Review article

Recent advances in oral cancer - A review

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(Received: October 2023 Revised: November 2023 Accepted: December 2023)

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ABSTRACT

Carcinoma of oral cavity presents as a long-lasting sore in the mouth cavity. In the US more than 55000 cases of mouth cancer are recorded every year out of which around 70% were males. It can be deadly if not investigated and treated promptly. Oral carcinoma is a deadly health affair in India. WHO has reported that around one third of cases of oral carcinoma in the world are found in India . ICMR had announced more than 75000 cases of oral carcinoma in India in 2020 . Mouth cancer can involve any portion of the mouth, such as the tongue, lips , gums, roof and bottom of the mouth, and the inner part of the cheeks, soft palate, hard palate sinuses, and pharynx . It occurs when cells in the mouth grow abnormally and form a malignant tumor. Tumors can also occur in the salivary glands, tonsils but these are less common. Mouth carcinoma can also disseminate to other portions of the body if proper treatment was not given. Oral cancer is significantly easier to treat when it is detected early. However, most people are diagnosed when their ailment is too advanced to be adequately treated. If one visits the dentist or doctor on a regular basis and learns how to recognize abnormal changes, it is possible to do an early diagnosis.

Keywords: Oral carcinoma; squamous cell carcinoma; biological markers; chemotherapy; immunotherapy.

INTRODUCTION

The development of malignant cells in the mouth cavity is known as oral cancer. It can have an impact on the lips, tongue, cheek lining, mouth floor, soft palates, hard palate gums, and teeth. Oro pharyngeal carcinoma, which results in throat cancer, is commonly mentioned in conjunction with oral carcinoma (1). It is the eighth most frequent cancer in the world, and there are about 275,000 fresh cases recorded each year (2). Oral cancer is the eighth most common carcinoma in women worldwide and the fourth majority common disease in men (3). Oral carcinoma accounts for roughly 3% of all cancers with a yearly incidence of around 500,000 worldwide. Consequently, this illness places a significant strain on global health. Throughout the world, there are zonal differences in the frequency of oral cancer. It seems that there is no connection between it and geographic location; rather, it is an issue with oral habits among people in some countries. Oral cancer is the most prevalent kind of malignancy in various nations, including Bangladesh, India, Pakistan, and Sri Lanka. It makes up more than 50% of all malignancies that have been documented in India. The high incidence rate in the aforesaid countries is caused by certain oral practices, such as chewing betel and other practices of a similar nature. The chief danger factor for oral carcinoma is style of living. The usage of nicotine and alcohol are two major lifestyle risks for this type of cancer. The most common kind of carcinoma of head and neck is oral squamous cell carcinoma (OSCC), has drawn a lot of attention from the scientific community (4). This is a result of both the disease's extremely high incidence of mortality rates in numerous nations throughout the world and the complicated social and economic effects it has on patients who are fortunate enough to survive this severely disabled condition. Oral cancer refers to any type of malignant growth that develops in the mouth cavity, including the lips, tongue, cheeks, bottom of the mouth, hard and soft palates, sinuses, and pharynx. The prevalence of oral squamous cell carcinoma in the US is 3%, and in India and other Asian countries it is 30%. The American Cancer Society has reported more than 48000 cases of oral carcinoma every year with a mortality rate of 17% .India has reported more than one lakh cases each year. In India, the most prevalent cancer is oral cancer (19/100,000 population). It is most of the cancer in males and the third most common carcinoma in women, accounting for 14%-17% of all carcinomas. Tobacco usage is responsible for 95% of all oral cancers (5,6).

Signs and symptoms of oral cancer

The common characteristic features of oral cancer are red or white specks on the inner aspect of the mouth or tongue , leukoplakia more than 2 cm, one or more ulcers or swellings in the mouth which fail to heal even after 3 to 4 weeks, difficulty in swallowing, chewing, speaking ,moving one's tongue, opening one's mouth, moving one's jaw, pain in the jaw, a chronic pain in the neck, rough voice, unusual weight loss and changes in taste sense, ability to tolerate hot

foods, exaggerated salivation ,pain in the ear and enlarged cervical lymph nodes.

