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Insight into the Risk Factors and Scope of Treatment of Oral Squamous Cell Carcinoma

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Abstract
Oral cancer is one of the major global dangers to public health. Oral malignancies develop on the tongue, the oral mucosa, the floor of the mouth, the base of the tongue and the oropharynx. Comprehension of oral carcinogenesis will give us the important advances for detecting high-risk patients, monitoring preventive interventions, evaluating cancer hazard, and pharmacogenomics. Oral cavity Squamous Cell Carcinoma (SCC) is very common and researchers proved that SCC occurs in 90% of cases. Tobacco and alcohol consumption is considered as a major cause for oral SCC. On the other hand, pre cancer detection is considered as the key point for cancer prevention and disease management. Thus, there is a need for noninvasive, highly sensitive, and specific diagnostic techniques. Nano drug particles are more biocompatible, easier to synthesize, and also able to target specific molecules. Therefore, using nano technologies can help physicians to detect and treat the diseases during different phases of oral cancer. The main objective of this review is to present a systematic review of oral cancers.

Keywords
Oral cancer, Oral Squamous Cell Carcinoma, Risk factor, Nanotechnology.

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INTRODUCTION
In South-Asian countries, oral cancer is the main causes of death and it is highly relevant problem of global public health. Researchers focused on discovery and development of different novel therapies or treatment for oral cancer. It is necessary to control the ever-rising oral cancer related mortalities. Though great progress made in the field of medical science, over 32.6 million people are still living with different cancer worldwide. Oral cancer mostly arises on the lip or oral cavity.[1] It is also called oral squamous cell carcinoma (OSCC), because in the dental area, 90% of cancers are histologically originated in the squamous cells. Oral cancer is a common and aggressive cancer. It has high morbidity, mortality, and recurrence rate globally. The incidence rates of cancer vary significantly between different countries. For example, oral cancer, which is less common in developed countries and is ranked in the top three causes of cancer related in South Asian countries like India, Bangladesh, and Sri Lanka. There is a large number of treatments are available for lung, prostate and breast cancer, however, treatment options are very limited.[3] It is located in the top 10 ranking incidence of cancer. Despite the progress in research and therapy, survival rate has not improved significantly in the last years and representing a continuing challenge for biomedical research study. Factors like

the high usage of tobacco, inability to diagnose cancer in early stage and limited treatment options are largely responsible for the high mortality rate of oral cancer.[6] Increasing oral cancer prevalence among young adults is a cause of special concern. However, couples of information have been distributed on the etiology and common history of the expansion. This paper is aimed to report key aspects of this cancer and allowing the reader to construct a map which could serve to place and integrate this growing information. [3, 4]

Oral cancer begins in the mouth or mouth cavity. It is also called as oral squamous cell carcinoma. About 90% people suffering from Squamous cell carcinoma. Oral cavity of the body includes the lips, the inside lining of the lips, buccal mucosa, the teeth, the gums, the tongue, the bottom of the mouth and the bony roof of the mouth or hard palate.[5] Oral cancer can also develop in the throat (oropharyngeal) and it is called as oropharyngeal cancer. The oropharynx and oral cavity play and important role in the functioning of the body. With the help of them we can breathe, eat and speak.[7]

CLINICAL FEATURES

One of the genuine perils of this disease is that in its beginning periods, it can go unnoticed. Oral squamous cell carcinoma introduces in an assortment of ways, yet most early injuries are asymptomatic. For the most part at the underlying stages it is effortless, yet it may build up a consuming sensation or agony when it is progressed. Normal locales for OSCC to create are on the tongue, lips and floor of the mouth.[10] Some OSCCs emerge in obviously ordinary mucosa, yet others are gone before particularly erythroplakia and leukoplakia.

Numerous premalignant sores relapse if tobacco utilizes is ceased.[9]. Late stage oral threat may result not just in extensive, indurated, hole like ulcers with moved edges yet additionally in hard devastation, prompting portable teeth, loss of teeth, or even neurotic cracks. These might be related with torment, deadness, or paraesthesia. OSCC introduces as a ulcer with fissuring or raised exophytic edges. It might likewise present as an irregularity, as a red injury (erythroplakia), as a white or blended white and red injury. OSCC ought to be viewed as where any of these highlights continue for over about two weeks.

