



## ONCOGENICITY OF TOBACCO-SMOKING: A REVIEW ON SQUAMOUS CELL CARCINOMA OF THE TONGUE, DIAGNOSIS AND TREATMENT

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### ABSTRACT

Squamous cell carcinoma (SCC) of the tongue is the commonest type of tongue cancer affecting young smokers and older men (over 45 years of age) than women. It represents more than ninety percent of all head and neck cancers, and occurs mainly in the lateral posterior border that may extend to the dorsum of the tongue. The major risk factors for SCC of the tongue are tobacco-smoking (to a greater extent) and frequent consumption of large amounts of alcohol (to a smaller extent). Minor risk factors for SCC of the tongue include irritation induced by chewing tobacco, dental caries, overuse of mouthwash, chewing betel nut and oral human papillomavirus (HPV) acquired via genito-oral route. The early stages of SCC of the tongue are usually asymptomatic, but later stages may present as lesions that appear as areas of erythroplakia or leukoplakia, with ulceration and pain usually at the base of the tongue, and consequently a lump or an induration on the tongue. Diagnosis of SCC of the tongue involves taking a medical history and physical examination of the tongue for unhealed ulcers and nearby lymph nodes for swelling. If SCC of the tongue is suspected, a biopsy of affected areas of the tongue is made, followed by processing of the biopsied tissue and preparation of smears on clean grease-free glass slides. Finally, the smears are stained with the 'Haematoxylin and Eosin (H & E) stain', and then examined under the microscope. The presence of intense pleomorphism, nuclear hyperchromatism, increased nuclear to cytoplasmic ratio, and increased proliferation of epithelial cells is diagnostic of SCC of the tongue. Treatment of this disease involves glossectomy, with postoperative radiation or chemo-radiation. It is not new that tobacco-smoking via cigarettes and shishas, as well as regular consumption of large volumes of alcohol among the elderly and especially young people is rapidly on the increase. Thus, this review was aimed at discussing the consequence of tobacco-smoking with focus on Squamous Cell Carcinoma of the Tongue, its diagnosis and treatment. It is therefore highly recommended that tobacco-smoking, as well as chronic consumption of alcohol be avoided, and that these artisans (smokers and alcoholics) should get themselves examined medically.

**KEYWORDS:** Squamous Cell Carcinoma, Pleomorphism, Hyperchromatism, Erythroplakia, Leukoplakia.

### 1. INTRODUCTION

Squamous cell carcinoma (SCC) of the tongue is a type of Head and Neck cancer, and the most common type of cancer in the oral cavity except those of the lip, and occurs with increasing age affecting about 30,000 people in the United States each year. It accounts for more than ninety percent of all head and neck cancers (Harris *et al.*, 2010), and typically occurs in the elderly men during the fifth to eighth decade of life, and rarely occurs in young patients below the age of forty. However, studies have shown that the incidence of squamous cell carcinoma (SCC) in young people is rapid increasing (Newman *et al.*, 1983).

SCC of the tongue may occur on the front of the tongue (called oral tongue cancer) or in the lateral posterior border at the base of the tongue (called oropharyngeal

cancer) that may migrate to the dorsum of the tongue. It is recorded in patients worldwide, but significant variations in incidence occur with highest incidence reported in Indian populations (Silva *et al.*, 1982). Oral cancer refers to cancer occurring between the vermilion border of the lips and the junction of the hard and soft palates or the posterior one-third of the tongue. The main risk factors for SCC of the tongue are smoking (especially tobacco-smoking), smokeless tobacco (snuff) (Syed *et al.*, 2015) and frequent intake of large quantities of alcohol. Squamous cell carcinoma (SCC) of the tongue may also result from any chronic irritation such as dental caries, overuse of mouthwash, chewing tobacco or betel nut. Oral human papillomavirus (HPV) acquired through genito-oral contact, may also play a role in the cause of SCC of the tongue (Ferlay *et al.*, 2001).

Oral lesions in squamous cell carcinoma (SCC) of the tongue are asymptomatic at early stages. At later stages however, symptoms present as lesions that appear as areas of erythroplakia or leukoplakia, with ulceration. The tumor spreads locally by extension and via the destruction of nearby tissues, with invasion into the cervical lymph nodes (in the neck). It can be diagnosed through biopsy, endoscopy to detect second primary cancer, chest x-ray and computed topography of the head and neck, and can be treated through surgical operation, with postoperative radiation or chemo-radiation (Hyams *et al.*, 1988).