Transformation of potentially malignant illnesses (PMDs) into squamous cell carcinoma of oral cavity

A censorious component of an improved prognosis and higher patient survival rate is early identification of cancer. The most of OSCC patients are not detected in the early stage, despite the ease with which the mouth cavity evaluation and checkup can be done by direct visual examination (7). This most likely results from the fact that patients rarely receive dental care and that most oral malignancies in their early stages have no symptoms (8). Additionally, dentists could misdiagnose malignancies as reactive or benign lesions because they are unaware of the various clinical manifestations of OSCC (9). Patients' knowledge of the importance of routine dental visits and staff training to conduct thorough patient examinations should both be increased to aid in the prior detection and improve the outcome of cancers (9).

There are numerous PMIs in the mouth cavity that have the possibilities to develop into OSCC, some of which are mentioned in detail below.

Leukoplakia

The WHO explains “a clinical diagnosis that include any white lesion (plaque or patch) on the oral mucosa that cannot be considered clinically or pathologically as any other disease is a leukoplakia” (10) (Fig 1). A microscopic study showed hyperkeratosis or acanthosis in around 80% of cases out of which 17% were probably malignant with 12,2% mild and 4.5% acute dysplasia or carcinoma preinvasive, and 3% of leukoplakia were diagnosed as OSCC (11). That is why it is necessary to diagnose leukoplakia early which can be treated easily than progressive malignant OSCC.

Fig. 1: Leukoplakia on the outer aspect of the tongue (https://www.treatcure.org/wp-content/uploads/2017/ 08/ white-spots-on-tongue-leukoplakia.jpg)

Proliferative verrucous leukoplakia (PVL)

Proliferative verrucous leukoplakia is a mutilating form of leukoplakia which is seen in clinical practice as gradually growing white lesions which appear repeatedly and chances of transformation to malignant state is high (12). Research of PVL cases showed that around 40% established into cancerous lesion like verruca’s cancer or OSCC within 2 years and many PVL cases advanced into OSCC on palate and gingiva.

Erythroleukoplakia

Erythroleukoplakia also known as mottled leukoplakia when examined histopathologically appears as a mixture of white and red lesions with more severe dysplastic changes than leukoplakia. This lesion typically has uneven edges and Candida colonization is prevalent (13). The chances of malignant transformation from speckled leukoplakia are 20 to 45%.

Fig.2: Erythroplakia (http://www.Oralmedicinelondo co.uk/conditions-treated/oral-medicine/red-patches/)

Erythroplakia

Explained as “Any red lesion of the oral mucosa that cannot be clinically diagnosed as any other condition is called erythroplakia” (14; Fig. 2). Clinically true erythroplakia is the most worrying sign than leukoplakia. According to reflective research, 90% of patients identified with "erythroplakia" had OSCC (50%), pre invasive carcinoma or acute dysplasia (40%), or gentle or medium epithelial dysplasia (9%). Erythroplakia and leukoplakia are frequently seen before OSCC (15) and occasionally observed next to an OSCC wound.

Oral submucous fibrosis (OSMF)

OSMF develops because of increasing fibrosis of the mucosa of mouth cavity caused by persistent areca nut use (16). Patients with Oral submucous fibrosis are more prone to establish cancerous OSCC.A 30% cases with a history of OSMF showed microscopically verified OSCC in a potential study conducted (17).

Oral lichen planus (OLP)

A functional abnormality produced by the immune system which presents clinically as netlike white spots that are sometimes connected with abraded and ulcerous wounds. There is a lot of discussion about whether Oral lichen planus must be considered a PMD. A prior study that looked at data from 20,095 individuals found that 1.2% of OLP cases developed OSCC. It must be highlighted that patients with

destructive OLP and chronic smokers and alcoholics are more prone to develop OSCC (18). Another earlier study found that the risk of reemergence of tumor in OSCC is greater in patients who had earlier OLP than in those with initial OSCC.

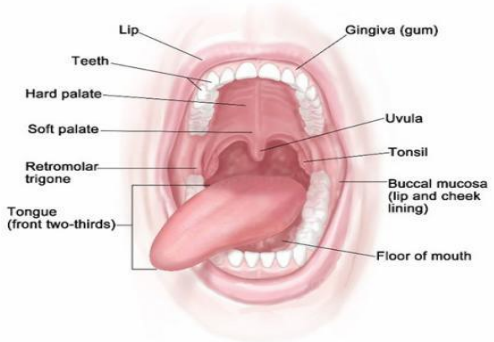

Fig. 3: Anatomy of oral cavityPC-https://spiritual curiosity.org/guides/mudra-khechari-part-1/

Anatomy of mouth cavity

The part of the mouth consists of lips, anterior two thirds of tongue, mucosa covering inner part of the buccal cavity and the part of the mouth under the tongue, both hard and soft palate, triangular area behind third molar (19). Oral carcinoma can occur in tissues of any of these of the above parts (Fig. 3).

