove cancerous tissue,(32) leaving histologically normal tumour margins while attempting to preserve normal tissue and function (33,34,35). Surgical techniques vary depending upon the ease of access and the size of the lesion to be excised. Ideally the surgeon can excise smaller tumours from within the oral cavity. However, larger tumours

TABLE 3: TNM staging system for cancers of the lips and oral cavity

Primary tumor (T)

TX Primary tumor cannot be assessed

TO No evidence of primary tumor

Tis Carcinoma in situ

T1 Tumor ≤ 2 cm in greatest dimension

T2 Tumor ≥ 2 cm but < 4 cm in greatest dimension

T3 Tumor ≥ 4 cm in greatest dimension

T4 (lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, ie, chin or nose'

T4a Moderately advanced local disease'

(lip) Tumor invades through the cortical bone. Mouth, or Skin of the face (ie. chin or nose) (oral cavity) Tumor invades adjacent structures (eg. through cortical bone [mandible or maxilla] into the deep [extrinsic) muscle of the tongue [geniogiossus, hyoglossus, palatoglossus. and styloglossus], maxillary sinus, or skin of the face)

T4b Very advanced local disease

Tumor involves masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

Regional lymph nodes (N)

NX Regional nodes cannot be assessed

NO No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, < 3 cm in greatest dimension

N2 Metastasis in a single ipsilateral lymph node, ≥ 3 cm ≤ 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none ≥6 cm in greatest dimension: or in bilateral or contralateral lymph nodes. none >6 cm in greatest dimension

N2a Metastasis in a single ipsilateral lymph node, > 3 cm but < 6 cm in greatest dimension

N2b Metastasis in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension

N2c Metastasis in bilateral or contralateral lymph nodes. none > 6 cm in greatest dimension

N3 Metastasis in a lymph node. >6 cm in greatest dimension

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

Distant metastases (M)

MO No distant metastasis

M1 Distant metastasis

Stage grouping

Stage O	Tis	NO	MO
Stage I	T1	NO	MO
Stage II	T2	NO	MO
Stage III	T3	NO	MO
	T1	N1	MO
	T2	N1	MO
	T3	N1	MO
Stage IVA	T4a	NO	MO
	T4a	N1	MO
	T1	N2	MO
	T2	N2	MO
	T3	N2	MO
	T4a	N2	MO
Stage IVB	Any T	N3	MO
	T4b	Any N	MO
Stage IVC	Any T	Any N	M1

TNM	Disease location
Tis	Carcinoma in situ
T1	Invades lamina propria or submucosa
T2	Invades muscularis propria
T3	Invades adventitia
T4	Invades adjacent structures
N1	Regional node metastases
M1	Distant metastases: celiac nodes. (controversial). cervical nodes, other distant sites, liver, lung, adrenal, bone

Stage	TNM	Standard therapy (2)	Other options (2)
O	Tis, NO, MO	Surgery	
I	T1, NO,MO	Surgery	
II	T2-3, NO, MO T1-2, N1,MO	Surgery	Chemotherapy plus radiation +/-Surgery
III	T3, N1, MO T4, any N, MO	Surgery for T3 disease	Chemotherapy plus radiation +/-Surgery
IV	Any T, any N, M1	Stent for dysphagia Radiation Chemotherapy	

and those in difficult-to-access sites may require an approach from outside the oral cavity and the removal of both soft tissue and bone

More advanced oral cancers may involve the lymph nodes. Positive and suspicious lymph node involvement may require neck dissection. Even when the lymph nodes are negative elective neck dissections are sometimes undertaken to prevent the risk of metastasis (29,31,32,34). The type and level of neck dissection is decided on the basis of the number, size, state and site (same side, opposite side or both sides) of the lymph nodes involved (29,31,32).

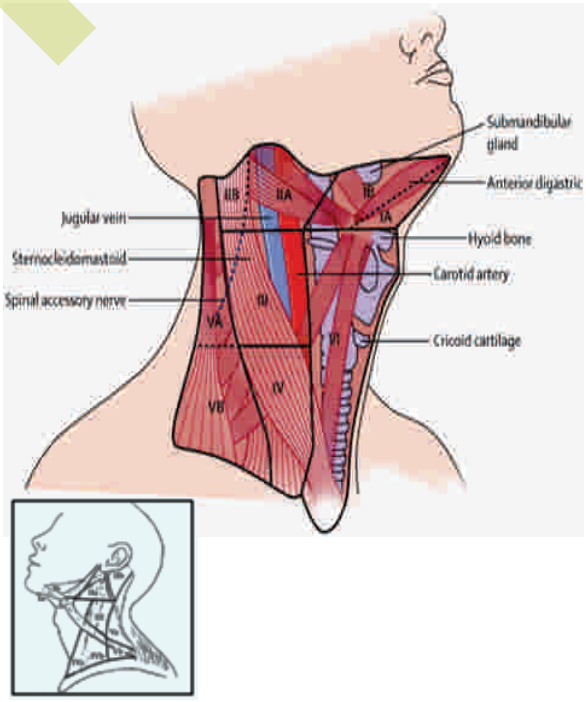


Figure: The levels of lymph nodes in the neck are as shown in the picture.

