CANCER NEWS

ISSN 0973-9653 Vol 8 No 1 April 2014

www.rgcirc.org

Rajiv Gandhi Cancer Institute and Research Centre
A Unit of Indraprastha Cancer Society
Registered under "Societies Registration Act 1860"

From the Desk of Director Research

Oral cancer is the largest group of malignancies which fall into head and neck cancer category. It accounts for 2-3% of all malignancies. India has got one of the highest incidences of oral cancer in the world. The incidence of oral cancer is significantly higher in the Indian population compared with that in the USA and Canada (age-standardized rate 9.8 v. 2.4). The gingival–buccal complex forms the most common subsite for oral cavity cancer in India, in contrast to the tongue and floor of the mouth, which are more common sites in the West. The two distinct pathways through which most people get oral cancer are the use of tobacco and alcohol, while the other is exposure to the HPV-16 virus (human papilloma virus version 16). A small percentage get oral cancers from currently non-identified cause, believed to be related to some genetic predisposition. 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. Heavy drinkers and smokers have 38 times the risk of oral cancer compared with abstainers.

There are several types of oral cancers, of which 90% are squamous cell carcinomas. Oral cancer is particularly dangerous as it is often diagnosed after the cancer has metastasized to another location, probably the lymph nodes of neck. The prognosis at this stage remains significantly worse than if it is detected in a localized intra oral area. Also, oral cancer has a high propensity of producing second primary tumors. The late stage diagnosis does not occur because most of these cancers are hard to discover but it is due to the lack of public awareness along with the absence of opportunistic screenings that would yield early detection.

The treatment of oral cancers is ideally a multidisciplinary approach, involving surgeons, radiation oncologists, chemotherapy oncologists, dental practitioners, nutritionists and rehabilitation and restorative specialists. The actual curative treatment modalities are usually chemotherapy with concurrent radiation, sometimes combined with surgery. Chemotherapy, while able to kill cancer cells, itself is currently not used as a monotherapy for oral cancers. The five-year survival rate is approximately 40% and has not improved considerably since decades, in spite of advances in surgery, radiotherapy, and chemotherapy.

Apoptosis, angiogenesis inhibitors, genetic "cocktails" which could stimulate the immune system activity specific to a particular tumor and techniques that would allow the replacement of a damaged tumor suppressor p53 gene, are all being researched now. The efforts to understand oral cancer genome are aimed at finding genomic and proteomic profiles and using this information in diagnosis and management. Despite the fact that oral cancer can be prevented, treated and controlled, there exists a significant gap in the Indian public's knowledge, attitudes and behaviors. The attempts must be made to introduce the preventive measures that may significantly reduce the burden and help bridge the gap between research, development and public awareness.

This issue of Cancer News highlights the newer advances in the field of Oral Cancer and features the regular articles, such as Special Feature, Guest Article, Perspective and In Focus.

We are grateful to the contributions made by Dr Tejinder Kataria, Chairperson Radiation Oncology, Medanta Cancer Institute, Medanta-the Medicity, Gurgaon and Dr Ravi Mehrotra, Scientist-G & Director; Institute of Cytology & Preventive Oncology, (ICPO-ICMR), Noida

Suggestions/ comments from the readers are welcome.

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Published by: **Rajiv Gandhi Cancer Institute & Research Centre**
Sector - 5, Rohini, Delhi - 110 085, India

SPECIAL FEATURE

ORAL CANCER – AN OVERVIEW

Introduction

Cancer of oral cavity is the leading malignancy diagnosed in men in India, and accounts for about 30% of all new cases annually. It is the leading cause of mortality in men, responsible for 22.9% of cancer-related deaths. The overall 5-year survival rate for all stages of oral cancer is 40%. These rates are better for localized tumors than those for tumors with regional or distant metastases. There are variations reported in the outcomes among the developing and developed countries and this could be due to the late presentation for the treatment. In India, habit of chewing smokeless tobacco in the form of betel quid *(pan)* containing areca nut and lime with dried tobacco leaves, has been shown to be highly carcinogenic.

Etiology

Worldwide studies have indicated a strong correlation between smoking and the incidence of cancer of the oral cavity. More than 50 carcinogens have been identified in tobacco and cigar smoke; polynuclear aromatic hydrocarbons and tobacco specific nitrosamines being the most important ones. The smokeless forms of tobacco (USA), betel quid and pan masala (India), *naswar, khaini, mawa, mishri* and *gutkha* (South and South-East Asia) and shammah (northern Africa) predispose to cancer of the oral commissure, alveolobuccal mucosa and inferior gingivolabilal sulcus. Strong evidence exists that chronic consumption of alcohol has a synergistic effect with tobacco. But alcohol consumption has also been found to have detrimental effect independent of cigarette smoking. The two factor combined constitute a 15-fold greater risk for developing an oral cavity cancer. Prolonged exposure to sunlight causes hyperkeratosis in the lip, which has a limited natural pigmented layer. The combination of outdoor activities and the issue of pigmentation explains the high incidence of lip cancer in fair-skinned people in sunny climates. Dietary deficiencies, such as iron, vitamins A, C and E, are associated with oral cancers. Fruit and vegetables are said to reduce the risk of oral cancer.

Patients with oral cancer have poor oral and dental hygiene. The enzymatic conversion of ethanol by oral microflora can lead to the carcinogenic accumulation of acetaldehyde. Secondly, chronic oral mucosal irritation from ill-fitting dentures can lead to dysplastic changes in the epithelium. Herpes simplex virus (HSV) has been shown to act as a cocarcinogen with tobacco and ultraviolet (UV) radiation in certain animal models. Human papilloma virus (HPV), principally type 6 and 16, has been detected in human cancer of the oral cavity.

Pathology

Approximately 95% of all oral cavity malignancies are squamous cell carcinoma (SCC). Other malignant tumors include: minor salivary gland carcinomas, such as adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma. Kaposi sarcoma, lymphoma and melanoma may also develop in oral mucosa. There are some premalignant lesions and conditions associated with the oral cancers - Leukoplakia, Erythroplakia, Lichen Planus, and Oral submucosal fibrosis.

The grading scheme of Broders, subsequently modified in the system adopted by WHO, scores mucosal carcinoma on the degree of differentiation and mitotic activity. Lesions are classified into four groups from well-differentiated (grade-1) tumors with a few mitoses and little pleomorphism to poorly differentiated (grade IV) tumors with high rate of mitoses and pleomorphism. Invasive pattern is divided into pushing- grade 1, solid cords- grade 2, small groups- grade 3 and dissociated – grade 4.

Genetic Changes in Oral Carcinogenesis

The recent characterization of some of these early molecular changes in the progression of cancer of the oral cavity has improved understanding of this complex process and may ultimately lead to novel diagnostic and therapeutic interventions. Some important molecular alterations in oral carcinogenesis are as follows:

EGFR/TGF - α : Epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor that can bind to ligands such as EGF, and transform growth factor alpha (TGF - α) and is related to the erbB family of oncogenes. Studies have demonstrated that increased production of EGFR and TGF - α is an early event in head and neck carcinogenesis; tumor levels of EGFR and TGF - α are significant predictors of disease-free and cause-specific survival. Recent studies suggest that EGFR is unregulated in head and neck squamous cell carcinoma, and that blocking EGFR at the level of the receptor or its pathways may offer therapeutic benefit. This clearly may represent the most recent breakthrough in molecular therapy for squamous cell carcinoma of the head and neck.