Fig. 4: Oral cancer risk factors PC-https:// www. indiancancersociety.org/oral-cancer/

Fig. 5: Oral Cancer PC -https://www.indiancancer society. org/oral cancer/

Screening for oral cavity cancer

All medical doctors and dentists must scrutinize the mouth cavity thoroughly during a normal inspection for lesions (Fig. 5) like leukoplakia, erythroplakia which can advance to malignancy. Usually, oral cancer is noticed only when it has extended to lymph nodes or other parts (20). Any person male or female above 35 years using tobacco or alcohol in any mode must be tested at all testing centers. The screening policy of oral cancer includes asking questions, examination of oral cavity, self-scrutiny, biopsy, and histopathological examination.

Fig. 6: Early sign of oral cancer (https://www.perio implantadvisory.com)

Diagnosis and evaluation

For a thorough evaluation of persons with mouth carcinoma, a thorough history and physical examination are essential. Oral cancer may exhibit few early symptoms that are frequently disregarded (Fig 6). A patch or non-healing ulcer which is the most typical manifestation , particularly one that has a history of cigarette or alcohol use and that has persisted for more than six weeks, calls for a comprehensive evaluation. Trismus is a marker of infratemporal fossa involvement and relative inoperability, especially when it is recent development. During the physical examination, the ability of the patient to perform daily activities, search for a simultaneous second primary malignancy, adherence to neighboring skin and soft tissue, and condition of regional lymph nodes should all be assessed to accurately find out the range of involvement of adjacent surrounding structures such as the bone, muscles of the tongue, and mouth floor. To validate the pathological diagnosis, tissue biopsies taken from the most illustrative non-necrotic area of the lesion should be used.

A fine-needle aspiration (FNA) must be conducted if there are any suspicions of localized cervical metastases (ultrasound-guided FNA boosts specificity and accuracy). Imaging is necessary for regionally extended disease; a CT scan has been found to be more efficient in showing involvement mandibular cortex and the state of regional lymph nodes. An MRI is recommended to identify the soft tissue extension, base of the skull, infratemporal fossa, RT planning, and involvement of medulla. Therefore, MRI is favored for tongue cancer whereas CT scan is preferred for carcinoma of buccal mucosa (21).

In initial lesions manageable with transoral excision with a clinically node-negative (confirmed by imaging) neck, ultrasound with or without FNA is the prior evaluation of choice. Ultrasound is also preferable for careful observation and investigation of

the neck in patients with negative lymph nodes. There is inadequate proof to help the use of more modern imaging techniques, like PET-CT scans, in pretreatment evaluation. It is helpful in determining post-treatment residual/recurrent illness, though the size of the initial tumor, as well as the involvement of neighboring structures, the condition of cervical lymph node , and distant metastases, are used to determine the stage of oral cavity cancers ..Exfoliative cytology is a straightforward method that depends on collecting exfoliated cells for microscopic examination and may be helpful in the early finding of oral cancer. However, it should be emphasized that cells can shred innately or when a benign or malignant illness is present. Hence, only a biopsy should be used to determine the OSCC diagnosis. The gold standard for diagnosing OSCC continues to be histopathologic study and biopsy, despite the evolution of new diagnostic techniques for the identification of oral cancer (22). The proper handling of the tissue, having appropriate length and thickness of the cut tissue, submission without concomitant diagnosis, and local anesthesia administration are all necessary components of an effective biopsy process.