SLOAN KETTERING CLASSIFICATION OF LYMPH NODES

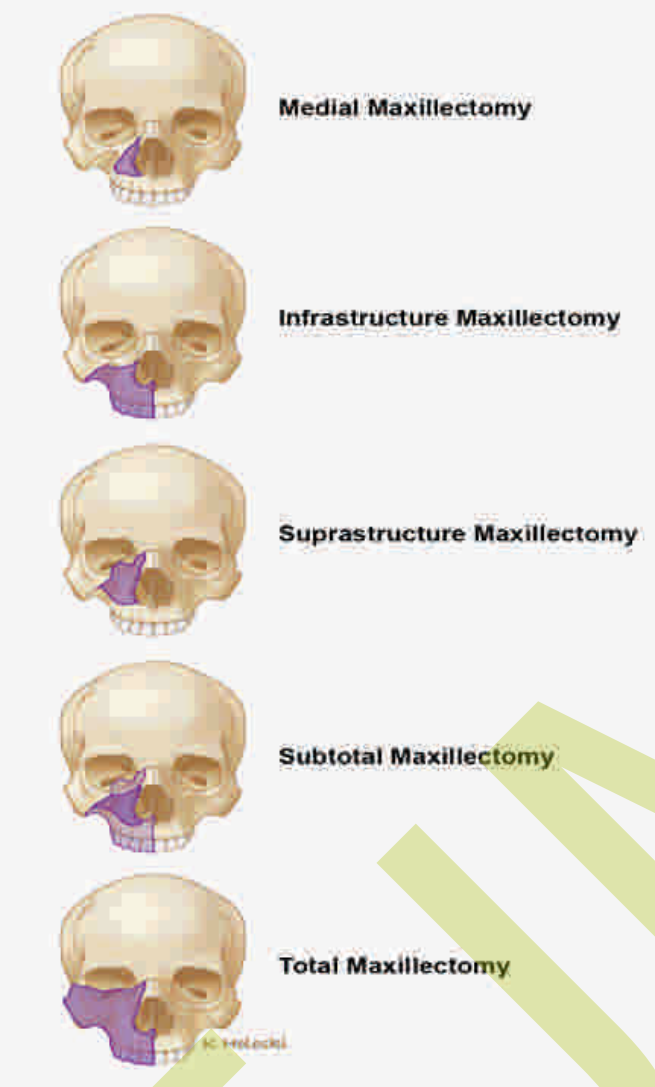
S.No.	Type
Ia	Submental
Ib	Submandibular
IIa	Upper Jugular (anterior to XI)
IIb	Upper Jugular (Pos terior to XI)
III	Middle Jugular
IVa	Lower Jugular (Clavicular)
IVb	Lower Jugular (Sternal)
Va	Posterior triangle
Vb	Posterior triangle (Transverse cervical)
VI	Central compartment

The neck dissection has been classified as :

CLASSIFICATION TABLE (K. Thomas Robbins) classification update 2001

Type of neck dissection	Structures that are removed
Comprehensive neck dissection	
"Classical" radical neck dissection	All lymph -bearing tissues (level I -V), spinal accessory nerve (cranial nerve [CN] XI) sternocleidomastoid muscle, and internal jugular vein
Modified radical neck dissection	Neck dissection with sparing one or more of the above structures
Type I	CN XI spared
Type II	CN XI and internal jugular vein spared
Type III(functional neck dissection)	All three structures spared(CN XI, internal jugular vein, and sternocleidomastoid muscle)
Selective neck dissection	Removal of lymph -bearing tissue from:
Lateral	Levels II-IV
Posterolateral	Levels II -V
Supraomohyoid	Levels I -III

From Medina JE, Rebual NM: Neck dissection, in Cummings CW, Fredrickson J, Harker LE, et al (eds): Otolaryngology: Head and neck Surgery, pp 1649-1672. St. Louis, Mosby Yearbook, 1993



Classification of Maxillectomy

Classification of Mandibulectomy

I.)

a) Partial

b) Total

II.)

a) Segemental mandibulectomy

b) Marginal mandibulectomy

Types of marginal mandibulectomy: Once it was shown that periosteal lymphatic paths were not important in the spread of oral cancers, full thickness removal of the mandible where it was not involved, was not necessary. So the concept of marginal mandibulectomy, preserving bony continuity was developed.

The various types of marginal mandibulectomy are

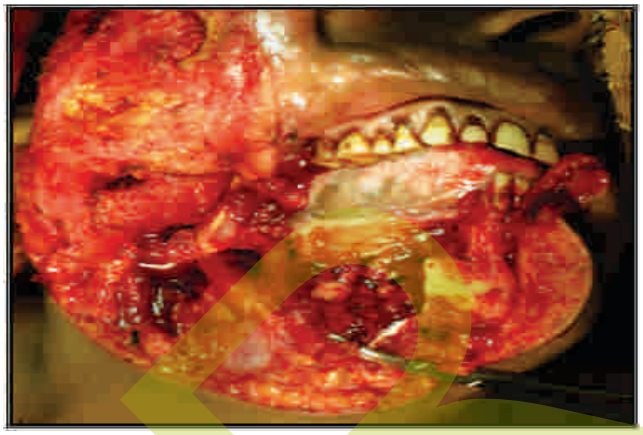


Figure : Mandibulectomy with Level III neck dissection

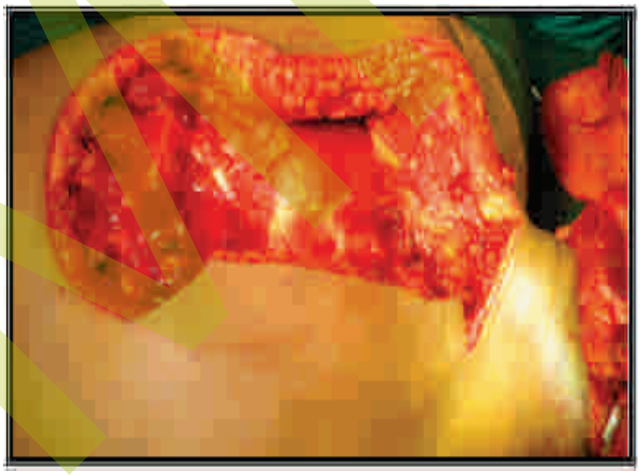


Figure : Reconstruction of the defect with pectoralis major myocutaneous flap (PMMC)

1. Classical (alveolar rim resection)
2. Reverse marginal (lower border)
3. Sagittal (lingual/ buccal plate)
4. Oblique

Cheek flaps may be required, either from the floor of the mouth upwards to access the mandible (lower cheek flap) or from below the eye and downwards to approach the maxilla (upper cheek flap).

