Chapter 1

Introduction:

Oral cavity:

Oral cavity represents the first part of digestive tube. It functions as the entrance to the alimentary canal and initiate digestion of bolus by salivation and propulsion. It is oval shaped and bound by lips anteriorly. The oral cavity consists of lips, gingivae, buccal mucosa, hard palate, teeth, tongue, and floor of the mouth. The mylohyoid muscle separates the floor of mouth into two spaces: the sublingual space and the submandibular space. Sublingual space is a space without facial linings whose boundaries are genioglossus muscles. Different types of lesions have been explained in this region such as hemangiomas, vascular malformations, Dermoid cysts, Thyroglossal duct cysts and Ludwig's angina. Few of them are explained in later sections.

Tongue:

Tongue is muscular mass covered with moist mucosal membrane. The rough texture of the tongue is due to the tiny bumps called papillae which are then covered by thousands of taste buds. On an average, human tongue has 2000-8000 taste buds and varies with individuals. These are collection of nerve-like cells connecting to cranial nerves and conducts information to the brain.

Nasal cavity:

Nasal turbinate divide nasal cavity into a labyrinth of slit like passages and is wrinkled by columnar epithelial which is just one cell layer thick. These cells produce a layer of mucus that traps and clears unwanted substances, protects the lining of the nose. Mucus also
contains antibodies, enzymes and other important substances too. The nasal linings are also covered with cilli, small hair-like structures sweeps mucus back and also slows down the air current inhaled warms and moistens the air before reaching the lungs.

The nasal mucosa lines entire nasal cavity from nostril to pharynx. The initial one third of nasal cavity is lined by smooth epithelium (stratified squamous epithelium), multilayer thick. The outermost layer of epithelium cells is covered with a layer of proliferative cells, which is attached to basement membrane. Posterior region of the cavity is lined with pseudo stratified columnar epithelium cells which are then projected to form cillum which overlies a basement membrane. The basement membrane is made up of glands, nerves, cellular elements and blood vessel networks.
**Pharynx:**

Pharynx is the tube behind the nasal and oral cavity. It connects nasal cavity to the larynx so that air can pass in and out of the lungs. It also connects the oral cavity to esophagus so that food bolus may be swallowed and passed on to the stomach for further digestion. Pharynx is further divided into three regions: nasopharynx, oropharynx and laryngopharynx.

**Larynx:**

Larynx is a short tube (1.5 inch) located in the throat, anterior to the esophagus and inferior to the tongue and hyoid bone. Nine supportive cartilages, intrinsic and extrinsic muscles and a mucus membrane shape the larynx. It connects pharynx to the trachea in the neck region. It also called as “voice box” because it contains vocal folds which produce sound for speech.

**Pathology of head and neck cancer:**

The upper aerodigestive tract lesions are similar irrespective of site and these altered epithelial lesions have potential of progressing to squamous cell carcinoma. Microscopic observation of haematoxylin and eosin stained sections for the presence of architectural and cytological changes which are known as epithelial dysplasia is the standard practice for assessment of malignant oral lesions [2]. The grading and diagnosis of oral dysplasia is based on the cytological and morphological changes. Approximately 50% of the lesions show evidence of dysplasia and remaining lesions are either specific hyperplasic or hyperkeratosis.

**Mild dysplasia:**

This shows proliferation of cells in spinous layer and the basal or parabasal layer. Regular stratification or slight cytological atypia can be observed. It does not extend beyond the lower third of the epithelial layer. Morphological changes are minimal and mitoses are not prominent (Figure 2 A).
Moderate dysplasia:

More severe than mild dysplasia, demonstrates proliferation of atypical cells. Architectural disturbances with cytological atypia can be observed extending to one third of the epithelium. Abnormal mitoses may be present which will be located to the basal layer (Figure 2B). Maturation and stratification is normal with hyperkeratosis.

Severe dysplasia:

In severe dysplasia abnormal proliferation is observed encompassing from the basal to upper layer of epithelium with prominent architectural and cytological changes (Figure 3C). Pleomorphic cells with large nuclei and multiple nucleoli are seen. Tripolar, suprabasal mitoses are evident with apoptotic bodies and architectural changes. Complete loss of stratification with abnormal keratinization with abnormal form of rete pegs with lateral extensions and small branches which could be early signs of invasion. Epithelium is thickened in severe dysplasia which is often escorted by epithelial atrophy.

Carcinoma in situ:

This is most severe form of epithelial dysplasia displays thickened epithelium and full cytological and architectural changes. Such changes are rare in oral cavity, presence severe atypia indicating malignant transformation has occurred but not the invasion. Atypical mitosis and marked changes in architectural and structural aspects off the epithelium. Although these changes are in the lower third of the epithelium, but cytological changes are rigorous. These are statistically more likely to progress to the cancer (Figure 2D).
Risk factors

HNSCC is primarily caused by two factors: 1) Tobacco and alcohol use 2) Human papilloma virus infection, mainly caused by sexual transmission. Other factors include gender, age, exposure to Epstein - Barr virus, betel quid, ill-fitting dentures, poor oral and dental hygiene and spices.