## 2. The Tongue

The tongue is a very mobile muscular organ that appears in the fourth week of life, and fills most of the oral cavity when the mouth is closed. It is lined by stratified squamous epithelium with several functions such as taste, chewing (mastication), swallowing (deglutition), speech and cleaning the oral cavity. Contraction of the muscles shortens the tongue which results in making it thicker and wider. Its major roles are to propel a bolus of food backwards and into the pharynx to initiate swallowing and forming words to enable communication (Landin *et al.*, 2005). It arises from the floor of the mouth, partly in the oropharynx, and consists of muscles covered by mucous membranes (Murray, 1973).

### 2.1 Anatomy of the tongue

The Sulcus terminalis (groove) separates the tongue into two areas:

- Anterior (two-third the body residing in the oral cavity)
- Posterior (one-third the root residing in the throat)

The tongue base ends at the vallecula. The Superior surface or Dorsum of the body contains a forest of fine projections called the lingual papillae. There are four types of papillae, which include filiform, fungiform, circumvallate and foliate. The filiform makes the tongue rough and provides friction, but does not contain taste buds on the body of the tongue (Lacy *et al.*, 2000). The fungiform is widely distributed over the tongue and gives it a reddish hue with presence of taste buds. The circumvallate contains 8-13 elevations forming a V-shaped row at the back of the tongue, placed anteriorly to the sulcus terminalis on the root of the tongue. These elevations contain so many taste buds with small salivary glands beneath them that steadily clean the papillae giving opportunity for new tastes to be experienced. The Foliate is situated on the lateral surface of the tongue close to the circumvallate papillae, but not well developed in humans (Jain and Roper, 1991).

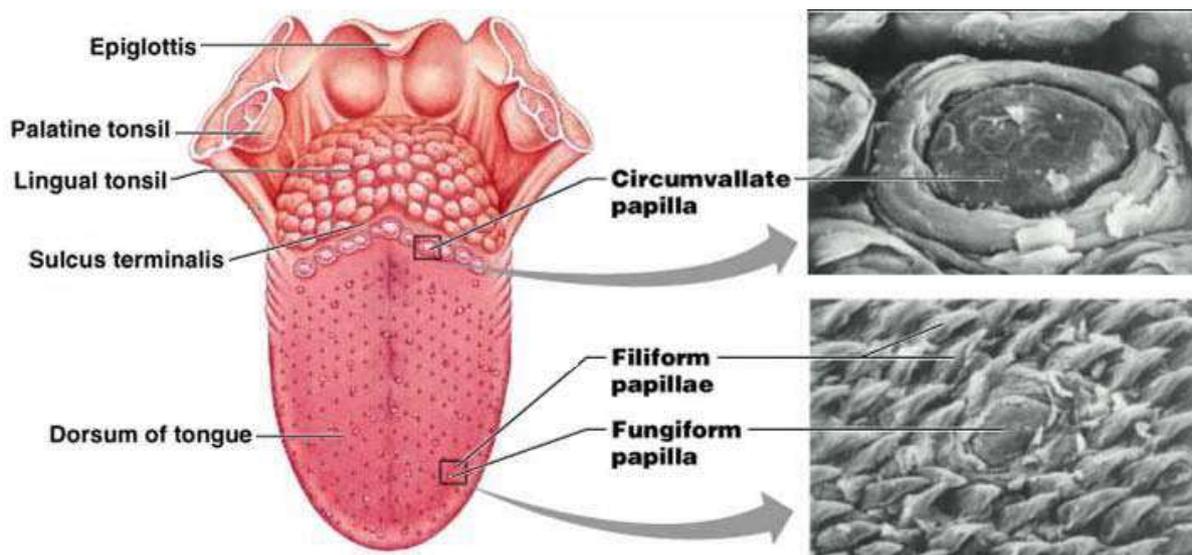


Figure 2.1: The tongue showing various papillae.