In recent years, new technology and techniques have minimized the extent and invasiveness of surgery. These efforts to reduce extensive surgery have resulted in decreased morbidity, increased function, and an overall benefit to the rehabilitation of the patient (31,32,35,36).

A new development in surgery is the use of autofluorescence to improve visualization and to delineate the lateral spread of the tumour (37). Under direct fluorescence visualization (FV), the oral mucosa is exposed to high-energy (blue) light, which excites the normal fluorophores in the cells and tissue, which in turn emit a lower-energy light (green) back out of the tissue (37). In cancerous tissue, however, the fluorophores are altered and are no longer fluoresce, making the cancerous tissue appear much darker than normal tissue under FV (37,38).

Following the excision of the tumour, reconstructive surgery is required to restore any loss of function and/ or aesthetics. The location, size, and extent of reconstruction are the main factors that contribute to the choice of graft, as is the need for soft and hard tissue coverage. Defects in the oral cavity or dentition may also require prosthetic devices, such as obturators, dentures or implants.

RADIOTHERAPY

There have been significant changes in RT in recent years, from new methods of delivery to variation of delivery schedules. To improve treatment outcomes, preserve tissue, and reduce side effects (33).In general, the intent of RT is to destroy DNA in rapidly dividing cancer cells in a localized region while preserving adjacent tissue and function.RT as a single, primary treatment is not generally used for oral cancer, although it may be used as a sole method of treatment in cases where the location of the tumour makes it difficult to excise, such as the oropharynx, or if the patient refuses surgery (29,30,39). RT alone has a similar 5-year survival rate to surgery for early-stage disease, with a 37% local recurrence rate. Brachiradiotherapy is preferred over teleradiotherapy as it minimises the damage to surrounding tissues.

Radiotherapy although has shown the same success rate in treating oral squamous cell carcinoma but in comparison to surgery alone, RT produces milder complications and offers better retention of function and aesthetics, and improved quality of life. The use of surgery and postoperative RT is a common combination in oral cancer treatment, used for large tumours and when surgical margins are positive for cancer (29,30). RT is usually administered after surgery, as surgery following RT would be hampered by poor healing and an increased risk of infection. RT combined with CT is the preferred treatment of oropharyngeal cancers.

The two main types of RT are external beam radiation and brachytherapy. Brachytherapy, a form of internal radiation, involves the precise surgical placement of a radioactive insert into the tumour, directly treating the tumour (30). However, it is restricted by the size of the field that it can target effectively. Brachytherapy can also be used in conjunction with external beam radiation. External beam radiation is provided as a daily outpatient treatment, over the course of about 6 weeks, using a linear accelerator (LINAC) that focuses radiation on the tumour site (30). While it is a very effective cancer treatment, it also unfortunately affects the normal surrounding tissue and the normal tissue through which it travels to reach the tumour site. External beam radiation is the more common form of RT for the treatment of head and neck cancers.

TRADITIONAL AND CURRENT RADIOTHERAPY

In traditional external beam radiation, "shrinking fields" are used to deliver different doses to different regions of disease. "Shrinking fields" refer to a technique in which the most sensitive organs are irradiated first and blocked, treating the overlying low-risk organs next with more superficial radiation (30). The high-risk areas surrounding the tumour, grossly involved lymph nodes, and the tumour itself are treated last with the highest dose of tolerable radiation. It is imperative that areas surrounding the tumours receive a high amount of radiation as they may contain genetic changes that may lead to secondary malignancies. Depending upon the size and depth of malignancy a full treatment of radiation is divided into smaller amounts known as fractions or doses. Radiation doses vary; generally 1.8 to 2.0 Gray (Gy) are delivered daily, 5 days a week. Treatment continues over the course of 6 weeks for a total of 30 fractions, until a maximum of 60 Gy is provided (29,30).

Current approaches to RT include 3-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), and volumetric arc therapy (VMAT) (29,30,39). These techniques have been developed both to deliver radiation to the tumour more precisely while protecting normal tissues and to allow for flexibility to alter the dose. 3D-CRT delivers beams from 3 dimensions versus the traditional 2, while

IMRT provides even greater control by using beams of different intensities from a variety of dimensions (39). VMAT is a further extension of IMRT, delivering a higher dose faster to the whole tumour volume simultaneously either in a single arc or series of arcs. Su et al. concluded that using IMRT for early-stage nasopharyngeal cancer had 5-year localregional control rates of about 97%, with similar local recurrence-free and distant metastasis-free survival rates. VMAT attained similar results, further reducing treatment time and sparing more normal tissue.

