

Oral and oropharyngeal cancers: global status, needs and recent developments in treatment

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ABSTRACT

Oral and oropharyngeal cancers are a large group of cancers that fall under the category of cancer of the head and neck. Current therapy includes surgery and radiotherapy associated with extreme morbidity and a decline in the quality of life. At advanced stages, oral cancer is often diagnosed and has a poor prognosis. Hence, an attempt was made to understand current status, needs and developments in oral cancer. This review provided epidemiology, risk factors and methods of screening of oral cancer. It reviewed current treatment strategies and risks associated oral cancer treatment. This review focused on recent developments in oral cancer research. Therapeutic peptides of microbial origin have proven to be effective in oral cancer. Hence, microorganisms and their peptides are reviewed which may be considered as novel leads for the treatment of oral and oropharyngeal cancers.

Keywords: Oral cancer, therapeutic peptides, oropharyngeal cancers, bacterial peptides

INTRODUCTION

One of the most common cancer types in India is oral cancer. In initial stages, oral

cancer is asymptomatic and hence late diagnosis accounts for its low outcome of survival. Despite improvements in the diagnosis and treatment plan, the worldwide

survival rate of oral cancer has not improved significantly and is still low for the last few decades. Oral cancers include the major areas of the tongue, oral cavity, nasopharynx, and pharynx, with an especially high risk factor exposure burden in South Central Asia. Oral carcinogenesis, including hyperplasia, dysplasia, in situ carcinoma and invasive carcinoma, progresses across a variety of pathological lesions. It typically occurs in the oral cavity with precancerous signs, such as white patches (leukoplakia) or red patches (erythroplakia). In any part of the oral cavity, oral cancer can occur, but it typically occurs in the buccal mucosa, upper and lower gingival, hard palate, tongue and floor of the mouth. Oral leukoplakia is a precancerous lesion that occurs in the oral mucosa as white patches. There are two forms of leukoplakia: homogenous lesions and heterogeneous lesions. Leukoplakia diagnosis typically depends on a biopsy to diagnose histopathology. Apart from that, in clinical leukoplakia, biopsy is a typical criterion for histo-pathological diagnosis. All cases with small heterogeneous leukoplakia or lesions with extreme dysplasia were indicated for surgery [1]. Erythroplakia has a relatively high incidence of malignant transformation, a type of relatively uncommon lesions (above 80

percent). In elderly patients who regularly use tobacco and alcohol, this lesion can be identified with a red band, relatively smooth, no signs in the floor of the mouth, the surface of the tongue and the soft palate. Thus, in this case, complete removal surgery is a big recommendation.

Epidemiology of oral cancer

An estimated 657,000 new cases of oral cavity and pharynx cancer are recorded each year, with more than 330,000 deaths worldwide. The area most significantly affected by oral and oropharyngeal cancers is Asia. Bangladesh has the highest incidence and mortality rates for oral and oropharyngeal cancers in South Asia. Over 100,000 cases are reported annually in India, and it is estimated that 182,697 cases are expected by 2030. Taken together, less developed countries account for almost two-thirds of the burden of oral and oropharyngeal cancers. In Asian countries, especially south East Asia, the incidence and mortality of oral cavity cancer is high. For diagnosing the causes of high incidence and mortality rates, etiological studies are recommended in these regions [2]. An annual estimate of the occurrence of oral and oropharyngeal cancers in the US is made by the Oral Cancer Foundation each year. The number has risen again this year, and OCF predicts that in 2019, 53,000

Americans will be newly diagnosed with oral or oropharyngeal cancer. In 2019, about 9,750 people will die from this cancer, also an improvement over last year [3].

The incidence of oropharyngeal cancer across the UK is growing rapidly. Oral cavity cancer rates are higher in Northern Ireland and higher still in Scotland (and relatively stable), but increasing in England and Wales. The INHANCE data indicate that while alcohol and tobacco use are the main risk factors for oral cavity and oropharyngeal cancers, the preventive benefits of reducing these risk factors are more certain [4].

The risk factors for developing oral cancer are also other factors, such as low socioeconomic status, genetics, oral hygiene, and human papilloma virus (oropharyngeal cancer only) [5]. India has one third of the world's cases of oral cancer. In India, oral cancer accounts for around 30% of all cancers. The highest incidence of mouth cancer has been recorded in the central region of India. It is due to a lot of etiological variables. The use of tobacco is the most relevant among them. More males suffer and die from oral cancer in general than female (Table 1) [6].