MAJOR RISK FACTOR

Oral cancer is a preventable disease, where smoking and alcohol-considered major risk factors and present in 90% of cases, having them both cause a synergic effect.[11] Developing the risk of oral cancer is 3 times higher in smokers compared with nonsmokers. People who quit smoking four years ago than those who continue smoking, their risk for oral cancer are 35% lower. As a result, smoking weakens immunity in the oral cavity by promoting gingivitis, periodontitis and oral cancer. This smoke contains several elements and these elements promote or initiate cancer and they basically can be grouped into three distinct groups: nitrosamines, benzopyrenes and aromatic amines. These chemicals are also called pre-carcinogens, which must suffer coordinated alterations by oxidative enzymes. In addition to oxidation, enzymatic or non-enzymatic metabolism can also produce carcinogens like free radicals. These free radicals have unpaired electrons that make them extremely reactive and being capable of promoting mutations by complex mechanism.[12]

There square measure quite sixty carcinogens in butt smoke and a minimum of sixteen in turn tobacco. Among these, tobacco-specific nitrosamines (such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN), polycyclic aromatic hydrocarbons (such as benzo[a]pyrene) and aromatic amines (such as 4-aminobiphenyl) appear to possess a vital role as causes of cancer.[61]

Alcohol can act as a both locally and systemically risk factor such as increased permeability of oral mucosa, dissolving lipids components of the epithelium, causing epithelial atrophy and interference in DNA synthesis and repair. It also has genotoxicity and mutagenic effects and causing decreased salivary flow. It affects the liver's ability to deal with toxic compounds and their chronic use is associated with an impairment of innate and acquired immunity resulting in increased susceptibility to infections. Many chemical carcinogens derived from alcohol consumption and are metabolized into active forms that have deleterious effects on organisms.[13]

A recent study showed that drinking is inversely associated with oral cancer in non-smoking betel quid non-chewing individuals. Tobacco is often added to betel leaf, areca nut and slaked lime.[14] An alkaloid present in areca nut which causes cell death, apoptosis and cell cycle arrest of epithelial cells which contributing to the pathogenesis of oral carcinogenesis.[15]

Age indicates a temporal component in the biochemical and biophysical processes of cells. It causes the reduction of the immune system. Specifically, the long-term haul introduction to chance components may influence the quality items that control epithelial cell multiplication and passing.[16]

Family history also plays an important role. It is considered a risk factor. However, more studies are necessary to describe in detail which molecules and genes are responsible for oral cancer susceptibility in families. Oral cancer is frequently seen in family members without habits, for example tobacco biting, smoking or liquor utilization and it is for the most part connected with a beginning of the malady at an early age (around 45 years of age).[17]

Poor oral hygiene can also be risk factors for the oral cavity. New trends like poor condition of the mouth, lack of toothbrush use emerged as possible risk factors for oral cancer. Different mouthwashes have high alcohol content which could also be a risk factor for oral cavity.[20] The consumption of mate, a tea beverage usually consumed by South Americans, has been related with an expanded danger of disease of the oral cavity.[19] Epidemiologic examinations suggest that the intake of vitamin A, -carotene, and -tocopherol may decrease the risk of developing oral malignancies. Exposure to ultraviolet (UV) light is a risk factor for the development of cancer of the lip.[18]

ORAL CANCER EPIDERMIOLOGY

Oral cancer is the eighth most common cancer in the world, and it is more prevalent in men than women. The worldwide cases of oral cancer growth in 2012 in both genders were about 300,000 (2.1% of the aggregate cancers) and roughly 145,000 cases were lethal.[24] The incidence of oral cancer is higher in developed countries when compared to developing countries according to the American Cancer Society, but the mortality rates remain higher in developing country.[21] In south-central Asia, oral cancer is one of the most frequent types of cancer.[23] In India the incidence rate is 12.6 per 100 000 population Of interest, the incidence rate remains high in several developed countries such as Denmark, Poland, Germany, Scotland, and also in Australia, Japan, New Zealand and the USA.[22]

As indicated by the most recent reports of the International Agency for Research on Cancer (IARC) for oral malignancy (ICD-10 code C00-08: Lip, Oral Cavity) which incorporates lips, tongue, gingiva, mouth floor, parotid and salivary glands, annual incidence is higher around the world, which is over 300.000 diagnosed cases, and the annual mortality is about 145,000 death.[25, 26]

