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Overview of Oral Cancer

Kalu U. E. Ogbureke[1,*] and Christopher Bingham[2]
*[1]Department of Oral Biology, College of Dental Medicine,
Georgia Health Sciences University, Augusta, Georgia,
[2]Department of Periodontology, College of Dental Medicine,
Georgia Health Sciences University, Augusta, Georgia,
USA*

1. Introduction

Cancer is the second most common cause of death in the Western world, after cardiovascular diseases (Johnson, 1991; 2001). Worldwide, an estimated cancer incidence of about 10 million was reported for the year 2009 (Jemal et al., 2010), and 1 out of every 3 persons is estimated to suffer from cancer by the age of 75 years (Johnson, 1991; 2001). It is also estimated that about 7.9 million people world-wide will die from cancer this year (Jemal et al., 2010), accounting for nearly 12% of deaths worldwide (Jemal et al., 2010). In the United States alone, an estimated 569,490 deaths from cancer are projected for the 2010 (Jemal et al., 2010). Recent published estimates of worldwide frequency of the 16 major cancers indicate that in developing countries with a high prevalence of infectious and nutritional diseases, cancer remains a major cause of death (Parkin, Laara and Muir, 1988). This may account partly for the current statistics whereby more than half the global incidence of cancer is from the so-called developing countries, since an estimated 70-80% of the global population resides in these areas (Parkin et al., 1998). The estimated annual incidence of cancer ranges from 48 to 225 per 100,000 in developing countries (Parkin et al., 1998).

2. Oral cancer – Epidemiologic overview

"Oral cancer" encompasses all malignancies originating in the oral cavity. Oral cancer ranks sixth in the overall incidence for the 10 most common cancer sites worldwide and third in the developing countries (Johnson, 2001)). There is also a marked disparity in geographic incidence between the "high" and "low" prevalence areas of the world, suggesting major geographic differences in risk factors (Johnson, 1991; 2001). Most of these factors have been identified through epidemiologic studies.

For statistical purposes, oral cancer is often grouped together with cancers of the pharynx as "oropharyngeal" cancer (Daftary et al., 1992). In the Western world, oral cancer is relatively uncommon, and in the context of all malignant tumors, incidence in the United States and Great Britain ranges from 2 to 3% (Batsakis, 1979; Jemal et al., 2008). Relative incidence of

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[*] Corresponding Author

up to 5% however has been reported for the United States (Batsakis, 1979), and higher rates have been reported for the so-called "high risk" areas of Europe with incidence equally varying with different socioeconomic groups within these areas (Johnson, 1991). Worldwide, it is estimated that about 300,000 people will be diagnosed with oral cancer in 2010 (Jemal et al., 2010). Of these, 126,000 will die from the disease (Jemal et al., 2010). In the United States alone, an estimated 35,000 new cases of oral cancer will be diagnosed in 2009 with an estimated 7,500 resultant deaths (Jemal et al. 2008). In the Asian subcontinent of Bangladesh, India, Pakistan, and Sri Lanka, oral cancer is the most common malignancy, accounting for about one-third of all malignancies within the subcontinent (Daftary et al., 1991; Jonson, 2001). About 100,000 new cases are estimated to occur annually in these regions that include Burma, Cambodia, Malaysia, Nepal, Singapore, Thailand, and Vietnam (Daftary et al., 1991).

The paradox in the foregoing gloomy statistics is that, although the oral cavity and oropharynx are easily accessible to dentist and physicians for routine examinations and the biopsy of suspicious lesions that often present with outstanding features, early diagnosis has been painfully slow when compared with the enhanced early detection of breast, colon, prostate cancers, and melanoma (Mashberg A, 2000). As a result, the mortality rate from oral cancer for the past three and a half decades has remained high (over 50%) in spite of new treatment modalities. In contrast, there has been a considerable decrease in mortality rates for cancers of the breast, colon, prostate, and melanoma during the same period (Mashberg A, 2000). Examination of the colonic mucosa, which requires endoscopic examination for evaluation of colon cancer, reveals 36% of localized colon cancers among the United States population (Mashberg A, 2000). An identical percentage of localized oral/oropharyngeal cancers are diagnosed without endoscopy among the same population (Mashberg A, 2000). This paradox was eloquently summed up in a four decades-old publication highlighting ". . . the poor prognosis of a form of cancer, which presents exceptionally good opportunity for early treatment" (Banoczy and Csiba, 1976; Wright 1994).

The impediment to early diagnosis of oral and oropharyngeal cancers, despite increased assiduousness on the part of dentists and oral physicians in their examination of patients at risk, stems from the persistence of archaic paradigms, and the lack of an easily available diagnostic adjunct. In order to increase the early detection of oral cancers, and by so doing increase the survival rates of oral cancer patients, there is therefore the need to identify diagnostic screening modalities that identify early oral malignant lesions with precision.