TP53 Gene: Approximately half of all cancers of the head and neck studied contain a mutation of the TP53 gene. Cancers of the head and neck have either a high level of abnormal TP53 expression and/or mutation of the TP53 gene. The loss of TP53 function can result in an accumulation of cells with defective DNA, increasing the likelihood of genetic abnormalities and a transformation from pre-invasive to invasive lesions. The insertion of wild-type TP53 into defective head and neck cancer cell lines via an adenovirus-mediated vector can induce apoptosis, which leads to an inhibition of tumor growth in vivo and in vitro.

TP16 and Cyclin DI: Both TP16 and cyclin DI are involved in regulation of the cell cycle. Many early cancers of the head and neck demonstrate the loss of chromosomal region 9p21, which causes the inactivation of TP16. Similarly, amplification of cyclin D1,which constitutively activates cell-cycle progression, is seen in 33% to 68% of cancers in the head and neck. Elevated levels of cyclin D1 are associated with more invasive disease. Elevated levels of cyclin D1 and a lack of TP16 expression are correlated with reduced disease-free and overall survival rates in patients with cancer of the tongue.

***BAX/BCL2*:** The apoptotic mechanism of the cell is regulated by a balance of the proapoptotic BAX and the antiapoptotic BCL2 subfamily of molecules. Activation of BAX and other proapoptotic molecules increase the permeability of the mitochondrial outer membrane, causing a release of cytochrome C into the cell. Several studies have demonstrated a differential expression of BCL2 and BAX in oral cavity cancer. In general, over-expression of BCL2 has been seen in more poorly differentiated cancer and in dysplastic epithelium adjacent to invasive cancer. BAX-expression levels are reduced in the same areas. Patients with high BCL2/BAX ratios have significantly poorer prognosis than those with lower ratio.

Natural History

The most common anatomical sites involves by SCC are the anterior two-thirds of the tongue and floor of the mouth, followed by the upper and lower alveolar ridge, retromolar trigone and buccal mucosa. Early accessibility of oral cavity should make the diagnosis early. Earliest diagnosis occurs with lip cancers, with 75% of the primaries measuring less than 2 cm in diameter. On the other side, hard palate, retromolar trigone and gingiobuccal tumors frequently have a delay in the discovery and patients present with invasion of adjacent structure (nasal cavity, sinus, mandible, soft palate).

Cervical lymph node involvement is the single most important prognostic factor in oral mucosal SCC. In patients with cervical metastasis, five-year survival is reduced by approximately 50%. The incidence of regional metastasis is associated with clinical stage and histopathological feature.

Lip and buccal mucosa primaries metastasize in about 10% of the cases; tongue and alveolus in about 30% and floor of the mouth in about 25-50%. The regional lymph nodes at highest risk of involvement by tumors of the oral cavity are levels I, II and III. In a clinically negative neck, level IV is rarely involved (<5%) with level V virtually never. Hence, supraomohyoid neck dissection as an elective option where metastatic disease is strongly suspected is efficacious. Distant metastases from oral cavity carcinomas occur in about 8% to 17% of patients, mostly in the lungs (66%), liver (22%) and bones (9.5%). The risk for distant metastasis depends on stage of disease, being respectively 2-8%, 9-29% and 17-51% for N0, N1 and N2-N3. Knowledge of the risk of distant metastasis is important for the planning of further treatment.

A temporal span of 5 years, a geographically distinct site or a distance of 2 cm from the original primary are generally accepted indicators for a second primary. The risk of developing a second primary cancer is the highest in patients with oral cavity cancer at 14%. Synchronous second primaries are much less frequent than metachronous lesions being 13% against 87% for the later.

Diagnosis and Evaluation

Evaluation of the patient with cancer of the oral cavity should include a thorough history and physical examination, dental assessment, radiological evaluation, tissue biopsy, and intraoperative visualization. TNM system is used as a standard part of the cancer patient work up. If superficial extension of a tumor to an adjacent site is limited to the mucosa, this is not considered invasion of adjacent structures. Generally, deep muscle invasion is associated with restriction of mobility of the tongue. Invasion of the intrinsic muscle of the tongue, which includes musculi longitudinalis superior and inferior, transversus linguae and verticalis linguae, or invasion of the submandibular gland is not classified T4 but rather T3. Similarly, invasion of the sublingual gland by a carcinoma of the floor of the mouth is not considered in the T4 classification.

The major drawback of the TNM system is that it does not take into account host factors and pathological

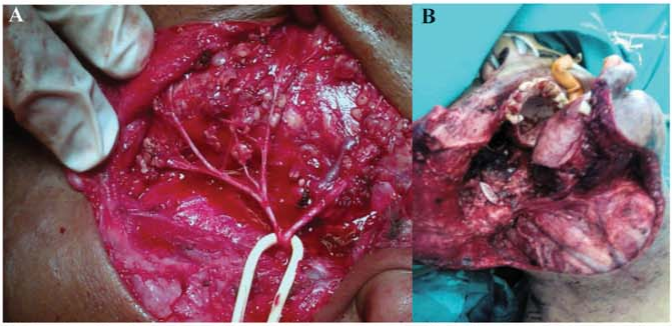

Figure: (A) Branches of facial nerve in parotidectomy. (B)Composite resection of buccal mucosa with infratemporal fossa clearance

features that are known to affect survival and outcome. Medical factors excluded are performance status, comorbidities, immune status and nutritional status. Important pathological factors include tumor thickness, pattern of invasion lymphovascular invasion and perineural invasion.

Treatment

Oral cancer is best managed by a team of health care professionals. A number of treatment options are available for the management of oral cavity cancer. These include surgery, radiation, chemotherapy, or a combination of these. All cases should be reviewed by pathologists, radiologists, surgeons, radiation oncologists and medical oncologists. Other team members include general dentists, nurses, speech therapists, prosthodontists, nutritionists and reconstructive surgeons.

Surgery and radiation are equally effective in treating early (T1-T2) oral cavity cancers. In the choice between surgery and radiation, some general considerations should be taken into account. With surgery, patients with small tumors of the oral cavity amenable to local resection requires less treatment time than is required by full course of radiotherapy, allowing a faster rehabilitation. Most early- stage oral cavity lesions do not require extensive reconstructive techniques. The degree of functional disability associated with surgery is directly related to the extent of tongue or mandible involvement, and rehabilitation becomes more difficult with extensive soft tissue or bony involvement. Radiotherapy can be used when there is significant risk associated with general anaesthesia or when a patient refuses surgery. Functional disability (speech and deglutition) is usually less pronounced with radiotherapy than with surgery, although this may not be necessarily true with small tumors.

In advanced disease (stages III and IV), a combination of surgery and radiation is often employed, although debate continues over the timing of the radiation. Conventional combined therapy for oral cavity cancer currently involves the use of postoperative radiation to avoid potential wound-healing complications and to deliver a higher total dose or radiation than is possible with planned preoperative radiotherapy. Many surgeons also prefer to have the ability to obtain clear surgical margins without concern for the histologic changes brought on by preoperative radiotherapy that obscures the diagnosis. Surgical resection is also preferred in patients who are at increased risk for developing radiation-induced complications and for those with second primary cancers of the upper aerodigestive tract due to their excessive consumption of tobacco and alcohol. In these patients, adequate surgical resection can avoid the potential adverse effects of radiotherapy while preserving radiation for future treatment protocols.

