REVIEW ARTICLE

ORAL SQUAMOUS CELL CARCINOMA (OSCC): REVIEW AND HISTOLOGICAL TYPES

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Evidence of head and neck cancers has been found in ancient skulls. The oldest known tumour is contained in a fossil found in East Africa by Leakey that dates back more than 500,000 years. It is speculated by some historians that there may have been high incidence of nasopharyngeal carcinoma in some ancient populations because of wood smoke inhalation in poorly ventilated huts. Hippocrates, in approximately 400 BC, described a common chronic ulcer at the edge of the tongue that he attributed to the presence of sharp teeth rubbing against the tongue[1].

EPIDEMIOLOGY

Squamous cell carcinoma is the most common type of oral cancer, accounting for about nine out of every ten oral malignancies, and is a major cause of cancer morbidity and mortality[2]. It is also amongst the 10 most common malignancies in Pakistan, mostly involving patients above the age of 50 years, with a peak incidence in 6th to 7th decades[3,4]. In certain countries like Pakistan, India, Sri Lanka and Bangladesh it is the most common cancer[5,6]. Males are affected more often than females because of heavier indulgence in both tobacco and alcohol habits in most countries with 5% of OSCC occurring in men and 2% in women. A study carried out in Pakistan showed both genders to be affected equally, with a male to female ratio of 1.09:1, and the tongue and lips as the most frequently invovlved sites[4]. However in India, the highest rates of OSCC are found in women who chew tobacco heavily[7].

AETIOLOGY

Tobacco Smoking

It is one of the dominant risk factors, the other one being alcohol abuse. Tobacco smoking puts an individual at much higher risk of developing oral cancer as opposed to persons who do not smoke[8]. Lewin et al[9] (1998) conducted a study on Swedish males age 40-79 years, which showed that those who were tobacco smokers at the time of study, the relative risk for head and neck cancer was 6.5%. After cessation of smoking, the risk was found to decline gradually, with no excess risk found after 20 years. In addition it has been shown through studies this relative risk for smoker's as compared to non-smokers is dose dependant for cigarette smokers, being at least five for persons smoking five cigarettes daily and rises up to 17 times for those who smoke 80 cigarettes or more per day. The risk also increases the longer the person smokes[10]. In India and certain South American countries, "Reverse smoking", the habit of holding the lighted end of the cigarette inside the mouth is associated with a significantly higher risk of oral cancer. The intensity of tobacco consumption adjacent to palatal and lingual tissues is responsible for this high risk[11]. In such cases 50% of all cases are found on the hard palate, which is a site usually spared by this disease[11]. Studies have also shown that pipe and cigar smoking carries a greater risk of oral cancer than cigarette smoking. Along with increased risk of developing cancer in any region of the mouth, persons who smoke pipe show higher risk of developing carcinoma of the lower lip[11]. The dominant risk factors are tobacco use and alcohol abuse, which are strongly synergistic[1].

Smokeless Tobacco

Chewing of various forms of smokeless tobacco; such as snuff, naswar, bidi or chutta (coarse cheroots) smoking and betel quid with tobacco, has been found to be most strongly associated with OSCC, increasing the risk significantly[12,13]. According to studies in Pakistan, tobacco use is the most important

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causative factor in OSCC, for example in the form of 'Naswar'[14]. The risk of 'naswar' chewing is ten times in males and fourteen times in females[12]. Oral smokeless tobacco use is a major cause of SCC in the Indian Sub-continent, parts of South East Asia, China and Taiwan, especially when consumed in betel quids containing areca nut and calcium hydroxide (lime). Areca nut has been declared a known human carcinogen by an IARC (2003) expert group[9].