About 95% of oral cancers are classified histologically as oral squamous cell carcinoma (OSCC; Mashberg, 2000; Johnson, 2001, Sargeran et al., 2008). The remaining 5% include such histologic variants as oral verrucous carcinoma, adenosquamous carcinoma, adenoid squamous cell carcinoma, mucoepidermoid carcinoma, and basaloid squamous cell carcinoma. Mucoepidermoid carcinomas are malignancies of salivary gland origin and, within the oral cavity, arise from minor salivary glands, while adenosquamous carcinomas are currently believed to arise from the oral mucosa with subsequent glandular changes among the tumor cells. Basaloid squamous cell carcinoma, a relatively newly recognized entity, is a rare histologic variant of OSCC with marked predilection for the base of tongue in addition to the supraglottic larynx and hypopharynx. Often included in the remainders are metastatic carcinomas from regional sites distant to the oral cavity.

3. Etiologic risk factors for oral cancer

Oral cancer is a multifactorial disease. Exposure to one of three broad groups of carcinogenic stimuli, namely, chemical, physical, and viral, is known to induce cancer in genetically and systemically conditioned oral mucosa. Within the oral cavity, it appears that carcinomas are caused predominantly by chemical carcinogens, although evidence implicating viral and physical stimuli in the development of some oral cancers continues to mount (Syrjanen, 2005; Reddout et al., 2007). The pathogenesis of oral cancer is equally complex, and exposure to carcinogens does not inevitably result in the development of oral cancer. This is because a number of familial, dietary, hormonal, and sex-related factors are known to modulate neoplastic processes generally. Tobacco and alcohol have emerged as the most important culprits contributing to the etiology of oral cancers. Other factors frequently cited are ultraviolet light, nutritional and dietary factors, precancerous lesions, immunosuppression, genetic, and dental factors.

3.1 Tobacco and tobacco products

An association between the use of tobacco and oral cancer can be traced to the early 18th century, when lip cancer was observed with some frequency in tobacco users (Sawyer and Wood, 1992). The strong association of cancers of the oral cavity and oropharynx with tobacco use is well established (Johnson, 2001). Epidemiological studies show that the risk of developing oral cancer is five to nine times greater for smokers than for nonsmokers, and this risk may increase to as much as 17 times for heavy smokers of 80 or more cigarettes per day (Neville and Day, 2002). Approximately 80 percent of oral cancer patients are smokers, and this is two to three times greater than that of the general population (Silverman and Griffith, 1972; Blot et al., 1988; Mashberg et al., 1993; Jovanovic et al., 1993; Andre et al., 1995, Lewin et al., 1998). In addition, treated oral cancer patients who continue to smoke have a two- to six- times greater risk of developing a second malignancy of the upper aerodigestive tract than those who stop smoking (Silverman and Griffith, 1972; Silverman and Shillitoes, 1998).

Oral smokeless tobacco (snuff and chewing tobacco) have also been associated with an increased risk for oral cancer (Brown et al., 1965). In one study of women in the southern United States, chronic users of snuff were estimated to have a four times greater risk of developing oral cancer (Winn et al., 1981, Johnson, 2001). In addition, a significant number of oral cancers in smokeless tobacco users develop at the site of tobacco placement. However, the use of smokeless tobacco appears to be associated with a much lower cancer risk than that associated with smoked tobacco. For example, although the state of West Virginia has the highest consumption of chewing tobacco in the United States, the incidence of oral cancer in West Virginia is below the U.S. national average (Bouquot and Meckestroth, 1998). Recent studies from Scandinavia have suggested that the use of Swedish snuff (which is nonfermented and has lower nitrosamine levels) is not associated with an increased risk for oral cancer (Johnson, 2001; Neville, 2002).

The habit of oral smokeless tobacco use is evolving as "fashionable" amongst the youth in many Western countries, and may partly account for spikes in the rate of oral cancers and potentially malignant lesions observed in this age group in recent decades (Johnson, 1991). The importance of teenage use of smokeless tobacco lies in the considerable length of time

that the oral mucosa of teenagers indulging in this habit are bathed in high concentrations of numerous carcinogens contained in smokeless tobacco (Sawyer and Wood, 1992). In addition to carcinogens usually associated with smoking, smokeless tobacco contains ^{210}polonium (originating from phosphate fertilizers used to grow tobacco), ^{226}radium, and ^{210}lead (Main and Lacavalier, 1988). Furthermore, tobacco-specific nitrosamines present in smokeless tobacco, and readily extracted in saliva and further enhanced in alkaline environments, often are of higher concentrations than in cigarette smoke (Sawyer and Wood, 1992).