Deformities of the head and neck region can have devastating effects on appearance and function of the patient and are among the most disabling and socially isolating defects with significant impact on patient's quality of life. Reconstruction of such defects continues to be an extremely demanding challenge for plastic surgeons who aim to restore form and function with minimal surgical morbidity. Successful reconstruction requires a team approach, which includes, ablative surgeon and reconstructive surgeon, for careful preoperative assessment and development of a treatment plan. Important considerations include tumor stage and prognosis; patient age, sex, body habitus, and functional status; available reconstructive donor sites; and the psychosocial make-up of the patient. The reconstruction

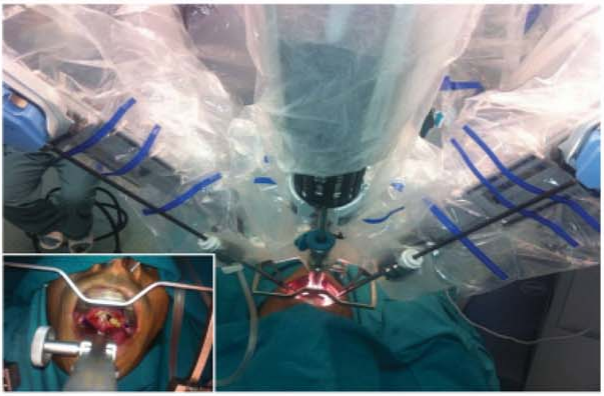

Figure: Oropharyngeal Robotic Surgery

ladder consists of Primary closure – Skin grafting–Local flaps–Free tissue transfer. As a general rule, when planning an individual patient's reconstruction, attempt the least complex and safest option from the reconstructive ladder first, while maintaining form and function. The plastic surgeon should be comfortable with the full armamentarium of reconstructive techniques, and should be able to decide which technique is the best for each particular patient and defect.

Sophisticated planning using three dimensional CT images of the tumor permits conformal radiation therapy (that is, it conforms to the tumor). This has allowed directed irradiation and the development of intensity-modulated radiation therapy, or IMRT. Reports have shown that the ability to reduce parotid gland exposure significantly reduces subsequent xerostomia and improves quality-of-life scores. Other attempts to improve tumor kill via radiation therapy have included the use of hyperfractionation and accelerated fractionation regimens (that is, higher doses or more frequent doses than conventional radiation therapy). Although these methods have shown increased local control, they have increased acute toxicity.

Chemotherapy usually is combined with radiation therapy. Combination chemoradiation therapy is used after surgery for patients with poor-prognosis stage IV cancer, for patients with unresectable stage IV disease and in protocols for organ preservation. Despite its popularity, neoadjuvant chemotherapy has not been shown to improve survival rates. Unfortunately, most series have combined all head and neck sites, and it is difficult to interpret data for the oral cavity alone when sites such as the larynx, oropharynx and nasopharynx (which are very sensitive to chemoradiation therapy) are included.

Emerging Therapies

Position emission tomography scanning appears to be most useful for identifying recurrent cancer after radiation therapy or chemotherapy. Sophisticated staining techniques have shown the presence of distant metastatic cells in the bone marrow in patients with early oral cancer. Thus, oral cancer may be a systemic disease from its onset- a revolutionary theory. The accumulated molecular abnormalities (that is, molecular markers) that occur in oral cancer may provide prognostic data, allow selection of the most useful therapeutic modalities and provide targets for specific therapy. Research in the field of molecular biology has allowed a deeper understanding of carcinogenesis and opened up areas for experimental therapies.

Conclusions

The mainstay of current therapy for oral cancer is surgery and radiation treatment. Advances in molecular biology have explained the genetic alterations that lead to the development of carcinomas. This provides hope that targeted therapy will be possible in the future. Today, our patients have a better quality of life and improved locoregional control. Tomorrow, our focus will be on using the continuing scientific and technological innovations to ultimately defeat this disease.

(Dr Ajay Kumar Dewan, Medical Director, and Sr Consultant, Dept of Surgical Oncology; Saud Azam, Research Officer, Dept of Research, RGCI&RC)

GUEST ARTICLE

CHEMORADIATION IN ORAL CANCER

Head and neck cancer(HNC) is the fifth most common cancer worldwide, with an estimated annual global incidence of 533,100 cases(1). Overall 57.5% cases of global head and neck cancer occur in Asia especially in India. Of the 2, 00,000 cancer cases occuring annually in India 80,000 cases are of oral cancers(2).

HNC is broadly divided into three clinical stages: early, locoregionally advanced, and metastatic or recurrent. Surgical resection, radiation, chemotherapy, or combined modality approaches are classical treatment options for patients with cancers of the oral cavity(3). The choice of treatment modality, either single or in combination, depends on the stage and size of the tumor and relevant patient factors, such as toxicity, performance status, comorbid disease, and convenience. Single modality treatment (i.e., surgery or radiation) for early stage while combined modality for advanced stage is the preferred treatment. The control rates are generally the same for early stage lesions with either modality alone. For T1,T2 tumors of the lip, tongue, floor of mouth, radiation alone in optimum combination of interstitial implant and external beam radiation has shown control rates from 85%-90% at 5 years in the series from Royal Marsden (UK) and Institute Curie(France). Treatment for locoregionally advanced disease remains challenging, and an aggressive treatment approach is necessary to achieve cure(4). Surgery alone for T3-T4,N1 tumors results in <20% control at 5 years and an adjuvant radiation therapy at 6-8 weeks is recommended to improve the locoregional control.In loco regionally advanced cases,5-year survival is reported to be only 40% and locoregional failure is the predominant cause of recurrence rather than metastases(5). Therefore, the efficacy of any curative approach is measured by its ability to achieve locoregional control(6,7).

Concurrent Chemotherapy and Radiation

The main purpose of concurrent chemotherapy is to increase tumor sensitivity to radiotherapy. However, sensitizing effects are not tumor specific and affect adjacent normal tissues within the radiation field. Concurrent chemoradiotherapy trials have consistently reported an increased incidence of acute grade 3 and 4 toxic effects, with mucositis and dermatitis being the most prominent. This increase creates a concern about chronic toxic effects, including consequential late effects, which evolve from persistent severe acute toxic effects. Interestingly, multiple studies have confirmed that, compared with radiation alone, the long-term side effects of concurrent chemoradiotherapy, such as on swallowing function or speech, are not increased(8,9).

The application of chemotherapy to treat HNC started in the 1960s. Over the decades the role of chemotherapy has advanced from initial use only in the recurrent or metastatic setting to active current use in the definitive treatment setting. There are a number of studies that demonstrate a benefit of concurrent chemotherapy in the definitive treatment of head and neck cancer with radiation (8-11). Although these trials vary with respect to radiation dose, fractionation schedule, and chemotherapy regimen, they have in common a randomized comparison between radiotherapy and radiotherapy plus chemotherapy. The advantage of concurrent chemotherapy with radiation has been further examined in the context of several meta-analyses (12-14). These meta-analyses generally identify a small overall survival benefit for the use of chemotherapy on the order of 1% to 8% (15). However, in many of the randomized studies comparing radiation alone to chemoradiation, oral cavity patients are either excluded or make up only a small proportion of the study population.

