

# Exploring the Squamous Cell Carcinoma in Head and Neck: A Literature Review on Pathogenesis, Clinical Symptoms, and Management

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## Abstract

This literature review provides a comprehensive examination of squamous cell carcinoma (SCC) within the head and neck, addressing key aspects such as pathogenesis, clinical manifestations, management, and prognosis. The intricate interplay of genetic, environmental, and lifestyle factors contributing to the development of SCC is explored, emphasizing the multicausal nature of gene mutations. Cellular responses to DNA damage, governed by genes involved in DNA repair, proliferation, and apoptosis, form a critical backdrop to the understanding of SCC progression. Clinical symptoms indicative of SCC in the head and neck, including persistent sore throat, difficulty swallowing, and voice changes, are discussed. Diagnosis and staging considerations are elucidated, emphasizing the importance of a multidisciplinary approach for optimal patient management. Therapeutic modalities, encompassing radiotherapy, chemotherapy, and their combination, are reviewed, highlighting the necessity for integrated care by otolaryngologists, radiation oncologists, and medical oncologists. Prognostic factors influencing the outcomes of SCC are examined, with an emphasis on tumor stage, lymph node metastasis, and distant metastasis. The paper also delves into the epidemiology of head and neck cancers, focusing on SCC, highlighting regional variations, and discussing factors such as age, gender, and socioeconomic influences. The anatomical considerations of SCC, spanning the oral cavity, pharynx, larynx, and major salivary glands, are outlined. Additionally, the review extends to cutaneous SCC, emphasizing the impact of ultraviolet sunlight exposure on the skin of the head and neck. In conclusion, this literature review offers a holistic perspective on SCC in the head and neck, consolidating current knowledge on its pathogenesis, clinical features, management strategies, and prognostic indicators. The insights provided serve as a valuable resource for healthcare practitioners and researchers engaged in understanding and combating this complex malignancy.

*Keywords: Squamous Cell Carcinoma, , Head and Neck, Cancer, Management*

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## 1. Introduction

Head and neck cancers constitute a diverse spectrum of malignancies affecting structures such as the oral cavity, pharynx, larynx, and major salivary glands. Among these, squamous cell carcinoma (SCC) emerges as the predominant histological subtype, accounting for over 90% of cases in this region (Bray et al., 2018). The global impact of head and neck cancers is substantial, with an estimated 800,000 new cases and 400,000 deaths reported in 2018 (Bray et al., 2018). Given its prevalence and associated morbidity, understanding the intricate facets of SCC in the head and neck is crucial. The pathogenesis of SCC in the head and neck is multifaceted, involving a complex interplay of genetic, environmental, and behavioral factors. Genetic predisposition, environmental carcinogens, chronic infections, and lifestyle choices collectively contribute to

the genetic alterations that drive normal cells toward malignant transformation. These alterations primarily affect proto-oncogenes, tumor suppressor genes, and genes regulating apoptosis, leading to uncontrolled cell growth (Kumar et al., 2007).

Clinical manifestations of SCC in the head and neck vary depending on the specific anatomical site involved. Persistent sore throat, difficulty swallowing, and voice changes are common symptoms prompting clinical evaluation. The epidemiological landscape of head and neck cancers exhibits regional variations influenced by factors such as ethnicity, gender, socioeconomic status, and environmental exposures. Diagnosing SCC in the head and neck poses challenges due to the complexity of the anatomy and nonspecific early symptoms. A comprehensive diagnostic approach, involving clinical examination, imaging studies, and histopathological evaluation, is crucial for accurate staging and treatment planning. The multidisciplinary nature of head and neck cancer management underscores the collaboration among otolaryngologists, radiation oncologists, medical oncologists, and other allied health professionals (Rousseau, 2017).

Therapeutic modalities for SCC in the head and neck include surgery, radiotherapy, and chemotherapy, employed individually or in combination based on disease extent. Prognostic considerations, including tumor stage, nodal involvement, and distant metastasis, significantly influence treatment outcomes. Striking a balance between effective disease control and preservation of vital functions remains a central tenet of therapeutic decision-making. This literature review aims to synthesize current knowledge on SCC in the head and neck, encompassing its pathogenesis, clinical manifestations, diagnostic challenges, therapeutic strategies, and prognostic factors. Drawing insights from diverse research perspectives, this review seeks to enhance our understanding of SCC in the head and neck, fostering improved clinical management and guiding avenues for future research.