In India and Southeast Asia, the chronic use of betel quid (*paan*) in the mouth has been strongly associated with an increased risk for oral cancer (Murti et al., 1985; Murti et al., 1995). The quid typically consists of a betel leaf that is wrapped around a mixture of areca nut and slaked lime, usually with tobacco and sometimes with sweeteners and condiments. The slaked lime results in the release of an alkaloid from the areca nut, which produces a feeling of euphoria and well-being in the user. Betel quid chewing often results in a progressive, scarring precancerous condition of the mouth known as oral submucous fibrosis. In India, one study showed a malignant transformation rate of 7.6 percent for oral submucous fibrosis (Murti et al., 1985).

Marijuana use is also considered to be a potential risk factor and may be partly responsible for the rise in oral cancers seen among young adults (Zhang et al., 1999; Silverman, 2001; Schantz and Yu, 2002). Marijuana smoke contains known carcinogens such as benzopyrene and benzanthracene (aromatic hydrocarbons), and the concentration of these carcinogens is postulated to be considerably higher than that in cigarette smoke (Sawyer and wood, 1992). However, further epidemiological studies are necessary to confirm the purported association of marijuana and oral cancer, particularly in younger patients.

3.2 Alcohol

The relationship between alcohol, particularly hard liquor, and squamous cell carcinoma has been recognized for a long time (Wynder, 1971), and has been identified as a major risk factor for cancers of the upper aerodigestive tract (Neville and Day, 2002). What presented as a significant challenge, until recently, was the assessment of the independent role of alcohol in oral cancers due to the difficulty in separating the effects of heavy alcohol consumption from those of smoking and other risk factors, including nutritional (Kato and Nomura, 1994). Most heavy consumers of alcohol beverages also are heavy smokers.

In studies controlled for smoking, moderate-to-heavy drinkers have been shown to have a three- to nine- times greater risk of developing oral cancer (Blot et al., 1988; Mashberg et al., 1993; Jovanovic et al., 1993; Andre et al., 1995; Lewin et al., 1998). One study from France showed that heavy drinkers, consuming more than 100 grams of alcohol per day (a typical serving of beer, wine, or liquor approximates 10 to 15 grams of alcohol), had a 30 times greater risk of developing oral and oropharyngeal cancer (Andre et al., 1995). Thus, it would appear that smoking is not a necessary prerequisite for alcohol induced cancers. Of greater significance however is the synergistic effect of alcohol and smoking; some subsets of patients who are both heavy smokers and heavy drinkers can have over one hundred times greater risk for developing a malignancy (Blot et al., 1988; Andre et al., 1995).

While the mechanism of alcohol-induced carcinogenesis remains unclear, it is apparent that alcohol acts primarily as a co-carcinogen or promoter. Carcinogenesis also may be related to nutritional deficiencies associated with alcoholism. Systemically, alcohol may lead to impaired absorption of nutrients and vitamins. It has been suggested that alcohol acts as a solvent facilitating the entry of carcinogens into exposed cells (Sawyer and Wood, 1992). In addition to creating a nutritional deficiency state (Harris et al., 1997; Johnson, 2001), alcohol may alter epithelial cell metabolism, or suppress immunity (Cotran, Kumar and Robbins, 1989). There is some evidence that carcinogenic contaminants rather than ethanol may be responsible for the increased incidence of alcohol-associated cancers (Bennie, 1976).

3.3 Human Papilloma Viruses (HPV)

The role of HPV as an etiologic agent in cancer was first recognized in the uterine cervix (where it is present in about 99.7% of cases), and the prognostic significance of HPV-associated cervical cancer is now well established (Clifford, Boyle and Franceschi S, 2003; Reddout, 2007). HPV-16 and -18 are the major high-risk types and predominate in invasive anogenital cancers (Clifford et al., 2003; Reddout, 2007). On the other hand there is as yet no clear evidence to support a causative role for HPV in OSCCs, and any potential pathogenic mechanism of HPV-associated OSCCs is still confounding. At best, an association between HPV infection and oral cancer is accepted by most investigators in this field.

In oral lesions, HPV-16 is by far the most common subtype associated with OSCCs and oral premalignant lesions (OPL) exhibiting epithelial dysplasias (Reddout, 2007). HPV-16 DNA has been identified in primary tumors of the tonsil, hypopharynx, oral cavity, tongue, and nasopharynx, as well as in cell-lines derived from these regions (Syrjanen, 2005; Reddout, 2007). Metastatic lymph nodes lesions have also been shown to contain DNA of the same HPV type as in the primary tumor in 76% of the cases, supporting the involvement of HPV in the development of OSCC (Clifford et al., 2003; Syrjanen, 2005; Reddout, 2007).