Cooper et al (**8**) reported the results of a randomized study in North America comparing radiation alone (60 to 66 Gy) to chemoradiation (same radiation dose plus three cycles of 100 mg/m^2 cisplatin) in patients with head and neck carcinoma demonstrating high-risk features after gross total resection. High-risk disease was defined as any or all of the following: two or more involved lymph nodes, extracapsular extension of nodal disease, and microscopically involved resection margins. This study demonstrated a benefit in locoregional control and disease-free survival for the chemoradiation arm, but no overall survival benefit was appreciated. A parallel study in Europe by Bernier et al. (**9**) randomized patients to essentially equivalent treatment arms following head and neck cancer surgery. Eligibility criteria included patients with pathologic T3 or T4 disease (except T3/N0), or patients with any T-stage disease with two or more involved lymph nodes, or patients with T1-2 and N0-1 disease with unfavorable pathologic findings (extranodal spread, positive margins, perineural involvement, or vascular embolism). Local control, progression-free survival, and overall survival were superior for patients on the chemoradiation arm. These studies suggest that

the addition of chemoradiation following surgery may be beneficial in selected patients with high-risk head and neck cancer, although with increased toxicity profiles.

A meta-analysis of 63 trials on nearly 11 000 patients with HNC showed that the addition of chemotherapy to locoregional treatment resulted in an absolute survival benefit of 4% at 5 years (HR 0·90, 95% CI 0·85–0·94; p<0·0001)(20). This benefit was confined to chemoradiotherapy (HR 0·81, 95% CI 0·76–0·88; p<0·0001) that resulted in an absolute survival improvement of 8% at 5 years(13), which was also supported by an updated meta-analysis that included 24 additional studies. Treatment benefit was maintained in stage III or IV disease, each major primary site, definitive or postoperative radiotherapy, and when altered fractionation radiotherapy was used in the control arm(14). However, chemoradiotherapy has an insignificant effect on distant recurrence rate. Nevertheless, being cured is of paramount importance to patients, overshadowing potential toxic effects(15).

In another meta-analysis, a total of 4331 patients with oral cavity cancer and 81 comparisons were included. The HR of death associated with chemotherapy was 0.87 (95% CI: 0.80–0.93), corresponding to an absolute 5-year overall survival benefit of 5.1% (95% CI: 2.0–8.3), increasing from 31.3% to 36.4%. According to subset and subgroup analyses patients, age and sex significantly affected chemotherapy benefit (p-values of interaction: 0.03 and 0.04, respectively), the benefit being lower for older patients and men. The Cox multivariate analysis shows that only patients sex has a significant independent interaction with chemotherapy effect (p = 0.009) (16).

Clinical trials conducted by the Radiation Therapy Oncology Group (RTOG) and others in the late 1980s suggested that a particularly high-risk subset of advanced operable head and neck squamous cell carcinomas existed that could be identified by the spread of tumor to 2 or more regional lymph nodes, extracapsular extension of nodal disease and/or microscopically involved mucosal margins of resection(17). Based on the concept that other high-risk tumors in various clinical settings respond better to concurrent chemotherapy and radiation therapy (RT+CT) than to radiation therapy (RT) alone (18,19).

As per the 10-year result of RTOG 9501, the local-regional recurrence rates of the randomized cohorts are no longer statistically significantly different; however, in the unplanned subset of tumors characterized by extracapsular extension (ECE) and/or microscopically involved margins, RT + chemotherapy continues to be associated with statistically better L-R control. In contrast, patients who were enrolled solely based on having multiple involved nodes (ie, without ECE and/or an involved margin) appear not to derive local-regional benefit from radiochemotherapy. Although subgroups with progressively more nodal involvement have progressively fewer members precluding meaningful analysis of the subgroups with the maximum nodal involvement, even in the subgroup of patients who had the relatively high degree of 6 or more involved nodes and neither involved margins or ECE (a subgroup containing 44 patients), there is no suggestion that the addition of chemotherapy was beneficial (20).

Neoadjuvant Therapy

Currently neoadjuvant radiation and chemotherapy remain largely experimental for cancers of the oral cavity. The use of preoperative chemotherapy has been studied in two randomized trials. Licitra et al. (21) conducted a phase III study of 195 patients with T2-4 (>3 cm) N0-2 squamous-cell carcinoma of the oral cavity and randomized patients to surgery alone versus three cycles of cisplatin and 5-fluorouacil (5-FU) followed by surgery. The authors found no difference in overall survival but did comment on the possibility of neoadjuvant chemotherapy as potentially improving resectability . In a similarly designed trial, Volling et al. (22) also reported no difference in overall survival with the use of neoadjuvant chemotherapy, although there was an improvement in disease-free survival. In a meta-analysis, induction chemotherapy resulted in a non-significant survival improvement of 2% at 5 years (HR 0·95, 95% CI 0·88–1·01; p=0·10). However, in 15 trials with a platinum agent plus fluorouracil, a marginal survival benefit was evident (HR 0·88, 95% CI 0·79–0·97; p=0·05) (13).

Preoperative chemoradiation has been studied prospectively by Mohr et al. (23). The authors randomized 268 patients with T2-4/N0-3 oral cavity and oropharyngeal cancers to either preoperative chemoradiation with cisplatin versus surgery alone. Results of this study revealed an improvement in overall survival and local control with the use of preoperative therapy. This regimen, however, has not shown common adoption in other centers around the world.

Dose and Fractionation

When postoperative radiation is used for oral cavity cancer, the most common dose fractionation is 1.8 to 2.0

Gy per day. Dissected tissues that harbored the original tumor should generally receive a dose of 60 Gy. However, for close or positive microscopic margins or extracapsular nodal extension, a 4- 6-Gy localized boost should be considered. If there is gross residual disease, either further surgical resection or focal boosting up to 70 Gy is advisable. Regions of somewhat lesser risk (i.e., clinically or pathologically uninvolved necks) should receive of the order of 50 to 54 Gy. When definitive radiation is used for oral cavity cancer, boosting the primary tumor with either interstitial implantation, submental, or intraoral cone therapy can result in increased tumor control and decreased complications, particularly osteoradionecrosis (24). When external beam radiation therapy is used as the sole treatment modality, even small lesions that cannot be excised or treated with brachytherapy require doses in the range of 66 Gy in 2-Gy fractions for reliable control. For larger tumors, improved local control rates are likely to be achieved with doses >70 Gy, but there is an increasingly significant price to pay in terms of normal tissue toxicity for doses in this range.

Altered Fractionation

Head and neck tumors are rapidly proliferating cancers. There has been a significant interest in the use of altered fractionation schedules to counter rapid tumor cell repopulation as a means of improving outcome in head and neck cancer patients treated with radiation. Altered fractionation regimens, such as hyperfractionation or accelerated fractionation, should be considered for patients being treated with radiation alone, as this approach has been demonstrated to improve the likelihood of locoregional tumor control (25). The Radiation Therapy Oncology Group's (RTOG 90-03) altered fractionation randomized trial comparing conventional fractionation to hyperfractionation, split-course, and concomitant boost technique demonstrated a significant improvement in disease-free survival for the hyperfractionation and concomitant boost arms (26). These altered fractionation regimens were associated with higher incidence of grade 3 or worse acute mucosal toxicity, but no significant difference in overall toxicity at 2 years following completion of treatment. However, oral cavity carcinoma constituted a minority of cases enrolled in these studies.