## **2. Review Content**

### **2.1 Cancer Pathogenesis**

There are many factors that contribute to the development of cancer, including genetic, free radicals, infections, environmental factors, behavior, lifestyle, and viruses that can lead to gene mutations. Gene mutations are not only caused by a single carcinogenic agent but by several carcinogens, resulting in a multifaceted influence that strengthens the occurrence of gene mutations in cancer, also known as multicausal. Cells can undergo uncontrolled growth if there is damage to the DNA. When cells experience DNA damage, the body has genes that regulate repair related to carcinogenesis. DNA repair genes indirectly affect cell proliferation or survival by influencing an organism's ability to repair non-lethal damage in other genes, including proto-oncogenes, tumor suppressor genes, and genes that control apoptosis. DNA repair can fail due to hereditary mutations in genes that affect DNA repair or genes that affect cell growth or apoptosis. Damage to DNA repair genes can facilitate extensive mutations in the genome and neoplastic transformation. There are three classes of normal regulatory genes: proto-oncogenes that promote growth, tumor suppressor genes that inhibit growth (antioncogenes), and genes that regulate programmed cell death or apoptosis. Genetic changes can lead to alterations in regulatory genes, such as the activation of growth-promoting oncogenes, changes in genes that control growth, and the inactivation of cancer-suppressing genes. The expression of altered gene products and the loss of regulatory gene products are what cause cancer. Cancer cells take a considerable amount of time to invade outside organs or undergo metastasis. Metastasis can occur in the early stages of cancer and consists of detached cancer cells or clumps of malignant cells originating from the parent tumor (Kumar et al, 2007).

## 2.2 Squamous Cell Carcinoma of the Head and Neck

### 2.1 Definition

Most head and neck cancers originate in the moist mucous membranes lining the inside of the mouth, nose, and throat. The membrane composed of squamous cells and the head and neck cancers that grow in these cells are called squamous cell carcinoma (National Cancer Institute, 2010). Squamous cell carcinoma of the head and neck develops in the mucosal membrane of the mouth, nose, and throat. Commonly affected locations include the oral cavity, oropharynx, paranasal sinuses, nasal cavity, nasopharynx, larynx, and hypopharynx (National Library of Medicine, 2017). Squamous cell carcinoma can also occur on the skin, especially on areas frequently exposed to UV sunlight, such as the face and head. Squamous cell carcinoma causes damage to local skin tissue but also has the potential to metastasize. If diagnosed early, it can be treated, and patients can recover (Perdoski, 2019).

### 2.2 Epidemiology

Head and neck cancer ranks seventh among the most commonly found cancers worldwide, with a global incidence of approximately 800,000 new cases and around 400,000 deaths in 2018 (Bray et al., 2018). More than 90% of head and neck cancers are squamous cell carcinoma, with other types including lymphoma, sarcoma, adenocarcinoma, basal cell carcinoma, and melanoma. In some countries, particularly in the Western states, there is an increase in the incidence of oral, laryngeal, and pharyngeal cancers. In the Asia-Pacific region and Africa, nasopharyngeal cancer is more common. Squamous cell carcinoma of the head and neck is one of the most prevalent cancers in Asia. In Indonesia alone, in 2018, there were 27,790 new patients with a prevalence of 72,821 (WHO, 2018). The incidence of head and neck cancer varies significantly by country and depends on various factors such as ethnicity, gender, environment, and socioeconomic status. This cancer occurs more frequently in males, up to three times more than in females. On average, patients with this cancer are in their 40s and 50s, but there is an increasing incidence in younger individuals. It tends to occur more in urban areas compared to rural areas (Rousseau, 2017).

### 2.3 Anatomy of the Head and Neck

Cancer in the head and neck is located in various parts, as shown in Figure 2.1, starting from the oral cavity, nasal cavity, paranasal sinuses, pharynx divided into 3 parts (nasopharynx, oropharynx, hypopharynx), larynx, and major salivary glands. In addition, squamous cell carcinoma (SCC) often occurs on the skin exposed to ultraviolet (UV) sunlight, such as the scalp, face, and neck. The first location of squamous cell carcinoma is the oral cavity, consisting of the lips, two-thirds of the front part of the tongue, gums, inner lining of the cheeks and lips, the floor of the mouth below the tongue, hard palate (upper part of the mouth bone), and the small oral cavity, the gum area behind the wisdom teeth. The next part is the throat or pharynx, which is a tube with a diameter of approximately 5 inches, extending from the back of the nose to the esophagus. The pharynx has three parts: nasopharynx (upper part), oropharynx (middle part, including the base of the tongue and tonsils), and hypopharynx (lower part). The voice box or larynx is a short tube formed by cartilage below the pharynx, containing vocal cords. The epiglottis, a small tissue that moves to cover the larynx, prevents food from entering the airway. The nasal cavity is an empty space inside the nose, while the paranasal sinuses are small hollow spaces in the skull surrounding the nose. Lastly, the salivary glands, with the major salivary glands located at the base of the mouth and near the jawbone, function to produce saliva. Minor salivary glands are located throughout the mucous membranes of the mouth and throat. The final part includes the skin of the head, face, and neck. Squamous cell carcinoma is formed in the cells of the epidermis. The skin itself has several layers, including the epidermis (including squamous and

basal cells), dermis, subcutaneous tissue, and other components.