The occurrence by sexual orientation fluctuates relying upon the anatomic location and has been changing because of the expansion in the quantity of ladies who smoke. The ratio between the male and female is currently 3:1.[23] The incidence of oral cavity cancer increases with age, mostly patients are between 50 and 70 years but can also occur in younger patient. There are substantial contrasts in the rate of oral disease among various geographical regions.[27]

MECHANISM AND CARCINOGENESIS

Tobacco consumption is related to with accumulation of deoxyribonucleic acid injury and exposure to tobacco connected chemical carcinogens. It will give direct damaging effects on the cellular deoxyribonucleic acid within the human oral fissure. Chiefly PAHs (Polyclyclic aromatic hydrocarbons), NNN (N-nitrosonornicotine) and NNN causes carcinoma.[61] Mechanism of action of Tobacco carcinogenesis is given in Figure 1.

The improvement of oral cavity SCC is a multistep movement that includes changes identified with particular qualities, epigenetic occasions, and flag transduction inside the cell.[28] Tobacco smoke contains operators that may go about as mutagens and further more tobacco smoke remove has been appeared to enact the epidermal development factor receptor (EGFR) in vitro and EGFR initiation has been appeared, thus, to expand the generation of prostaglandins, including PGE2 which may act in a positive criticism design by expanding EGFR flag transduction. Cyclin-D1 is often overexpressed in head and neck malignancy and expanded cyclin-D1 movement is a downstream occasion activated by EGFR initiation.[29] Genetic adjustments that are available from the get-go over the span of carcinogenesis are changes or cancellations of chromosome 3p and 9p. Telomerase actuation likewise happens from the get-go in carcinogenesis.[35] Changes or cancellations at chromosome 17p (including the p53 tumor silencer quality), and chromosome 13q and chromosome 18q by and large are seen later all the while. Patients whose tumors contain HPV mRNA have an altogether lower rate of erasures of chromosomes 3p, 9p, and 17p, proposing another atomic instrument in these patients.[30] The viral proteins E6 and E7 have been appeared to cause deregulation of the cell cycle by inactivating p53 and retinoblastoma protein, which might be the instrument of HPV-intervened carcinogenesis.[31]