Complications

Patients with SCCHN develop acute and late complications as a result of their disease and its treatment. Common acute toxic effects associated with radiation are mucositis (which is severe in 50% or more of patients receiving chemoradiotherapy), increased secretions, dysphagia, occasionally with aspiration, loss of taste, hoarseness caused by laryngeal oedema, and dermatitis (27). Supportive care during chemoradiotherapy is often demanding and includes oral and skin care, narcotic analgesics, intravenous hydration, and enteral nutrition, as necessary. Swallowing function and quality of life usually improve in the first year after treatment, but swallowing dysfunction might be permanent(28,29). Other possible late sequelae of treatment include osteoradionecrosis, dental caries, subcutaneous fibrosis, trismus, thyroid dysfunction, sensorineural hearing loss, pharyngeal or oesophageal stenosis, and myelitis. Radiation-induced xerostomia is universal in long-term survivors, which is moderate or severe in about 60% of patients(30). Several strategies seek to prevent xerostomia, including surgical transfer of salivary glands, radioprotectants (eg, amifostine), and radiation techniques that spare the salivary glands(31). Supportive care measures include oral hygiene with fluoride agents and antimicrobials to prevent dental caries and oral infections, saliva substitutes, and cholinergic stimulants (eg, pilocarpine). Treatment and disease-induced anatomical and functional defects might lead to many social and psychological problems(32). Such, patients with SCCHN should be cautiously monitored and encouraged to participate in long-term supportive care programmes. At present, there is no radioprotectant with proven efficacy in decreasing the severity of mucositis during chemoradiotherapy. Granulocyte-macrophage colony stimulating factor or granulocyte colony stimulating factor has been investigated for amelioration of radiation mucositis without convincing results; moreover, there are concerns about poor disease control when such factors are added to radiation(33). Erythropoietin could also have an adverse effect on survival, presumably because of the presence of erythropoietin receptors in cancer cells. Therefore, the use of cytokines during curative radiation or chemoradiotherapy should be generally avoided. Many novel agents with potential cytoprotective effect, such as palifermin (recombinant human keratinocyte growth factor), are under assessment in clinical studies.

Summary- The available literature at present supports addition of concurrent radiation and chemotherapy in the postoperative setting for advanced cancers of the oral cavity. The specific subsets that seem to benefit from such an approach include(i) stage III and IV disease, (ii) vascular embolism, (iii) perineural invasion, iv) positive lymph nodes at level IV and V ,(v) extracapsular invasion,(vi) more than two lymph nodes positive on histopathology.

Down staging with concurrent chemoradiation is still experimental as the patient may not agree for surgery and the margins cannot be assessed at the time of surgery.

Follow-Up

First follow-up is recommended after 1-2 weeks of the radiation therapy followed by 2-4 months for first 2 years and once in 4-6 months for another 3 years and once in a year after 5 years. During follow-up complete history, physical examination and flexible endoscopy or indirect mirror examination is to be considered on each visit. Investigation imaging includes CECT neck at 3 months after definitive treatment, followed by six monthly thyroid function tests, annual CECT/MRI neck, chest x-ray and ultrasonography abdomen during the first 5 years(34).

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PERSPECTIVE

RECONSTRUCTION IN ORAL CANCER

In no field of cancer other than head and neck the challenge to surgery proposes procedures that commonly effect form and function. The patient who undergoes extirpative surgery of oral cavity is left with defect and alteration in his appearance and functions that are devastating and isolating. Reconstruction of these alterations together with promoting early healing requires considerable understanding and compassion by the surgeon.

A variety of options are available to the reconstructive surgeon. The decision is based upon the disease prognosis, functional status of patient, co-morbid conditions, psychological state and available reconstructive donor sites.

The most important aspect of planning the reconstruction is to assess the defect. It may comprise of mucosal lining, soft tissue fill, skin cover, skeletal support of bone or cartilage and repair of nerve or blood vessels. Replacement of 'like tissue with like' is the norm and is practiced as much as possible. This entails importing tissues as pedicled or free vascularised flaps composed of fasciocutaneous, myocutaneous, osseocutaneous or such other composite compositions.

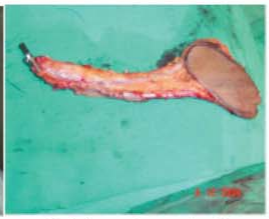
In oral cavity reconstruction, the goal is to obtain a water tight seal, oral competence, tongue mobility and mastication by optimum mandibular activity and stability. This helps to achieve optimum function of speech and swallowing, and restores the facial contour and aesthetics. The most common oral cavity cancer is buccal mucosa cancer. Many times, the lesion with its margin is not confined to one anatomical boundary and can involve adjacent structures e.g. mandible. This makes the defect complex and the reconstruction complicated.

Buccal mucosa reconstruction depends on the site and size of lesion and also on the presence of submucosal fibrosis and trismus. Buccal mucomuscular flaps can be raised from inside the oral cavity based on facial artery perforators for reasonable sized defects but only in cases where submucosal fibrosis is absent and adequate amount of buccal mucosa is left.

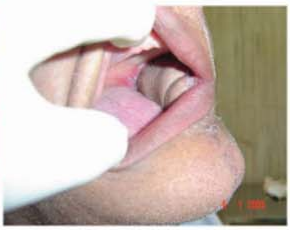
For larger defects, tissues from elsewhere needs to be brought in to reconstruct the defect. Flaps like nasolabial flap(NLF), radial artery forearm free flap (RAFF), anterolateral thigh free flap (ALT) or pectoralis major myocutaneous flap may be required.

The tongue is another common site of cancer in the oral cavity. When a part of the tongue is resected, its muscles also get resected and this leads to a loss in function of speech and swallowing. The aim of tongue reconstruction is to provide cover, bulk and tissues to ensure adequate freedom of tongue movement for proper function. The flaps that cover these defects are adynamic but provide contour to the remaining tongue and prevent the remaining musculature of tongue to get teethered, thereby allowing movements of reconstructed tongue. These flaps may at times be 'weight-less' enough to let the remaining tongue 'carry' it to ensure its unrestricted mobility. At other times when most or whole of the tongue is resected, these flaps should be bulky enough to fill the soft tissue deficiency and let the pharyngeal and floor of mouth musculature work on it for tongue function. Most commonly used flaps for partial glossectomy defects are local tongue flaps, buccal mucomuscular flap, nasolabial flap, and radial artery forearm free flap. For subtotal and total glossectomy defects, faciocutaneous flap like anterolateral thigh free flap or musculocutaneous flaps like pectoralis major myocutaneous pedicled flap are done. If floor of mouth also needs reconstruction, musculocutaneous flap is preferred.

