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# Oral Cancer

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## Abstract

Cancers implicate a group of diseases including more than 100 different pathologies. Cancers encompass uncontrolled development of cells (abnormal cell growth & tumor malignency) which have the potential to invade or spread to other parts of the body. The progression of metastatic cancers cause the death of patients. A tumor can be cancerous or benign. This review is mostly focusing on oral cancerous malignant disease. Oral squamous cell carcinoma (OSCC) is the most frequent malignant tumor of the oral cavity.

**Keyword:** Leukemia; Carcinomas; Cancer; Mucosa; Oral Cancerous

**Abbreviations:** OSCC: Oral Squamous Cell Carcinoma; EFGR: Epidermal Growth Factor Receptor; CDKN: Cyclin-Dependent Kinase Inhibitor; STAT: Signal Transducer and Activator Of Transcription; VEGF: Vascular Endothelial Growth Factor; MVD: Microvessel Density; TSCC: Tongue Squamous Cell Carcinoma; ALK: Anaplastic Lymphoma Kinase; DNA: Deoxyrebonucleic; ADH: Acid Alcohol Dehydrogenase.

## Introduction

The four main types of cancer are

- Carcinomas. A carcinoma begins in the skin or the tissue that covers the surface of internal organs and glands. Carcinomas usually form solid tumors. They are the most common type of cancer. Examples of carcinomas include prostate, breast, lungs, and colorectal cancers.
- Sarcomas. A sarcoma begins in the tissues that support and connect the body. A sarcoma can develop in fat, muscle, nerve, tendon, joint, blood vessel, lymph vessel, cartilage, or bone.
- Leukemias. Leukemia is a cancer of the blood. Leukemia begins when healthy blood cells change and grow uncontrollably. The 4 main types of leukemia are acute lymphocytic, chronic lymphocytic, acute myeloid, and chronic myeloid leukemia.

Lymphoma is a cancer that begins in the lymphatic system. The lymphatic system is a network of vessels and glands. There are 2 main types of lymphomas: Hodgkin and non-Hodgkin lymphoma. The oral cavity includes. The lips, the lining of the lips and cheeks, also called the buccal mucosa, gingiva, including the upper and lower gums, retromolar trigone, which is the small area behind the wisdom teeth, the oropharynx that begins where the oral cavity stops. It involve also the soft palate, at the back of

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the mouth. More than 90% of oral and oropharyngeal cancers are squamous cell carcinoma.

This means that they begin in the flat squamous cells found in the lining of the mouth and throat (pharynx). The most common locations for cancer in the oral cavity are: the tongue, tonsils, oropharynx, gums, floor of the mouth. The bloodstream can spread the cancer malignant cells to distant parts of the body. Benign tumors are also present, but they don't spread and remains localized. Considering that metastases are the major cause of death in cancer patients, new technologies for investigating cancer cell invasion are playing a central role in developing new therapeutic approaches for preventing or delaying the formation of malignant tumors, and extending the life of cancer patients.

## Oral cancer

Oral cancer is a malignant neoplasia which arises on the lip, oral cavity and oropharynx [1]. They represent the 6th most common cancer in the world. Oral cancer remains a lethal disease for over 50% of case diagnosed annually. Ninety per cent of cancers are originated from the squamous cells : they are named oral squamous cell carcinoma (OSCC). They have a propensity for lymph node metastasis. It is more prevalent in men than women in Table 1.

| Oral Malignant Neoplasms | |
|---|---|
| Common | Uncommon |
| Squamous cell carcinoma | Malignant salivary gland tumours |
| | Malignant melanoma |
| | Lymphomas |
| | Neoplasms of bone and connective tissue |
| | Some odontogenic tumours |
| | Maxillary antral carcinoma (or other neoplasms) |
| | Metastatic neoplasms (from breast, lung, kidney, stomach, or liver cancer) |
| | Langerhans' cell histiocytoses |
| | Kaposi's sarcoma |

Table 1: Oral Malignant Neoplasms [2].