### 2.2 Risk factors for Squamous Cell Carcinoma (SCC) of the tongue

The major risk factor for SCC of the tongue is tobacco-smoking (which is usually achieved via smoking of cigarettes and shishas); tobacco smoking accounts for over eighty percent of all cases of SCC. Other risk factors for SCC of the tongue include irritation induced by chewing tobacco, dental caries, overuse of mouthwash, chewing betel nut and oral human papillomavirus (HPV) acquired via genito-oral route. Chronic exposure of the epithelial surfaces of the tongue to these irritants causes a "field cancerisation" sequence

of hyperplasia, dysplasia and carcinoma; that is, the development of premalignant lesions may undergo malignant change to become a cancer (Kirita *et al.*, 1994).

Smoking and consumption of alcohol act synergistically in the development of head and neck cancer (mainly squamous cell carcinoma of the tongue); smoking tobacco with concomitant consumption of alcohol poses a greater risk than when only either of both is taken. A dose-response relationship between tobacco-smoking and the SCC of the tongue also occur; in that the more

you smoke, the more you stand the risk of developing SCC of the tongue. Tobacco smokers are up to twenty-five times more likely to develop squamous cell carcinoma (SCC) of the tongue than non-smokers (Zeng *et al.*, 2001).

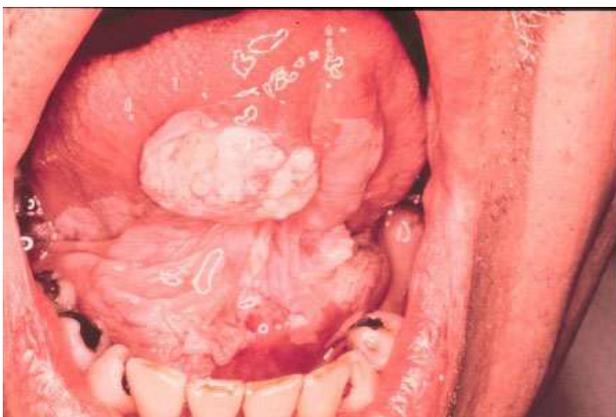
### 2.3 Signs and Symptoms of squamous cell carcinoma (SCC) of the tongue

At the early stage, it is usually asymptomatic, but at the later stages, oral lesions develop usually at the base of the tongue with ulcers and pain, and consequently may migrate to the dorsum of the tongue presenting with a lump or an induration on the tongue. These lesions may also present with erythroplakia (a condition of an abnormal erythematous/red lesion) or leukoplakia (a condition of an abnormal white lesion) of the oral mucosa, or both.

These lesions may be exophytic (grow outward beyond the surface epithelium from which it originates), ulcerated or indurated and firm with a rolled border. As the lesions increase in size, pain, dysarthria (slurred or slow speech that can be difficult to understand) and dysphagia (difficulty in swallowing) may result (Pitman *et al.*, 2000).



**Figure 2.2: Erythroplakia and Squamous cell carcinoma.**



**Figure 2.3: Leukoplakia and squamous cell carcinoma.**



**Figure 2.4: Lesion in tongue dorsum and lateral border, exhibiting deep and necrotic ulceration, with large infiltration in surrounding tissues.**

### 3. Diagnosis of squamous cell carcinoma of the tongue

Diagnosis of SCC of the tongue is based on clinical, histopathological and radiological examinations.

#### 3.1 Clinical Examination

This begins with taking medical history as well as the lifestyle of the patient, followed by physical examination of the tongue for unhealed ulcers or indurations, erythroplakia or leukoplakia, as well as nearby lymph nodes for swelling.

#### 3.2 Histopathological diagnosis of squamous cell carcinoma (SCC) of the tongue

Any suspicious area of the tongue should be biopsied, either incisional or brush biopsy. In incisional biopsy, a small piece of tissue in the suspected area is removed, while in brush biopsy, a small brush is rolled over the suspected area, thereby allowing cells to be collected. The biopsy is then fixed in formalin and processed through tissue processing techniques, and smears made on clean grease-free glass slides. The slides are finally stained with the Haematoxylin and Eosin stain, and then examined under the microscope (Bona and Fauci, 2011).

##### 3.2.1 Principle of Haematoxylin and Eosin Staining

The haematoxylin and eosin (H & E) stain is the most used stain in histology and histopathology laboratories. The objective is to differentiate the tumor, cancer or benign cells from the biopsy. The haematoxylin is a basic dye that stains the acidic component of the cells (such as the nucleus) blue-black, while eosin is an acidic dye that stains the basic component of the cells (such as the cytoplasm, collagen and muscle fibres) pink.

