Review Article
Essentials of oral cancer

César Rivera

Department of Basic Biomedical Sciences, University of Talca (UTALCA) Talca, Maule Region, Chile; Department of Oral Diagnosis, School of Dentistry, State University of Campinas (UNICAMP) Piracicaba, São Paulo, Brazil; Mass Spectrometry Laboratory, Brazilian Biosciences National Laboratory (LNBio), National Center for Research in Energy and Materials (CNPEM) Campinas, São Paulo, Brazil

Received July 1, 2015; Accepted August 20, 2015; Epub September 1, 2015; Published September 15, 2015

Abstract: Oral cancer is one of the 10 most common cancers in the world, with a delayed clinical detection, poor prognosis, without specific biomarkers for the disease and expensive therapeutic alternatives. This review aims to present the fundamental aspects of this cancer, focused on squamous cell carcinoma of the oral cavity (OSCC), moving from its definition and epidemiological aspects, addressing the oral carcinogenesis, oral potentially malignant disorders, epithelial precursor lesions and experimental methods for its study, therapies and future challenges. Oral cancer is a preventable disease, risk factors and natural history is already being known, where biomedical sciences and dentistry in particular are likely to improve their poor clinical indicators.

Keywords: Mouth neoplasms, oral cancer, oral squamous cell carcinoma, carcinogenesis, neoplasm staging, tumor microenvironment

Introduction

Oral cancer is a highly relevant problem of global public health, especially for dental surgeons. It is located within the top 10 ranking incidence of cancers and despite the progress in research and therapy, survival has not improved significantly in the last years, representing a continuing challenge for biomedical science. This paper aimed to report key aspects of this cancer, integrating clinical, histological and molecular concepts for a better understanding of their biological pathways, allowing the reader and researcher construct a map which could serve to place and integrate this growing information.

Definition

Oral cancer is a malignant neoplasia which arises on the lip or oral cavity. Is traditionally defined as a squamous cell carcinoma (OSCC), because in the dental area, 90% of cancers are histologically originated in the squamous cells [1]. It has different levels of differentiation and a propensity for lymph node metastasis [2].

Epidemiology

Oral cancer is two to three times more prevalent in men than women in most ethnic groups [http://seer.cancer.gov/statfacts/html/oralcav.html]. In worldwide reports, cancers of all regions of the oral cavity and pharynx are grouped and collectively represent the sixth most common cancer in the world [3]. According to the latest reports of the International Agency for Research on Cancer (IARC) for oral cancer (ICD-10 code C00-08: Lip, Oral Cavity) which includes lips, tongue, gingiva, mouth floor, parotid and salival glands, annual incidence is higher around the world, which is over 300,000 diagnosed cases, and the annual mortality is about 145,000 death [http://globocan.iarc.fr/Pages/summary_table_pop_sel.aspx]. Table 1 shows the incidence and mortality for oral cancer according to the regions of the World Health Organization (WHO), and those that present the most critical numbers are WHO South-East Asia region (SEARO) and WHO Europe region (EURO). Specifically by area, those that are characterized by a high incidence of oral cancer are found in South and Southeast Asia (Sri Lanka, India,
Oral cancer

The incidence also varies according to the Human development index of the United Nations Development Programme (UNDP). According to this index, incidence is higher in countries with better development indicators (Table 1). The GLOBOCAN grouping shows that the crude rate and age-standardized incidence rate (worldwide) are higher in more developed regions, but mortality is higher in less developed areas, which shows social inequality.

Risk factors

Oral cancer is a preventable disease, where smoking and alcohol—considered major risk factors—are present in 90% of cases [4], having them both a synergic effect [5].