*Tobacco:*

Tobacco consumption is the primary cause of development of HNSCC. Approximately 90% of the patients diagnosed have history of tobacco use with increased risk of more than four-fold of developing oral cavity, oropharynx and hypopharynx cancers, among smokers.
compared to non-smoker individuals [3, 4]. Tobacco smoking and alcohol drinking together synergistically elevates the risk of HNSCC [3, 5]. Carcinogenic effect of tobacco in HNSCC is dose dependant, and relates to the frequency duration and intensity of the smoking. Smokeless tobacco such as snuff, chewing tobacco, is also another important risk factor, in particular cancer of oral cavity [6]. People in many countries have history such as North America, Northern Europe, South Africa, India and Asian countries have long history of using smokeless tobacco and related products. Smokeless tobacco users have fourfold increase in risk of HNSCC compared to the non-users [7]. The chewing tobacco related cases are maximum in India and it is consumed in multiple forms such as khaini, dohra, betal leaf, gutkha, pan masala, zarda and mishri [8].

**Alcohol:**

Although alcohol is not considered as carcinogen, excessive consumption increases the risk of cancer. Alcohol independently increases the risk of HNSCC with 1% to 4% cases ascribed to alcohol users and tobacco non-users only [9], particularly hypopharyngeal cancer is prominent compared to other sites [10, 11]. Combined effect of tobacco and alcohol has greater than multiplicative effect in increasing the risk of HNSCC [9, 12].

**Gender, age and race:**

In most countries, men are at higher risk of HNSCC than women, this is attributable to the more use of tobacco and alcohol in men compared to women [13, 14]. The risk of HNSCC also increases with the increase in age; particularly mean age of diagnosis for all anatomical sites is the sixth or seventh decade of the life.

Studies have depicted differences in HNSCC incidence pattern and survival in White Americans and African-Americans. Oropharyngeal and oral cavity cancer mortality in
African-Americans 6.5 per 100,000 compared to 3.7 per 100,000 in White Americans between 2002 and 2006 [15]. Lower socioeconomic status, poor access to health care, late disease presentation is the main factors for such outcome differences [16-19].

**Human papilloma virus:**

The association of Human papilloma virus (HPV) and HNSCC has been under investigation for couple of decades. The morphological similarity between oral and genital HPV related lesions led to the postulation that HPV might be involved in oral and oropharyngeal squamous cell carcinomas which later confirmed in 1985 [20]. HPVs are non-enveloped DNA viruses and have affinity towards human squamous cells epithelium. A spectrum of lesions ranging from benign hyperplasia to precancerous lesion with potentially higher malignancy is caused by about 120 different types of strains [21]. Based on the epidemiological and molecular evidences two strains i.e. HPV 16 and 18 were established to be carcinogenic in humans [22]. Capsid proteins, E6 and E7 get integrated into host genome and interfere with function of p53 and retinoblastoma (Rb) tumor suppressor genes by binding and degrading these genes [23, 24]. Squamous columnar junction of pharynx which is similar to the transformation zone of uterine cervix is the most common site of HPV infection due to simple access to basal cells [25]. Increased expression of p16 and downregulation of p53 and Rb observed in HPV-associated HNSCC cases [26]. The 5 year survival rate for HPV-associated HNSCC is 79% compared to HPV negative tumors for which survival rate is 20% and recurrence rate is less in HPV+ cases (14%) compared to HPV- cases (45%) [27].

**Epidemiology:**

**Global scenario:**
HNSCC is the sixth most common cancer worldwide with approximately 65,000,000 cases diagnosed per year resulting 3,00,000 deaths annually [28]. More than 90% of these head and neck cases are squamous cell carcinoma and arises from mucosal surfaces of the oral cavity, oropharynx and larynx. There is large geographical variation in the incidence and anatomical distribution of HNSCC worldwide, which is attributed to the differences in the alcohol consumption and tobacco use, the major risk factors[5, 29]. In the United states HNSCC is eighth most common cancer, with 53,000 cases diagnosed and 11,500 deaths per annum[30]. Among the European countries, France has the highest incidence rate for HNSCC. High rate of incidence is also noted in Hungary, Slovenia and Slovakia[30].

![Graph showing worldwide distribution of head and neck cancer standardized incidence rate](image)

**Figure 3: Worldwide distribution of head and neck cancer standardized incidence rate (1/100,000) (Oral cancer foundation, WHO)**

**Indian scenario:**

Greater than 57% of head and neck cancer occurs in Asia, especially India and China. In India head and neck cancer contributes to more than 30% of all the cancer sites except
Dibrugarh, Assam where it is 49% [31]. Among all the sites in head and neck cancer, tongue and mouth contributes to more than one third except in Dibrugarh where hypopharynx (34%) is the major contributor. Among females mouth cancer is the leading site of cancer and constitutes 11 to 16% of all the cancers [32, 33].

Figure 4: Top cancer incidences in India in both male and female

Head and neck cancer is most frequent among male and seen after age of 55 years. According to The National Cancer Registry Program (NCRP), ICMR, New Delhi, report 2007-2011 which covers statistics for all the cancers all over the India, Mumbai has the highest incidences of mouth and tongue cancer for both the sexes.