The prevalence of HPV-16 in OSCC is now considered to be as high as 50% if not more, making it likely that every alternate OSCC patient is HPV-16 positive (Syrjanen, 2005; Reddout, 2007). The association is strongest in the oropharynx, most notably in the tonsil and base of tongue, which present more frequent basaloid histomorphology and less frequent p53 mutations (Clifford et al., 2003). In addition, HPV-16 has been detected in extremely low copy numbers (compared to copy numbers in OSCC and dysplastic OPLs) in some human "normal" oral mucosa (NOM), suggesting that a threshold viral DNA copy number is required for the role of oncogenic HPVs in oral carcinogenesis. HPV-18 is far less commonly associated with oral cancers, and has been found in up to just 14 percent of cases (Kang and Park, 2001).

It is now established that the products of two early genomic regions of high-risk HPVs, E6 and E7, are capable of forming specific complexes with vital cell cycle regulators (Kang and Park, 2001). For example, E6 binds to p53 to induce p53 degradation, while E7 interacts with pRb resulting in blockage of the downstream activities of pRb (Kang and Park, 2001). Both p53 and pRb are oncosuppressors, and the overall outcome of their functional dysregulation is an uncontrolled DNA replication and impairment of apoptosis. The combined effects of apoptotic impairment and uncontrolled DNA replication are increased tendency towards cellular transformation and tumorigenesis.

3.4 Nutritional factors

The role of metabolic and dietary deficiencies in the etiology of OSCC was long suspected before concrete evidence began to emerge. Peterson (1919) and Kelly (1919) independently described the symptom complex of chronic dysphagia, mucosal atrophy of the hypopharynx, and chronic anemia in middle-aged women who also had cricoid carcinomas. The term sideropenic dysphagia was introduced, and used to describe the disease complex now referred to as Paterson-Kelly (or Plummer-Vinson; P-V) syndrome. P-K syndrome is marked by diminished iron stores and the absence of stainable bone marrow iron. Other components of the syndrome include riboflavin and other vitamin deficiencies. Subsequent studies by Ahlbom (1936) confirmed not only the importance of P-K syndrome in the development of pharyngeal cancers, but also showed that this applied to the buccal mucosa, tongue, and all levels of the esophagus.

There is a high incidence of oral cancer in parts of the world where iron deficiency is endemic (Prime, MacDonald and Rennie, 1982). Iron metabolism is essential for the overall integrity and health of epithelia of the digestive tract, and its importance may lie in its contribution to normal enzymes. Rennie and MacDonald (1982), and Rennie, MacDonald and Dagg (1982) demonstrated quantitative histologic changes in the oral epithelium in human iron deficiency anemia and in experimental iron deficiency in hamsters. The authors noted that the oral epithelium in iron deficiency is atrophic with reduced maturation compartment, but an increased keratinized compartment (Rennie et al., 1982). Subsequent cell kinetic studies by Rennie and MacDonald (1984) showed increased cell proliferation, indicating that, in spite of the atrophy, epithelial turnover is rapid. This observation suggested a possible increase in susceptibility to chemical carcinogens due to both an increase in the population of potentially vulnerable dividing cells and to a more permeable epithelium.

Increased cancer risks also are attributable to dietary factors, notably low intake of fruits and vegetables (Winn et al., 1984; Winn, 1995). Increased consumption of fruits and vegetables were said to be protective against oral cancer when controlled for demographic characteristics, tobacco and alcohol use, relative weight, and the intake of other food items (Winn et al., 1984). The reduction of risk is seen to be consistent with the hypothesis that Vitamin C and/or Vitamin A and ß-carotene intake is associated with a reduced risk of oral and pharyngeal cancers (Ibrahim, Jafarey and Zuberi, 1977). Interestingly, intervention trial studies with ß-carotene and Vitamin A in patients with oral precancer have been shown to result in substantial regression of the lesions (Stich et al., 1988a, 1988b).

Degenerative changes occur in riboflavin deficiency, a frequent finding in alcoholics. This may partly explain the relationship between alcoholism and oral cancer (Wynder and Klien, 1965). It also may be that alcohol increases the risk of oral cancer by lowering nutritional status via a substitution of non-nutritive calories for vitamins, minerals, and other elements; alternatively, that poor nutrition allows the deleterious effects of alcohol to be manifested.

3.5 Impaired immunity

Generally, patients with malignancies have some degree of immunosuppression that tends to worsen with the progression of their malignancy. Immunosuppression appears to predispose some individuals to an increased risk for oral cancer. Carcinomas of the lip have been reported in a number of kidney transplant patients receiving immunosuppressive

medications, and oral carcinomas have been documented in young AIDS patients (van Zuuren, de Visscher JGAM, Bouwes Bavinck JN, 1988; Flaitz et. al., 1995; de Visscher, Bouwes Bavinck JN and van der Waal, 1997; Flaitz and Silverman, 1998). It is however still debated as to whether immunosuppression in malignant disease represents an effect or a cause of the malignancy. Some studies have suggested that immunosuppressive states may represent the effect rather than the cause of cancer (Johnson, 1991), while others have suggested that OSCC, despite its local manifestations, is most likely a "regional" disease process that becomes "clinically significant" only when the patient's immunologic status is altered (Mashberg and Samit, 1989).