Tobacco

In 2007 the IARC concluded that “there is quite evidence to establish that snuff smoke is carcinogenic, and for example, it causes cancer of the oral cavity and pancreas” [6]. The risk for developing oral cancer is 3 times higher in smokers compared with nonsmokers [7]. Besides, the risk for oral cancer is 35% lower in people who quit smoking four years ago than those who continue smoking, and not higher in persons with no smoking antecedents for over 20 years when compared with people who have never smoked [8]. An environment with cigarette smoke is also risky; the risk for oral cancer is 87% higher in those who never smoked, but were exposed to an environment with cigarette smoke (involuntary smoking) compared with those who never smoked and not have been exposed [9]. Cigarette smoke weakens immunity in the oral cavity by promoting gingivi-

| Table 1. GLOBOCAN cancer incidence and mortality, all ages, both sexes by population |
|---------------------------------|-----------------|-------------|-------------|-------------------|
| Population                      | Incidence       | Mortality   |
|                                 | Numbers         | Crude rate  | ASR (W)     | Accumulative risk |
| WHO African Region (AFRO)       | 13,484          | 1.5         | 2.7         | 0.30              |
| WHO Americas Region (PAHO)      | 49,200          | 5.2         | 4.1         | 0.48              |
| WHO East Mediterranean Region (EMRO) | 20,681    | 3.3         | 4.6         | 0.52              |
| WHO Europe Region (EURO)        | 65,933          | 7.3         | 4.6         | 0.53              |
| WHO South-East Asia Region (SEARO) | 103,464 | 5.6         | 6.4         | 0.73              |
| WHO Western Pacific Region (WPRO) | 47,524    | 2.6         | 2.0         | 0.22              |
| UNDP Very High Human Development | 92,338          | 8.0         | 4.8         | 0.54              |
| UNDP Low Human Development      | 40,954          | 3.1         | 5.2         | 0.59              |
| GLOBOCAN More Developed Regions* | 100,823         | 8.1         | 4.7         | 0.54              |
| GLOBOCAN Less Developed Regions* | 199,550         | 3.4         | 3.7         | 0.42              |

WHO, World Health Organization; UNDP, United Nations Development Programme; GLOBOCAN Global Burden of Cancer Study 2012. *The designation for more developed and less developed regions are intended for statistical convenience and do not necessarily express a judgment about the stage reached by a particular country or area in the development process. More developed regions: all regions of Europe plus Northern America, Australia/New Zealand and Japan. Less developed regions: all regions of Africa, Asia (excluding Japan), Latin America and the Caribbean, Melanesia, Micronesia and Polynesia. ASR (W), World age-specific rates.
tis, periodontitis and oral cancer [10]. This smoke contains several elements that promote cancer and they basically can be grouped into three distinct groups: nitrosamines, benzopyrenes and aromatic amines. These chemicals are called pre-carcinogens, which must suffer coordinated alterations by oxidative enzymes, so that the final product becomes poor in electrons and into an agent to be covalently bound to the DNA, generating an adduct mutated region [11]. In addition to oxidation, enzymatic or non-enzymatic metabolism can also produce carcinogens, such as free radicals, which have unpaired electrons that make them extremely reactive being capable of promoting mutations by complex mechanisms [11]. Snuff consumption expose the oral epithelium to free radicals of oxygen and nitrogen that can affect antioxidant defense mechanisms. Elevated levels of these free radicals are found in oral precancer and cancer [12].

Alcohol

Alcohol (ethanol) can act as a both locally and systemically risk factor: increased permeability of oral mucosa, dissolving lipids components of the epithelium, causing epithelial atrophy and interference in DNA synthesis and repair; it also has genotoxicity and mutagenic effects, causing decreased salivary flow, affects the liver's ability to deal with toxic or potentially carcinogenic compounds, and their chronic use is associated with an impairment of innate and acquired immunity, resulting in increased susceptibility to infections and neoplasms [13].