## 2.4 Histology of the Head and Neck

In the oral cavity, it is lined by non-keratinized stratified squamous epithelium that is protective, safeguarding the oral mucosa from damage during chewing. This type of epithelium is found only on the gingiva and hard palate. The lips and cheeks form part of the oral cavity, with the lips covered by very thin skin overlaid by keratinized stratified epithelium. The outer surface of the lips contains hair follicles, sebaceous glands, and sweat glands. The lips also contain skeletal muscle called orbicularis oris. On the inner free border of the lips, the outer layer transitions into non-keratinized stratified squamous epithelium without a thicker horn layer. Beneath the oral epithelium, there are labial glands (*glandula labialis*) that produce mucus. The tongue's dorsal surface has four types of papillae: filiform, fungiform, circumvallate, and foliate (Eroschenko, 2018). The pharynx is lined by non-keratinized stratified squamous epithelium in areas that continue to the esophagus and is then covered by pseudostratified columnar epithelium with cilia. Near the nasal cavity, there are goblet cells. The tonsils have many minor salivary glands in their lamina propria, consisting of dense connective tissue. Outside this layer, there are constrictor and longitudinal muscles (Mescher, 2018). Similar to the pharynx, the larynx, the entire surface of the tongue, and the apical part of the laryngeal surface are covered by stratified squamous epithelium. The ventricle is a recess that separates the superior and true vocal folds. The mucosa of the superior vocal fold is lined by pseudostratified columnar ciliated epithelium, while the true vocal fold is covered by non-keratinized stratified squamous epithelium. The epithelium in the lower part of the larynx changes to pseudostratified columnar ciliated epithelium, and there is hyaline cartilage called the cricoid (Eroschenko, 2018). The nasal cavity consists of two structures: the vestibule on the outside and the nasal cavity (or *fossa nasalis*) on the inside. The vestibule is the anterior and widest part of each nasal cavity. It contains sebaceous glands, sweat glands, and vibrissae (nose hairs) to filter the air. In the vestibule, the epithelium transitions into respiratory epithelium before entering the nasal fossa. The middle and inferior turbinates are lined with respiratory epithelium; the superior turbinate is covered with specialized olfactory epithelium (Mescher, 2018). The paranasal sinuses are lined with thinner respiratory epithelium and contain few goblet cells. The lamina propria has few small glands and merges with the periosteum below it. The olfactory mucosa is lined by pseudostratified columnar ciliated epithelium (Mescher, 2018).

## 2.5 Etiology and Risk Factors

More than 75% of all squamous cell carcinoma patients in the United States are associated with smoking and alcohol consumption. Active smokers have a higher risk of developing squamous cell carcinoma of the head and neck than passive smokers. The simultaneous use of cigarettes and alcohol can synergistically interact to increase the risk of cancer. DNA and major genes that function in protecting against cancer cells are damaged when exposed to chemicals found in cigarettes. These damaging substances include benzene, polonium-210, benzo(a)pyrene, and nitrosamines (Cancer Research UK, 2016). In addition to tobacco and alcohol, infections are also considered a risk factor for squamous cell carcinoma of the head and neck. Chronic infections in the oral cavity are marked by red and white patches, sometimes associated with the yeast or hyphae of fungi. Some microorganisms related to oral cancer include *Candida albicans*. *Candida* can increase dysplasia grade and elevate the risk of malignancy. Virus infections, such as Human Papilloma Viruses (HPV), can also play a role in causing oropharyngeal cancer in the tonsils and base of the tongue through sexual transmission. In the United States, the incidence of oropharyngeal cancer caused by HPV infection is increasing, while the incidence of oropharyngeal cancer related to other causes is decreasing (Chatuvedi AK et al., 2011). A family history of cancer can also increase the risk of developing cancer by 3

to 4 times compared to those without a cancer history. Individuals with compromised immune systems, such as those with AIDS, transplant recipients, and immune system deficiencies, are also at an increased risk of developing cancer. Although aging is not a major risk factor, older individuals are more vulnerable to exposure to the above-mentioned risk factors. However, cancer of the head and neck is not exclusive to elderly patients. Squamous cell carcinoma growth on the skin is caused by exposure to sunlight, arsenic, hydrocarbons, temperature, chronic radiation, scars, and viruses.