Smocking and alcohol are considered to be the major risk factors, present in 90% of the cases, with a synergic effect. With the knowledge of risk factors, primary prevention through the elimination of tobacco consumption, the moderation of alcohol- intake and chemoprevention are urgently needed. Development of tumour markers with high sensitivity and specificity could assist the detection of patients and lesions at risk [3]. Considering that metastases are the major cause of death in cancer patients, new technologies for investigating cancer cell invasion are playing a central role in developing new therapeutic approaches, needed for preventing or delaying the formation of metastasis, and extending the life of cancer patients.

Smoke chemicals, called pre-carcinogens, are basically grouped into three distinct groups : nitrosamines, benzopyrenes and aromatic amines. Alcohol increase the permeability of oral mucosa, together with EFGR (epidermal growth factor receptor), CDKN2A (cyclin-dependent kinase inhibitor 2a), STAT3 (Signal transducer and activator of transcription 3). Oral carcinogenesis starts with the transformation of a limitednumber of normal keratinocytes. Leukoplakia is a white plate displaying uncertain risks, by excluding other diseases or disorders that are already known to not increase the risk for cancer.

Microscopically extensive, they exhibit several reactive epithelial changes such as hyperplasia, hyperkeratosis and acanthosis (Figure 1). Histologically, a distinction is essential between dysplastic and non-dysplastic leukoplakia. The term leukoplakia refers to epithelial dysplasia precursor lesions showing cytology combinations and degrees of atypia such as hyperchromatism, increased nuclear size, pleomorphism, dyskeratosis, abnormal mitotic figures or increased mitosis. Early diagnosis of oral cancer [4] include over 90% squamous carcinoma. Early carcinoma remain painless until the lesion becomes ulcerated. Localized changes such as erosion, erythema, or keratosis have been identied as pre-carcinogens or carcinogens. Leukoplakia designate a clinical white patch, representing hyperkeratosis. Premalignant lesions can be stained with 1% toluidine blue.

## Oral Cancer Detection

Screening can be made more efficient by examining the high-risk areas where 90% of all oral SCCs arise: the floor of the mouth, the ventrolateral aspect of the tongue and the soft palate.

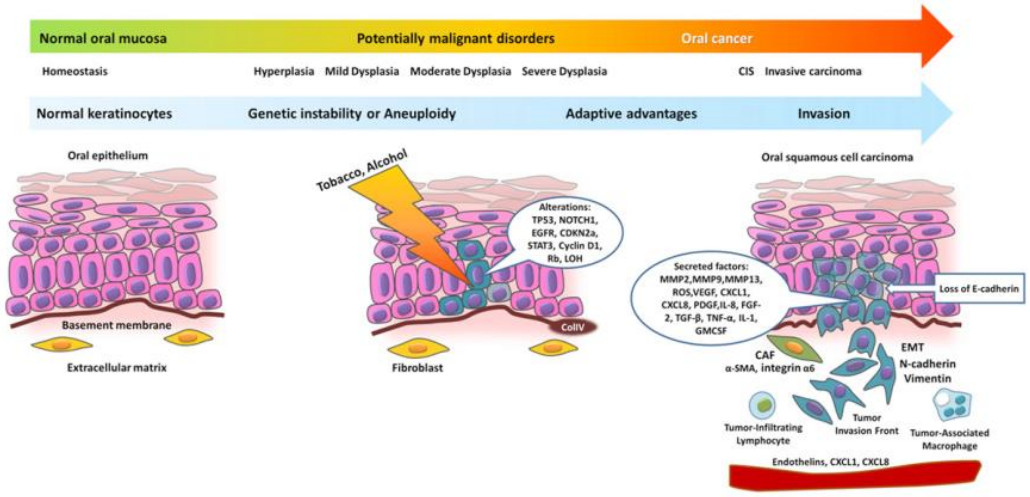


Figure 1: Hyperplasia, hyperkeratosis and acanthosis.

Surgery, chemotherapy and radiotherapy are the options for treatment of head and neck cancers [5]. Xerostomia, oral infection, oral mucositis are associated with head and neck radiotherapy. Osteoradionecrosis is irreversible, with progressive devitalization of irradiated bone. Five markers are increased in cancer patients by 39–246%: carbonyls, lactate dehydrogenase, metalloproteinase-9 (MMP-9), Ki67 and Cyclin D1 (CycD1). Threemarkers decrease by 16-29%: 8-oxoguanine DNA glycosylase, phosphorylated-Src and mammary serine protease inhibitor.

