

## Systemic Review

# Oral Squamous Cell Carcinoma: Prevalence, Risk Factors, Pathogenesis, Clinical Features, and Treatments: A Systemic Review

Dr. Ziyad Abdulaziz AlHammad

DMD, King Abdulaziz Medical City, National Guard, Riyadh, Saudi Arabia

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### ABSTRACT

Systemically reviewing the topic Oral Squamous Cell Carcinoma (OSCC) and its components: prevalence, risk factors, pathogenesis, clinical features, and treatments. All studies pertaining to the topic and its components were included. Exclusion criteria were applied to exclude studies that were not PubMed indexed. The materials and methods which were used for this systemic review were to search in the PubMed database, using specific words "Oral Squamous Cell Carcinoma, Prevalence, Risk Factors, Pathogenesis, Clinical Features, and Treatment" and published in the English language. The articles were reviewed, 30 papers were identified in PubMed but a total of 25 papers were included in the final systemic review according to the specific keywords and components mentioned above. The prevalence of OSCC showed to be very high compared to other lesions. Risk factors were identified and presented showing their impact and relationship to OSCC. Pathogenesis was reviewed revealing a very complex multi-stages genetic process. Clinical features were investigated, identifying the most affected sites, most common symptoms, and typical presentations of OSCC. Management was reviewed showing a variety of treatment modalities with variable indications, advantages and disadvantages for each.

### INTRODUCTION:

Worldwide, oral cancer accounts for 2% - 4% of all cancer cases [1]. Although oral cancer incidence is highly variable worldwide, it is accepted that oral cavity considered to be the 6<sup>th</sup> to the 9<sup>th</sup> most common anatomical location for cancer [2]. Oral squamous cell carcinoma (OSCC) is the most common malignant epithelial neoplasm affecting the oral cavity. OSCC is accounted for more than 90% of all oral neoplasms [3]. OSCC is associated with risk factors, mainly the use of tobacco and alcohol resulting in high incidence of OSCC and eventually high mortality and morbidity rates. The pathogenesis of OSCC is highly related to genetic changes and gene expression patterns. Clinical features of OSCC including defining the variable profiles of OSCC and recognizing the most common affected sites are highly recommended to properly screen for lesions and hopefully diagnose them in early stages. Different

treatment modalities such as palliative treatment, surgery, radiotherapy and chemotherapy can be utilized to manage OSCC patients. Each type of treatment modality has shown to have specific indications, advantages and disadvantages. In this systemic review article, we will be exploring the different aspects of OSCC including prevalence, incidence, risk factors, morbidity and mortality rates, survival rate, pathogenesis, clinical features, and treatment modalities.

### PREVALENCE AND RISK FACTORS OF ORAL SQUAMOUS CELL CARCINOMA:

Oral cancer is a major public health problem. Hernández-Guerrero JC *et al.* [4] concluded that oral cancers represent the sixth most common malignant neoplasm. Additionally, Dhanuthai K *et al.* [5] reported the overall prevalence of oral cancer to be (1.3%). Moreover, Warnakulasuriya S *et al.* [6] reported the

\* Corresponding author: Dr. Ziyad Abdulaziz AlHammad, DMD, King Abdulaziz Medical City, National Guard, Riyadh, Saudi Arabia

annual estimated incidence of oral cancer to be approximately (275,000 per year). The prevalence of OSCC has been reported in many studies. Choi S *et al.* [3] suggested that (90%) of all oral neoplasms are OSCC, representing the most frequent neoplasm of all oral neoplasms. Also, Selvamani M *et al.* [7] suggested that 95% of the head and neck cancers are squamous cell carcinomas. OSCC are highly affected by risk factors. Patel SC *et al.* [8] suggested that the incidence of OSCC is increasing among young white individuals age (18 to 44 years), particularly among white women. Furthermore, Tandon P *et al.* [9] reported that the incidence of OSCC varies markedly by geographic region, and more than half of all cancer cases occur in developing countries. A study conducted by Dhanuthai K *et al.* [5] suggested the mean age of the patients to be (58.37±15.77) years. He also mentioned a total of OSCC (68.90%) were diagnosed in males, whereas (31.07%) were diagnosed in females. The male-to-female ratio was (2.22:1). In addition, Selvamani M *et al.* [7] reported that patient were affected over a wide range of (27–80) years with mean age of (55.75) years and peak incidence seen in the fourth and fifth decades of life, with the male: female ratio of (1.7:1). He also concluded the main risk factors of OSCC to be frequently exposed to various carcinogenic agents, specifically tobacco, alcohol, betel nut, and human papillomavirus (HPV). Additionally, Petti S *et al.* [10] concluded that alcohol consumption, tobacco smoking, unhealthy diets, sedentary lifestyles, and viral infections are the main risk factors for OSCC development. He also emphasized that drinking alcohol and smoking tobacco can synergistically contribute as a significant risk factor in developing OSCC. Regarding morbidity and mortality rates, Dhanuthai K *et al.* [5] reported that “although the prevalence of oral cancer is not high compared to other entities, oral cancer shows

