REVIEW ARTICLE

ORAL CANCER - A JOURNEY TO UNRAVEL THE PAST

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is the most common malignant tumour in the oral and maxillofacial region. It is the sixth most common malignancy and is a major cause of cancer morbidity and mortality. OSCC accounts for 95% of malignant lesions of the mouth and is a major problem worldwide. The relative prevalence of oral SCC is 3–5% of all cancer. The purpose of this article is an attempt to review a brief frame work about epidemiology, etiology, pathogenesis, clinical presentation, staging and grading of Oral cancer.

Key words: oral cancer, staging, grading

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INTRODUCTION

The term 'cancer' has originated from Greek word Karkinos, a crab, referring to an irregular jagged shape often assumed due to local spread of carcinoma.[(1)] Oral cancer is an epithelial neoplasia generally beginning as a focal clonal overgrowth of altered stem cells near the basement membrane, expanding upward and laterally, replacing the normal epithelium. The neoplastic process is a beginning with normal epithelium progressing through hyperplasia to dysplasia to carcinoma in situ and invasive carcinoma.[(2)] The term 'oral cancer' includes a diverse group of tumors arising from the oral cavity, usually includes cancers of the lip, tongue, pharynx and oral cavity.[(3)]

EPIDEMOLOGY

Globally, the varied incidence rates of oral cancer (per 100,000 cases) are seen ranging from 2.0 (UK) to 9.4 (France); 4.4 in Colombia to 13.4 in Canada; 1.6 Japan to 13.5 India; and from 2.6 New Zealand to 7.5 in South Australia. Each year, about 5, 75,000 new cases and 3,20,000 deaths occur world-wide.[4] The estimated new cancer cases in 2007 worldwide will be more than 12 million, 6.7 million will occur in economically developing countries, of which 4.7 million will result in death. On an average about 8-8.5% men and 4-8.1% women could develop oral cancer in their lifetime in developing countries.[5] Some countries with the highest incidence rates for oral cancer in the world are located in the region of South Asia. India has always been cited as the country with the highest incidence in the world, though in some recent reports Sri Lanka and Pakistan are ranked at the top. In India alone over 100,000 cases are registered every year. According to cancer incidence in five continents one district of India (Bhopal) has the highest incidence for cancers of both the tongue (10.9 per 100,000) and mouth (9.6 per 100,000) in the world.[6] It is estimated that more than one million new cases are being detected annually in the Indian subcontinent out of which 92-95% of all oral malignancies are oral squamous cell carcinoma (OSCC).[7]

ETIOLOGY

Oral squamous cell carcinoma is an age related disease, with about 90% to 95% of cases occurring in persons above the age of 40 years.[8] The etiology of OSSC is multifactorial. Genetic, environment, social and behavioral effects may all be implicated. Tobacco is by far the main risk factor for OSCC and this applies to not only smoke but also to smokeless tobacco.[9] The other risk factor for cancer is alcohol. Alcohol is oxidized to acetaldehyde and may act as a solvent and enhance the penetration of carcinogens into target tissues.[10] There is a significant joint multiplicative risk for OSCC in people who are both alcohol drinkers and heavy tobacco smokers.[11] There is also a relationship of OSCC with betel nut. The International agency for research on cancer (IARC) long ago declared that betel nut was carcinogenic to humans and that has been confirmed.[12] There is a relationship with HPV 16, HPV 18 and OSCC, particularly oropharyngeal carcinoma.[13] The dentition may also play a role in OSCC. Head and neck and oesophageal dysplasia/cancer has been found associated with dental neglect.[14] Periodontal diseases has been implicated in OSCC.[15] Other conditions associated with an increased risk of OSCC includes diabetes[16] and candidal infection.[17] Diet may play a role in OSCC development as evidenced by multiple epidemiological studies worldwide.[18] Apart from the dietary risk factors for OSCC such as alcohol and other factors, studies show that consumption of fruits and vegetables will have a protective effect.[19] Thus, environmental insults such as alcohol and/or tobacco products presumably increase DNA damage, increase p53 expression, and thereby activate clusters of genes associated with cell growth, and/or cell death.[20]