Cancer-related changes in salivary tumour markers may be used as a diagnostic tool for prognosis and post-operative monitoring in Figure 2, Figure3, Figure 4 [6]. Dry mouth (xerostomia) may cause a subjective complaint, difficulty with speech and swallowing dry foods, a burning sensation in the mouth, dental caries, oral candidiasis, and bacterial sialadenitis. Residual salivary tissue may be stimulatable by gustatory (sugar free chewing gum) or pharmacological (cholinergic agents) stimuli. Pilocarpine in doses of up to 5 mg three times daily can be effective. Patients with a dry mouth should avoid anything that further impairs salivation-such as drugs, tobacco, and alcohol.

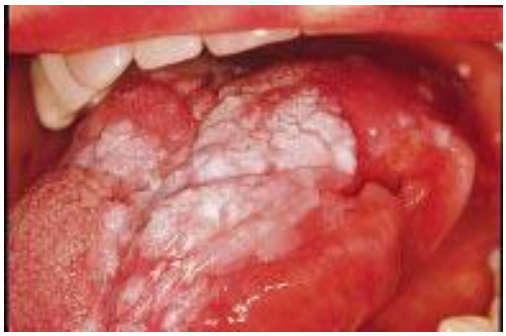

Figure 2: Carcinoma of tongue with associated white lesions.

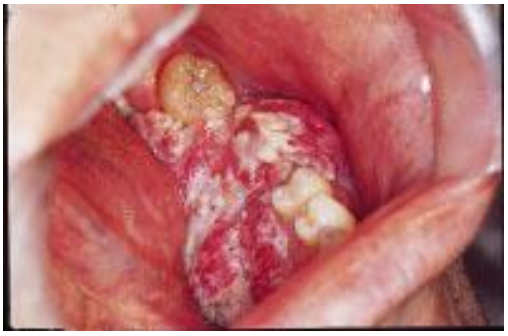

Figure 3: Carcinoma of gingiva.

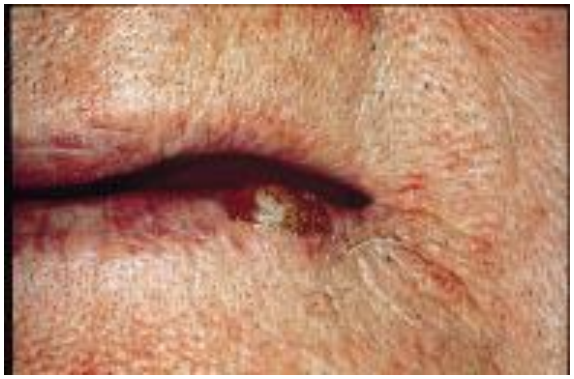

Figure 4: Carcinoma of lip.

Smoking, drinking and consumption of smokeless tobacoo, and genetic predisposition to oral cancer has been found [7]. The other diagnostic aid which is used is topical 1% toluidine blue, which binds selectively to dysplastic and malignant oral epithelial cells. Accordingly, toluidine blue can be used as a diagnostic aid for patients at risk from oral cancer as well as fordelineating biopsy sites. However, as toluidine blue is a suspected carcinogen, its repeated use for assessing 'high-risk' patients and premalignant lesions is associated with some risk. Whatever the screening method is used, a positive result must always be confirmed histologically by biopsy.

## Cancer and Genes Expression

Polymorphic variation of genes in the xenobiotic metabolism pathways may be implicated, such as in CYP1A1 or the genes coding for glutathione S-transferase-M115, 16 and N-acetyltransferase-2.17. Individuals that carry the fast-metabolizing alcohol dehydrogenase type 3 (ADH3) allele18 may be particularly vulnerable to the effects of chronic alcohol consumption and could be at increased risk to develop oral cancer. Early stage (I and II) oral cancer may be curable by surgery or radiation therapy alone but advanced cancers (stage III and IV) are generally treated by surgery followed by radiation therapy.