## 2.6 Diagnosis

The success of therapy or treatment for patients with squamous cell carcinoma of the head and neck heavily depends on accurate and timely diagnosis. Diagnostic tests depend on several conditions, including age, medical history, symptoms, and other medical conditions. Typically, clinicians can establish a diagnosis based on history in about 70% of cases. From the history, clinicians can understand the course of the disease and risk factors for cancer, such as lifestyle and other factors like age, gender, and occupation. The clinical symptoms complained by the patient can also determine the location where the malignant tumor appears. For example, if a patient complains of a blocked nose and a lump on the palate, squamous cell carcinoma may be present in the paranasal sinuses. The next stage involves a physical examination, including inspection and palpation based on the patient's complaints. Inspection can be performed to observe abnormalities in the nose, mouth, throat, and neck using a headlamp and mirror for clearer visibility. Subsequently, palpation is conducted to feel lumps in the neck, lips, gums, and cheeks (Cancer.Net, 2016). Examination of the neck is done to look for the involvement of metastatic lymph nodes. There are also several examinations aimed at determining the general condition of the patient, such as the presence of metastasis and secondary primary tumors, as some head and neck cancer patients may experience significant health problems other than cancer. Supplementary examinations include: (1) Complete blood and urine tests, (2) Thyroid function tests or thyroid scans, (3) Liver function or chemical tests, (4) Heart examination or electrocardiography, (5) Bone scan. A definite diagnosis is obtained from the results of a biopsy. Specimens are taken from the clinically suspected area, avoiding areas with necrosis and ulceration; more than one biopsy area may be needed. If the primary tumor location is not found in patients with enlarged lymph nodes, aspiration of the lymph nodes can be performed to establish a diagnosis. In patients whose aspiration results are non-diagnostic and there is suspicion of Squamous Cell Carcinoma, a biopsy is performed by excising the lymph node (Barnes et al., 2005). The histopathological diagnosis looks at invasive growth and squamous differentiation. Invasive features are characterized by the destruction of the basal membrane and the growth of tumor cells forming island-like structures. The larger the tumor, the easier it is to invade deeper structures such as bone and muscle, and it can invade vascular, perineural, or lymphatic structures as well.

## 2.7 Management

The management of squamous cell carcinoma cancer may involve radiotherapy, chemotherapy, a combination of both, and some supportive symptomatic therapy according to the perceived symptoms. The treatment of squamous cell carcinoma of the head and neck requires integration and coordination from ENT specialists, radiation oncologists, and medical oncologists. Before any action (radiotherapy and/or chemotherapy), patients should be given a comprehensive multidisciplinary approach, including: (1) improving physical, psychosocial, spiritual, and quality of life functions, (2) preventing limitations in function, activities, and participation that may arise, and (3) managing limitations or impairments in function and activities (Ministry of Health Indonesia, 2017). Chemotherapy is a systemic therapy for systemic cancer and clinically or subclinically metastatic cancer. Sometimes chemotherapy becomes the only effective therapy for advanced local stage cancer patients. The cure rate for patients who cannot be treated with

surgery can be improved with chemotherapy. However, the chemotherapy strategy or method can be chosen based on the location of the disease, TNM criteria, and appropriate clinicopathological considerations (Romdhoni, 2017).

## 2.8 Prognosis

The prognosis of Squamous Cell Carcinoma of the Head and Neck is based on the tumor stage, lymph node metastasis, and/or distant metastasis. Patients with well-managed squamous cell carcinoma of the head and neck, such as single surgery or radiation therapy, have a good prognosis. Patients with squamous cell carcinoma usually have accompanying diseases such as severe cardiovascular and lung diseases due to smoking and alcohol consumption, leading to a high mortality rate.

## 3. Conclusion

In conclusion, this literature review provides a comprehensive overview of squamous cell carcinoma (SCC) in the head and neck. Delving into its multifactorial pathogenesis, clinical manifestations, diagnostic challenges, and therapeutic modalities, the review consolidates diverse perspectives to enhance our understanding of this prevalent malignancy. The complexities of SCC underscore the importance of multidisciplinary collaboration for accurate diagnosis and optimal patient management. As ongoing research continues to unravel the intricacies of SCC, this synthesis serves as a valuable resource for healthcare practitioners, guiding improved clinical strategies and inspiring future investigations.

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