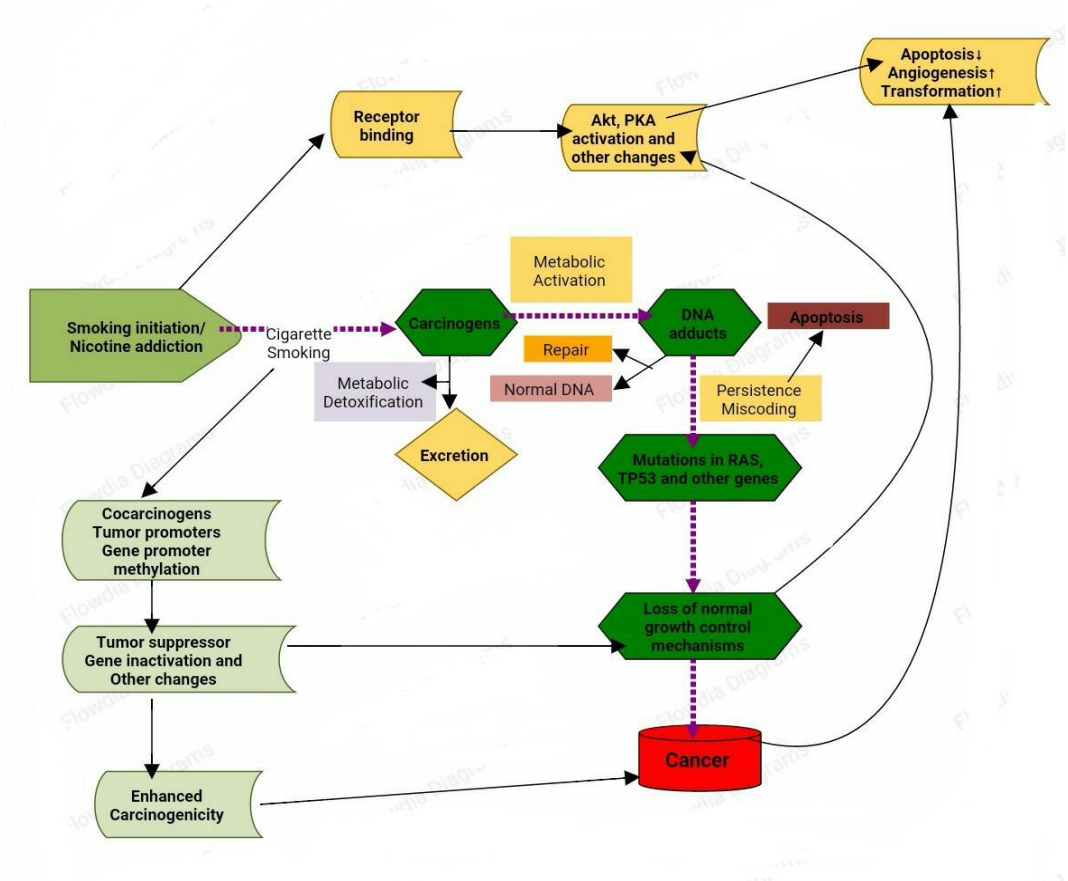

Fig. 1: Mechanism of Tobacco carcinogenesis.

An essential epigenetic occasion in the movement to malignancy is the quieting of quality advertiser districts through hyper methylation.[34] which has been appeared to influence the tumor silencer's p16, DAP-kinase, and E-cadherin. Additionally, the quality for retinoic corrosive receptor-beta (RAR-beta) is quieted by methylation of its promoter not withstanding erasures or changes of individual qualities, proof exists showing that numeric chromosomal lopsided characteristics, known as aneuploidy, might be a reason as opposed to an outcome of threatening transformation. Aneuploidy may happen because of changes in qualities controlling chromosome isolation amid mitosis and centrosome irregularities. [32,33]

MANAGEMENT AND TREATMENT

There are various new techniques of diagnosis are evaluated to improve the clinical examinations. Treatment of OC depends on the OC staging. However, some articles show significant results for oral cancer examinations. Treatment for oral cancer is principally surgical but few peoples are treated solely with radiotherapy and even fewer with chemotherapy. Radiotherapy and chemotherapy are widely used for adjunctive therapy. The main aim of surgical treatment is to eliminate possible channels of spread, such as the tissue, nerves, and blood vessels. This ablative surgery is followed by reconstructive surgery.[36] It is used to improve healing and restore function and improve the patient's quality of life. Some surgical procedures only involve soft tissues, and some involve both hard and soft tissues.[37]

Radiotherapy is very rarely used as a primary treatment. It is used either to debulk the tumor before surgery or to eliminate residual tissue after an incomplete resection. Oral mucositis and osteoradionecrosis are the complications of radiotherapy, which causes difficulty in management of cancer. If extra capsular spread is thought to have occurred, then radiotherapy is used. In this situation, it is done within three to four weeks of surgery. Systematic review of the management of oral neoplasms is needed to provide more information required for patients and their medical advisers to make more informed choices about treatment. [38, 39] According to the American Joint Committee on Cancer the different stages and treatment option of oral cancer s are available. In the stage 1, the cancer

is used to be less than two centimeters in size without metastasis.[40] The treatment options are surgery and radiation therapy in this case. Radiation treatment is performed if medical procedure is not realizable or as adjuvant therapy. In the stage 2 the cancer is more than 2 centimeters and less than 4 centimeters in size, but radiation therapy is preferable with T2 lesions. The ionizing radiation destroys cells in the target area sand topping the growth of cells. In the stage 3, the cancer is more than 4 centimeters in size, or any size, and can have spread to more than one lymph node. In T2 and small T3 tumors surgery and radiation therapy are present the elective treatment options. The size and area of the tumor control the techniques of both. The benefit of chemotherapy is the capacity to achieve the metastatic cells of the cancer, since radiation and the medical procedure have impact on localized areas only. Cisplatin, carboplatin, fluorouracil, and cetuximab represent the principle operators utilized in chemotherapy protocols. In the stage 4, the cancer is any size and has spread to any lymph node. In spite of the fact that medical procedure is exceedingly incapacitate for the patient, insignificantly obstructive technique.[41] Palliative radiation therapy or chemotherapy can be used in patients with metastatic disease. Now a day's different novel molecular target agents have been developed as treatment options.[42]