Two more recent advances in RT are altered fractionation and concurrent systemic chemotherapy. Altered fractionation refers to changes in the dose per fraction, the number of fractions delivered per day, and the overall duration of treatment. Altered fractionation can further be divided into hyperfractionation and accelerated fractionation (30,39). Hyperfractionation provides smaller doses per treatment but delivers 2 fractions per day for the same or longer time period so that a greater overall dose can be delivered to the tumour. In contrast, accelerated fractionation delivers the total dose over a shorter time period, usually with greater doses per fraction or multiple doses per day (40). By increasing irradiation intensity, accelerated fractionation reduces the risk of repopulation of cancer cells, which may follow delays in treatment. In a meta-analysis comparing the efficacy of hyperfractionation and accelerated fractionation in late-stage disease, the authors found that both significantly improved patient survival rates.Both altered fractionation and hyperfractionation had a slightly higher 5-year survival rate than traditional RT (41).

Lastly, with the purpose of attaining radiosensitization, concurrent chemoradiation (CRT) is the addition of a chemotherapeutic drug to RT(39,42). These drugs make the target tissue more sensitive to RT than the surrounding normal tissue, thereby increasing RT efficacy.

CHEMOTHERAPY AND TARGETED THERAPIES

In the past, CT was primarily a palliative treatment for oral cancer. With the discovery of new drugs, CT has become a significant curative treatment in advanced oral cancer. The purpose of CT is to destroy dividing abnormal cancer cells rapidly in order to manage spread and metastasis. CT affects frequently dividing cells, such as those in the oral cavity, skin, bone marrow, alimentary tract, and hair follicles (32,34). Current CT techniques have been shown to reduce toxicities, spare sensitive organs such as the spinal cord, optic nerve, and parotid glands, and decrease treatment time while still maintaining quality and accuracy. Overall, CT offers enhanced local control, improved disease-specific survival rates and can contribute to an enhanced quality of life.

The delivery of CT can be divided into three categories: induction CT (before surgery), concurrent CRT (in conjunction with radiation treatment), and adjuvant CT (after surgery and/or radiation). Induction therapy is used primarily in patients who have advanced stage disease and nodal involvement, and in patients at the greatest risk of recurrence, second primary tumours, and metastases. As CT is the initial therapy, it can be distributed systemically in blood vessels not yet harmed by radiation, with less concern about toxicities, healing, and immunosuppression. Advantages include the ability to measure tumour response, inhibit extracapsular spread, and prevent metastasis early on, resulting in a significant improvement of local regional control and overall survival (43,44).

Concurrent CRT, however, has produced more effective results than induction CT (44). By combining a chemotherapeutic agent with radiation, the efficacy of RT is increased and results in better tumour control and survival rates (42).The combination of induction and concurrent CRT produces even more beneficial effects (44).Adjuvant CRT is used as a last effort to completely eradicate advanced disease and metastasis.

In general, the common classes of chemotherapeutic agents include platinum compounds (cisplatin and carboplatin); antimetabolites (methotrexate and 5-fluorouracil); taxanes (docetaxel); plant alkaloids; hydroxyurea; anthracyclines; and most recently taxoids (44).

A combination of 5-fluorouracil, docetaxel, and cisplatin has been shown to be efficacious in induction therapy, while more commonly the platinum derivative cisplatin is used for induction therapy alone. Other novel treatments still in development include the use of targeted therapies. The main agent is Cetuximab, a monoclonal antibody that is intended to target the

epidermal growth factor receptor (EGFR) (44). The EGFR is overexpressed in epithelial cancers such as oral

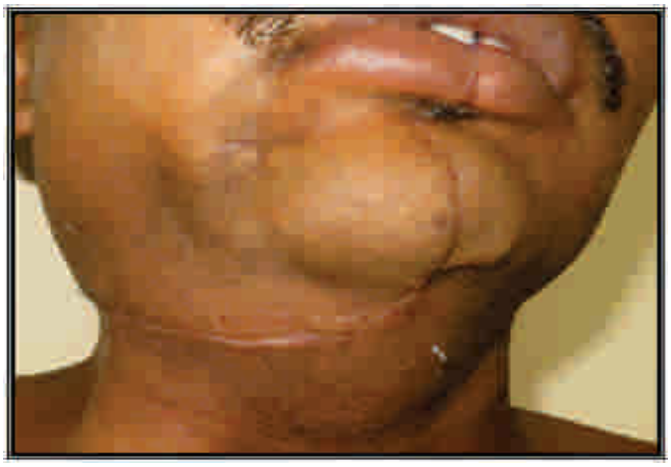


Figure : Post Ablative Healing of Sub-mandibular Region

SCC, and can be enhanced with the addition of RT leading to poor treatment results. Cetuximab inhibits EGFR, thereby increasing the efficacy of RT (44).

Patients who receive CRT following surgery have better localregional control and better overall survival rates than patients who receive only radiation postsurgery. In a recently updated meta-analysis by Pignon et al., both radiation alone and CRT improved local regional control and reduced mortality (45,46). The combination of cetuximab and radiation, however, was significantly more efficient in patients with advanced stage disease.(47,48).

RECENT TRENDS IN PREVENTION OF ORAL CANCER

Primary prevention

Prevention and control of tobacco and alcohol use can be brought about by:-

A. National Programs

- Designating federal funding for a national program of oral cancer prevention, early detection, and control that includes support for outcomes assessment and policy-based research. Increasing excise taxes on tobacco and alcohol products to provide targeted funding for oral cancer prevention programs.

- The production of tobacco and related products as well as alcohol should be forbiden. Strengthening and enforcing laws regarding access to tobacco and alcohol.

- Prohibiting all advertising and promotional activities by the tobacco industry and conduct a well-funded counter advertising campaign that focuses on cigarettes, cigars, pipe tobacco, and spit tobacco.