significant mortality and morbidity in patients, especially when discovered late in the course of the disease”. Mehrotra R *et al.* concluded that the percentages of morbidity and mortality in males are (6.6/100,000) and (3.1/100,000) respectively, while in females the same percentages are (2.9/100,000) and (1.4/100,000), respectively. For that reason, early detection is essential to reduce the mortality and morbidity rate and increase the survival rate in OSCC patients. In relevance to survival rate, Marsh D *et al.* [11] concluded that “despite advances in surgery and radiotherapy, which remain the standard treatment options, the mortality rate has remained largely unchanged for decades, with a 5-year survival rate of around (50%)”. Moreover, Wang B *et al.* reported that the 5-year overall survival rate was (54.5%) with survival time ranging from (6 to 120 months), and a median of (36 months). When it comes to recurrence rate, he reported the recurrence rate of OSCC to be (32.7%) which ranged from (2 to 96 months), with a median of (14 months). Another study conducted by Kernohan MD *et al.* [12] reported a median time to recurrence from initial treatment to be (7.5 months) (range: 0.9-143.9 month), with (86%) of recurrences occurring within the first 24 months. The impact of OSCC is hugely remarkable on society and individual level. For that reason, proper understanding of the pathogenesis of OSCC is very essential.

#### **PATHOGENESIS OF ORAL SQUAMOUS CELL CARCINOMA:**

Reviewing the literature revealed variable concepts regarding the pathogenesis of OSCC. As reported by Ram H *et al.* [13] “understanding the genetic changes and gene expression patterns are keys to the understanding of molecular pathogenesis of OC. Though, there are some significant leads achieved, the complete

understanding of molecular pathology of OC and its association with causative agent will require additional intensive research". Rivera C *et al.* [14] suggested that oral carcinogenesis is a multistage process, which simultaneously involves precancerous lesions, invasion and metastasis. Degradation of the cell cycle and the proliferation of malignant cells results in the loss of control mechanisms that ensure the normal function of tissues. Another study conducted by Choi S *et al.*[3] found that the development of oral squamous cell carcinoma is a multistep process requiring the accumulation of multiple genetic alterations, influenced by a patient's genetic predisposition as well as by environmental influences, including tobacco, alcohol, chronic inflammation, and viral infection. He also concluded that Tumorigenic genetic alterations consist of two major types. First, tumor suppressor genes which promote tumor development when inactivated. Second, oncogenes which promote tumor development when activated. Tumor suppressor genes can be inactivated through genetic events such as mutation, loss of heterozygosity, deletion, or by epigenetic modifications such as DNA methylation or chromatin remodeling. Oncogenes can be activated through overexpression due to gene amplification, increased transcription, or changes in structure due to mutations that lead to increased transforming activity. Moreover, Feller LL *et al.* [15] concluded that most OSCCs develop in fields of precancerized epithelium in which there is clonal expansion of phenotypically normal but genetically altered keratinocytes. These genetically unstable precancerous keratinocytes manifest aneuploidy, gain or loss of chromosomal material, or alterations in the sequences of nucleotides. The genomic instability favors further acquisition of genetic alterations leading to growth superiority or inferiority of the affected cells. The

genetically advantaged cells may ultimately acquire a cancerous phenotype. Furthermore, Williams HK *et al.* [16] concluded that oral squamous carcinogenesis is a multistep process in which multiple genetic events occur that alter the normal functions of oncogenes and tumor suppressor genes. This can result in increased production of growth factors or numbers of cell surface receptors, enhanced intracellular messenger signaling, and/or increased production of transcription factors. In combination with the loss of tumor suppressor activity, this leads to a cell phenotype capable of increased cell proliferation, with loss of cell cohesion, and the ability to infiltrate local tissue and spread to distant sites. Based on the evidence that we have today, it appears that OSCC is a complicated multi-step process that involves sophisticated genetic changes and gene expression patterns. On the other hand, it also appears that we are still lagging behind when it comes to fully understand the exact pathogenesis and pathophysiology of OSCC. Such lesion can be presented complexly with different clinical features and affect different sites.

#### **CLINICAL FEATURES OF ORAL SQUAMOUS CELL CARCINOMA:**

OSCC can be clinically located in different sites and present different symptoms. The typical appearance OSCC as described by Markopoulos AK *et al* [1] "OSCC presents as an ulcer with fissuring or raised exophytic margins which may also appear as a lump, red lesion (erythroplakia), white (leukoplakia), mixed white and red lesion, non-healing extraction socket, or as a cervical lymph node enlargement, and usually characterized by hardness or fixation". OSCC should be considered where any of these features persist for more than two weeks. Bagan J *et al.* [17] also described OSCC in its initial stages that it shows an