It would appear however that a factor such as advanced age, which diminishes immune competence and immune cellular surveillance, increases the risks of oral cancer. Overt immune suppression induced by chemicals or drugs, or caused by specific viral infections such as the human immunodeficiency virus (HIV), or Epstein Barr virus (EBV), increases the risk of oral cancers. Barr et al. (1989); Bradford et al. (1990) variously suggested that HPV may play an etiologic role in squamous cell carcinoma in renal allograft recipients.

3.6 Oral Premalignant Lesions

Oral premalignant lesions (OPLs) are lesions, often presenting on the oral mucosa, which possess a higher than normal propensity for transformation to OSCC with time if untreated. The current model for oral carcinogenesis postulates a step-wise transformation from normal to pre-malignant to invasive carcinoma phenotype. Histologically, the transition process involves progression from benign epithelial hyperplasia to various degrees of epithelial dysplasia (mild, moderate, severe) to carcinoma in situ, and finally to invasive OSCC. With respect to transition to OSCC, oral leukoplakia, oral erythroplakia, and speckled leukoplakia are the most notable and most studied OPLs (Figure 1.1). The transition rate of oral leukoplakia to OSCC is estimated at between 4 and 18%, while that of OLP is to be between 1 and 4%.

Although erythroplakia is not nearly as common as leukoplakia, it is much more likely to show dysplasia or carcinoma histologically. In a study by Shafer and Waldron (1975) of biopsies of erythroplakic lesions from 65 patients, all cases showed some degree of epithelial dysplasia: 51 percent showed invasive squamous cell carcinoma; 40 percent were carcinoma in situ or severe epithelial dysplasia; and the remaining 9 percent demonstrated mild-to-moderate dysplasia (Shafer and Waldron, 1975). Thus, true clinical erythroplakia is a much more worrisome lesion than leukoplakia (Mashberg and Samit, 1995). Likewise, in a mixed leukoplakia-erythroplakia (erythroleukoplakia), the erythroplakic (red component) is more likely to demonstrate dysplastic changes than is the white component, making it imperative that that biopsy sites be selected to ensure that the specimen incorporates the red component. In addition, a number of studies have suggested that oral lichen planus (OLP), especially the erosive form, may be associated with an increased cancer risk, although other investigators have questioned the strength of this association (Silverman et al., 1991; Barnard et al., 1993; Eisenberg, 2000).

4. Site distribution in oral cancer

Symptomatic lesions present with symptoms and signs such as intraoral pain and/or dysfunction, extraoral swelling, and cervical lymphadenopathy. These signs and symptoms

alert the clinician to the need to evaluate the oral cavity for obvious primary lesions. Site distribution in OSCC is usually described in relation to the symptomatic lesions, which are often amenable to classification under the "T" category of the TNM classification of malignant tumors (Neville and Day, 2002). The TNM classification allows for the clinical staging of oral malignant tumors on the basis of the size of the primary tumor, T, the absence or presence of corresponding regional node spread, and the absence or presence of distant site/organ metastases (Neville and Day, 2002). In OSCC, T1 lesions are 2cm or less in greatest dimension; T2 lesions are more than 2cm but not more than 4cm in greatest dimension; T3 lesions are more than 4cm in greatest dimension, and T4 lesions are those that have invaded adjacent contiguous structures such as the cortical bone, inferior alveolar nerve, deep extrinsic muscles of the tongue, maxillary sinus, or salivary glands regardless of their apparent visual dimension (Neville and Day, 2002).

Early asymptomatic lesions are relatively small (T1) and, not infrequently, elude clinical diagnosis by conventional systems (Mashberg and Meyers, 1976; Neville and Day, 2002). These early asymptomatic lesions, often presenting as erythroplastic lesions, were studied by Mashberg and Meyers (1976) who consequently provided guidance toward enhanced accurate designation of sites of origin of these early asymptomatic lesions (Mashberg and Meyers, 1976). In this respect, the authors further concluded thus: "The described locations in the literature may be points of termination or extension of the lesion rather than sites of origin, e.g., a symptomatic lesion (T2 or T3) in the floor of mouth may have extended to and invaded the alveolus; hence, based on clinical and x-ray evidence, it may have been reported as a gingival or alveolar lesion" (Mashberg and Meyers (1976).