Alcohol

Excessive alcohol consumption has been implicated in oral cancer[15]. Whether alcohol itself is a carcinogen has not been proven yet, but it is well established that alcohol in combination with tobacco is a significant risk factor[8]. It has been shown that the relative risk associated with alcohol consumption of 50 grams or more per day versus less than 10 grams per day was 5.5%, and an almost multiplicative effect was found for tobacco smoking and alcohol consumption. It has been shown that the risk is dose dependant as well as time dependant and that the combination of alcohol and tobacco abuse over long periods may increase a person's risk for oral cancer by a factor of 15 or more[10]. It is believed that the effects of alcohol may occur through its ability to irritate mucosa and to act as a solvent for carcinogens (especially those in tobacco). Contaminants and additives with carcinogenic potential that are found in alcoholic drinks are also thought to have a role in oral cancer development. It has also been suggested through molecular studies that the carcinogenic risks associated with alcohol may be related to the effects of an alcohol metabolite, acetaldehyde, through the alteration of keratinocyte gene expression[11].

Oncogenic Viruses

Oncogenic (tumour producing) viruses are thought to play a major role in a wide variety of cancers, although no virus has been definitely proven to cause oral cancer so far. In the past Retro viruses, Herpes simplex virus (HSVs), Adenoviruses and Human papilloma viruses (HPVs) all have been suggested to play a role in the development of oral cancer however, HPV is the only one still implicated, not only in oral cancer but also in carcinoma of pharyngeal tonsil, larynx, oesophagus, uterine cervix and uvula[10,16]. In fact, some epidemiological studies suggest that HPV-positive oro-pharyngeals cancers comprise a distinct entity with a markedly increased prognosis. The HPV subtypes 16 and 18 are the strains most closely associated with dysplasia and squamous cell carcinoma and are found in variable but a small proportion of oral and up to 40% of oro-pharyngeal cancers. The HPV is believed to contribute to carcinogenesis through two virally encoded genes, E6 (which promotes degradation of p53 tumour suppressor gene product) and E7 (which promotes degradation of the Retinoblastoma protein [Rb] tumour suppressor gene product[7,10,11].

Radiation and Ultraviolet (UV) Light

Radiotherapy to the head and neck area increases the risk of the later development of a new primary oral malignancy, either a carcinoma or a sarcoma. This effect is dose dependant, but even low dose radiotherapy for benign entities may increase the local risk up to some extent[10,11]. The UV light is a known carcinogenic agent and is a significant factor in SCC of the skin and lips. The cumulative dose of sunlight and the amount of protection by natural pigmentation are significant in the development of these cancers[10,17].

Nutritional Deficiencies

Although poor nutritional status has been linked to an increased risk of oral cancer, the only convincing nutritional factor that has been associated with oral cancer is iron deficiency of Plummer–Vinson syndrome (Patterson Kelly syndrome, sideropenic dysphagia). This syndrome is associated with an elevated risk for SCC of the oesophagus, oropharynx and posterior part of mouth and at an earlier age than in patients without iron deficiency anaemia[10,11,17,18].

A compromised immune system puts patients at risk for oral cancer. Persons with Acquired immunodeficiency syndrome (AIDS) and those undergoing immunosuppressive therapy for organ transplantation or

malignancy are at increased risk for OSCC and other head and neck malignancies, especially when tobacco smoking and alcohol abuse are also present[10,11,17].

Miscellaneous

Various other factors have been associated with the development of oral cancer. According to recent evidence, there is increased risk of oral cancer and nasal and nasopharyngeal carcinoma in workers in the wood products industry who are chronically exposed to certain chemicals, such as 'phenoxyacetic acids'. Tertiary syphilis has also been accepted as having a strong association with the development of dorsal tongue carcinoma[12]. Hyperplastic candidiasis is also considered as a precancerous condition. Certain strains of Candida albicans have been shown to produce nitrosamines, chemicals that have been implicated in carcinogenesis[19].

LOCALIZATION

Tumours can arise in any part of the oral cavity. It most commonly involves the lower lip, lateral border of the tongue and floor of the mouth, however the site most commonly involved varies from one geographical region to the other depending upon the various risk factors involved[7,10,20]. According to a study conducted by Wahid et al[12] in the northern areas of Pakistan, buccal cavity is the site most commonly involved, followed by the lip, tongue and gums. Another study shows the tongue followed by lips to be the most commonly involved sites[4].