- Denying federal health and medical research funding to organizations that accept health research funding from the tobacco industry or its research institutes.

- Encourage professional sports teams to ban the use and advertisement of tobacco products among team members during practices and games.

- Adding strong statements to tobacco and alcohol warning labels about the risk of oral cancer. Ensuring that tobacco warning labels cover 25% -30% of the front or back of a product's package and advertising copy.

A. Public Education

Seven major strategies were recommended by the work group on public education.

- Develop and disseminate guidelines and lists of resources to assist communities (e.g., states, cities, towns, and members of organizations and institutions) in developing, implementing, and evaluating models for oral cancer education. This effort could include an inventory of available guidelines, literature, processes, and educational models.

- Develop, implement, and evaluate state wide models to educate all relevant groups. These models should be tailored to local needs, practical, culturally appropriate, and user friendly and should include the following content areas:

  - risk factors for oral cancer (e.g., tobacco use, alcohol use, and nutritional deficiencies);

  - signs and symptoms of oral cancer;

  - procedures for a thorough oral cancer examination and the ease with which the examination can be performed; and methods of public advocacy.

- Develop and conduct a national campaign to raise public awareness of oral cancer and its link

to tobacco use and heavy alcohol consumption. The campaign might include a mascot or logo, sports figures or other distinguished persons as spokespersons, or a national oral cancer awareness week.

- Ensure that behavioral and educational research in oral cancer is included in the budget of organizations that sponsor such research (e.g., the National Institutes of Health, universities, and foundations).

- Ensure that a national research agenda is developed that includes the following:

- Ongoing surveillance to monitor knowledge, opinions, attitudes, and practices of the public, especially populations at high risk for oral cancer;

- Surveys of the knowledge, opinions, attitudes, and practices of relevant health-care providers regarding oral cancer;

- Determination of the proficiency of persons who have been taught to perform an oral cancer self-examination; and

- Assessment of the quality (e.g., reading level or scientific accuracy), quantity, and availability of educational materials directed to the public about oral cancer.

B. Professional Knowledge and Practice

- Ensuring that clinicians learn procedures to detect oral cancer that are appropriate to their professional practice.

- Urge all health professionals to routinely assess tobacco and alcohol intake by their patients.

- Encourage health-care agencies and professionals to recommend that all clinicians who deliver primary health care routinely examine their patients for oral cancer.

- Develop, promote, and maintain a database of all professional education materials related to oral cancer.

- Define, identify, develop, and promote centers of excellence in oral cancer management.

C. Data Collection, Evaluation and Research

These recommended strategies would facilitate research regarding the etiology, prevention and treatment of oral cancer and would translate research findings into effective public health action.

- Strengthen organizational approaches to reducing oral cancer by developing cooperative and collaborative arrangements, funding formal centers, and involving commercial firms. The following means are suggested:

- Consortia of researchers and medical and dental practitioners could share patient sources, standardize clinical protocols, achieve adequate sample sizes, recruit patients and at-risk persons for research studies, and enhance science transfer; individual practitioners as well as organizations (e.g., alcohol treatment centers) that serve populations at risk for oral cancer or its sequelae could be sources of study subjects;

- Other formal centers could be established in addition to those funded by NIDR and the National Cancer Institute; and

- Commercial firms could use their marketing and distribution systems to enhance science transfer, health promotion, and disease prevention activities; in addition, they could join with academic or government groups to fund or otherwise facilitate research(49).

Thus, all primary-care providers must assume more responsiblity for counseling patients about behaviors that put them at risk for developing this cancer, examining patients who are at high risk for developing the disease because of tobacco use or excessive alcohol consumption and referring patients to an appropriate specialist for management of a suspicious oral lesion. Comprehensive education of medical and dental practitioners in diagnosing and promptly managing early lesions could facilitate the multidisciplinary collaboration necessary to detect oral cancer in its earliest stages. Furthermore, because of the public's lack of knowlege about the risk factors for oral cancer and because this disease can often be detected in its early stages , the public awareness of oral cancer (including its risk factors, signs, and symptoms) must also be increased.

Oral cancer occurs in sites that lend themselves to early detection by most primary health-care providers and, to a lesser extent, by self-examination. Heightened awareness in the general population could help with

early detection of this cancer and could stimulate dialogue between patients and their primary health-care providers about behaviors that may increase the risk for developing oral cancer. Recent advances in understanding the molecular events involved in developing cancer might provide the tools needed to design novel preventive, diagnostic, prognostic and therapeutic regimens to combat oral cancer. Acquiring greater knowledge of the biology, immunology, and pathology of the oral mucosa may also help to reduce the morbidity and mortality from this disease.

Some simple clinical practices can be followed in day-to-day practice, which encourage the tobacco users to quit tobacco, like the absence of ash trays and any book of advertisement on any tobacco product in the clinic.The other practices are: Using routine questionnaire about the use of tobacco; complimenting those who do not use tobacco of any kind; encouraging the tobacco users to stop it; display of suitable educational materials in the waiting room and also distribution of such material to the patients. Regular follow-up examination of precancerous and other tobacco-related oral lesions will greatly assist the people who are using tobacco and intend to quit.

SECONDARY PREVENTION

Secondary prevention aims at early detection of cancer of easily accessible sites and oral cavity. It is also called cancer control. The ideal time to detect precancerous lesions is when it is small and has not spread. In this context dentists have the prime responsibility in detecting cancer by screening the oral cavity which should be performed in every new patient and at all recalls. Screening camps can also be organised from time to time to conduct toluidine blue, papani colaou test, exfoliative cytology which is inexpensive easy and can be employed on a large group of people tool in short span of time. Despite the fact that there are false positive and false negative results but in the absence of any other better alternative, these still are one of the best screening tests available(50).