There are geographic variations in the frequency of sites of involvement, probably related to such risk factors as occupation and lifestyle, oral habits, and certain socio-cultural practices, such as the mode of tobacco use (Paymaster, 1962; Brown et al., 1965). For example, presentation of intraoral cancers among the population of the high risk areas of Southeast Asia and the Southeast United States is slightly different. Consistent with the role of the risk factors alluded to above the most prone sites in the high risk areas of Southeast Asia are the buccal, retromloar, and commissural mucosa (Paymaster, 1962; Brown et al., 1965).

4.1 The lip

The World Health Organization (WHO) revision of the International Classification of Diseases (ICD) defines cancer of the lips as malignant lesions of the vermilion area of the upper and lower lips (Daftary et al., 1992). Cancers in these areas are not considered intraoral cancers (Daftary et al., 1992). Over 90% of lip cancers involve the lower lip (Neville and Day, 2002). Lip lesions are easily detectable partly because the lip is the most visible structure of the oral cavity complex. Lip squamous cell carcinomas usually arise in actinic cheilosis, a premalignant condition, which is a "cousin" to actinic keratosis of the skin. Actinic cheilosis is characterized by atrophy of the vermilion border, clinically visible as dry, scaly changes. Ulcerated foci alternating with partial healing may appear as the lesion progresses. Not infrequently, patients mistake these recurring ulcerated lesions for "fever blisters." Subsequently, the evolving cancer slowly becomes a crusted, non-tender, indurated ulcer or mass (Neville et al., 2009; Silverman, Dillon and Fischbein, 1998).

In Romania, Hungary, Yugoslavia, and parts of Canada and the United States, the vermilion area of the lips are the commonest sites of oral cancer (Johnson, 1991; 2001), and it has been reported that about half of all cases of oral cancer in the Nordic countries occur on the lips (Ringertz, 1971). The lateral aspect of the lower lip is more frequently involved than the mid-portion (Daftary et al., 1992). Race and ethnic variations in the incidence of lip cancer occur worldwide. Among most white population, the lip constitutes the most common site for oral cancer (Spitzer et al., 1975; Johnson, 1991; 2001). Considerable agreement over the association between lip cancer and occupation exists; the disease being common amongst white males who engage in outdoor occupations, such as farming and fishing, which expose them excessive sunlight (Spitzer et al., 1975; Johnson, 1991; 2001). On the other hand, lip cancer is relatively rare in black males, and females of both white and black races (Bernia, 1948; Spitzer et al., 1975; Johnson, 1991; 2001).

In a 1984 study reported by Douglass and Gammon there was variation in the incidence of lip cancer between the male non-Maori (1.7/ 100,000) and the Maori (0.2/100,000) population of New Zealand (Douglass and Gammon, 1984). The authors similarly highlighted ethnic differences in the incidence of lip cancer in Israel where males born in Israel had a higher rate of lip cancer (3.5/100,000) than male immigrants from Europe/America (2.9/100,000), or Africa/Asia (0.8/100,000).

4.2 The tongue and floor of mouth

The tongue is the most common site for intraoral carcinoma and accounts for about 40 percent of all cases in the oral cavity proper, with tumors occurring on the posterior lateral border and ventral surfaces of the tongue (Neville and Day, 2002). The incidence of floor-of-mouth squamous cell carcinoma closely approximates that of the tongue (Neville and Day, 2002). In the black population however the floor of mouth distinctly is the most common site for OSCC (Batsakis, 1979). Thus, anatomically, the lateral tongue and floor of mouth (extending to the lateral soft palate and tonsillar area) combine to form a horseshoe-shaped region of the oral mucosa, which is at greatest risk for cancer development (Neville and Day, 2002). Two major factors may explain the high-risk status of this composite region: first, carcinogens in saliva pool at the floor of the mouth with the tongue providing a lid; second, this complex is covered by a thinner, non-keratinized mucosa, thus providing limited barrier to carcinogen ingress (Jovanovic et al., 1993).

4.3 Buccal mucosa

The mucosal surface of the cheek extends from upper to lower vestibular sulci, where the mucosa reflects itself to cover the upper and lower alveolar ridges. The buccal mucosa also forms the commissure of the lip and covers the ramus of the mandible. A number of buccal squamous cell carcinomas originate in the commisural areas before spreading posteriorly to involve the mucosa along the occlusal plane of the teeth, or at the retromolar area (Batsakis, 1979). It has been suggested that, because commissural cancers have better prognoses than buccal mucosa cancers, the former ought to be separated from the latter for purposes of site designation (Daftary et al., 1992). However, this suggestion appears not to have gained wide acceptance. Buccal cancers usually arise on the mucosa lying against the wisdom teeth, and correspond to the common site of placement of tobacco-containing quid. The lesion then grows to obscures the site of origin (Singh and von Essen, 1966; Batsakis, 1979; Daftary et al.,

1992). Results of some studies indicate a consistent increase in the incidence of buccal cancers in relation to smokeless tobacco use (Brown et al., 1965; Winn et al., 1981). These findings underscore the importance of local etiologic factors in the site distribution of intraoral cancers.