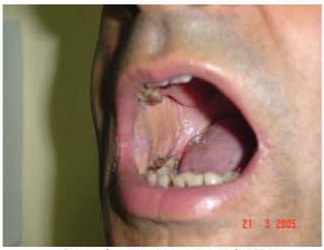
Cancer of Lt. Buccal mucosa



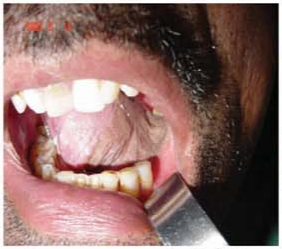
Radial artery forearm free flap



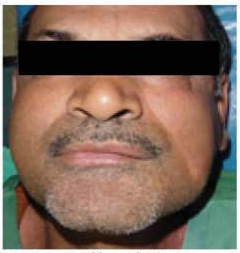
Reconstruction of buccal defect with RAFF



Buccal cancer recon. with NLF



Tongue reconstructed with NLF



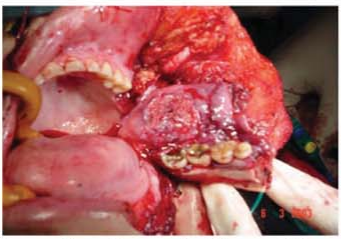
Patient profile with NLF scar

It is more common in lesions of buccal mucosa or tongue to have the defect that extends to involve the mandible. In such cases a composite flap of bone with fasciocutaneous component is required.

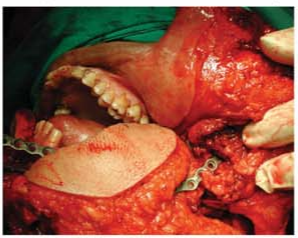
Alveolar carcinoma of mandible mostly mandates segmental mandibulectomy. Mandibular reconstruction is needed to maintain the function of mastication, mainteinance of airway, deglutition, articulation and to restore the bony contour. The ideal reconstruction for mandibular defects is by an osseous or osseoseptocutaneous vascular free fibula flap (FFF)(3). Another commonly used composite is the deep circumflex iliac artery based iliac crest free flap (DCI). In patients with advanced disease not fit for long surgeries involving free flaps and increased risk of vascular thrombosis, mandible is often reconstructed using titanium reconstruction plate ensconced in pectoralis major myocutaneous flap. In cases where fibula or iliac crest is used for mandibular reconstruction, osseointegrated dental implants may be done secondarily to restore the dentition too(1). Upper alveolectomy defects are reconstructed by superiorly based nasolabial flap, palatal mucoperiosteal flap or buccal mucomusccular flaps for small defects. When the defect is large as is common involving the whole of 'bite' segment, other flaps used for buccal mucosa and mandible defects may be used(2).

Lip is one area where both function of oral competence and aesthetics are very important. The best reconstruction of lip is possible when the flap used is from the remaining lip. The oral competence is best achieved when the continuation of orbicularis oris is maintained and like tissue of mucosa and skin from lip itself is used. This also gives the best aesthetics. The commonly used flaps are Abbe, Estlander, Gilles and Karapandziac, all of which use some part of remaining upper or lower lip together with perioral tissues to reconstruct upto 75% of either lip, ofcourse at the cost of some microstomia which improves remarkably with time. If the loss is of subtotal variety, non-lip tissue is required to provide for the loss like nasolabial flap, or radial artery forearm free flap.

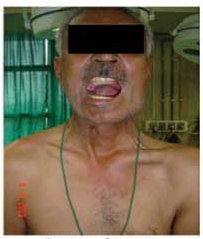
Maxillary carcinoma which needs partial maxillectomy can be reconstructed by using only a skin graft with subsequent use of obturator. When total or extended maxillectomy is done, the defect in floor of orbit is reconstructed with bone or titanium mesh covered and supported by temporalis muscle flap or anterolateral thigh free flap. An osteocutaneous free fibular flap is done to restore the maxillary arch and palatal shelf which later receives the osseointegrated dental implants, When total maxillectomy is extended to orbitectomy as in craniofacial resections, then a free rectus abdominis



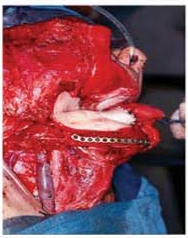
Cancer of buccal mucosa involving mandible



Reconstructed with recon plate and PMMC



Post op function



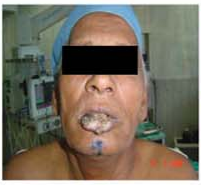
FFF for mandible and floor of mouth

Temporalis muscle flap for palate and maxilla

myocutaneous flap (RAM) is preferred over ALT flap to provide bulk and epithelial surface partition in nasal, palatal and cheek defects. This ensures closure of oro-nasal, oro-antral and oro-antro-cutaneous fistulisation.

All these reconstructions are not without complications. Flap failures because of infection, vascular thrombosis and implant exposures are some uncommon but dreaded complications which may happen in 5-20% of cases. This would delay the healing process and lead to morbidity in terms of loss of form and function. Adjuvant treatment of radiotherapy may also be delayed in such cases. The donor site morbidity is increased when bone is required as vascular tissue replacement.

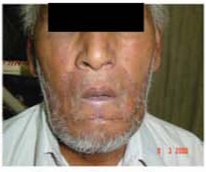
In recent times tissue engineering has been applied to reconstruct complex defects of head and neck region. The ability to grow tissues from stem cells and remodel them at the site of their final functional position has now become a reality(4). Titanium meshes and more recently certain biodegradable substances like silk and polymers like polyglycolide and polylactolide etc. have been used as scaffolds, prefabricated and shaped like a mandible.



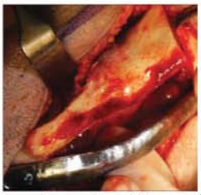
Cancer of lower lip

Resected lower lip defect

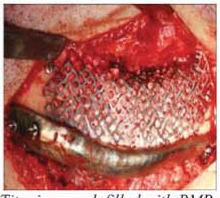
Bilateral karapandziac flaps



Restored lower lip

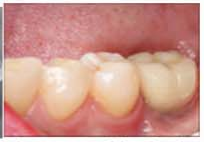


Resected mandible



Titanium mesh filled with BMP

Osseo-neo genesis



Osseointegrated dental implant

These scaffolds are impregnated with bone morphologic protein (BMP), adipose derived mesenchymal stem cells and 'cocooned' in a free ALT, RAM flap before being transferred to the site of mandibular defect by means of micro vascular anastomosis between vessels of flap and that of neck. The scaffold gets degraded in body tissue over a 5-6 months period during which time osteoblastic activity from stem cells and BMP leads to ormation of new bone within the vascular flap transferred to the defect. This bone becomes strong enough to receive dental implants(4,5).

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MANAGING ORAL CANCER: TRENDS

Different Anaesthetic Techniques

To investigate the effects of different general anaesthesia techniques on immune responses in patients, 60 American Society of Anesthesiologists physical status 1 or 2 patients undergoing elective reconstructive surgery for tongue cancer were randomised to three groups. Group 1 received propofol induction and maintenance (TIVA), group 2 received propofol induction and sevoflurane maintenance (MIXED), and group 3 received sevoflurane induction and maintenance (SEVO). Blood samples were obtained at eight time-points. All immunological indicators except CD3(+)CD8(+) cells were significantly decreased in all groups at T1~T5 compared to T0 ($P<0.05$). The percentages of CD3(+) cells, CD3(+)CD4(+) cells and natural killer cells, and the CD4(+)/CD8(+) ratios were significantly lower in the MIXED groups and SEVO groups but not the TIVA group at T6 as compared with T0 ($P<0.05$). There were minor but statistically significant differences in the percentages of CD3(+) cells, CD3(+)CD4(+) cells and natural killer cells, and the CD4(+)/CD8(+) ratios between the SEVO group and the TIVA group at T2approxT6 ($P<0.05$). These findings suggest that propofol has slightly less effect on cellular immune responses than sevoflurane.