Other factors

Among other risk factors, there is the human papillomavirus (mainly associated with carcinoma of the oropharynx [14]) and ultraviolet radiation (UV). The IARC classifies human papillomavirus 16 (HPV16) as a cause for cancers of
Oral cancer

Table 2. TNM Definitions for Oral Cancer*

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4a</th>
<th>T4b</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Cannot be assessed</td>
<td>Tumor 2 cm or less in greatest dimension</td>
<td>Tumor more than 2 cm but not more than 4 cm in greatest dimension</td>
<td>Tumor more than 4 cm in greatest dimension</td>
<td>Moderately advanced local disease. Lip: Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (chin or nose). Oral cavity: Tumor invades through cortical bone, into deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face.</td>
<td>Very advanced local disease. Lip and oral cavity: Tumor invades masticator space, pterygoid plates, or skull base; or encases internal carotid artery</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ (CIS)</td>
<td>Tumor 2 cm or less in greatest dimension</td>
<td>Tumor more than 2 cm but not more than 4 cm in greatest dimension</td>
<td>Tumor more than 4 cm in greatest dimension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2 cm or less in greatest dimension</td>
<td>Tumor more than 2 cm but not more than 4 cm in greatest dimension</td>
<td>Tumor more than 4 cm in greatest dimension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 2 cm but not more than 4 cm in greatest dimension</td>
<td>Tumor more than 4 cm in greatest dimension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumor more than 4 cm in greatest dimension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Regional lymph nodes (N)

<table>
<thead>
<tr>
<th>N0</th>
<th>No regional lymph node metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis as specified in N2a, 2b, 2c (see below)</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node more than 6 cm in greatest dimension</td>
</tr>
</tbody>
</table>

Distant metastasis (M)

<table>
<thead>
<tr>
<th>M0</th>
<th>No distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
</tbody>
</table>

Clinical stages (T+N+M)

<table>
<thead>
<tr>
<th>O</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3 (enough alone), T2 or T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IV A</td>
<td>T4a</td>
<td>N0 or N1</td>
<td>M0</td>
</tr>
<tr>
<td>IV B</td>
<td>any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>IV C</td>
<td>any T</td>
<td>any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

*Modified of IARC (International agency for research on cancer) screening group (http://screening.iarc.fr/atlasoralclassiftnm.php)

the oral cavity and pharyngeal tonsils, and HPV18 as possible causes of oral cancer [http://monographs.iarc.fr/ENG/Classification/index.php]). The most-common sites of HPV-related head and neck squamous cell carcinoma (HNSCC) are the tonsils and base of tongue within the oropharynx, with a prevalence rate of 75%; HPV-related HNSCC is rare in nonoropharyngeal sites. The presence of HPV is an established prognostic biomarker of favourable outcome in locally advanced oropharyngeal cancers [15]. Evidence shows that HPV contributes to carcinogenesis by two virus-encoded proteins: E6 protein promotes the degradation of p53 tumor suppressor gene product; E7 that promotes the degradation of the tumor suppressor gene pRb (retinoblastoma protein) [16], causing a deregulation of the cell cycle control, which also leads to an overexpression of the inhibitor of cyclin dependent kinase p16\[^{\text{INK4a}}\] [14]. Ultraviolet radiation, mainly the UVB is also involved in lip cancer.
Clearly the OSCC develops over many years and during this period there are several neoplastic sites transforming and taking place in the oral cavity [17]. Oral carcinogenesis (Figure 1) is a highly complex multifactorial process that occurs when epithelial cells are affected by various genetic alterations [18], including key disorders on TP53, NOTCH1 (Notch homolog 1, EGFR (epidermal growth factor receptor), CDKN2A (cyclin-dependent kinase inhibitor 2a), STAT3 (signal transducer and activator of transcription 3), Cyclin D1, Rb (retinoblastoma) [19]. Probably oral carcinogenesis starts with the transformation of a limited number of normal keratinocytes. This transformation can be expressed via cytogenetic changes and epigenetic processes that modify the progression of the cell cycle, DNA repair mechanisms, cell differentiation and apoptosis, which may be caused by random mutation, by exposure to a variety of biological factors, carcinogens or errors in the DNA repair process [20], resulting in an unstable keratinocyte into a pre-cancerization field and leading to malignant neoplastic changes [20], which can inherit these alterations to their clones. Subsequently, selection pressures on the microenvironment of the oral mucosa may act on the heterogeneous clonal population, allowing perpetuate those cells with better tools and advantages of adaptability, survival and proliferation above their normal neighboring cells [20, 21]. Tumorigenesis requires multiple essential elements: a limitless replicative potential, self-sufficiency in growth signals, lack of sensitivity to anti-growth signals, the ability to evade apoptosis, increased angiogenesis, invasion and metastasis [22]. Recent evidence supports that the biophysical and biochemical signs of tumor-associated into the extracellular matrix influence the essential characteristics of cancer and therefore are essential for malignancy [23].