CLINICAL PRESENTATION

The OSCC may present clinically as a red lesion (erythroplakia), white lesion (leukoplakia) or a mixed red and white lesion (speckled leukoplakia), an ulcer, fungating mass or an infiltrative lesion[21,22]. However most patients present with symptoms of locally advanced disease. Cancer of the buccal mucosa may present as an ulcer with indurated, raised margins, exophytic or verrucous growth or with the site of origin depending on the preferred site of placement of betel quid or tobacco. As the disease progresses, the lesions infiltrate into the adjacent bone and overlying skin. Carcinoma of the tongue may present as a red, partially nodular area or a deeply infiltrating ulcer, which may later lead to reduced tongue mobility[7].

HISTOPATHOLOGY

Squamous cell carcinoma arises from dysplastic surface epithelium and is characterized histopathologically by invasive islands and cords of malignant squamous epithelial cells Squamous differentiation, often seen as keratinization with variable "pearl" formation, and invasive growth are the prerequisite features of SCC. Invasion is manifested by disruption of the basement membrane, and extension into the underlying tissue, often accompanied by stromal reaction. Angio-lymphatic and peri-neural invasion are additional signs of malignancy. The tumours are traditionally graded into well-, moderately-, and poorly- differentiated SCC[7]. The tumour cells generally show abundant eosinophilic cytoplasm with large often hyper chromatic nuclei and an increased nuclear to cytoplasmic ratio. Round foci of concentrically layered keratinized cells (keratin pearls) may be produced within the lesion, along-with individual cell keratinization[10]. Well differentiated SCC resembles closely normal squamous epithelium. Intercellular bridges are readily recognizable, keratin pearls are seen frequently. Nuclear and cellular pleomorphism is not prominent and there are relatively few mitotic figures[7,19]. Moderately differentiated SCC contains distinct nuclear pleomorphism and mitotic activity, including abnormal mitoses; there is usually less keratinization, but is still readily identified as squamous in type[7,10,19]. In poorly differentiated SCC, immature cells predominate, with numerous typical and atypical mitoses, and minimal keratinization[10]. Locally, most OSCC are extensively destructive. The pattern in which the tumour invades the adjacent normal tissues is variable. Tumours may have: **Cohesive Invasive front:** consisting of broad sheets or groups of malignant cells and is associated with a better prognosis. **Non-Cohesive front:** consisting of small islands, narrow strands or

individual cell infiltration and is associated with a worse prognosis[23,24].

VARIANTS OF ORAL SQUAMOUS CELL CARCINOMA

Verrucous Carcinoma

It is a low grade variant of OSCC[10,25]. It is found predominantly in men older than 55 years of age. Chronic smokeless tobacco use is accepted as the primary etiological factor. It is characterized by very well-differentiated epithelial cells that appear more hyperplastic than neoplastic, key feature being the invasive nature of the lesion in the form of broad pushing margins and chronic lymphocytic infiltrate in the subjacent connective tissue[10].

Spindle cell carcinoma

It is a rare variant of SCC characterized by dysplastic surface squamous epithelium in conjunction with an invasive spindle cell element[10,26,27]. It is more common in the larynx than in the oral cavity.

Basaloid Squamous cell carcinoma

It is a variant of SCC found mostly in the upper aero-digestive tract. It has two microscopic components; the first is a superficial well-differentiated or moderately-differentiated SCC. The second deeper component is an invasive basaloid epithelium arranged in islands, cords and gland like lobules. It is believed to be associated with smoking related and HPV associated tumours[10,27,28].

Adenosquamous carcinoma

It is a rare, aggressive variant of SCC characterized histopathologically by a combination of adenocarcinoma and squamous cell carcinoma and is associated with poor prognosis. It is most frequently seen as a component of a large squamous cell carcinoma[10,26,29].

Carcinoma cunniculatum

This rare variant of oral cancer has similarities to the lesion more commonly seen in the foot in which tumour infiltrates deeply into bone. The oral tumours show proliferation of stratified squamous epithelium in broad processes with keratin cores and keratin filled crypts which seem to burrow into bone, but lack obvious cytological features of malignancy[7].

Papillary Squamous cell carcinoma

It is usually recognized in the oral cavity and pharynx as a component of a large SCC. The tumour is characterized by a predominant papillary growth pattern. These papillae have thin fibro vascular cores covered by neoplastic, immature basaloid cells or more pleomorphic cells. Stromal invasion consists of a single or multiple nests of tumour cells with dense lympho-plasmacytic inflammation at the tumour-stromal interface[7,26].