Risk Factors

The use of tobacco in all its forms and alcohol are significant risk factors for oral

cancer growth. Tobacco and alcohol are associated with the majority of oral cancers (front/anterior of the mouth), with around 10 percent of these cancers attributed to unknown causes.

Many studies have shown the link between tobacco use and a high incidence of oral cancer. There is a prevalence of oral cancer among those who have avoided or decreased their use of tobacco in rural areas [7].

Unknown etiology cancers can arise from a genetic aberration or frailty, or from a common shared risk factor for lifestyle that has not yet been identified. Paan with betel nut/areca nut (supari) are common causative agents of Oral cancer. Another consideration is persistent gum and cheek pain due to ill-fitting dentures or sharp teeth. A connection has long been proposed between an unbalanced diet and oral cancer. The meta-analysis found that daily fruit and vegetable intake reduced the risk of oral cancer by 50%. Infection with Human Papilloma Virus (HPV) increases the risk of certain types of oral cancer, especially among younger people [8,9].

Individuals with compromised immunity are more vulnerable to oral cancer. The deficient immune system may be responsible for some immune deficiency diseases at birth, radiotherapy and chemotherapy, medicines given to organ

transplant recipients, and Acquired Immunodeficiency Syndrome (AIDS). Lip cancer may be caused by exposure to ultraviolet rays of the sun.

Methods of screening

At an early stage, only 30 percent of oral and pharyngeal cancers are detected, while 50 percent are diagnosed at an advanced metastasis stage (stage III or IV). This is primarily due to late presentation between dentists and medical doctors, delayed diagnosis, and lack of proper referral routes. Therefore, oral cancer screening must be an integral component of the regular inspection

of the head and neck performed in the primary dental care setting.

Major events in oral cancer treatment and future goals

Only in the last 20-30 years have the biggest advancements been made in our understanding of oral cancer. Some big studies on the molecular characterization of oral cancer were also made nearly 20 years after similar findings in other cancers (Table 2). Understanding of microbial genome and the role of microbial peptides in the subsequent inhibition of oral cancer progression is under study.

Table 1. Number of new cases in India, both sexes, all ages; [source: Globocan, 2020, India, WHO]

S. No	Type of Cancer	Number of new cases-2020
1	Breast Cancer	178361(13.5 %)
2	Lip, oral cavity	135929(10.3 %)
3	Cervix uteri	123907(9.4 %)
4	Lung	72510(5.5 %)
5	Colorectum	65358((4.9 %))
6	Other cancers	748348(56.5 %)

Table 2. Major events in oral cancer treatment and future goals

S. No	Year	Major events in oral cancer treatment and future goals
1	1920-1930	Radiotherapy was introduced.
2	1950-1960	Chemotherapy was introduced.
3	2000-2010	Cetuximab, Nimerazole, Pembrolizumab and Nivolumab were approved.
4	2020-2050	Hypoxia specific therapies, Immunotherapies, Effect of microbiome oncogenesis

Conventional Oral Examination

An oral cancer screening test should require visual inspection of the face, neck, lips, labial mucosa, buccal mucosa, gingiva, floor of the mouth, tongue, and palate, according to the World Health Organization and the National Institute of Dental and Craniofacial Study. Mouth mirrors can allow all surfaces to be visualized. Conventional oral testing is the most practically applied and accepted screening technique for oral squamous cell carcinoma. In addition to a limited number of malignant lesions, COE generally chooses lesions from clinically and histopathologically benign stages, such as

traditional leukoplakia. Several experiments have been carried out in order to test the reliability and reproducibility of COE [10].

Histopathological examination and biopsy

Histopathological examination and biopsy is the gold standard method of identifying suspicious lesions for cancer diagnosis in premalignant conditions at early stages, whereas this is an invasive technique and cannot be used for mass screening. As an alternative test to other screening processes, it can be used as a confirmatory test. In order to prevent any diagnostic related errors, it is very important to target the main representative zone in a wide

variety of lesion areas. Every abnormality lasting more than two weeks should be re-evaluated and biopsy referred [11].