4.4 The gingiva and alveolar ridge

Cancer of the gingivae and alveolar ridge are usually grouped together. Squamous cell carcinomas of the gingival and alveolar ridge generally are less common than those of the lip, tongue, and floor of mouth (McCarthy and Shklar, 1964). Similar to buccal and commissural cancers, Daftary et al., (1992) suggested that lesions of the gingivae and alveolar ridge be separated because of differences in prognosis. The incidence of carcinoma of the gingivae and alveolar ridge among the rural women of the Southeast United States is relatively high (Rosenfield and Callaway, 1963). The reported incidence of cancer of the gingival and alveolar ridge in three Indian populations ranged from 0.6/100,000 to 1.4/100,000 per annum among women (Daftary et al., 1992). Carcinoma of the gingivae generally arises in the premolar and molar regions and more frequently, on the lower than on the upper arch (Cady and Catlin, 1969). These correspond to the sites of retention of tobacco quid in those who practice the habit.

4.5 The palate

Squamous cell carcinomas of the palate are in the Western countries and the United States (Daftary et al., (1992). Again, incidence significantly reflects different habits. In India, for example where the habit of "reverse smoking" is prevalent among the population, the relative frequency of squamous cell carcinoma of the palate is high (Gupta et al., 1980; Daftary et al., 1992). The habit of reverse smoking is exemplified by the practice of placing the glowing end of a local form of cigar called "chuttas" inside the mouth. In areas where reverse smoking is practiced palatal cancer comprise 38 to 48 percent of all oral cancers (Gupta et al., 1980; Daftary et al., (1992). Lesions of the hard palate may arise in the midline or to one side close to the palatal gingivae (Batsakis, 1979).

Primary squamous cell carcinomas arising in the soft palate are uncommon, accounting for 2 percent of overall oral cancer in reverse-smoking areas (Ramulu et al., 1973), but only 0.4 percent in non-reverse smoking areas (Wahi et al., 1965). However, reports of later studies by Mashberg and Meyers (1976) indicated a greater frequency of lesions primarily arising from the soft palate than is ordinarily documented with the "late" symptomatic lesions. On analyzing the site distribution of 222 cases of early asymptomatic OSCCs, the authors found that 64 of these (28.8 percent) occurred in the "soft palate complex" comprising the soft palate, anterior pillar of fauces, and retromolar trigone. Thus, some of the lesions designated hard palate lesions at the time of diagnosis may have earlier arisen from the soft palate before spreading to the hard palate at a late symptomatic stage.

5. Diagnosis and management of oral cancer

Early diagnosis of oral cancer has emerged as a priority public health objective whereby oral health professional play leading role (Neville and Day, 2002). It is presumed that early diagnosis of cancer should lead to less damage from interventional treatment and to a better

prognosis. Because most individual are seen more commonly by primary care physicians and general dentists than by specialists, it is imperative for these clinicians to perform screening examinations to identify potential oral and pharyngeal cancers. In addition to the need for improved early detection by clinicians, it is also important that the patient and general public are knowledgeable about the disease (Yellowitz and Goodman, 1995; CDC, 1998). Delays in identification and recognition of suspicious lesions contribute to advanced stage at diagnosis and lower survival statistics (Shafer, 1975; Hollows, McAndrew and Perini, 2000).

5.1 Diagnosis of oral cancer

A distinction has been made in the early detection of oral cancers between "screening" (test aimed at evaluating presence of the disease in asymptomatic individuals) and "detection of cases" (applying specific procedure to patients with a suspicious lesion; Lestón and Dios, 2010). Nevertheless, conventional visual examination accompanied by palpation of suspicious lesions remains the gold standard screening methodology for oral precancer and cancer, while biopsy and histopathologic examination remains the universal diagnostic confirmatory test of choice (Lestón and Dios, 2010). Thus, in spite of the availability of several techniques that have been advocated as aids to oral cancer diagnosis (summarized in Table; adapted from Lestón and Dios, 2010) suspected malignant lesions must be biopsied in order to establish a definitive diagnosis.

Toluidine blue
Light-based detection systems
Chemiluminescence (ViziLite Plus®; Microlux/DL®)
Tissue fluorescence imaging (VELscope®)
Tissue fluorescence spectroscopy
Cytology or brush biopsy (OralCDx®)
Specific analysis (, SCCAA, IAP, CYFRA, , and others)
Specific analysis (, , , CYFRA 21-1, TPS, IL-1B, DUSP 1, HA3, , , SAT, miRNA, and others)
Imaging (DPT, CT, CBCT, MRI)

Table 1. Some techniques advocated for the clinical diagnosis of OSCC supplementing conventional oral examination, and histopathologic examination of suspicious lesions (*adapted from Lestón and Dios, 2010*).