**Tumor microenvironment (TME)**

For an effective approach to cancer, it should be considered as a disease that involves complex interactions among a community of heterotypic cells, characterized by the original cancerous tissue, the newly formed tissue and cells surrounding it [24]. The TME of OSCC include cancer-associated fibroblasts (CAFs), immune cells and other supporting cells (Figure 1). Oncogenic changes in gene expression profiles contribute to microenvironmental alterations such as ROS accumulation, overproduction of cytokines and epithelial mesenchymal transition (EMT). CAFs are some of the most critical elements of TME, contributing to proliferation, invasion and metastasis. The adaptive immune response is suppressed in OSCC through overexpression of cytokines, induced...
Oral cancer

Table 3. Some cellular lines for the study of OSCC

<table>
<thead>
<tr>
<th>Line</th>
<th>Clinical features</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC4</td>
<td>Tongue</td>
<td>55 M T3N0M0 From a patient who had radiation and methotrexate treatment for the tumor for 16 months before the biopsy was taken for culture. Epithelial cell morphology: weak colonies.</td>
</tr>
<tr>
<td>SCC9</td>
<td>Tongue</td>
<td>25 M T2N1 The patient who developed this line did not had treatment before the biopsy was taken (NRT). Compared to SCC25, SCC4 y CAL27, this line show a higher resistance to cisplatine. Epithelial cell morphology: weak colonies.</td>
</tr>
<tr>
<td>SCC15</td>
<td>Tongue</td>
<td>55 M T4N1M0 NRT. Epithelial cell morphology: tight colonies.</td>
</tr>
<tr>
<td>SCC25</td>
<td>Tongue</td>
<td>70 M T1N1M0 NRT. Compared with SCC15, this line has a higher invasive potential. Epithelial cell morphology: tight colonies.</td>
</tr>
<tr>
<td>CAL27</td>
<td>Tongue</td>
<td>56 M - NRT, isolated from patient with PD-OSCC.</td>
</tr>
<tr>
<td>BHY</td>
<td>Alveolus</td>
<td>52 M - Isolated from a patient with WD-OSCC of the lower alveolus, highly invasive to the mandibular bone and the muscle layer of the oral floor; however, it did not metastasize.</td>
</tr>
<tr>
<td>HN</td>
<td>Soft palate</td>
<td>60 M - Isolated from a patient with MD-OSCC of the soft palate that metastasized to cervical lymph nodes, lungs, and brain, but did not invade bone.</td>
</tr>
<tr>
<td>HSC-3</td>
<td>Lymph node</td>
<td>64 M - Obtained from Japan Health Science Research Resources Bank (Tokyo, Japan). The primary tumor was on the tongue with lymph node metastasis, and was MD-OSCC.</td>
</tr>
<tr>
<td></td>
<td>metastasis</td>
<td></td>
</tr>
<tr>
<td>HaCaT</td>
<td>Skin</td>
<td>- - - Human adult low calcium high temperature cells (HaCaT), are spontaneously transformed aneuploid immortal keratinocyte cell line from adult human skin that have the characteristics of basal epidermal keratinocites. This cell line currently used as a non-tumorigenic control.</td>
</tr>
</tbody>
</table>

OSCC, oral squamous cell carcinoma; T, primary tumor; N, regional lymph nodes metastasis; M, distant metastasis, NRT, patient did not receive treatment before the biopsy; WD, well differentiated, MD, moderately differentiated; PD, poorly or undifferentiated.