Brush Cytology

In early detection of oral cancer or oral potentially malignant diseases, Oral Brush Cytology (OBC) is used using both liquid-based and traditional preparations. OBC is a well-tolerated, minimally invasive, and healthy approach to oral mucosal cell harvesting. A quick, well-tolerated, minimally invasive, and relatively painless diagnostic technique for harvesting representative cells of oral mucosal layers is attributed to the key advantages of OBC. More value was added to the OBC technique by the implementation of Liquid-Based Cytology (LBC) [12].

Toluidine Blue

A critical colorant that can stain nucleic acids and irregular tissues is Toluidine blue (tolonium chloride). It has been found to be effective in detecting oral cavity mucosal anomalies. Cyto-histo pathological similarity, high sensitivity and specificity have been shown by 1 % toluidine blue (modified Mashberg method) and cytology in the identification of oral premalignant and malignant lesions [13].

Oral cancer and its treatment

Surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy and supportive treatment can be used to treat oral cancer. The surgical goal is to fully eliminate the negative margin of the primary tumor, as well as to determine the stage and treatment of regional lymph nodes. In oral cancer surgery, mandible management is an important factor because resection of any portion of the mandible involves the proximity of the primary tumor to the mandible or the invasion of the mandible by the primary tumor [14].

A central component of the treatment of oral cavity cancer is control of the neck. Sixty percent of patients with early stage oral cancer with metastatic cervical lymph nodes (cN0) cannot be clinically identified. Many factors, such as tumor size, histology grade, invasion depth, perineural invasion, and vascular invasion, are associated with the risk of neck lymph node metastasis.

In oral cavity cancer treatment, reconstructive surgery plays a significant role. Presurgical function and cosmesis are returned to the target of reconstructive surgery. For most cases of oral cancer, primary reconstruction rather than

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secondary surgery has been the first option of treatment.

In patients with a high risk of local, regional recurrence, postoperative adjuvant therapy is recommended. Two clinical studies have shown that adjuvant radiotherapy with cisplatin substantially increases control rates along with survival time relative to single adjuvant radiation therapy in those with invasive extra capsular head and neck cancer.

There are large variations in intraoral tumor pathologies, so from 29 population-based cancer registries in India (2012-2014), all cancers linked to the oral cavity and other associated sites such as lip, tongue, throat, tonsils, salivary gland and oropharynx cancers were included. It has been shown that oral tongue cancer can be easily controlled if detected at an early stage and without any neck nodes (T1-2N0M0) without substantially affecting patients' Quality of Life (QOL).

The risks associated with treatment strategies of oral cancer

Depending on the form, location, and stage of the cancer at diagnosis, treatment for oral cancer will differ. Early stage treatment usually requires surgery to remove the tumor and cancerous lymph nodes. Furthermore, chemotherapy and radiation therapy are given. Radiotherapy

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is one of the choices for treatment that also results in complications. It accounts for over thirty per cent of all cancers reported in the country.

Next, it is diagnosed at later stages, leading to low outcomes of care and significant costs for patients who are usually unable to afford this form of treatment. Second, rural areas still have insufficient access to qualified practitioners and restricted health facilities in middle and low-income countries. As a consequence, delay has also been largely associated with advanced oral cancer stages. These problems impact the quality of life of the patient, food intake, and ultimately undermine the effects of treatment. The verbal accounts of patients' experiences about their overall oral health during radiotherapy have not been properly identified.

The related morbidity and mortality was greatly affected by early oral cancer diagnosis. Oral cancer is typically associated with malignancy-related classical clinical features that result in correct diagnosis. However, some cases of oral cancer may be clinically misleading and may be misdiagnosed, especially in its early stages [15].

Patient adherence to oral cancer treatment regimens can be adversely affected by

medication-related factors of existing medications, such as increased toxicity, drug-drug interactions, and safe handling problems [16]. For the treatment of early oral cancer, surgery and radiotherapy are commonly used. Other potential risks can involve dehydration and malnutrition, often induced by swallowing difficulties (dysphagia). Radiation can injure the saliva-producing glands (xerostomia), or damage the jaw and neck muscles and joints (trismus). These treatments can also lead to hypo-vascularization (reduction of blood vessels and blood supply) of the maxillary bones. In addition, other types of dental disease (caries or complications of soft tissue) may be affected by treatment or may cause bone death (osteonecrosis) [17].

The side effects of oral cancer chemotherapy, radiation and drug resistance are among the main current clinical issues. Therefore, it is very important to look for new substances and drugs for cancer. Among them, a promising group of bioactive compounds and potential anticancer drugs are bacterial proteins and peptides [18].