##### 3.2.2 Procedure for Haematoxylin and Eosin Staining Method

1. Heat-fix the smear on slide warmer at 60°C for more than 30 minutes, then dry in 60°C oven for 20-60 minutes
2. Cover slide with xylene for 3 minutes (2 changes)

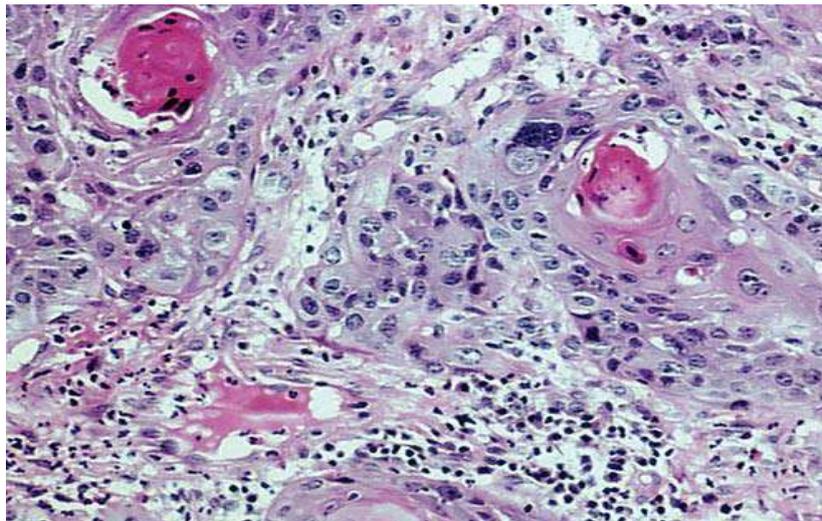
3. Apply 100 percent ethanol for 2 minutes (2 changes)
4. Apply 95 percent ethanol for 2 minutes
5. Wash in running tap water for 2 minutes
6. Apply haematoxylin stain for 4 minutes
7. Wash in running tap water for 2 minutes
8. Differentiate in acid-alcohol for 10 seconds
9. Wash in running tap water for 2 minutes
10. Blue for 10-30 seconds
11. Wash in running tap water for 1 minute
12. Apply 95 percent ethanol for 30 seconds
13. Apply eosin-Y stain for 2 minutes
14. Apply 95 percent ethanol for 30 seconds
15. Apply 100 percent ethanol for 1 minute (2 changes)

16. Apply xylene for 2 minutes (2 changes)
17. Mount slides with mounting media (DPX-Distyrene, Plasticizer and Xylene)

After the staining, allow to air-dry, then examine the specimen under the microscope using x100 objective.

**RESULT**

Stained cancer cells should show intense pleomorphism with great number of mitoses of epithelial cells and nuclear hyperchromatism.



**Figure 2.5: Microphotography of the histopathological examination, showing intense pleomorphism with great number of mitoses of epithelial cells and nuclear hyperchromatism using the H & E Staining Technique.**

**3.3 Radiological Examination**

From results of the histopathological examination of the biopsy, if cancer cells were seen, then a computed tomography (CT) or magnetic resonance imaging (MRI) scan of the tongue and neck is done to assess the grades and stages of the cancer, which are the determining factors for effective treatment. SCC of the tongue is classified using grades and stages. The grade refers to the aggressiveness of the cancer, and how likely it is to spread; it may be low (slow-growing and unlikely to spread), moderate, or high (very aggressive and likely to spread). The stage refers to the extent of metastasis of the

cancer cells; the size of the tumor is denoted by the letter T. The presence of a small tumor is denoted by T1, while the presence of a large tumor is denoted by T4. T2 and T3 are used to denote moderately sized tumours with T3 larger than T2. The probability of whether or not the cancer has metastasized to the cervical lymph nodes (in the neck) is denoted by N. The non-metastasized nature of the cancer is denoted by N0, while the metastasized nature of the cancer cells to the cervical lymph nodes is denoted by N3. Metastasis to distant tissues is denoted by M.