Table 4. Oral cancer key points

Conceptual framework

It is a preventable disease.
The most important risk factors are snuff and alcohol (chronic exposure), they have a synergistic effect.
Has higher occurrence in people over 50 years.
The genetic instability in keratinocytes allows tumor development.
The erythroplasia and leukoplakia disorders are usually related to oral cancer.
It occurs most frequently on the tongue, floor of the mouth and lower lip.
The diagnosis is confirmed by biopsy and histopathological analysis.
Is diagnosed in advanced clinical stages.
Treatment options include surgery, radiotherapy and chemotherapy.
Until today there are no specific biomarkers.
Population screening reduces mortality.

apoptosis by T cells and modifications in antigen processing machinery [25]. The overexpression of cytokines assessments such as transforming growth factor-β (TGF-β), contribute to the EMT, immunosuppression, and the evolution of the CAFs. Inflammation and hypoxia are the dynamic forces of angiogenesis and altered metabolism [26]. OSCC uses the glycolytic and oxidative metabolism to feed tumor genesis through mechanisms which are coupled between regions of cancer cell (parenchyma) and TME cells (stroma) [19].

Some markers for elements in OSCC tumor microenvironment are shown in Figure 1, including E-cadherin, cytokeratin, PD-L1, FasL
Oral cancer

(OSCC); CD33, CD144, ALDH (cancer stem cells markers); N-cadherin, vimentin (EMT); α-SMA, integrin α6 (CAFs); CD4+CD25+FoxP3+ (T regulatory cells); CD8+, TCR, Fas, PD-1 (cytotoxic T cells), CD4+ (cytotoxic Th2 cells) and CD34+ (myeloid precursor cells) [19].

Potentially malignant disorders and dysplastic changes

The OSCC can be presented as a “natural history”, which originates from non-aberrant keratinocytes which are chronically exposed to a stimulus that breaks its homeostasis, following an epithelial hyperplasia, dysplasia in different degrees, carcinoma in situ (CIS) and an invasive carcinoma leading to the generation of distant metastases [17], with the consequent clinical manifestations. This natural history offers a map for the different research approaches in both basic science, translational and clinical-therapeutic environment.

The first detectable clinical changes that can advise of an epithelium on its way to establishing an OSCC are potentially the occurrence of malignant disorders, including leukoplakia and erythroplasia which are the most common ones [27]. Leukoplakia is a white plate uncertain risk, by excluding other diseases or disorders which are already known to not increase the risk for cancer [28]. Microscopically expensive exhibits several reactive epithelial changes such as hyperplasia, hyperkeratosis and acanthosis. Histologically, a distinction is essential to be made between dysplastic and non-dysplastic leukoplakia. The term refers to epithelial dysplasia precursor lesions showing cytology combinations and degrees of atypia (in example, hyperchromatism, increased nuclear size, pleomorphism, dyskeratosis, abnormal mitotic figures or increased mitosis). When alterations occurs in the basal or parabasal keratinocytes, which is called mild dysplasia, the atypia found in the middle level is called moderate dysplasia; when changes are extended to the surface layer, the terms advanced dysplasia and carcinoma are applied in situ (atypia is complete, from the base to the surface) [16]. About 1% may progress to malignant transformation [27]. Besides white plates, there are red ones. Erythroplasia (high malignant potential) is defined as a red plate that cannot be characterized clinically or pathologically as other disease [27]. If a mixture of red and white change occurs, the lesions are called erythroleukopla-kia. Erythroplakias commonly shows some degree of presence of dysplasia and carcinoma. In general, it should be treated because their high-risk malignant transformation [27].

In general, if a lesion in the oral mucosa does not heal within three weeks, a malignant tumor or some other serious condition should be excluded, indicating a biopsy and its histopathological analysis [29].