Recent developments in oral cancer treatment

Despite advancements in surgery, chemotherapy and radiotherapy for

HNSCC care, there has been no substantial change in the prognosis of this disease over the last 50 years. In order for oral cancer to include health education and awareness, risk factor mitigation and early detection, a holistic approach is needed. Oral cancer screening in high-risk individuals has been tested in selected regions with a high incidence [19].

On the cell surface, oral cancer tumor suppressant antigen (TA) is poor. Therefore, better TA presentation is one of the avenues for targeted therapeutics promotes monoclonal antibodies [20]. In the second-line setting for patients with recurrent/metastatic oral cancer, nivolumab and pembrolizumab have recently been approved for use as mono therapy [21,22].

Inhibitors of Epidermal Growth Factor Receptors (EGFR, highly overexpressed in 80-90 % of patients with oral cancer), such as Cetuximab, Bevacizumab, and Erlotinib, have shown improvement in the treatment of the disease [23]. The treatment of oral cancer cells with cisplatin-loaded nanoparticles (NC-6004) results in the activation of the apoptosis-inducing caspase-3 and caspase-7 pathways. A combinatorial method was recently developed using Solid Lipid Nanoparticles (SLN) loaded with

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Paclitaxel (PTX), 5-Fluorouracil (5-FU) and Ascorbic Acid (AA) for oral cancer therapy. Better therapeutic efficacy has been shown in pharmacokinetic and bio-distribution studies of prepared SLN [24]. Chemotherapy with 5-Fluorouracil (5-FU) was meant to kill cancer cells, but it infected the surrounding normal cells during the treatment of oral cancer. The chemo protective effects of Curcumin (CU) as herbal remedy on oral cancer treatment with 5-FU-induced cytotoxicity loaded inside the nanocarrier system have been studied. As a combinational drug delivery system, CU was paired with 5-FU chemotherapy [25].

The use of nano-based Drug Delivery Systems (DDS) in conjunction with immunotherapy has recently been studied for oral cancer treatment [26,27]. Other therapeutic strategies have recently been used, including Photodynamic Therapy (PDT), to improve drug penetration deeper into the tissues needed for the treatment of advanced and recurrent oral cancer. Using an oil-in-water emulsion solvent evaporation technique, highly stable PLGA based Quinacrine (QC)-silver hybrid Nanoparticles (QAgNP) are formed. Oral Squamous Cell Cancer (OSCC) proliferation and decreased neo-angiogenesis is inhibited by

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PLGA/quinacrine/silver nano particles [28,29].

The enhanced bioavailability of curcumin loaded into nano structured lipid particles, an evolving method for the treatment of OSCC, has been documented. The manufacture of nano structured lipids with other therapeutic agents, such as docetaxel and etoposide, has been documented in other studies and has shown promise in the treatment of oral cancer. Exosomes may be a valuable method for the treatment of oral cancer, but they are still difficult to disinfect, examine and administer. Chemotherapy Photodynamic Therapy (PDT) is currently being produced to simultaneously release anticancer and photosensitizer medicines at the tumor site for the treatment of resistant cancer of the head and neck. As nucleic acid delivery vectors, micro bubbles are another technique that can trigger EGFR inhibition by RNA interference. Ultrasound-targeted micro bubble destruction (UTMD) ruptures micro bubbles delivered to the site, leading to drug release from the shell of the micro bubbles to the tumor areas [30,31,32].

Role of microorganisms and its proteins in treatment of oral cancer

In the treatment of cancer, bacteria and their metabolites are used without causing

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toxic effects. Several *Escherichia* and *Salmonella* strains endogenously express Cly A and causes cellular lysis of infected cells. They produce and release toxins externally. To increase the cytotoxic effect, *E. coli* were modified to constitutively express Cly A. [33,34,35].

From several different microbial sources, various forms of anticancer molecules have been isolated. *Salmonella typhimurium* defective strains in ppGpp synthesis (ppGpp *S. Typhimurium*) and *E. Coli* K-12 (MG1655), accumulated in different types of tumor-bearing mice exclusively in tumors following intravenous administration [36,37].

The other approach shown by bacteria is the suppression of tumors and micro-environmental changes. *Salmonella* spp. directly kills tumor cells by inducing apoptosis and/or autophagy through a variety of mechanisms, including toxin production or nutrient deprivation from tumor cells [38,39,40].