TERTIARY PREVENTION

Tertiary prevention aims at the terminal stages. Over 70% of cancers have severe pain and other distressing symptoms in the advanced stages. Pain control and palliative care are major strategies of tertiary prevention.

New ways to prevent oral cancer are being studied in clinical trials

CHEMOPREVENTION

Chemoprevention refers to the administration of an agent to prevent a cancer from occurring. The agent can be a drug or a natural product. These agents must be easy to administer, cause little or no toxicity, cause no long term adverse sequelae, be affordable, and ideally, should have the need to be administered only for a short time.

Promising agents for chemoprevention of oral cancer

RETINOID

Mechanism of action of these compounds for chemoprevention is not well understood. Studies have documented lower β carotene (a precursor of vitamin A) serum concentrations in patients who develop cancer of the head and neck, than in patients who do not develop these cancerous tumours. Retinoids can act through induction of differentiation and can inhibit proliferation, as well as cause programmed cell death.

β-CAROTENE

β Carotene is one of several carotenoids in the body and is a precursor of vitamin A. It is found in leafy green vegetables and yellow and orange fruits and vegetables, and it is also available in tablet form. To some extent it is converted to vitamin A in the body and is not associated with hypervitaminosis A syndrome. Several studies have noted lower blood levels of β-carotene in patients who develop aerodigestive tract cancers compared to patients who do not develop cancer. These findings led to the hypothesis that β-carotene deficiency may predispose to cancer formation. The mechanism of action of β-carotene as a chemopreventive agent may involve antioxidant mechanisms as well as inhibition of free radical reactions.

N-ACETYLCYSTEINE

N-acetylcysteine is an antioxidant and free-radical scavenger that has shown chemopreventive activity in lung and tracheal tumors in animals.

NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

In animal studies, nonsteroidal anti-inflammatory agents (NSAIDs) have chemopreventive activity in several tissues and have shown activity in tumor inhibition in preclinical head and neck cancer models. Because these compounds may be inhibitors of proliferation, they may be useful as chemopreventive agents.

VITAMIN E

Epidemiologic studies have noted an inverse relationship between serum vitamin E levels and oral

cancer. Its mechanism of action postulated to be as an antioxidant agent.

Interferons
Interferons have shown additive or synergistic antitumor effects in combination with retinoids.

Curcumin
Curcumin is the major component of turmeric, which is widely used in curry. Curcumin has inhibited carcinogen-induced tumorigenesis in an oral cancer model and is nontoxic. This is under consideration as a cancer preventive agent(50,51).

What is new in oral cavity and oropharyngeal cancer research and treatment?

Important research into oral and oropharyngeal cancers is taking place in many universities hospitals, medical centers, and other institutions around the country. Each year, scientists find out more about what causes the disease, how to prevent it, and how to improve treatment.

DNA CHANGES
A great deal of research is being done to learn what DNA changes cause the cells of the oral cavity and oropharynx to become cancerous. One of the changes often found in DNA of oral cancer cells is a mutation of the *TP53* gene. The protein produced by this gene (called p53) normally works to prevent cells from growing too much and helps to destroy cells with too much damage for the cells to repair. Changes in the *TP53* gene can lead to increased growth of abnormal cells and formation of cancers. Some studies suggest that tests to detect these gene changes may allow oral and oropharyngeal tumors to be found early. These tests may also be used to better find cancer cells that may have been left behind after the tumor is removed and to determine which tumors are most likely to respond to surgery or radiation therapy (52).

VACCINES
Most people think of vaccines as a way to prevent infectious diseases such as polio or measles. As mentioned earlier, vaccines against human papilloma virus (HPV) infection are already being used to help prevent cervical cancer. They may have the added benefit of preventing some oral cancers as well, although they won't help treat the disease.

However, some vaccines are being studied as a way to treat people with cancer by helping their immune system recognize and attack the cancer cells. Many of these vaccines use dendritic cells (cells of the immune system), which are removed from the patient's blood and exposed in the lab to something that makes them attack tumor cells. The dendritic cells are then injected back into the body, where they should induce other immune system cells to attack the patient's cancer cells (52).

GENE THERAPY
New discoveries about how changes in the DNA of cells in the mouth and throat cause these cells to become cancerous are being applied to experimental treatments intended to reverse these changes. Gene therapies that interfere with the growth-stimulating effect of certain HPVs are also being developed. Another type of gene therapy adds new genes to the cancer cells to make them more susceptible to being killed by certain drugs. These forms of treatment are still in the earliest stages of study, so it will probably be several years before we know if any of them are effective (52).

CONCLUSION
For patients suffering from oral cancer our aim should be :-

Disease free existence of the patient
Complete aesthetic functional and psychological rehabilitation
Post treatment good quality of life as close as possible to normal

Advances in the treatment of oral cancer have improved outcomes for those diagnosed with the disease. These improvements have led to a significant increase in local regional disease control and overall survival rates. This is particularly true for oral cancer diagnosed at an early stage, which is often treated with surgery or radiation alone(40).

The large group of people who are employed by the tobacco and alcohol production industries should be motivated to quit those jobs and get involved with public health care services. Government should come up with policies of educating such people as well as with skill development programs so that such people can be employed and can earn their living through a much better source, such as small scale industries like paper industry, candle making etc. Changing the mind sets of the people and motivating them towards healthy life style can help us win, our constant struggle/ battle against oral cancer.