Classification of tumors: WHO and gene-expression profile

The OSCC derived from an epithelial dysplasia and is characterized by a neoplastic proliferation mechanism which destroys oncogenic sub-epithelial basement membrane locally [24]. The ability to metastasize is directly associated with the degree of tumor differentiation of the cancer cells [24]. The International Classification of Tumors of the WHO ranks well differentiated tumors, moderately differentiated and poorly or undifferentiated [30]. Another frequently studied histological feature is the front pattern of invasion (degree of cohesion between invading cancer cells), which is measured as a good prognostic factor in OSCC [4]. WHO classification is essentially histological and extremely limited. Since cancer is a complex disease characterized by genetic heterogeneity, HNSCCs (including OSCC) can also be classified based on their gene-expression profile as “basal”, “mesenchymal”, “atypical” and “classical”. The atypical subtype included most of the HPV-positive HNSCCs [15]. These subtypes-added to HPV infection status-have been validated using independent datasets in The Genome Cancer Atlas (TGCA) reports [31]. The TCGA study represents the most comprehensive integrative genomic analysis of HNSCCs.

Staging of oral cancer

The most common sites for the presentation of oral cancer are the tongue (ventral-lateral edge, 40% of cases), floor of the mouth (30% of cases) and lower lip [16, 32, 33]. Regardless of the accessibility of the oral cavity during clinical examination, oral cancer is usually diagnosed in advanced stages. The most common reasons for this are the initial misdiagnosis and ignorance of the patient or the treating professional [34], which evidently decreases the
chances of survival, despite therapeutic strategies [24].

In the clinical-therapeutic field, most models take part in center their base decisions on clinical and pathological information along with the health of the patient [24]. In OSCC, as in most other cancers, the prognosis depends largely on factors which are more related to lifestyle such as smoking, alcohol consumption, medical comorbidity and undeniably the step (staging) of tumor [35].

The TNM staging system (tumor-lymph node-metastasis) is based on the best estimate of the extent of disease before treatment (Table 2). Assessment of the primary tumor is based on inspection and palpation, where the proper nodal drainage areas are examined by careful palpation and also imaging studies can help in metastases [http://www.cancer.gov/cancer-topics/pdq/treatment/lip-and-oral-cavity/HealthProfessional/page3]. But so far, the data delivered by the conventional TNM is insufficient to predict the response to nonsurgical treatment, which keeps the door permanently open to molecular studies in order to search for biomarkers. Information obtained from clinical examination and imaging are used to assign a clinical stage (cTNM), which is then used to stratify patients (clinical stage) for selection of therapeutic and report the results of treatment alternatives. The differentiation between localized disease (stages I and II) of advanced disease (III and IV) is essential [24]. If the patient undergoes through surgical resection, its pathologic stage (pTNM) derived from tumor histopathology and/or regional lymph nodes, is useful in the selection of postoperative adjuvant therapy and in order to estimate the prognosis [35].

**Biomarkers**

Until today, there is no specific biomarkers for oral cancer. But latest studies show that elevated levels of interleukin-8 and SAT can categorize between patients with OSCC and healthy patients, with high sensitivity and specificity [36]. Predicting the malignant transformation of dysplasia also shown promising results. Recent evidence shows that a loss-of-heterozygosity (LOH) status of chromosomes 3p and 9p is a predictive spin, high-risk lesions (3p & 9p LOH) had a 20-fold increase OSCC risk compared to low-risk lesions (3p & 9p retention) [37]. Although there are no biomarkers, neoplastic progression allows windows to finding them (Figure 2, modified from [38]).