An attenuated *S. Typhimurium* strain, developed by deletion of the *msbB* and *purI* genes, has been extensively studied in tumor-bearing mice and shows promising specificity of tumor-targeting and inhibitory effects of the tumor [41,42].

In some human cancer cells, Azurin, forms of cupredoxin electron transfer and

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purified low-molecular-weight redox protein from the pathogenic bacteria *Pseudomonas aeruginosa* selectively induces and activates apoptosis. Azurin can get into human cancer cells efficiently, but not into normal cells. Azurin forms a complex with the tumor suppressor protein p53 after internalization and stabilizes it, thereby inducing apoptosis or cell cycle arrest in the G1 process. Its ability to modulate the growth of oral cancer has not yet been characterized, despite comprehensive study of azurin's antitumor activity. Azurin's antitumor activity on YD-9 and MG-63 cells has been elucidated. Azurin regulates protein levels of p53 and cyclin B1, contributing to OSCC apoptosis. In addition, 5-fluorouracil or etoposide combination therapy with azurin effectively improves the sensitivity of OSCC to anticancer drugs [43].

Recombinant *Bifidobacterium longum* showing partial mouse Wilms' tumor 1 (WT1) protein (*B. longum* 420) has been developed using a bacterial vector as an oral cancer vaccine. Vaccination by oral route with *B. Longum* successfully induced WT1 specific anti-tumor immunity in mice by the display of WT1 protein and could be improved by IL-2 treatment [44].

Role of therapeutic peptides in treatment of oral cancer

Promising classes of therapeutics, therapeutic peptides offer many advantages over classical drugs such as proteins, antibodies and small organic molecules. With a host of new applications in the diagnostic as well as the therapeutic field, peptides and proteins have appeared. A total of 239 therapeutic proteins and peptides have been approved for clinical use by the US-FDA since the early 1980s. A benefit of peptides over other medicines is that they are extremely flexible, offering a large range of pharmaceutical targets, high specificity and low levels of toxicity. A total of 60 peptide-based pharmaceutical products are already on the market and many other therapeutic peptides are currently being tested at various clinical trial stages. THPdb is a database of therapeutic peptides and proteins approved by the Food and Drug Administration (FDA). It is curated manually. The text file contains all of the THPdb curated data. Peptides that exist naturally in all living organisms and have unique biological activities are AMP/pore-forming peptides. These pore-forming peptides attack cancer cell membranes and, either by necrosis or apoptosis, can cause cell death [45].

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Buforins are stomach-derived peptides of *Bufo bufo gargarizans*. Buforin I is a 39 AA peptide derived from 21 AA buforin II. BuforinIIIb has been shown to be cytotoxic against in vitro human cervical carcinoma (HeLa) and leukaemia (Jurkat cells) cells and to inhibit the growth of xenografts in mice in human lung cancer. BR2, a 17 AA peptide dependent on the CPP motif of buforinIIIb, is called BA novel CPP. This peptide, but not NIH 3 T3 mouse fibroblasts, HaCat human keratinocytes and BJ human fibroblasts was cytotoxic against HeLa cells, HCT116 human colon cancer cells and B16-F10 mouse melanoma cells [46].

Active markers expressed on the tumour cell membrane are Tumour-Targeting Peptides (TTPs). The Arg-Gly-Asp sequence recognizes and binds to integrin α -v β 3 and α -v β 5 expressed on the lung cancer melanoma membrane, brain tumors, ovarian carcinoma, oral cancer, and breast cancer cells. MAPKs are serine/threonine kinases which, in response to external growth factors, hormones, nutrient status or stress, have an important role in cellular signal transduction cascades and activate intracellular events. Extracellular signal-Regulated Kinases (ERKs), c-Jun amino terminal kinases, and the three major

characterized subfamilies of MAPKs found in mammalian cells are (JNKs) and p38 MAPKs. In cell proliferation and differentiation, ERK plays a significant role and is deregulated in one-third of all human cancers, including breast, pancreatic, pulmonary adenocarcinoma, thyroid, bladder, liver, kidney and melanoma. In the phosphorylation of ERK, MEK plays an important role in inducing the transcription of proteins that regulate apoptosis [47].

