Review Article

Recent Advances in Oral Squamous Cell Carcinoma: A Literature Review

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Abstract

Head and neck squamous cell carcinoma (HNSCC) are the most widely recognized disease emerging in the head and neck region. Smoking, high addiction of drinking, and human papilloma virus (HPV) infection are the most widely recognized risk factors. Oral tumorigenesis and progression have prominent features of aberrations of the epidermal growth factor receptor (EGFR) pathway. Evidence suggests association of cigarette smoking (CS) with worst prognosis in OSCC patients including overexpression of EGFR in tumor tissue. With the increase in incidence of HNSCC, there is a prompt shift in comprehension of the pathophysiology, treatment, and prognosis of this disease. The recent advances in diagnosis and treatment planning have provided significantly better outcomes. Although surgery and adjuvant radiotherapy and chemotherapy are still the mainstream modality of treatment, the advancement in treatment modalities of HNSCC has paved way for better prognosis and saving lives of many. The current review article emphasizes on the recent advances in treatment strategies and new therapies in HNSCC.

Key words

Oral cancer, Oral squamous cell carcinoma, Immunotherapy, Biomarkers, Head and neck squamous cell carcinoma.

Introduction

Introduction

Out of all malignant tumors of the body, around 5% of them are head and neck malignancies [1]. Representing almost 95% of the head and neck cancers, squamous cell carcinoma is the most common malignancy. Oral cancer incidence has a wide regional variation from region in the world. Approximately 2 to 4% of all cancer cases accounts for oral cancer. In countries like India, Pakistan, Sri Lanka and Bangladesh, oral

cancer malignancy is the most commonly occurring malignancy, causing 10% of all cancers. In Indian scenario, oral cancer represents nearly 50% of all the malignancies reported [2]. Specific oral habits for instance betel and alcohol are the main reason for high incidence rate among these countries.

Oral cancer is referred to all neoplasms of oral cavity pharyngeal regions and salivary glands. The term oral squamous cell carcinoma (OSCC) is often used interchangeably with oral cancer. It is estimated that 90% of all oral neoplasms are OSCC [3].

Risk factors

The greatest risk factor for OSCC is use of tobacco and alcohol. While 75% of cases occur due to prolonged tobacco smoking, the risk of oral cancer increases 6-15 times in patients with chronic alcoholism [4]. The combined effect of tobacco and alcohol further increases the threat of oral cancer [5]. Some of the other significant risk factors include betel quid chewing, areca nut, narcotics, nutritional deficiencies, impaired immune system, inability to metabolize carcinogen. Viral infections due to Human Papilloma Virus (HPV), Epstein-Barr virus are also predisposed to have oncogenic potential and also with Hepatitis C Virus. HPV 16 was more frequently associated with development of oral cancer.

The last few decades marked a significant reduction trend in smoking and thereby smoking related HNSCC in high-income countries. In contrary, incidence of HPV- associated HNSCC marked a significant increase globally [6].

Diagnostic Aspect

The mortality rate of OSCC with a 5-year survival rate is almost about 50% and this has remained unchanged for almost few decades [7]. In order to reduce the high mortality, detection of oral cancer at its earliest is the most competent means. Both morbidity and treatment of the disease gets minimized by early detection. Critical diagnostic tools are needed to be devised urgently for early detection of oral dysplasia and malignancy. These tools are practical, non-invasive and are easy to perform in an outpatient set-up. The various tools for diagnosis of oral cancer have been mentioned in **Table - 1**.

Table – 1: Tools for diagnosis of oral cancer.

Visual examination
Excision biopsy and Histopathology
Oral brush biopsy
Toluidine blue
Light-based detection systems
• Chemiluminescence • Tissue fluorescence imaging (VELscope) • Tissue fluorescence spectroscopy
Biomarkers
• DNA-analysis
Laser capture microdissection

For malignant lesions, a highly sensitive and moderately specific diagnostic aid is Toluidine blue which is useful in detection of the suspected areas. The range of sensitivity of toluidine blue staining in oral cancer screening varies from 93.5% to 97.8%, and specificity from 73.3% to 92.9% as stated by Rosenberg and Cretin [8]. Another reliable technique equivalent to surgical biopsy is brush biopsy which involves collection of cells from the oral epithelium at its full thickness. Moreover, the sensitivity of brush biopsy was found to be 71.4% in detection of OSCC [9]. In saliva-based oral cancer test, among the most significantly elevated tumor markers are Tissue polypeptide-specific antigen (TPS) and cancer antigen 125 (CA125); while other tumor markers show insignificant elevation [10].

Optical diagnostic

Technologies based on optical diagnostic techniques are useful in detection of oral dysplasia and malignancy at their early stages. These include the light-based systems. Besides being practical, noninvasive, they have an added

advantage as one can easily perform it in an outpatient set-up. The chemiluminescence and VELscope (Tissue fluorescence imaging) are support the theory that different structural changes in malignant tissues will have different light absorbance and reflectance properties than normal tissues due to abnormal metabolic process. There is no claim by the manufacturers about the device being sensitive to any type of abnormal oral lesion identification. The most consistent optical diagnostic biopsy having high sensitivity and specificity is Tissue fluorescence spectroscopy and relies on the depletion of NADH and FAD that are supposed to produce green fluorescence. An improvement in the detection of premalignant and malignant oral lesions has been observed with sensitivity of 81% by use of tissue fluorescence spectrometry [11]. Raman spectroscopy and elastic scattering spectroscopy uses the method of chemical characterization to offer the optical signature of the tissue by biopsy.