**Experimental studies for oral cancer**

In addition to traditional clinical studies and descriptive studies of samples, assumptions that are related to oral cancer can be tested from cell lines which are originally isolated from patients with carcinoma and also from animal models of chemical carcinogenesis and transgenic animals. Table 3 shows some of the cell lines most commonly used for the experimental study of OSCC with an allusion to their origin and biological behavior (see references for more information: SCCs 4, 9, 15 and 25 [39-43]; CAL27 [44]; BHY, HN and HSC-3 [45], Hacat [46]). Genetic manipulation of cells allows silencing and overexpression of certain products, which can also be brought in vitro or in vivo (animal models). Chemical carcinogenesis is useful to study the progressive changes that occurs throughout oral carcinogenesis from normal tissues, through dysplastic changes until the invasive carcinoma [47]. The most frequently used chemicals are the 9,10-dimethyl-1,2-benzanthracene (DMBA) and 4-nitroquinoline-1 oxide (4NQO). DMBA is highly irritating and it has some limitations for the study of OSCC (it produces inflammatory response and necrosis of granulation tissue appearance) [48]. 4NQO form adducts which are similar to those induced by carcinogens containing snuff, and is more effective in inducing carcinogenesis and it causes extensive inflammation when compared with DMBA [48, 49]. Genetic approaches are particularly useful for studying the basics of oral cancer in its different stages and new therapeutic methods in a large number of animals by generating transgenic animals [50].

**Management**

The prognosis for patients with OSCC still remains poor, despite therapeutic advances in this and many other malignancies. Early diagnosis and treatment remains to be the key to improving survival of patients [51].

**Therapeutic alternatives**

Among the approaches to the treatment of OSCC such as surgery, radiation therapy (exter-
nal beam radiotherapy and/or brachytherapy, and coadjuvant therapy (chemotherapy with agents such as cisplatin, carboplatin, 5-fluorouracil, paclitaxel and docetaxel) is included [16, 52], it still remains as a high economic cost and highly damaging treatment/alternatives [53].

The OSCC is typically treated by one or a combination of these alternatives. The choice of one or the other depends not only on the location, size and stage of the primary tumor; it is also subjected to the comorbidities presented by the patient, nutritional status, its ability to tolerate treatment and the patient's wishes to face therapy [54]. In resectable tumors, surgery is superior to all alternative therapies [53, 55]. Approximately one third of patients with OSCC are diagnosed in stage I/II disease. The local/regional therapy includes surgery, radiotherapy or a combination of both. A good prognosis for these patients, with cure rates of 80% (stage I) and 65% (stage II) is expected [56]. Unfortunately most of OSCC cases are diagnosed in advanced stages of disease (III or IV) [57], with survival at 5 years less than 50% [58] and a cure of 30% [55, 56]. Patients with metastatic disease, which are untreated show a survival of about 4 months [57].

Oral cancer causes substantial damage in speech, swallowing and chewing function, where pain is the main symptom. Among the causes of the onset or exacerbation of pain there are mediators in the tumor microenvironment, lack of palliative therapy, a dense trigeminal innervation and continuous oral function, and pain due to treatment and opioid tolerance [58].

Prevention and future challenges

There is now sufficient understanding of the causes to prevent a third of all cancers in the world and it has sufficient information to enable early detection and well-timed treatment of another third of cases [59], where the OSCC counterenances this opportunity. For oral cancer there is evidence that the visual examination as part of a population screening program reduces mortality in patients at high risk [60], it is also possible to change lifestyles and impose barriers to the triggering factors. Education to the general population and for those with particular risk, a good theoretical basis to meet key aspects of oral cancer (Table 4) plus the constant updating in oral pathology healthcare providers, should be significant to decrease the red numbers that have accompanied this disease in recent decades. The search for specific biomarkers for the disease should not be abandoned, and future research should enable progress toward defining the susceptibility field (etiological factors and their interaction) [53], in order to put a stop to the story that begins with genetic instability keratinocytes.

Disclosure of conflict of interest

None.

Address correspondence to: César Rivera, Department of Basic Biomedical Sciences, Faculty of Health Sciences, University of Talca, Avenida Lircay S/N, Maule Region, Talca, ZIP 3460000, Chile. ORCID: 0000-0002-5491-4233; E-mail: contacto@cesar Rivera.cl

References

Oral cancer


Oral cancer