**Table 1: American Joint Committee on Cancer (AJCC) TNM staging Classification for the Lip and Oral Cavity (7<sup>th</sup> ed., 2010).**

Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)	Histologic Grade (G)
<b>TX</b> Primary tumor cannot be assessed	<b>NX</b> Regional lymph nodes cannot be assessed	<b>M0</b> No distant metastasis	<b>GX</b> Grade cannot be assessed
<b>T0</b> No evidence of primary tumor	<b>N0</b> No regional lymph nodes metastasis	<b>M1</b> Distant metastasis	<b>G1</b> Well differentiated
<b>Tis</b> Carcinoma <i>in situ</i>	<b>N1</b> Metastasis in a single ipsilateral lymph node, 3cm or less in greater dimensions		<b>G2</b> Moderately differentiated
<b>T1</b> Tumor 2cm or less in greatest dimension	<b>N2</b> Metastasis in a single ipsilateral lymph node, more than 3cm but not more than 6cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than		<b>G3</b> Poorly differentiated

	6cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6cm in greatest dimension		
<b>T2</b> Tumor more than 2cm but not more than 4cm in greatest dimension	<b>N2a</b> Metastasis in single ipsilateral lymph node more than 3cm but not more than 6cm in greatest dimension		<b>G4</b> Undifferentiated
<b>T3</b> Tumor more than 4cm in greatest dimension	<b>N2b</b> Metastasis in multiple ipsilateral lymph nodes, none more than 6cm in greatest dimension		
<b>T4a</b> Moderately advanced local disease. Tumor invades adjacent structures	<b>N2c</b> Metastasis in bilateral or contralateral lymph nodes, none more than 6cm in greatest dimension		
<b>T4b</b> Very advanced local disease	<b>N3</b> Metastasis in a lymph node more than 6cm in greatest dimension		

#### 4. Treatment of SCC of the tongue

Treatment of SCC of the tongue depends on involvement of the floor of mouth, mandible and other surrounding tissues, the size of the cancer, and palpable cervical lymph node. It may be treated with radiation or surgery, with preference to surgery/surgical removal of the tongue (known as glossectomy) as it remains the most favoured and primary treatment of choice. There are four forms of glossectomy which include: partial glossectomy (in which one-third or less of the tongue is surgically removed), hemi-glossectomy (in which one-third to half of the tongue is surgically removed), near total glossectomy (in which half to three-quarter of the tongue is removed surgically), and total glossectomy (in which three-quarter or greater of the tongue is surgically removed). If metastasis to the lymph nodes occurred, the lymph nodes will be dissected to remove the cancer cells (Martinez, 2011).

For T1/T2 lesion, a partial glossectomy is performed, which provides adequate margins of resection. For T3/T4 cancers, a hemi-glossectomy or total glossectomy is usually necessary; this is because they usually involve adjacent structures such as the floor of the mouth, tonsillar pillar, and/or mandible. Hemi-glossectomy or total glossectomy can lead to defects in speech, breathe, talk and swallow, thus speech therapy is often done after the surgery. Also, postoperative radiation therapy is done for T3/T4 primary cancer to destroy any remnant cancer cells (Martinez, 2011).

In addition to glossectomy and radiation, chemotherapy is also done; some drugs that are usually administered include paclitaxel, ciplastin, methotrexate, 5-Fluorouracil and docetaxel. Combinations of cisplatin and 5-Fluorouracil, carboplatin and 5-Fluorouracil, and cisplatin and paclitaxel may also used.

#### CONCLUSION

Squamous cell carcinoma (SCC) of the tongue is the most common type of cancer accounting for over ninety

percent of all cases of Head and Neck carcinomas, capable of leading to death. Although, it occurs most commonly in elderly men from age 45 and above who are chronic tobacco-smokers, or have a history of tobacco-smoking, recent researches have proven an increase in its incidence in younger tobacco-smokers. Apart from tobacco-smoking, other factors may induce SCC of the tongue due to irritation of the tongue resulting from chewing tobacco or betel nut, oral human papiloma virus and chronic alcohol consumption. It occurs more in male smokers than in female smokers; but may also occur in female non-smokers. Effective treatment may however be effected through proper diagnosis which can only be achieved through clinical, histopathological and radiological examinations. It is highly recommended however, that tobacco-smoking, as well as chronic consumption of alcohol be avoided, and that these artisans (smokers and alcoholics) should get themselves examined medically.

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