Oncogenes are genes that are able to increase malignant potential. Many of the major oncogenes that are implicated in other cancer types also contribute to oral cancer. A large number of these genes promote unscheduled, aberrant proliferation, prevent apoptosis and enable cellular survival under unfavorable conditions. Growth receptors are known to induce different cellular responses in response to the binding of specific ligands that represent external stimuli. The ErbB family of receptors and the epidermal growth factor receptor in particular has received attention due to its inherent ability to stimulate the proliferation of epithelial cells. Amplification of EGFR is found in a considerable percentage of oral tumors and also in pre-malignant lesions. Although several studies demonstrate the association between EGFR overexpression and tumor grade or stage, there are few studies that determine its practical clinical usefulness. Signal transduction from activated transmembrane receptors like EGFR depends on a variety of downstream mediators that are frequently altered in various cancer types. Indeed, constitutive activation of the K-ras protein in a mouse model is sufficient to induce oral tumor formation.

## Angiogenesis

The formation of new vessels from preexisting ones, is a crucial step in tumor growth, progression and metastasis. Regulation of angiogenesis in vivo is complex and controlled by a variety of factors. Among them, VEGF (vascular endothelial growth factor) is considered to play a dominant role. It has been well established that VEGF promotes the progression of OSCC by up-regulating MVD (microvessel density). Its enhanced expression in oral malignant tumors. Furthermore, VEGF-C expression has been reported to be a reliable predictor of regional lymph node metastasis in early OSCC. The expression of Flt-4, a member of the family of VEGF receptors, has also been correlated with lymph node metastasis, which agrees with its preferential expression in lymphatic endothelium.

## Matrix Metalloproteinases

Matrix metalloproteinases are zinc metalloenzymes with the ability to degrade components of the ECM (extracellular matrix). Their action is crucial during the progression of cancer since they allow the remodeling of the surrounding healthy tissues and enable local invasion. It has been demonstrated that gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10 and -11), collagenases (MMP-1 and -13) and membrane-bound MMPs (MT1-MMP) are expressed in OSCC and may play a role in its progress. MMP-3, 9, -10 and -13 and possibly MT1-MMP are expressed by the malignant cells, while MMP-2 and -11 are probably produced by stromal cells. The immunohistochemical expression of gelatinases (MMP-2 and -9) is related to the invasive potential of Oral Squamous cell carcinoma (OSCC). However, MMP-2 expression seems to be more prominent than MMP-9 in OSCC samples and correlates with lymph node metastasis. The association between the overexpression of MMP-2 and MMP-9 and alcohol consumption, leads the

researchers to hypothesize that the contribution of alcohol in the carcinogenetic process of OSCC may be attributed to the overexpression of these two enzymes.

GALNT2 enhances migration and invasion of oral squamous cell carcinoma (OSCC) by regulating EGFR glycosylation and activity [8]. The dominant cause of death including patients with oral tongue squamous cell carcinoma (TSCC) established that miR-138 suppresses TSCC cell migration and invasion by regulating 2 key genes in the Rho GTPase signaling pathway such as RhoC and ROCK2. Direct targeting of miR-138 to specific sequences located in the 3′-untranslated regions of both RhoC and ROCK2 mRNAs was confirmed using luciferase reporter gene assays. Ectopic transfection of miR-138 reduced the expression of both RhoC and ROCK2 in TSCC cells [9]. In summary, miR-138 is a multifunctional molecule regulator that controls a variety of biological processes. One of its major roles in cancer progression is the synchronization of cancer cell migration and invasion.

Cancer cells can move out of the primary tumor and invade proximal and distant tissues where they can form metastases, which are ultimately responsible for 90% of cancer-associated deaths. Considering that metastases are the major cause of death in cancer patients, new technologies for investigating cancer cell invasion play a central role in developing new therapeutic approaches for preventing or delaying the formation of metastasis, and extending the life of cancer patients. Proliferation, migration, adhesion, survival, invasion and vascularization are the initial steps in tumor metastasis. The cell migration is regulated by elements of the local microenvironment, including the extracellular matrix architecture [10].