PATHOGENESIS

Tumorigenic genetic alterations consist of two major types: tumor suppressor genes, which promote tumor development when inactivated; and oncogenes, which promote tumor development when activated. Tumor suppressor genes can be inactivated through genetic events such as mutation, loss of heterozygosity, or 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.[21] The cell of origin of OSCC is the oral keratinocyte. OSCC, as any cancer, is caused by DNA mutation, often spontaneous but increased by exposure to any of a range of mutagens like chemical, physical or microbial. The various changes in the DNA can progress from a normal keratinocyte to a pre-malignant or a potentially malignant keratinocyte that is characterized by an ability to proliferate in a less controlled fashion than normal. The cells become autonomous and a true cancer results, characterized by invasion across the epithelial basement membrane and, ultimately, metastasis to lymph nodes, bone, brain, liver and other sites.[22]

CLINICAL PRESENTATION

Symptoms: Pain is a common symptom in oral cancer patients, representing 30–40% of their main complaints. Although pain is the main symptom, it usually arises only when the lesions have reached a remarkable size, thus, early carcinomas often go unnoticed because they are asymptomatic. Other symptoms include ear pain, bleeding, and mobility of teeth, problems in breathing, difficulty in speech, dysphag, and problems using prosthesis, trismus, and paraesthesia. Occasionally patients may present with cervical lymphadenopathy without any other symptoms. In terminal stages, patients may develop skin fistulas, bleeding, severe anaemia and cachexia.[23]

Oral carcinoma presents with varied clinical features as follows:

- Exophytic (mass-forming, fungating, papillary, verruciform)
- Endophytic (invasive, burrowing, ulcerated)
- Leukoplakia (white patch)
- Erythroplakia (red patch)
- Erythroleukoplakia (combined red and white patch).[24]

Initial stages: The clinical presentation of these early malignant lesions is usually in the form of an erytholeukoplastic lesion. It consists of red or red and white areas with a slight roughness and is well-demarcated.

Advanced stages: The classic features of oral malignancy include ulceration, nodularity and fixation to underlying tissues.

Ulceration: This is one of the most common and best known features of OSCC. The ulceration has an irregular floor and margins, and is elevated and hard on palpation. When the lesion is large the patient often has severe pain, radiating from the lesion to the ipsilateral ear.

Lump: In these advanced stages, exophytic tumours with warty surfaces, poorly defined boundaries and hard to palpation may be seen.

Less common presentations: OSCC may manifest with paraesthesia or numbness of the chin. Others manifest with delayed healing after a dental extraction, or sometimes a lump with abnormal supplying blood vessels, dysphagia or weight loss.[23]

TNM STAGING

The stage of the disease depends on several factors, including the size of the primary lesion, local extension, lymph node involvement, and evidence of distant metastasis. Tumor size, the organ or tissue affected, and the extent of spread are considered to be the best indicators of the patient's prognosis. (TNM) classification of oral cancer has 3 basic clinical features: the size (in centimeters) of the primary tumor; the presence, number, size, and spread (unilateral or bilateral) to the local lymph nodes; and the presence or absence of distant metastasis. Among the commonly applied schemes in oncology are the classifications proposed by the International Union against Cancer (UICC) and the American Joint Committee on Cancer Society (AJCCS).[25]

The *tumor-node-metastasis (TNM)* staging system was first reported by Pierre Denoix in the 1940s. The *International Union against Cancer (UICC)* eventually adapted the system and compiled the first edition of the TNM staging system in 1968 later it was modified in *1974* and was given as follows.[26]

T – Extent of primary tumor

N – Condition of regional lymph nodes

M – Absence or presence of distant metastasis

T – Primary Tumor

TIS – Carcinoma in situ

T1 – Tumor 2 cm or less in greatest diameter

T2 – Tumor greater than 2 cm but not greater than 4 cm in greatest diameter

T3 – Tumor greater than 4 cm in greatest diameter

N – Regional lymph nodes

N0 – No clinically palpable cervical lymph nodes; or palpable nodes but metastasis not suspected