erythroleukoplastic area without symptoms but in advanced stages there are ulcers and lumps with irregular margins which are rigid to touch. Pires FR *et al.* [18] investigated the clinical aspect of the lesions and concluded that tumors revealed as ulcers (62%), ulcers associated to leukoerythroplakia (21%) or only leukoerythroplakia (17%). Also, the lesions can be classified to well-differentiated type and poorly-differentiated. As reported by Andisheh-Tadmir A *et al.* [19] “The well-differentiated type (55.5%) was the most common, with the poorly differentiated OSCC being the least common (7.5%)”. In relevance to the most affected sites, Pires FR *et al.* [18] reported the site distribution showing that the most common location of the tumors was the border of the tongue (37%), followed by the alveolar mucosa and gingiva (20%), and floor of the mouth with ventral tongue (19%). Furthermore, Andisheh-Tadmir A *et al.* [19] concluded that the tongue was the most commonly affected site (53%), followed by the buccal mucosa (9.5%) and maxillary gingiva (9%). In regard to the most common symptoms associated with OSCC, Adeyemi BF *et al.* [20] reported that (59.4%) of patients had were asymptomatic at the onset of the disease. For symptomatic patients, the most common symptom was painful tooth/teeth which are not mobile (27.5%). The interval between onset of symptoms and clinical presentation ranged from (3 weeks) to (36 months) with a mean duration of  $(7 \pm 6.3)$  months). Paradoxically, patients that experienced painful symptoms at the onset of disease presented later than those who had painless symptoms. Moreover, Sharma RG *et al.* [21] reported the three most common clinical symptoms at presentation were presence of oral ulcer (76 %), pain at local site (43 %) & swelling/growth (33 %). Also, the average duration of onset of symptoms before admission to hospital was (5 months). This period

ranged from (7 days to 9 months). In respect to diagnosis, verity of different techniques have been discussed in the literature. However, the best diagnostic technique is that which we have sufficient experience and training. As concluded by Carreras-Torras C *et al.* [22] “Definitely tissue biopsy and histopathological examination should remain the gold standard for oral cancer diagnose. With oral cytology we can obtain single cells that can be analyzed using sophisticated techniques such as cytomorphometry and molecular analysis or using more simple techniques such as toluidine blue (dye most used) or rose bengal (which has proved more promising), with all these techniques have been achieved very interesting results. On the other hand, optical techniques and diagnostic techniques for imaging have also proved particularly useful, but their results are not yet clinically relevant”. Proper diagnosis is extremely important to provide the most appropriate treatment for the patient.

#### **TREATMENTS OF ORAL SQUAMOUS CELL CARCINOMA:**

The primary treatment modality of oral cancer is generally determined according to the stage of the disease, with surgical treatment remaining the mainstay of multimodal treatment. When selecting the treatment, many factors are taken into consideration, and the treatment should be tailored individually to the patient's needs and consider the quality of life as well as the survival of the patient. Spencer KR *et al.* [23] suggests that palliative care is offered to patients who either have incurable disease or are medically unfit to be subjected to potentially curative treatment. He also concluded that surgery and radiotherapy are the two treatment options available with curative potential and may be used alone or in combination. Surgery will involve complete

excision of the tumor along with a surrounding margin of normal tissue, and, where indicated, some or all of the ipsilateral and occasionally contra lateral cervical lymph nodes. Radiotherapy preferentially kills dividing cells, and for those patients treated by radiotherapy, the aim is to kill every cancer cell. Both the primary tumor and the regional lymph nodes can be included in the treatment field. A full course of radiotherapy is typically expressed in the usual units as being about 60 Grey (Gy) (1 Gy=100 rads), which is fractionated into 30 daily doses of 2 Gy each over six weeks. Another study conducted by Omura K *et al.* [24] suggesting that an early-stage disease is primarily managed with surgery or brachytherapy without functional morbidity, whereas for advanced-stage disease multidisciplinary treatment is recommended, not only for enhanced survival but also for improved quality of life. He also emphasized that after resection of large primary tumors, reconstructive surgery is required. Free tissue transfer currently represents one of the most popular and reliable techniques for oral reconstruction. Regarding advanced cases of OSCC, Ow TJ *et al.* [25] concluded that “Treatment of advanced OCSCC requires a multidisciplinary approach which combines surgery with radiotherapy and cisplatin-based chemoradiotherapy for high-risk cases. Advances in surgical resection and reconstruction, the delivery of radiation, and in chemotherapeutic strategies have improved the management of patients with advanced OCSCC, but the high rate of treatment failure and morbidity of treatment must be improved by future advances in the management of this disease”. When it comes to treatment decision, all factors should be considered, including and not only limited to, patient’s overall health status, location of lesion, advancement of the lesion, ability or inability of

reconstruction and rehabilitation, complications, and prognosis.

#### CONCLUSION:

To sum up, oral squamous cell carcinoma is considered to be the most common neoplasm in the oral cavity. It showed a high prevalence compared to other lesions, and recognizable risk factors. The pathogenesis is investigated in many studies, showing different theories behind OSCC development. Clinical features including OSCC typical profile, diagnosis methods and symptoms were reviewed. Treatment modalities such as, surgery, radiotherapy and chemotherapy all were investigated showing the indication of each type of treatment. Lastly, further research regarding OSCC is required to improve diagnosing methods, treatment options and eventually the overall health of patients.

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