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Review Paper

The Epidemiology, Risk Factors and Diagnosis and Treatment of Oral Cancer: An Update

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ABSTRACT

Oral cancer remains one of the most common and challenging malignancies of the head and neck region. Tobacco and alcohol consumption remain the two major risk factors for oral cancer. This review summarizes the incidence, prevalence, epidemiology, risk factors and diagnosis and treatment of oral cancer.

Key Words: Oral cancer, oral cancer epidemiology, tobacco smoking

INTRODUCTION

Oral cancer (OC) is a highly relevant problem of global public health, especially for dental surgeons. It is located within the top 10 ranking incidence of cancers and despite the progress in research and therapy, survival has not improved significantly in the last years, representing a continuing challenge for biomedical science. This paper aimed to report key aspects of this cancer, integrating clinical, histological and molecular concepts for a better understanding of their biological pathways, allowing the reader and researcher construct a map which could serve to place and integrate this growing information. [1]

Definition:

OC is a malignant neoplasia which arises on the lip or oral cavity is traditionally defined as a squamous cell carcinoma (OSCC), because in the dental area, 90% of cancers are histologically originated in the squamous cells. It has different levels of differentiation and a propensity for lymph node metastasis. [2]

Epidemiology:

OC is the eighth most common cancer in the world, with the highest prevalence among men (5-year prevalence in men: 401,075). [3] According to Ferlay et al. the worldwide cases of oral cancer in 2012 in both sexes were about 300,000 (2.1% of the total cancers) and approximately 145,000 cases were fatal. [4] According to the American Cancer society the incidence of OC is higher in developed countries when compared to developing countries, but the mortality rates remain higher in developing countries. In developing countries the incidence of OC is 107,700 in males and the estimated deaths are 61,200. [5] In India the age standardized incidence rate of oral cancer is 12.6 per 100000 populations. [6]

Risk Factors:

Tobacco and Alcohol

The major risk factors associated with Oral Cancer are tobacco use, in any available forms, and heavy alcohol consumption (people who drink five to eight drinks per day with one drink containing 1.5 oz or 10-15 g of alcohol). [7,8] The combined effects of alcohol and tobacco smoking have

been shown to be synergistic. Of interest, a recent study showed that drinking is inversely associated with Oral Cancer in non-smoking betel quid non-chewing individuals. [9] Another common risk factor is betel-quid and areca-nut chewing. Betel-quid and areca-nut chewing are common social and cultural habits in many parts of Asia. Betel-quid consists of betel leaf, areca nut and slaked lime to which tobacco is often added. Frequent areca nut chewing is carcinogenic to humans. [10]

HPV infection

Among other risk factors, there is the human papillomavirus (mainly associated with carcinoma of the oropharynx and ultraviolet radiation (UV). The IARC classifies human papillomavirus 16 (HPV16) as a cause for cancers of the oral cavity and pharyngeal tonsils, and HPV18 as possible causes of oral cancer. The most-common sites of HPV related head and neck squamous cell carcinoma (HNSCC) are the tonsils and base of tongue within the oropharynx, with a prevalence rate of 75%; HPV-related HNSCC is rare in nonoropharyngeal sites. The presence of HPV is an established prognostic biomarker of favorable outcome in locally advanced oropharyngeal cancer. [1]

Immunosuppression

Immunosuppressed subject's individuals are at increased risk for malignant tumor of the oral cavity and elsewhere in the body In particular HIV-infected individuals may develop OC, non-Hodgkin lymphoma and Kaposi sarcoma. Also transplant patients are at risk for multiple malignancies including OC. [11]

Potentially Malignant Disorders

The lesions of most relevance are erythroplakia, leukoplakia, oral lichen planus and submucous fibrosis.

Erythroplakia is defined as a"fiery red patch". These lesions are often symptomatic, have a degree of increased vascularity, and carry a high risk of harbouring dysplasia. All erythroplakic or leukoerythroplakic lesions should be referred for biopsy and or excision. Should mild or moderate dysplasia be confirmed on biopsy, its risk of malignant transformation is 10.3%, with high grade dysplasia and carcinoma in situ carrying a 24.1% risk. [12]