In turn, the accurate diagnosis of potentially malignant and malignant oral lesions depends on the quality of the biopsy, selection of appropriate technique (e.g. incisional versus excisional), the applicability of the adequate clinical information, and competent interpretation of the biopsy results. Oral biopsy specimens can be affected by a number of artifacts resulting from crushing, fulguration, injection, or incorrect fixation and freezing (Trullenque-Eriksson et al., 2009). Results of cytologic examination of specimens obtained from non-invasive procedures such as brush biopsies or comparable techniques must not constitute the sole basis for a diagnosis of malignancy (or the absence) leading to definitive treatments. This is because these non-invasive techniques often are fraught with several pitfalls accounting for high rates of false-negative and false-positive results.

5.2 Management of oral cancer patients

While an exhaustive discussion on the management of oral cancer and precancerous lesions is not intended in this review, it is generally recommended that leukoplakias exhibiting degrees of epithelial dysplasia equal to, or worse than, moderate epithelial dysplasia be removed completely when possible (Epstein et al., 2007). On the other hand, the management guideline for mild dysplastic lesions is far less standardized with varied schools of thought ranging from those advocating a "wait-and-see" approach to those advocating total removal of all dysplastic lesions regardless of the degree of epithelial dysplasia. In addition, management decisions for mild epithelial dysplasia appear to be influenced by the size, location, and apparent etiologic factor accounting for the lesion. Some early dysplastic lesions where an etiologic agent (e.g. smoking) is identified have been known to regress and may reverse to normal on elimination of the etiologic factor responsible.

Patients with invasive oral cancer are best managed by a coordinated, multidisciplinary team of health care professionals, which may include a head and neck surgeon, oral and maxillofacial pathologist, general pathologist, radiation oncologist, neuroradiologist, reconstructive surgeon, medical oncologist, general dentist, oral and maxillofacial surgeon, maxillofacial prosthodontist, dental hygienist, nurse specialist, speech pathologist, nutritionist, and tobacco cessation counselor (Ord and Blanchaert, 2001).

Up to 15 percent of individuals with oral cancer harbor a second primary, making a complete head and neck examination that includes the larynx imperative (Lippman and Hong, 1989). Endoscopy of the larynx, esophagus, trachea, and lungs to rule out the possibility of other lesions in the high-risk patient is now performed routinely. For patients who present with a neck mass but no obvious primary site (or if the neck mass is more amenable to biopsy than the primary tumor), a fine needle aspiration remains the diagnostic method of choice rather than an open biopsy, because open biopsy has been reported to be related to a lower survival rate when not accompanied by a simultaneous neck dissection (Lefebvre et al., 1990; Kleid and Millar, 1993).

Also, imaging studies are now routines during the evaluation of primary oral tumors and neck disease. Both contrast-enhanced computed tomographic (CT) scans and magnetic resonance imaging (MRI) may be utilized in determining the extent of the primary tumor, invasion, regional node status, and distant metastasis, thereby providing important staging information (Som, Curtin and Mancuso, 1999, Robbins, 1999). Positron emission tomography (PET) scans are also becoming an increasingly popular tool for the identification of primary, recurrent, and metastatic diseases.

The treatment options for primary OSCCs are variable and depend on the size and location of the tumor, lymph node status, presence or absence of distant metastases, the patient's ability to tolerate treatment, and the patient's desires. Surgery and/or radiation therapy remain the gold standards for treatment of cancers of the lip and oral cavity. Oropharyngeal cancer may be treated with surgery and/or radiation therapy for early-stage disease. For advanced-stage disease, surgery with adjuvant radiation therapy may be indicated, although recent evidence suggests that the addition of chemotherapy to radiation therapy may provide a survival advantage over radiation therapy alone in this population (Forastiere, 1998; Calais et al., 1999). It is important to take into account disease status and

prevalence of occult disease in the neck when evaluating primary cancers of the lip, oral cavity, and oropharynx (Robbins et al., 2001). Regardless of the treatment modality used, many patients will require consideration of problems related to airway protection, enteral feedings, xerostomia, mucositis, dysphagia, and voice change.

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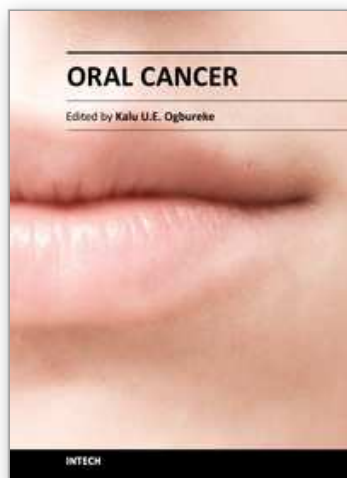
Oral Cancer

Edited by Dr. Kalu U. E. Ogbureke

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

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