(Anaesth Intensive Care, Mar 2014)

Foods, Nutrients and Risk of Oral Cancer

A collabrative study was conducted in Itlay and Switzerland between 1997 and 2009 to assess the role of selected food groups and nutrients on oral cancer and pharyngeal cancer (OCP). The study included 768 incident, histologically confirmed squamous cell carcinoma cases and 2078 hospital controls. Odds ratios (ORs) were estimated using logistic regression. Significant inverse trends in risk were observed for all vegetables and all fruits, whereas significant direct associations were found for milk and dairy products, eggs, red meat, potatoes and desserts. With reference to nutrients, significant inverse relations were observed for vegetable protein, vegetable fat, polyunsaturated fatty acids, a-carotene, β-carotene, â-cryptoxanthin, lutein and zeazanthin, vitamin E, vitamin C and total folate, whereas direct ones were observed for animal protein, animal fat, saturated fatty acids, cholesterol and retinol. This study confirms and further quantifies that a diet rich in fruits and vegetables and poor in meat and products of animal origin has a favorable role against OCP cancer.

(Br J Cancer, Nov 26, 2013)

Novel Optical System for Early Detection

A new spectral imaging that holds promise for rapid and non-invasive screenings for oral cancers has been developed by researchers at the Centre for Earth Sciences Studies, Kerala, India. The Diffuse Reflectance Imaging System (DRIS) works with an Andor Luca-R electron multiplying CCD (EMCCD) which captures monochrome images of the patient's mouth at 545 and 575 nm. Andor's SOLIS software uses the images to generate a pseudo color map where blue, red and yellow colors denote healthy, pre-malignant and malignant tissues respectivley. This allows rapid visual differentiation of oral lesions and identification of regions with pre-malignant characteristics. The novel DRIS also demarcates the margins of neoplastic changes and locates the sites with most malignant potential for biopsy, thereby avoiding unnecessary repeated biopsies and delay in diagnosis. The imaging may assist surgeons to identify the margins of lesion that cannot be easily seen with naked eye during surgical interventions. This rapid and easy-to-use system reveals the accuracy equivalent to the gold standard histopathology of a biopsy sample and has the potential to be valuable tool in oral cancer screenings.

(www.optics.org, Jan 23, 2014)

Surgical Margins in Oral Cancer

Oral cancer is a public health problem with high prevalence in the population. Local tumor control is best achieved by complete surgical resection with adequate margins. Fluorescence spectroscopy is a noninvasive diagnostic tool that can aid in real-time cancer detection. Researchers in Brazil compared oral squamous cell carcinoma lesions to surgical margins and the mucosa of healthy volunteers by fluorescence spectroscopy. The sample consisted of 56 individuals, 28 with oral squamous cell carcinoma and 28 healthy volunteers with normal oral mucosa. Thirty-six cases (64.3%) were males and the mean age was 60.9 years. The spectra were classified and compared to histopathology to determine fluorescence efficiency for diagnostic discrimination of tumors. In the analysis of the other cases, a discrimination was observed between normal mucosa, injury and margins. At two-year follow-up, three individuals had local recurrence, and in two cases investigation fluorescence in the corresponding area showed qualitative differences in spectra between the recurrence area and the area without recurrence at the same anatomical site in the same patient.

(Oral Oncology, March 17, 2014)

IN FOCUS

WORTHWHILENESS OF GENE PROFILING IN ORAL CANCER

Background

Oral cancer ranks as the sixth most common cancer worldwide, accounting for 4% of all cancers in men and 2% of all cancers in women with more than 500,000 new oral and pharyngeal cancers diagnosed annually. The disease burden of oral cancer in India is extremely disconcerting, being the most common cancer among men, accounting for nearly 30-40% of all malignancies (1).

The aetiology of oral cancer is multifactorial, being influenced by age, sex, race, local environmental factors, diet and genetics. Most oral cancer cases and deaths are due to specific individual predispositions; genetic characteristics and exposure to carcinogens caused by lifestyle modifications. The specific risk factors for oral cancer range from alcohol consumption, smoking, chewing of tobacco with or without betel quid to HPV infection, culminating to variability in prognosis. Of these note, smoking and alcohol has been shown to have synergistic effects in the development of OSCC.

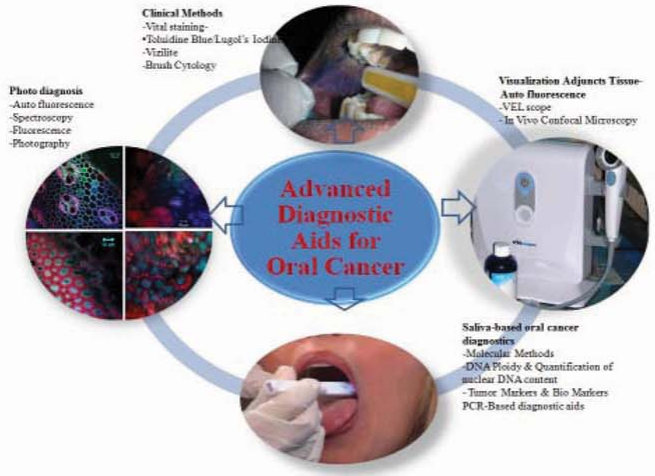
OSCC, like many other malignancies, is caused by DNA mutations, often spontaneous but increased by exposure to a range of chemical, physical or microbial mutagens. It typically evolves from normal epithelium through dysplasia, carcinoma in situ and finally progressing to invasive carcinoma. During this tumorigenesis, cumulative genetic alterations, including microsatellite instability and loss of heterozygosity, occur. Additionally, key molecular regulators, such as p53, NF-êB, microRNAs and various signaling pathways such as RAS, EGFR/TGF-á, PI3K/AKT, ERK/MAPK, Cyclin D1, VEGF and carcinogen detoxification pathways have been implicated in oral carcinogenesis(2). Furthermore, common genetic variants in immune and inflammatory response genes can also affect the risk of developing oral cancer.

Despite substantial improvements in treatment strategies involving surgery, radiotherapy and/or chemotherapy, the prognosis of oral cancer patients in clinically advanced stages remains largely dismal, owing to the late presentation of patients and loco-regional recurrence. Given the poor prognosis associated with oral cancer, there is an urgent and unmet need to elucidate the molecular determinants and critical signaling pathways underlying the malignant transformation of precancerous to cancers, which may lead to the identification of novel diagnostic and therapeutic targets. Additionally, there exists a severe paucity of data regarding the status of pre-diagnostic markers in the context to immunomodulatory genes for oral malignancy in Indian population. The immediate need of the hour is a planned program for the identification of specific and robust biological markers for progression from pre-malignant lesions, such as leukoplakia and oral submucosal fibrosis, to malignancy and validation of these markers for drug and radiation responses (3,4).