Leukoplakia is usually asymptomatic and is defined either as a "white plaque that will not rub off" or "a white plaque of questionable risk, having excluded other known diseases or disorders that carry no increased risk for cancer". Confounding benign causes of a white plaque include a frictional lesion from habitual trauma or cheek biting, linea alba (normal white streaks bilaterally bilaterally along the occlusal line), and leukoedema amongst others. [13] The prevalence of Leukoplakia has been estimated at 2%, although the true rate when the latter of the two above definitions is applied is likely to be a little lower at a more modest 0.5%. The annual malignant transformation rate estimated to be from 0.3% to 1%. [14]

Oral Lichen Planus (OLP) is an oral autoimmune condition with a number of morphological variants including reticular (fine white lacy lines), erosive (shallow ulcers), atrophic (thinned erythematous mucosa), and bullous (fluid filled vesicles). It can be symptomatic typically with a burning feeling or hypersensitivity of the affected mucosa. There remains debate as to its status as a potentially malignant condition. It is generally accepted that its risk of malignant transformation is below 1% per year. [15]

Submucous Fibrosis causes progressive trismus due to fibrosis of the connective tissues of the cheeks. It is strongly associated with betel nut/tobacco chewing and it is likely that the use of these carcinogens give it an association with oral cancer. The rate of malignant transformation is estimated at 0.5% per year. [14]

Diagnosis

The clinical appearance of OC is variable and requires an expert eye to recognize its features. Over time patients may complain of difficulties chewing, limited tongue movement or an abnormal sensation secondary to swelling. After the

cancer growth, more symptoms occur and include bleeding, paresthesia, mobile teeth (when the tumor invades the bone), and induration and fixation of soft tissues; only one third are diagnosed with localized tumors. [16]

In the last years, several adjunctive techniques emerged to facilitate the detection of oral premalignant and malignant lesions, however incisional biopsy remains the gold standard for the diagnosis of OC. [17]

Oral Cytological studies mainly comprise use of methods such as, Fine Needle Aspiration Cytologys, Exfoliative cytology and Liquidbased cytology. For High-risk groups for malignancy, cytology has proven to be efficient diagnostic tool with advantages of being inexpensive, fast, comparatively less traumatic, painless and easy in handling. [17]

Tissue reflectance: a) Microlux DL (AdDent, Danbury, CT), using LED and a fiber optic light guide, enhances the visibility but does not help with the true diagnosis of the oral lesion; b) ViziLite Plus (Zila Pharmaceuticals, Phoenix, AZ) is a chemiluminescent light detection system that may increase the visibility of mucosal lesions, but his detective effect alone is unknown. [18]

Tissue fluorescence: VELscope (LED Dental Inc, Vancouver, Canada) is a multiuse device detecting tissue fluorescence useful in assessing lesion margins in patients with oral malignancies. [19]

Toluidine Blue is frequently used for vital tissue staining for OSCC. It is an inexpensive and rapid diagnostic tool. Epstein, et al. showed Toluidine blue to have specificity and sensitivity of 63.2% and 92.5%. Methylene Blue is less toxic and cheaper than toluidine blue. [20]

Brush cytology: OralCDx Brush Biopsy (CDx Laboratories, Suffren, NY) is a brush that collects transepithelial cellular samples, to assess dysplastic changes in clinically suspicious lesions. [21]

Treatment:

All 3 main treatment modalities-surgery, radiation (RT), and chemotherapy (CT)-are used to treat oral cancer, either alone or in combination. The type and extent of treatment are determined by factors associated with the tumour, the patient, and the medical team. Tumour characteristics such as site, proximity to bone, the depth of invasion, and stage (tumour size, lymph node involvement, and risk of metastasis) are considered along with the age of the patient, co-morbidities, compliance to treatment, and the desire to make lifestyle changes. Expertise of the medical team will also influence the treatment decision. [22]

Surgery:

Surgery is the most common treatment modality for oral cancer. The intention of surgery is to completely remove cancerous tissue, leaving behind histologically normal tissue. Larger tumors often require an approach from outside the oral cavity and the removal of both soft tissue and bone. More advanced oral cancers may involve the lymph nodes. Positive lymph node involvement might necessitate a radical neck dissection. Elective neck dissections are undertaken when the lymph nodes are negative in order to prevent the risk of metastasis. The level of neck dissection depends on the number, size, and site of the lymph nodes involved. The efforts to minimize extensive surgery have resulted in the invention of newer advanced surgical techniques, which decreased the morbidity and provided an overall benefit to rehabilitate of the patient. [23] Following the excision of the tumour, reconstructive surgery is required to restore any loss of function and/ or aesthetics. When a segment of the mandible is removed, bone from the fibula is typically the first source for mandibular reconstruction. The location, size, and extent of reconstruction are the main factors that contribute to the choice of graft, as is the need for soft and hard tissue coverage. Defects in the oral cavity or dentition may

also require prosthetic devices, such as obturators, dentures or implants. [24]