## Cancer Treatment

In 2019, it has been be estimated that 18.1 million new cancer cases were found (17.0 million excluding non-melanoma skin cancer), and in 2018, 9.6 million cancer deaths (9.5 million, excluding non-melanoma skin cancer). In both sexes combined, lung cancer is the most commonly diagnosed cancer (11.6% of the total cases) and was the leading cause of cancer death (18.4% of the total cancer deaths), closely followed by female breast cancer (11.6%), prostate cancer (7.1%), colorectal cancer (9.2%), stomach cancer (8.2%), and liver cancer (8.2%). Among females, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death, followed by colorectal and lung cancer. Cervical cancer ranks fourth for both incidence and mortality. A large proportion of cancers can be prevented through measures including tobacco control, vaccination, early detection, and promotion of healthy lifestyles. In addition, the burden of suffering can be reduced through appropriate treatment and palliative care.

The proportion of patients with cancer in whom external beam radiotherapy is indicated according to the best available evidence was calculated to be 52%. The availability of recombinant lymphokines that provide large amounts of biologically active materials can hopefully lead to the development of effective new therapies for cancer in humans. Other new approaches to immunotherapy include the use of combinations of lymphokines, such as the use of tumor necrosis factor or alpha interferon in conjunction with IL-2. The selection of therapies is based on prognostic features (chemotherapy, radiotherapy), hormone receptor status (hormonal therapy) and HER-2 status. HER-2, p53 and BCL-2 are tumour-related proteins that have the potential to further improve individualization of patient management [12].

EGFRs are targets for cancer therapy. Several molecular predictors have been detected for identifying patients who would be most likely benefit from treatment with anti-EGFR drugs. However, most available clinical data are from retrospective studies and subgroup analyses. There is an urgent need to validate these observations in properly designed prospective studies. Another clinical issue is the need to determine the most effective sequences and combinations of EGFR inhibitors, used with chemotherapy, radiotherapy, or both, in order to optimize cytotoxicity potentiation [11]. Combining immunotherapy and targeted therapies [1], positive tumor response were obtained in selected patients.

Drugs such as the epidermal growth factor receptor (EGFR), BRAF, KIT, HER2 and anaplastic lymphoma kinase (ALK) were used successfully. Chromosomal instability and cytoskeletal defects were reported in oral cancer cells. Genetic instability can result from changes in chromosome structure, through errors in DNA metabolism, repair, recombination, or other rearrangements of the DNA sequence, or from misregulation of the cell cycle. Abnormalities in the chromosomal segregational apparatus are also likely to play an important role in genetic instability. These include centrosomal defects, defects in kinetochore-microtubule attachment, and movement of chromosomes relative to the poles.

It is likely that all of these changes contribute to carcinogenesis, the extent to which plays a part that is still largely uncharacterized. An additional observed defect was the untimely and unnatural division of the nuclear

mitotic apparatus protein NuMA at the centrosomes, apparently an early step in the splitting of the spindle poles. These observations support the conclusion that many of the cell-to-cell variations in chromosome structure and numbers in cancer cells result from (i) dicentric chromosomes forming anaphase bridges, which break and reform and (ii) specific structural defects in the spindle and chromosome segregational machinery.

Micronuclei are commonly observed in oral cancer cells and are an important biomarker for this disease. Gene amplification, chromosome fragmentation and loss, and segregational errors from separation of microtubule-organizing material were identified. In fact, it appears that all of the karyotypic changes seen in these cultures may be explained by the observed segregational defects. The extra poles could have only a minor influence on the metaphase alignment, pulling one or a few chromosomes from the main body of chromosomes or as major effects, splitting the chromosomes equally in four or more directions simultaneously [14].

## Conclusion

Oral cancers are a malignant neoplasia which arises on the lip, oral cavity and oropharynx**.** They represent the 6$^{th}$ most common cancer in the world. Oral cancer remains a lethal disease for over 50% of case diagnosed annually. Ninety per cent of cancers are originated from the squamous cells: they are named oral squamous cell carcinoma (OSCC). Cancer treatments implicate radiotherapy, surgery, targeted therapy, chemotherapy, immunotherapy, hormone and radiation therapies. Some of these therapies, but not all, induced spontaneous regression of cancer and/or declining mortality.

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