For late-stage disease requiring CT or a combination of surgery and CRT, the results remain promising but are still in need of improvement. Individual patient factors, tumour features, lymph node involvement, and metastasis have to be taken into account for optimal treatment effectiveness. Comorbidities and both short- and longterm treatment side effects must also be

examined when creating individual patient therapies (49,50).

The purpose of monitoring patients following therapy is to a) provide care for the sequelae of treatment side effects; b) to coordinate care between specialists and primary care providers to ensure that both oral and overall health needs are met; and c) to prevent and identify recurrence or the development of a second primary tumour (51). To provide satisfactory care to this complex group of patients, it is important that dental hygienist's understand the various treatment modalities for oral cancer and their possible effects. The patient's hygiene maintenance schedule will result in the dental hygienist's being one of the dental health professionals who is frequently in contact with the patient. Continued surveillance is essential in order to reduce the risk of secondary oral cancers and assist in improving a patient's quality of life and overall survival.

Conflict of interest

The authors declare that they have no competing interests.

REFERENCES

1. Pathak KA, Gupta S, Talole S, Khanna V, Chaturvedi P, Deshpande MS, *et al.* Advanced squamous cell carcinoma of lower gingivobuccal complex: Patterns of spread and failure. *Head Neck* 2005;27:597602.
2. SEER Stat Fact Sheet based on 2008-2012 statistics.
3. Sankaranarayanan R, Ramadas K, Thomas G, Muwonge R, Thara S, Mathew B, *et al.* Effect of screening on oral cancer mortality in Kerala, India: A cluster-randomised controlled trial. *Lancet* 2005;365:192733.
4. Dikshit R, Gupta PC, Ramasundarahettige C, Gajalakshmi V, Aleksandrowicz L, Badwe R, et al. Cancer mortality in India: A nationally representative survey. Lancet, 2012:379, 180716.
5. Lingen MW, Kalmar JR, Karrison T, Speight PM. Critical evaluation of diagnostic aids for the detection of oral cancer. Oral Oncol, 2008: 44 (1022).
6. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol, 2009:45, 30916.
7. Cancer Research UK. Available at http://www.cancerresearchuk.org/cancer-info/cancerstats/types/oral/uk (accessed on 1 Mar 2013).
8. J. Ferlay, H. R. Shin, F. Bray, D. Forman, C.Mathers, and D.M. Parkin, "GLOBOCAN, 2003, 2008, 2010 cancer Incidence and MortalityWorldwide," IARC Cancer Base
9. Franceschi S, Talamini R, Barra S, Barón AE, Negri E, Bidoli E, et al. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in northern Italy. Cancer Res,1990:50, (65027).
10. Jussawalla DJ, Deshpande VA. Evaluation of cancer risk in tobacco chewers and smokers: An epidemiologic assessment. Cancer 1971 28:24452. (Bagnardi V, Blangiardo M, La Vecchia C, Corrao G. A meta-analysis of alcohol drinking and cancer risk. Br J Cancer,(2001):85:17005.
11. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, et al. , Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res, 1988:48 (32827).
12. American Joint Committee on Cancer (AJCC). American Joint Committee for Cancer Staging Manual. 6th ed. Springer: Chicago, Illinois 2002.
13. Shiels MS, Cole SR, Kirk GD, et al. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals (link is external). J Acquir Immune Defic Syndr, 2009:52(5), 611-22
14. Negri E, Boffetta P, Berthiller J, et al. Family history of cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium (link is external). Int J Cancer, 2009:124(2), 394-401.
15. Paget-Bailly S, Cyr D, Luce D. Occupational exposures to asbestos, polycyclic aromatic hydrocarbons and solvents, and cancers of the oral cavity and pharynx: a quantitative literature review (link is external). Int Arch Occup Environ Health, 2012:85(4), 341-51.
16. Chronic Trauma As Precipitating Factor Of Squamous Cell Carcinoma Of Tongue 3 Case Reports Indian Journal of Dental Sciences, October 2014:6 (4)
17. Ravi Mehrotra and Dwijendra K Gupta. Exciting new advances in oral cancer diagnosis: avenues to early detection. Head Neck Oncol, 2011:3(33).
18. He H, Sun G, Ping F. Laser-capture microdissection and protein extraction for protein fingerprint of OSCC and OLK. Artif Cells Blood Substit Immobil Biotechnol. 2009:37(5),20813
19. Handschel J, Oz D, Pomjanski N, Depprich R, Ommerborn MA, Braunstein S, Kübler NR, Meyer U, Böcking A. Additional use of DNA-image cytometry improves the assessment of resection margins. J Oral Pathol Med, 2007:36(8), 4725
20. Ziober BL, Mauk MG, Falls EM, Chen Z, Ziober AF, Bau HH. Lab-on-a-chip for oral cancer

screening and diagnosis. Head Neck. 2008:30(1), 11121.

21. Papamarkakis K, Bird B, Bedrossian M, Laver N, Wein R Diem M. Cytopathology by optical methods: spectral cytopathology of the oral mucosa. Lab Invest. 2010:90(4), 58998.

22. Prasad G, McCullough M.Chemokines and cytokines as salivary biomarkers for the early diagnosis of oral cancer. Int J Dent, 2013, 813756.

23. Wu JY, Yi C, Chung HR, Wang DJ, Chang WC, Lee SY, et al. Potential biomarkers in saliva for oral squamous cell carcinoma. Oral Oncol,2010:46, 226-31.