Radiotherapy:

In general, the intent of RT is to destroy DNA in dividing cancer cells in a localized region while preserving adjacent tissue and function. [25] RT as a single, primary treatment is not generally used for oral cancer, although it may be used as a sole method of treatment in cases where the location of the tumour makes it difficult to excise, such as the oropharynx, or if the patient refuses surgery. [26] RT as a single, primary treatment is not generally used for oral cancer, although it may be used as a sole method of treatment in cases where the location of the tumour makes it difficult to excise, such as the oropharynx, or if the patient refuses surgery. RT is usually administered after surgery, as surgery following RT would be hampered by poor healing and an increased risk of infection. RT combined with CT is the preferred treatment of oropharyngeal cancers. [25]

The two main types of RT are external beam radiation and brachytherapy. Brachytherapy, a form of internal radiation, involves the precise surgical placement of a radioactive insert into the tumour, directly treating the tumour. However, it is restricted by the size of the field that it can target effectively. In traditional external beam radiation, "shrinking fields" are used to deliver different doses to different regions of disease. "Shrinking fields" refer to a technique in which the most sensitive organs are irradiated first and blocked, treating the overlying low-risk organs next with more superficial radiation. A full treatment of radiation is divided into smaller amounts known as fractions or doses. Radiation doses vary; generally 1.8 to 2.0 Gray (Gy) are delivered daily, 5 days a week, Monday to Friday. Treatment continues over the course of 6 weeks for a total of 30 fractions, until a maximum of 60 Gy is provided. [26]

Chemotherapy:

With the invention of new drugs, chemotherapy has taken a vital role in the treatment of oral cancer. The motive behind the use of chemotherapy is to destroy dividing cancer cells thereby restricting invasion and metastasis. [27] Currently used agents include cisplatin, carboplatin, 5-fluorouracil and the taxanes (paclitaxel and docetaxel). 5-fluorouracil and the taxanes also are radiation sensitizers. [28] There are three different modes of chemotherapy: Induction chemotherapy which is given before surgery, concurrent chemoradio-therapy which is in conjunction with radiation treatment and adjuvant chemotherapy, which is given after surgery. [27]

Combination chemoradiation therapy is used after surgery for patients with poor-prognosis stage IV cancer, for patients with unresectable stage IV disease and in protocols for organ preservation. However, the use of concurrent chemotherapy and radiation therapy has been shown to increase survival rates in patients with head and neck cancer. [28]

Limitations

Conventional therapies such as radiotherapies, chemotherapy, surgery are far away from ideal requirements. There are certain limitations to these therapies of which most important are cosmetic and functional defect with surgery. Radiotherapy and chemotherapy are more active in G2 and M phase of the cell cycle, but by the tumour is diagnosed it would have crossed the actively dividing phase making chemotherapy and radiotherapy less effective. Drug suppression and myelosuppression are important limitations of chemotherapy. Few other side effects like, xerostomia, mucositis, impaired taste sensation, delayed wound healing, fibrosis, osteoradionecrosis. [29]

CONCLUSION

Oral Cancer (OC) is the most common malignant disorder of the oral cavity, with high incidence rates in several developed countries. It represents the eighth most common cancer worldwide. In United States the median age at diagnosis is 65

years old, and the tongue remains the most affected site. Tobacco and heavy alcohol consumption are the most common risk factors for OC, with betel-quid and areca-nut chewing in some Asian countries. The predilection of oral cancer is most commonly seen in male than female with low background who smoke and consume alcohol. Patients unfortunately continue to present with late stage disease. An oral screening examination is a simple non-invasive test to apply, has a comparable sensitivity and specificity to that of the well established cervical and breast cancer screening programs, and is felt to probably be cost effective.

Abbreviations

OC	Oral cancer
OSCC	Oral squamous cell carcinoma
HPV	human papillomavirus
UV	ultraviolet radiation
IARC	International agency for research on cancer
HNSCC	Head and neck squamous cell carcinoma
HIV	Human immune virus
OLP	Oral lichen planus
LED	Light emission diode
RT	Radiation therapy
CT	Chemotherapy

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