Acantholytic Squamous cell carcinoma

This is an uncommon and rare histopathologic variant of SCC, characterised by acantholysis of the tumour cells, creating pseudo lumina and false appearance of glandular differentiation. It mostly involves the sun exposed areas of the skin, the lip being the most frequently involved oral site[30,31].

Human Papillomavirus (HPV) Positive Oropharyngeal Cancer (OPC)

It is also known as HPV 16+ oro-pharyngeal cancer or HPV 16+ OPC. It is a recognized subtype of oro-pharyngeal carcinomas and is associated with HPV type 16 virus. The pathologic features of HPV16+ OPC differ from those of the moderately differentiated OSCC in that the former consistently: Arise from tonsillar crypts, Are un-associated with dysplasia of the surface epithelium, Exhibit lobular growth, are permeated by infiltrating lymphocytes, Lack significant keratinization, Demonstrate a prominent basaloid morphology. At the molecular genetic level, HPV-positive HNSCCs express the viral onco-proteins E6 and E7, overexpress the p16 gene product, and only infrequently harbour p53 gene mutations. HPV16-positive HNSCCs are associated with an improved prognosis. The mechanisms underlying this favourable prognosis may involve the combined effects of immune surveillance to viral-specific tumour antigens, an intact apoptotic response to radiation, and the absence of widespread genetic alterations

associated with smoking (i.e., field cancerization)[32,33].

IMMUNOPROFILE

The SCC expresses epithelial markers such as cytokeratins. The patterns of expression of cytokeratin subtypes may change during malignant transformation and relate to the histologic grade, degree of keratinization, and the likelihood of metastases. Low-grade SCC expresses medium-high molecular weight (MW) cytokeratins, but not low MW cytokeratins, similarly to normal squamous epithelium. In contrast, high-grade SCC tends to lose the expression of medium to high MW cytokeratins, and express low MW cytokeratins . High-grade SCC may express vimentin[7].

METASTASIS

The OSCC spreads by invading the lymphatic vessels. It most frequently involves the submandibular and the superficial and deep cervical lymph nodes. The first draining lymph node from a tumour is called the 'sentinel node'. Lymphatic spread of the tumour occurs through the sentinel node to other lymph nodes. Haematogenous spread, although less important, may occur, and mostly involves the lung. Spread of tumour to the local lymph nodes indicates worse prognosis. Tumours that spread beyond the regional lymph nodes often metastasize to the lungs and liver. A lymph node that has been invaded by tumour usually appears enlarged, firm and fixed on clinical examination[7,17]. The lymph nodes of the neck are divided into various compartments known as 'levels', these are; Level I to level –VI (sub-mental nodes (IA) and submandibular nodes (IB); upper jugular nodes; middle jugular nodes; lower jugular nodes; posterior triangle lymph nodes; and pre-tracheal, para-tracheal and peri- thyroid nodes[7].

TREATMENT OPTIONS

Management of OSCC requires a multidisciplinary approach. The treatment options are usually discussed in a tumour board comprising of pathologists, surgeons, radiation and medical oncologist, dental surgeons, prosthodontists and speech therapists[34]. The main treatment options are surgery and radiotherapy; chemotherapy being usually reserved for patients with metastases and is not a primary treatment approach for oral cancer[35,36].

Low stage cancers (stage I and II) are treated with surgery or radiation alone, since five –year survival rates are similar for both modalities and the decision is based on tumour site, size, grading and advice of multidisciplinary team approach. However most patients present with advanced disease (Stage III and IV), when more complex therapy is required and prognosis is worse[35]. In such patients a combination of surgery and radiotherapy is the best treatment option[37].

Cervical lymph node metastasis has a tremendous impact on prognosis for patients with OSCC, reducing the survival by 50%[38]. Neck dissections are generally performed for management of both occult and clinically positive neck disease, which means patients with stage III or IV OSCC. However, recent studies have shown high rates of lymph node metastasis in early stages (Stage I and II) of OSCC, therefore some experts suggest elective neck dissection in these patients[37,39].

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