Involvement of salivary biomarkers in detection of OSCC

OSCC is many times diagnosed through both inspection of oral cavity clinically and biopsy examination of doubtful tissue material (23). Because of this policy, tragically the most of the OSCC cases remain unnoticed in the beginning stage and are detected only in the later stage (24). Furthermore, due to late diagnosis, survival rate is less than 5 years in 50% of cases of OSCC as a result of widespread metastasis (25). The saliva can be used for rapid detection of the infection (26). OSCC is relatively prevalent and early detection can greatly improve prognosis (27). Several workers have reported that a particular group of biological markers made up of protein are elevated in the saliva of persons with OSCC. A study showed that biomarker of head and neck cancer is CD44, and possible biological markers of oral carcinoma are carcinoma antigen 25 and Cyfra 21-1A previous investigation showed a raise in appearance of all seven transcriptomes and three proteins are possible indicators for OSCC (28). These workers also showed improvement in specificity and sensitivity in diagnosing OSCC by demonstrating elevated levels of IL 8 and adipose tissue beneath the skin in saliva. Some other study showed the appearance of IL-1 and IL-8 are more in the saliva of persons with OSCC than in control groups. Another study also found that these proteomic markers like IL-1and IL-8 concentrations were more in OSCC than in dysplasia patients (29). Another comparative study between OSCC, precancerous condition and normal controls showed increased levels of Cyfa-21-1, total protein, and lactate dehydrogenase in the saliva of patients with OSCC than in other groups (30).

Treatment of oral cancer

Surgical removal of cancerous growth which is followed by radiotherapy and/or drug therapy to remove left over cancer cells.

Chemotherapy

Chemotherapeutic drugs are increasingly being utilized to supplement radiation therapy (chemo-radiation), however only drug therapy is scarcely useful for HNSCC. Collective chemo-radiation treatment (CCRT) had a better treatment impact than either irradiation or chemotherapy alone in patients with inoperable regionally restricted advanced HNSCC. Survival can be extended significantly using multi-agent chemotherapy procedures that include targeted medicines administered concurrently with normal fractionation or hyper-fractionated radiation. Three and five-year survival rates of 30-60% are increasingly being reported. HNSCC patients are also more likely to have underlying health issues because of heavy smoking and alcohol intake. Diabetes, respiratory and cardiovascular disorders affect a high proportion of individuals. Coexisting conditions can impact treatment choices and upset post-surgical care. HNSCC patients undergoing various treatments need specialist guidance during the course of treatment. Several patients require long-term rehabilitation, and even with great care, numerous patients experience prolonged issues. However, because most patients have regionally advanced conditions, integrative treatment including surgical treatment, radiation, and drug treatment is often recommended (31).

The combinations of treatment include surgical treatment followed by supportive chemoradiotherapy (CRT) or radiation treatment; CRT followed by surgical treatment as a rescue treatment; induction chemotherapy followed by a definitive local therapy such as CRT; and selected therapy with epidermal growth factor receptor (EGFR) inhibition combined with radiotherapy or CRT. Acceptance, consent, and endurability of a proposed treatment plan by the patient are captious components in establishing a suitable treatment approach (31). The tumor factors that can affect opening treatment options are area, size, location, closeness to bones like maxilla or mandible, variety, class, and deepness of infiltration of initial phase of tumor, condition of regional lymph nodes and earlier treatment. Because the results of tumors managed with surgical treatment or radiation treatment are the same, treatment complications are an essential problem. Cancer specialists must also examine the location of the disease. The lesions in the mouth cavity are regularly treated with surgery followed by radiation treatment or CRT, but tumors in the pharynx or larynx are commonly managed with CRT first. Bleomycin, carboplatin, cisplatin, taxemes,

methotrexate, and 5-fluorouracil are chemotherapeutic drugs utilized to treat HNSCC patients, either alone or in combination with radiotherapy.

Prevention of oral carcinoma

Oral cancer can be avoided by averting danger factors like munching tobacco, extreme use of alcohol, smoking, and infections of the oral cavity and by improving protective factors.

Discontinuation of tobacco

Research have shown that stopping smoking for 5 to 9 years have reduced the incidence of mouth cancer by 50% and for 20 years the risk is nil.

Quitting alcohol

According to some studies, stopping alcohol consumption reduces the incidence of mouth carcinoma by approximately 20 years, by improving preventive factors like proper dental cleanliness, self-examination of oral cavity and visual examination of teeth by health care professionals may help in avoiding oral carcinoma. The incidence of oral carcinoma can be reduced by taking more fish, eggs, raw and cooked vegetables and fruits and restricting exposure to sun, do self-testing for at least once in three weeks, meet your dentist regularly and consult doctor or health problems (32). OSCC can also be prevented by using the strategy of immunotherapy which was recently used for advanced head and neck carcinoma with metastasis.

However, there is no notable improvement in general prognosis of OSCC in the current period despite all attempts. In the initial part of OSCC, the announced estimation of survival after successful treatment can be more than 90%, and more than 50% of the cases showed established disease at the time of identification in clinical practice. So, it is necessary to identify the lesion early to battle against OSCC. Furthermore, because in most of the human beings the disease is caused due to several danger factors, risk factors induce disease in most patients (33), an effective action plan for prevention of the disease is essential in the universal attempt to oppose OSCC.