N1 – Clinically palpable homolateral cervical lymph nodes that are not fixed; metastasis suspected

N2 – Clinically palpable contralateral/ bilateral cervical lymph nodes that are not fixed; metastasis suspected

N3 – Clinically palpable lymph nodes that are fixed; metastasis suspected

M – Distant metastases

M0 – No distant metastases

M1 – Clinical and/or radiographic evidence of metastases other than to cervical lymph nodes

Clinical stage – Grouping of carcinoma of oral cavity: [27]

Stage I: T1 N0M0

Stage II: T2N0M0

Stage III: T3N0M0

T1N1M0

T2N1M0

T3N1M0

Stage IV: T1 N2M0 T1 N3M0 or any T or N category with M1

T2N2M0 T2N3M0

T3N2M0 T3N3M0

REVIEW OF HISTOPATHOLOGIC MALIGNANCY GRADING IN ORAL SQUAMOUS CELL CARCINOMA

Histologic grading has been used for many years in an attempt to predict them clinical behavior of squamous cell carcinomas in the head and neck region. Histopathologic evaluation of the degree to which the tumor e.g. oral squamous cell carcinoma resembles its parent tissue (squamous epithelium) and produces its normal product (keratin) is called *grading.* The first level of histological assessment of OSCC is usually the grading of the tumor using the method based on the degree of differentiation introduced by Broders in 1920. It takes into account the degree of keratinization, cellular and nuclear pleomorphism and mitotic activity. Tumors are generally divided into three categories: grade 1 (well differentiated), grade 2 (moderately differentiated) and grade 3 (poorly differentiated). [28]

Broders A.C. system was based on the proportion of differentiated cells to undifferentiated or anaplastic cells. Broders classification with modification is. [29]

Grade I: Well differentiated tumors – 75-100% of cells are differentiated

Grade II: Moderately differentiated tumors – 50-75% of cells are differentiated

Grade III: Poorly differentiated tumors – 25-50% of cells are differentiated

Grade IV: Anaplastic tumor – 0-25% of cells are differentiated

A reported lack of correlation between Broder's grade and prognosis of head and neck squamous cell carcinomas has been explained by the fact that squamous cell carcinomas usually exhibit a heterogenous cell population with probable differences in invasive and metastatic behavior. A new grading system of head and neck squamous cell carcinomas was originally introduced by Jakobsson et al. (*1973*) which includes the morphologic parameters "structure", "tendency to keratinization", "nuclear aberrations", and "number of mitosis", but also an evaluation of tumor-host relationship as estimated by parameters such as "mode," "stage of invasion", "vascular invasion" and "degree of lymphoplasmocytic infiltration".

ANNEROTH et al (1987) histologic grading system: [30]

It was based on Jakobsson et al. system for application to squamous cell carcinoma in the tongue and floor of mouth. One of the parameters, "vascular invasion" was omitted. Statistical analysis revealed that the reproducibility of the system was good for all morphologic variables. Mean total malignancy, tumor population and tumor-host relationship scores showed statistically significant correlation with mean rating for all the different

Jakobbson et al (1973) histologic grading system: [4]

Histologic grading of malignancy based on tumour cell population				
Tumor Cell Population	1	2	3	4
Structure	Papillary and solid	Strands	Small cords and groups of cells	Marked cellular dissociation
Differentiation	Highly; Keratinization	Moderately; some keratinization	Poorly; minimum keratinization	Poorly; no keratinization
Nuclear polymorphism	Few enlarged nuclei	Moderate number of enlarged nuclei	Numerous	Anaplastic immature enlarged nuclei
Mitoses	Single	Moderate number	Great number	Numerous
Histologic grading of malignancy based on tumor-host relationship				
	1	2	3	4
Mode of invasion	Well-defined borderline	Cords, less marked borderline	Groups of cells, no distinct borderline	Diffuse growth
Stage of invasion	Possibl	Microcarcinoma (few cords)	Nodular, into connective tissue	Massive
Vascular invasion	None	Possibly	Few	Numerous
Cellular response (plasma-lymphocytic infiltration)	Marked	Moderate	Slight	None