24. Dietz A, Rudat V, Conradt C, Weidauer H, Ho A, Moehler T, Prognostic relevance of serum levels of the angiogenic peptide bFGF in advanced carcinoma of the head and neck treated by primary radichemotherapy. Head Neck, 2000:22(7), 666-673.

25. Gandour-Edwards R, Trock B, Donald PJ. Predictive value of cathepsin-D for cervical lymph node metastasis in head and neck squamous cell carcinoma. Head Neck, 1999:(8), 718-722.

26. Gottschlich S, Folz BJ, Goeroegh T, Lippert BM, Maass JD, Werner JA. A new prognostic indicator for head and neck cancer p53 serum antibodies? Anticancer Res, 1999:19(4A), 2703-2705.

27. Ito T, kawabe R, Kurasono Y, Hara M, Kitamura H, Fukita K, Kanisawa M. Expressioin of heat shock proteins in squamous cell carcinoma of the tongue: an immunohistochemical study. J Oral Pathol med, 1998:27(1), 18-22

28. Lee J J, Hung HC, Cheng SJ, Chiang CP, L14 by, y4CH, Jeng J. H, Chang HH, Kak & SH. Factors associated with underdiagnosis from incisional biopsy of oral leukoplakic lesions.Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2007:104(2), 217-25

29. Deng H, Sambrook PJ, Logan RM. The treatment of oral cancer: an overview for dental professionals. Aust Dent J, 2011:56(3), 244-52, 341.dol: 10. 1111/J 1834-7819.

30. Haddad R, Annino D, Tishler RB. Multidisciplinary approach to cancer treatment: focus on head and neck cancer. Dent Clin North Am, 2008: 52(1), 117, vii.

31. Haddad RI, Shin DM. Recent advances in head and neck cancer. N Engl J Med, 2008:359(11), 1143-54. dol: 10.1056/NEJ mra 0707975.

32. Shah JP, Gil Z. Current concepts in management of oral cancersurgery. Oral Oncol, 2009:45(4-5), 394-401.

33. Logan RM. Advances in understanding of toxicities of treatment for head and neck cancer. Oral Oncol, 2009:45(10), 844-8.dol: 10.1016/J arciloncology .

34. Woolgar JA, Rogers S, West CR, Errington RD, Brown JS, Vaughan ED. Survival and patterns of recurrence in 200 oral cancer patients treated by radical surgery and neck dissection. Oral Oncol, 1999:35(3), 257-65.

35. Sutton DN, Brown JS, Rogers SN, Vaughan ED, Woolgar JA. The prognostic implications of the surgical margin in oral squamous cell carcinoma. Int J Oral Maxillofac Surg, 2003:32(1), 304.

36. Rogers SN, Brown JS, Woolgar JA, Lowe D, Magennis P, Shaw RJ, et al. Survival following primary surgery for oral cancer. Oral Oncol, 2009: 45(3), 201-11. dol:10.1016.

37. Poh CF, MacAulay CE, Zhang L, Rosin MP. Tracing the "at-risk" oral mucosa field with autofluorescence: steps toward clinical impact. Cancer Prev Res (Phila),2009:2(5), 401-4. dol:10.1158.

38. Lane PM, Gilhuly T, Whitehead P, Zeng H, Poh CF, Ng S, et al. Simple device for the direct visualization of oral-cavity tissue fluorescence. J Biomed Opt, 2006:11(2), 024006.

39. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. Lancet, 2008:371(9625), 1695-709.

40. Peters ES, Ang KK. The role of altered fractionation in head and neck cancers. Semin Radiat Oncol, 1992:2(3), 180-194.

41. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet, 2006:368(9538), 843-54.

42. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med, 2004:350(19),1937-44.

43. Mohr C, Bohndorf W, Carstens J, Harle F, Hausamen JE, Hirche H, et al. Preoperative radiochemotherapy and radical surgery in comparison with radical surgery alone. A prospective, multicentric, randomized DOSAK

study of advanced squamous cell carcinoma of the oral cavity and the oropharynx (a 3-year follow-up). Int J Oral Maxillofac Surg, 1994:23(3), 140-8.

44. Pignon JP, le Maitre A, Bourhis J, Group M-NC. Meta-analyses of chemotherapy in head and neck cancer (MACH-NC): an update. Int J Radiat Oncol Biol Phys.2007: 69(2 Suppl), S112-4.

45. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous cell carcinoma: three meta-analyses of updated individual data.MACH-NC Collaborative Group. Meta-analysis of chemotherapy on head and neck cancer. Lancet,2000:355(9208), 949-955.

46. Pignon JP, le Maitre A, Maillard E, Bourhis J, Group M-NC. Metaanalysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol, 2009: 92(1), 4-14.

47. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol, 2010:11(1), 21-28.

48. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med, 2006:354(6), 567-578.

49. Funk GF, Karnell LH, Christensen AJ. Long-term health-related quality of life in survivors of head and neck cancer. Arch Otolaryngol Head Neck Surg,2012: 138(2), 123-33.

50. Seiwert TY, Salama JK, Vokes EE.The chemoradiation paradigm in head and neck cancer. Nat Clin Pract Oncol. 2007:4(3):15671.

51. Committee on Cancer Survivorship: Improving Care Quality of Life, National Cancer Policy Board, Institute of Medicine and National Research Council. From cancer patient to cancer survivor: lost in transition. Hewitt M, Greenfield S, Stovall E, editors. Washington, DC: The National Academies Press; 2005.

52. Oral Cavity and Oropharyngeal Cancer. [Last accessed on 2014 Jul 17]. Available from: http://www.cancer.org/cancer/oralcavityandoropharyngealcancer/detailedguide/oral-cavity-and-