Gene Profiling in Oral Cancer

Gene profiling refers to the measurement of the activity (the expression) of thousands of genes at once, to create a global picture of cellular function. Expression profiling experiments often involve measuring the relative amount of mRNA expressed in two or more experimental conditions. Gene profiling simultaneously compares the expression levels of many genes between two or more sample types. This analysis can help scientists to identify the molecular basis for phenotypic differences and select gene expression targets for an in-depth study using other technologies and use it as a major tool for discovery in medicine. Genomic alterations may add prognostic information and indicate biological aggressiveness, thereby emphasizing the need for genome-wide profiling of oral cancers. Identifying oral cancers associated with high risk of relapse and predicting clinical outcome remain challenging issues in clinical practice.

Numerous methods are available for directly analyzing tumor DNA, either directly in the tumor itself or in archival tissue using formalin fixed tissue. The most common methods are in situ hybridization, Southern and Northern blot analysis, polymerase chain reaction, and automatic DNA sequencing. Microarray technology, for its part, is particularly useful for establishing general gene expression patterns and for screening for differential gene expression. Array results, however, need to be validated using an alternative method, such as Northern blot analysis or quantitative real-time (RT) PCR, used to evaluate product accumulation during the log phase of the reaction. Quantitative RT-PCR, currently considered the most reliable and reproducible gene quantification method available, is the most widely used technique for validating gene expression results obtained using microarray technology.



Some recent reports suggest frequent chromosomal aberrations (deletions) at 2q21-24, 2q33-35, and 2q37 which affect numerous tumour suppressor genes including LRP1B, CASP8, CASP10, BARD1, ILKAP, PPP1R7, and ING5 (5). Polysomy 3, for its part, is more common than polysomy 9 and is characteristic of dysplasia and in-situ carcinoma. A high frequency of loss of heterozygosity (LOH) at chromosomal loci 13q and 17p has been described in premalignant oral lesions and early carcinomas. Chromosome 9 appears to be one of the regions that is altered most often and earliest in tumor development. The 9p21 region harbours genes that code for the cyclin dependent kinase inhibitors p16 and p14, two important regulators of cell proliferation. Recent studies have identified allelic polymorphisms in the genes HLA and major histocompatibility complex-class-I-chain-related gene A. Alteration of CCND1 gene has been observed to induce overexpression of the cyclin D1 protein, which has been associated with poor prognosis in early-stage oral tumors (5).

Tumor suppressor gene anomalies are also found in malignant oral lesions. Most oral carcinomas are characterized by aberrant expression of at least one of the members of the retinoblastoma family of growth suppressor proteins. CDKN2A, for example, which encodes the protein p16, is located at locus 9p21 - one of the most vulnerable areas of the human genome in oral cancer, while p14, the alternative transcript of the same gene, is frequently deleted in malignant lesions. Functions of tumor suppressor gene TP53 has been found to be suppressed in numerous tumors - constituting one of the earliest findings in the natural history of oral cancer (6). Three single nucleotide polymorphisms (SNPs) detected in the promoter region of the DNMT3B gene-C46359T [-149C>T], -238T>C, and -579>T, might play a causative role in several cancers, including OSCC. However, in OSCC, the base excision repair pathway, which comprises the genes MUTYH, OGG1, and MTH1, and which repairs mutations that involve 8-oxoguanine, has been seen to play a very small or possibly even non-existent role in tumor development. AgNOR and Ki-67 analyses can be used to determine proliferative states of epithelial cells in oral cancer, and increased levels of proliferating cell nuclear antigen (PCNA) have been observed. Also, ATP6V1C1 5 gene seems to be the main gene involved in the regulation of V-ATPase enzymes and the acidity of solid oral tumors. Alterations of Ras association family genes have also been seen in OSCC (5).

Other molecules that have been associated with OSCC are cyclo-oxygenase 2 (COX-2), which has been found in high levels in dysplastic lesions; the human trophoblast cell-surface antigen (TROP2), which appears to be associated with shorter survival and the epithelial adhesion molecule (EpCAM), which has been associated

with tumor size, regional lymph node metastasis, histologic differentiation, and an invasive pattern (5). The connective tissue growth factor, CCN2, was recently associated with head and neck squamous cell cancer (7). Overexpression of MMP-1, MMP-2 and MMP-9 has been associated with the invasive potential of tumors and levels of alcohol, leading several authors to hypothesize that alcohol might play a role in oral carcinogenesis through the stimulation of these genes (8). Other studies have detected the soluble fragment of cytokeratin 19, Cyfra 21-1, in patients with OSCC, although further studies are required to determine the true diagnostic and prognostic value of this marker.

Studies have also shown that the determination of proteins and oxidated DNA levels in saliva might indicate high levels of reactive oxygen species, which appear to be involved in the development of OSCC (5). Therefore, it has been suggested that proteomic analysis of human oral fluid, such as saliva, holds promise as a non-invasive method to identify biomarkers for human oral cancer. Most recently, detection of five proteins in the saliva of cancer patients has been found to be useful markers of oral cancer with 90% sensitivity and 83% specificity for OSCC. These proteins include: calcium binding protein MRP14, CD59 (overexpressed on tumor cells that enables them to escape from complement-dependent and antibody-mediated immune responses), Profilin 1 (protein involved in several signaling pathways with cytoplasmic and nuclear ligands, generally secreted into tumor micro-environments during the early progressive stage of tumorigenesis), and catalase (member of the enzymatic antioxidative system, whose level has been found elevated in many human tumors including oral cancer. Yet another set of molecules, such as actin and myosin, are promising salivary biomarkers for distinguishing premalignant and malignant oral lesions (9, 10).

Other recent findings in this area include the observation of an association between oral cancer and a set of new molecules called advanced glycation endproducts (AGEs) and their receptors (RAGEs). RAGE expression decreases with an increase in OSCC differentiation (5).

Gene profiling is, therefore, of utmost importance and the need of the hour, especially in oral cancer which is a very rampant disease in India. Correctly diagnosing the disease and proper therapeutic approach and monitoring can greatly help in reducing the overall burden of this disease.

Conclusion

This brief perspective attempts to elucidate the key molecular mechanisms involved in the pathogenesis of oral cancers, focuses on the major lacunae in the current management and envisages the future genomic vistas that should be combined with proper awareness programs, especially for the Indian population. Findings in the bench (laboratory) should be extrapolated to the bedside (clinic) for the benefit of these patients. Gene profiling is indeed a promising approach to discover innovative therapeutic options. Given the advances in technology for personalized medicine and therapeutics, it is high time that we work together and combat this challenge right now instead of merely speculating and contemplating for the future. The ideal strategy for oral cancer should be a multidisciplinary approach involving the efforts of dental practitioners, head and neck surgeons, radiation oncologists, chemotherapy experts, nutritionists, rehabilitation and restorative specialists.

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The specialist's consultation will be provided to your physician in your presence. Individual sessions with each patient/physician may last up to one-half hour and are structured in a manner intended to assure security and confidentiality.

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- Are there alternatives to surgery and/or radiation therapy?
- If first line therapy fails, what is recommended as next therapy?
- Is the patient eligible for any new treatments available in the US?
- Of the newer drugs available, which seem to have the most promise in early clinical use?
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