Anneroth et al (1987) histologic grading system:

Histologic grading of malignancy of tumor cell population				
Morphologic Parameters	1	2	3	4
Degree of keratinization	Highly keratinized (>50% of the cells)	Moderately keratinized (5-20% of the cells	Minimal keratinization (5-20% of the cells	No keratinization (0-5%)
Nuclear polymorphism	Little nuclear polymorphism (>75% mature cells)	Moderately abundant nuclear polymorphism (50-75% mature cells)	Abundant nuclear polymorphism (25-50% mature cells)	Extreme nuclear polymorphism (0-25% mature cells)
Number of mitoses/HPF	0-1	2-3	4-5	>5

Histologic grading of malignancy of tumor-host relationship				
Morphologic Parameters	1	2	3	4
Pattern of invasion	Pushing, well delineated infiltrating borders	Infiltrating, solid cords, bands and or strands	Small groups or cords of infiltrating cells (n>15)	Marked and widespread cellular dissociation in small groups of cells (n<15) and/or in single cells
Stage of invasion (Depth)	Carcinoma in situ /or Questionable invasion	Distinct invasion, involving lamina propria only	Invasion below lamina propria adjacent to muscles, salivary gland tissues and periosteum	Extensive and deep invasion replacing most of the stromal tissue and infiltrating jaw bone
Lympho-plasmacytic infiltrate	Marked	Moderate	Slight	None

Bryne's (1989, 1992) (ITF) Invasive Tumor Front Grading System:

Morphologic Feature	1	2	3	4
Degree of keratinization	Highly keratinized (>50% of the cells)	Moderately keratinized (5-20% of the cells)	Minimal keratinization (5-20% of the cells)	No keratinization (0-5%)
Nuclear polymorphism	Little nuclear polymorphism (>75% mature cells)	Moderately abundant nuclear polymorphism (50-75% mature cells)	Abundant nuclear polymorphism (25-50% mature cells)	Extreme nuclear polymorphism (0-25% mature cells
Number of mitoses (high - power field)	0-1	2-3	4-5	>5
Pattern of invasion	Pushing, well delineated infiltrating borders	Infiltrating, solid cords, bands and or strands	Small groups or cords of infiltrating cells (n > 15)	Marked and widespread Cellular dissociation in small groups of cells(n<15) and or in single cells
Host response (lympho-plasmacytic infiltrate)	Marked	Moderate	Slight	None

morphologic parameters with certain specified exceptions.

BRYNE'S (1989, 1992) (ITF) Invasive tumor front grading system: [4]

Bryne M. (1998) presented a hypothesis suggesting that molecular and morphological characteristics at the invasive front area of various squamous cell carcinomas may reflect tumor prognosis better than other parts of the tumor. He further states that several molecular events of importance for tumor spread like gains and losses of adhesion molecules, secretion of proteolytic enzymes, increased cell proliferation and initiation of angiogenesis occur at the tumor host interface. Consequently, they have developed a simple morphological malignancy grading system that restricts the evaluation to the deep invasive front of the tumor. Several studies have shown that this system is a significantly better predictor of prognosis.

CONCLUSION

Oral cancer constitutes the most life threatening of all dental conditions. Oral cancer has a prolonged natural history with premalignant and early invasive phases. The etiological factors are well outlined. There is a long natural history of development of the disease running in to several years, cases treated in localized stages of the disease are completely curable and for the incurable persons pain relief and palliative care can be offered with considerable improvement of the quality of life. Early diagnosis is critically important to improve survival and to reduce morbidity and mortality associated with oral cancer. The treatment outcome of this disease is much better if detected at an early stage.

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