The member of the third MAPK subfamily is p38. In head and neck squamous cell carcinoma (HNSCC), breast, gastric and non-small cell lung cancer p38 levels are elevated. It consists of two binding sites: an Asp-Phe-Gly (DFG) motif and an ATP-binding site. Recent research has focused on the production of peptides that are inhibitory to p38 α . In a time- and dose-dependent manner, the synthetic tetra peptide VWCS prevented the proliferation of HNSCC and KB human oral cancer cells. The FWCS tetra peptide is based at the DFG site and has inhibited the dose- and time-dependent growth of HNSCC and KB cells. As a promising technique for the design of drug candidates, inhibitory or interference peptides (iPeps) have appeared. Peptides (Mw 500-5000 Da) combine the advantages of biological and

chemical origin. There are three members of the MYC oncogene family: c-Myc, N-Myc, and L-Myc, which have a similar feature, but vary in potency and expression patterns. In the overwhelming majority (~70%) of human malignancies, including breast, colon, cervix, lung, bone, brain, and blood cancers, oncogenic deregulation of MYC is observed [48,49].

In OSCC patient tissues, the interferon-mediated tetra tri copeptide repeat protein (IFIT) gene family protein levels were altered, but it is still unclear how and why their expression was induced in OSCC [50].

IFIT1 or IFIT3 over-expression improved OSCC tolerance to different chemotherapy drugs, including Cisplatin, Carboplatin, Oxaliplatin, 5FU, and Ganetespib. The expression of IFIT1 and IFIT3 made Gefitinib susceptible to OSCC cells (EGFR-TKI) In OSCC cells, IFIT1 and IFIT3 promoted EGFR activation and increased the tumor-preventive activity of Gefitinib. IFN-alpha and Gefitinib combination therapy demonstrated synergistic anti-tumor activity in OSCC cells [51].

In OSCC cells, IFIT2 knockdown improves atypical PKC signaling. Targeting particular IFITs can therefore be a successful therapeutic strategy for OSCC

care.⁸⁸ It has been established that the WISP family is associated with oral tumorigenesis. An experimental in vitro research has shown that WISP1 knockdown induces apoptosis and prevents the invasion of cells of oral squamous cell carcinoma (OSCC). In oral cancer patients, WISP-1 expression was clinically associated with the tumor stage [52].

In people who smoke, WISP1 rs2929970 polymorphism is prone to OSCC, while WISP1 rs16893344 is causally related to the incidence of OSCC in individuals who chew betel nuts. WISP1 amplification is associated with a substantial decline in oropharyngeal squamous cell carcinoma survival (OPSCC) [53]. Tenascin C (TNC) TNC is a glycoprotein which, by assembling other ECM molecules, forms a broad structural body and takes part in cell adhesion, motion, permeation, survival, migration and differentiation. Large Tenascin-C variant is over expressed in oropharyngeal squamous cell carcinoma [54].

Symbiotic (probiotics and prebiotics), diet or microbial suppression is the latest avenues for personalized care. For cancer prevention and/or treatment, probiotic strains may be useful adjuvants. In patients with HNSCC *Lactobacillus brevis* CD2

lozenges have been shown to reduce the severity and frequency of radio/chemotherapy-induced mucositis [55,56]. Some of the bacterial proteins such as Azurin proven to be promising lead as novel anti-cancer agents [57,58]. Micro environment of oral cavity and its effect on oral cancer and its malignancy have to be established further for better therapeutic approaches. The effect of checkpoint inhibitors with other therapeutic agents is being currently under study [59, 60].

CONCLUSION

Invasive growth rates, metastases of the regional lymph node and second primary cancers are distinguished by oral cancer. Current therapy includes surgery and radiotherapy associated with extreme morbidity and a decline in the quality of life. At advanced stages, oral cancer is often diagnosed and has a poor prognosis. Several variables such as age, co morbidities, social issues, and especially whether to prefer surgery or radiation-based protocols need to be weighed when selecting the most suitable treatment for patients with oral cancer. Hence, this review is conducted to understand current status, needs, challenges and recent

developments in oral cancer treatment. The development of the evasive resistance of cancer cells to traditional therapies is the major challenge in the management of HNSCC patients today. To address unmet needs for the treatment of oral cancer, novel therapeutic targets, formulations and delivery methods are needed. Therapeutic peptides of microbial origin have proven to be effective in Oral cancer which may be considered as novel leads for the treatment of oral and oropharyngeal cancers.

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