The currently established screening method of clinical examination of oral cavity for OSCC has had no role in survival rate in recent decades. The successful method that can change the design of incidence and danger factors connected to OSCC rates are preventive action taken for the use of alcohol and smoking and the newly started HPV vaccination drive (34). Another important aim is to find out and detect precancerous lesions long before they turn into malignant conditions and to point out the high-risk persons who can develop oral carcinoma. A non-encroaching, duplicable method used in clinical procedures such as high-resolution imaging tools like Reflectance Confocal Microscopy in vivo can be used to distinguish precancerous growth from malignant lesions (35). Imaging tools of computed tomography can be used to demonstrate complicated metabolic irregularities such as high glucose uptake in OSCC like in several other carcinomas. This is a possible screening method for mouth cancer presently used for diagnosing ,observing and screening OSCC. PET-CT's value also gives conclusive evidence in screening of cancer and in patients with symptoms this tool is linked with superior long period results (36). Saliva can be used as a non-intrusive diagnostic device for the prior investigation, detection, and observation of OSCC and malignant lesions of the oral cavity. The several modifications in immunological pathways shown by changes in cytokines are detected in precancerous and cancerous condition in oral mucosa.IL-8 was found to be a most consistent biomarker for cancerous changes in OSCC and changes were observed in both salivary specimen and tumor tissue (37). The significance of prolonged inflammation in the evolution of OSCC is indicated by elevated levels of cytokines promoting inflammation like IL-6 and alpha TNF in saliva of OSCC patients than in normal controls or in cases with dysplastic mouth lesions. Salivary changes can also be used to study genetic alterations in OSCC which discloses prognostic features. The prognosis of persons alters considerably if nodal involvement is there in OSCC. It is very difficult to differentiate OSCC from cutaneous squamous cell carcinoma in a pathogenic process. The effect of delay in the diagnosis has several roles in prognosis, standard of life of a patient and monetary burden for healthcare systems throughout the world (38).

CONCLUSION

One of the top ten cancers in the world by prevalence is oral cancer. The mortality and morbidity rates of oral carcinoma is high because it was detected in the last stage which is harmful to the patients. The typical age of diagnosis for oral cancer is around 60 years, and 95% of instances occur in persons more than 40 years. Therefore, it's critical to find oral cancer early on to lessen the impact of this fatal condition. Therefore, it is urgently necessary to develop crucial diagnostic methods that are practical, noninvasive, and simple to use in an outpatient setting for the early detection of oral dysplasia and carcinoma.

The chance of survival is 50% of persons in whom carcinoma was detected in the last stage. About 50% of affected cases of oral squamous cell carcinoma (OSCC) survive. Traditional OSCC treatments such as surgical treatment ,radiation treatment and drug treatment have advanced, but there was no improvement in the rate of survival but has led to grave complications. Although several biomarkers have been developed as potential OSCC prognosticators, the prognosis of oral cancer is still determined by conventional factors including tumor grade and depth of invasion.

Latest work has shown that immunotherapy is an efficient regimen choice for OSCC. The theory of immunotherapy was established long back suggesting the part of the immune system in suppressing carcinoma cells and helping the patient to recover. The importance of immunotherapy of cancer was noticed only when the Nobel prize in medicine was given for such treatment in 2018. Immunotherapy for OSCC was first introduced for patients with repeated and metastatic lesions identical with other carcinoma of head and neck. Neo-adjuvant immunotherapy has been currently used for untreated OSCC before operation. It is necessary to frame criteria for selection of persons who might gain from immune treatment in the management of OSCC and to discover an anticipating marker for succeeding response for treatment. The significance of salivary barometers for early observation has also been highlighted.

Oral carcinoma is quite common. It is possible to cure mouth cancer if treatment was given early, when it was small and localized .A dentist usually detects oral cancer in its nascent stages because they can examine the mouth and lips easily. Most of the oral cancers are squamous cell carcinomas.

Warning signs of oral cancer

Long standing ulcer of more than 20 days, growth / uneven surface on inner aspect of the mouth, white or red patch, sudden drop of tooth, modified speech, discomfort in eating, pain at the posterior aspect of throat extending to the ear and swelling of the neck.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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