CHALLENGES IN THE TREATMENT OF ORAL CARCINOMA

The cancer treatment mostly will have effects on normal cells as well as cancer cells. The most commonly oral problems occurring after giving radiation and chemotherapy and those problems are mucositis (an inflammation of the mucous membranes in the mouth), infection, pain, and bleeding. Others are dehydration and malnutrition as a result of difficulties in swallowing. Radiation therapy to the head and neck may injure the glands that produce saliva or can damage the muscles and joints of the jaw and neck. In addition, treatments may cause bone death (osteonecrosis). Most of the patients being treated for head and neck cancer will experience some oral complications. Furthermore, surgical solutions to tumor evacuation may prompt oral and harmful issues also.[43] The most important risk factors leading to problems are oral or dental disease which is already exists and poor oral care during therapy. Other hazard factors incorporate the kind of malignant growth, the chemotherapy type and schedule utilized, the area illuminated and how much radiation is given, how blood counts are diminished and for how long, the patient's age, and the general condition of the patient's health pre-treatment etc. Prior oral conditions may build the danger of contamination or other issues.[44] Bacteria and fungi are used to live in the mouth and may develop into an infection when the immune system is not working well. Both of these factors can be caused by the treatment technique used. These complications can result in reduction in the quality of life for the patient. Major drawback is the people who've had oral cavity or oropharyngeal cancer can still get other cancers. [45, 46]

NOVEL APPROACH IN THE TREATMENT OF ORAL CANCER

The main goal of cancer treatment is to kill as many cancer cells as possible and it should not effect on healthy cells. However, the drugs have ability to target specific sites in the body to achieve therapeutic effects. Nano delivery systems provide a targeted drug delivery and they have shown several promising characteristics, including anti-oral tumor effects, which are not available with traditional chemotherapy.[47] Thus, the US Food and Drug Administration (FDA) recently approved a clinical trial of a nanoparticle based system to use in humans for treatment of solid tumors. Hence, in the future, patients will benefit from suitable nanotechnology-based drug delivery systems and that could lead to improved therapeutic outcomes with reduced costs. Nanotechnology is also predicted to alter health care with novel methods of identifying the cancer as well as customization of a patient's therapeutic profile. The fate of the nanotechnology for oral cancer growth looks more splendid than ever. [48, 49]

Gene therapy is an important key and plays a very important role in the treatment of oral cancer. Gene therapy is an associate degree experimental technique that uses genes to treat or stop unwellness. It involves the transfer of a therapeutic or working copy of a gene into specific cells of an individual in order to repair or remove the faulty gene copy. Many experiments have been done on gene therapy to its application in various diseases. The delivery system of gene includes a vector that delivers a therapeutic gene to a targeted site. The introduction and the activation or inactivation of new gene may inhibit or suppress tumor growth. Gene therapy is a quality treatment and it can attack harmful cells while respecting normal tissue or cell. It may also be useful to manage disease recurrence and as a co adjuvant therapy. [50, 51]

Comprehensive analysis has provided proof that cancer is managed victimization plant-derived

dietary compounds, nutraceuticals is associate in nursing optimistic approach. They need the potential to treat different cancers because of their chemical diversity, multi-targeting action and safety profile.[52] The counter neoplasm effects of curcumin, is as of now set up. Tea polyphenols may also be used as therapeutic agents for carcinoma. Resveratrol made by a range of plants, like grapes and mulberries. It is varied ideal properties, that have been utilized in treating varied sicknesses together with malignant growth.[52]

FUTURE AND SCOPE

Now a day, different biomarkers are available for treatment therapy. Advances in biomarker development helps to detect oral cancer easily at an early stage. Although most oral abnormalities found by dentists are unlikely to be malignant and biomarkers can identify lesions with the genetic mutations. There are tremendous advances in surgical techniques, notably reconstruction, and in radio therapy and chemo therapy.[53] In last 10 years, targeted therapies were offered to patients and that are directed to particular pathways.[59] Further studies are needed to grasp the concepts of nanotechnology (targeted drug delivery) and to elucidate correct drug doses and ideal release from these systems for the treatment of many cancers with completely different molecular and cellular mechanisms. Physicians have large number of multiple diagnostic options and multidisciplinary approaches for the treatment of oral cancer, however further research is needed to better understand the oral cancer.[54, 55] Clinicians or physician should screen their patients to detect early lesions and educate them about the risk factors of the oral cancer. Despite the fact that oral cancer and consequences can be prevented or controlled, there exists a significant gap in the Indian public's knowledge and behaviors.[56] Efforts must be made to introduce the preventive measure that has the potential to reduce the burden or the gap between research, development and public awareness. Knowledge dissemination help people to improve their health and decisions making process and to provide required public health education. [57,60]

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