Optical coherence tomography uses light technology rather than sound as in case of ultrasound imaging, other than that they are similar. DNA-analysis could be used in determination of the malignancy probability of cells by comparison with a reference group of cells. Positron emission tomography (PET) is a "functional image modality that characterizes the different tissues of the body according to perfusion and metabolic activity of the glucose analogue fludeoxyglucose F 18 (^{18}FDG)". In diagnosis of OSCC, PET imaging has been declared as most valuable functional imaging technique. Although FDG-PET has no confirmed supplementary value in staging of patients with a known primary tumor, it has a key role in identifying unknown primary tumor. One limitation of using FDG-PET scanning is controversy regarding diagnosis of lymph node involvement. While wide agreement was observed on usage of ultrasound guided fine needle aspiration biopsies as the most reliable technique in the evaluation of lymph node metastasis.

Resistance of hypoxic cancers to radiotherapy and chemotherapy is well known. Currently topic of interest lies in using radiosensitisers such as carbogen for improvement of the therapeutic response of hypoxic cancers to radiotherapy. A noninvasive test called Blood Oxygen Level-Dependent MRI (BOLD) uses MRI for identification of hypoxic cancers (deoxyhaemoglobin) which will possibly respond to this sort of treatment. It detects an increase in signal which results from reduced paramagnetic effect due to reduced blood deoxyhaemoglobin within a cancer by using a T-sensitive sequence during oxygen inhalation [12]. Laser capture microdissection (LCM) has led to more precise study of oral cancer and used for detection of biomarkers and establishment of protein fingerprint model required for early diagnosis of oral cancer [13].

Advancement in treatment of OSCC

The usual treatment of OSCC includes use of radiotherapy and/or surgery in the primary stage. A combined therapy involving radiotherapy, chemotherapy or surgery is used in the later stage (3rd or 4th) of oral cancer. In addition to this, the patients receiving radiotherapy must be conscious towards their oral care since the oral mucosa is liable to xerostomia, mucositis and osteoradionecrosis as side effects from the treatment. It is quite acceptable that OSCC has the best prognosis when diagnosed early, particularly amongst the well-differentiated ones which are not metastasized. Metastasis which usually occurs in the cervical lymph nodes, undergoes treatment of cervical lymphadenopathy (radical neck dissection). Recent times noticed development of selective neck dissection which reduces the morbidity caused by radical neck dissection [14]. Under chemotherapy, the standard for regionally advanced HNSCC is cisplatin-based chemoradiation.

Immunotherapy has been underlined in the recent research as a significant treatment of many cancers. In this new era, Immune checkpoint

inhibitors (ICI) have been used as a weapon for targeting metastatic melanoma which turned to revolutionize the therapy of all cancers along with OSCC. It was based on the fact that patient's own ability of the immune system will cause repression of cancer cells and be helpful in recovery. This made a global recognition in 2018 when the Nobel Prize was rewarded for developing such therapies [15]. Vigorous research is being conducted for evaluation of the tumor immune microenvironment (TIM) which will aid in identifying potential biomarkers for ICI response. Higher CD8+ T-cell infiltration was confirmed to be a self-sufficient predictive factor for enhanced prognosis which was observed among PD1/PD-L1 (Programmed Death-Ligand 1) inhibitor therapy responders [16].

Microbiome has emerged to be a key factor which influences reaction to cancer therapy. Vigorous investigation is being carried out for the function of the oral cavity microbiome in development and progression of HNSCC, and a potential part of Fusobacteria species was pointed out by initial studies, found in both primary and metastatic cancerous tissues [17].

Encouraging results were found from research on therapeutic vaccines. Similarly, cell-based therapy is developed as a latest weapon to fight OSCC. Use of T cells already primed to patient-specific antigens was involved here. Multiple trials are being conducted to investigate the application of T cell therapies in case of solid malignancies [18].

At present, therapy with monoclonal antibodies and gene therapy are some of the targeted molecular therapies that the oral cancer patients have already been applied. There is a restricted or nonexistent side effect of this treatment modality on the body's normal cells. These therapies could also be a complementary to other existing cancer therapies. They are primarily focused on four molecules; cyclooxygenase-2 (COX-2), epidermal growth factor receptor (EGFR), progesterone receptor and peroxisome proliferator-activated receptor γ (PPARγ). Association of these molecules with the differentiation and proliferation of OSCC has been prominent [19].

Future area of research

With the rapid evolution of immunotherapy, biomarkers identification for the prediction of immune response could be a clinically efficient treatment of OSCC. The last three decades saw introduction of many parameters/biomarkers for the evaluation of immune response. Efforts for ongoing research are growing in the field of immune response usage in grading of OSCC, and immunoscore identification for OSCC. A cornerstone in identification of patients benefitted from immunotherapy is definitely a clinically relevant assessment of the immune response. Current collaborative studies and/or meta-analyses which emphasize the significance of assessment of TILs and other immune biomarkers provide evidence to be a strong tool in revealing the status of the immune response along with a strong correlation with survival outcome. Increase in urgency is needed to conduct more validation studies to validate the findings on these biomarkers for identifying an ideal biomarker/s to select OSCC cases which can be cured from immunotherapy. Further research is required in digital evaluation of immune biomarkers in OSCC which is yet at its initial stage. Similarly, additional investigation is still required on the findings of predictive value of tumor mutational burden and mutational signatures before adding them in the personalized prediction of OSCC treatment response.

Conclusion

The key for a better prognosis of oral cancer is early detection. Oral cancer screening must be conducted in tobacco prevalent regions to catch the disease at an initial stage. Though traditional therapies are still going on, yet the survival rate from oral cancer remains unchanged since decades. With the latest advancement in

therapies, there is a promising change in the field of oral cancer diagnosis and treatment.

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