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Contemporary Multimodal Approaches in Oral Cancer: An Updated Review

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ABSTRACT

Oral cancer is one of the global health burdens with considerable morbidity and mortality due to its aggressive nature and diagnosing it in later stage. This complex disease with anatomical and functional implications requires a multidisciplinary and multimodal approach for management. In recent years detection and management of oral malignancies gained prominence due to its contemporary multimodal approach. This updated review gives an insight on traditional diagnosis with the advanced techniques like optical imaging, salivary biomarkers and genomic profile. Trending aids like Artificial Intelligence including Machine Learning algorithms may facilitate a more precise diagnosis. The multimodal treatment approach integrates traditional cancer treatment with newer techniques like immunotherapy, gene therapy and precision medicine guided by molecular profiling. This multimodal approach can improve survival rates, reduce recurrence and preserve quality of life with advanced or high-risk oral cancers. This evidence based multimodal approach can achieve better clinical and functional outcomes in oral cancer patients.

KEY WORDS: Oral cancer, Multimodal approaches, Artificial Intelligence, Interdisciplinary management

INTRODUCTION

A global health challenge in today's world continues to be Oral Cancer primarily Oral Squamous cell carcinoma (OSCC). It Often arises from epithelial cells, especially squamous cells, representing 90% of all head and neck carcinomas.[1] Oral cancer still has high rates of morbidity and mortality, with a global 5-year survival rate of about 50%, despite recent improvements in cancer treatment.[2] This poor survival rate is mostly caused by aggressive disease progression and delayed diagnosis, especially when the cancer is discovered later. This emphasises the critical need for improved early detection techniques and innovative treatment approaches.

One of the main strategies to reduce the burden of oral cancer, according to the World Health Organisation, is early detection. When evaluating the risk of malignant transformation, this early detection is crucial. Evidence suggests that more than 60% of patients are usually diagnosed with stage III and IV cancer, indicating that the disease is usually detected at an advanced stage.[3,4,5]

The etiology of OSCC is multifactorial, involving genetic and epigenetic alterations influenced by environmental factors such as tobacco use, alcohol consumption, and human papillomavirus (HPV) infection.[6] These risk factors contribute to the transformation of normal epithelium into malignant tissue through complex molecular mechanisms

Chemotherapy, radiation therapy, and surgery are traditional treatment options for oral cancer. Despite being the mainstay of treatment for oral cancer, these methods can entail serious adverse effects, particularly when the illness is advanced.

In recent years, there has been a paradigm shift towards multimodal therapy, which integrates various treatment strategies to enhance efficacy and overcome the limitations of single modality treatment. This approach may combine surgery, chemotherapy, radiation therapy, targeted therapy and immunotherapy to address the complex nature of oral cancer.[7]

The goal of this review is to present a thorough summary of the most current developments in the treatment of oral cancer. In the continuous fight against this difficult and deadly illness, multimodal treatment would provide the way forward for a better quality of life.

GLOBAL EPIDEMIOLOGY:

According to Global Cancer Observatory (GLOBOCAN) for 2022, oral cancer ranks as the sixth most frequent cancer worldwide, accounting for about 389,846 new cases and 188,438 deaths every year.[8] It is the most common form of cancer in South and Southeast Asia, especially in Bangladesh, Pakistan, India, and Sri Lanka, where it accounts for up to 40% of all cancer cases. Oral cancer is the most frequent cancer in men in India alone, accounting for over 30% of all cancer cases.[9] Western nations like the United States, the United Kingdom, and portions of Europe, on the other hand, have comparatively lower incidence rates, despite some upward tendencies, especially when linked to HPV infection. The incidence of HPV-positive oropharyngeal malignancies is rising in these areas, although effective public health initiatives are lowering the prevalence of conventional risk factors like alcohol and tobacco use.[10] Oral cancer is still a major issue, especially for underserved people with little access to medical treatment.

RISK FACTORS

Oral squamous cell carcinoma (OSCC) is a multifactorial disease with several well-established risk factors contributing to its development. Tobacco use, both smoked and smokeless forms, remains the most significant risk factor, often acting synergistically with excessive alcohol consumption to greatly increase carcinogenic potential. However, new variables like dietary practices and HPV infection are becoming more widely acknowledged as significant predictors of the risk of oral cancer.[1]

PATHOPHYSIOLOGY OF ORAL CANCER

Oral cancer, primarily oral squamous cell carcinoma (OSCC), develops from the epithelial lining and is caused by a complex interaction between various factors including environmental variables, epigenetic modifications, and genetic alterations.[11] There is transformation of normal oral epithelium into potentially malignant lesions such as leukoplakia or erythoplakia, which later on develop into Oral cancer. Numerous molecular pathways that regulate cellular proliferation, differentiation, apoptosis, and immune evasion play a vital role and understanding these mechanisms is essential for developing targeted therapies improving better quality of patient life.

The pathogenesis of oral cancer is mostly caused by genetic abnormalities that change important cellular processes. These mutations can cause unchecked cell proliferation and malignant transformation by affecting DNA repair systems, tumour suppressor genes, and oncogenes.[1]

Through the epithelial-mesenchymal transition (EMT), epithelial cells lose their polarity and adhesion properties and acquire mesenchymal traits like enhanced motility and invasiveness, which aids in the progression from localised OSCC to invasive and metastatic illness.[12]

In oral cancer, the tumour microenvironment (TME) is essential for promoting tumour growth, invasion, and treatment resistance. The extracellular matrix (ECM), immune cells, endothelial cells, and cancer-associated fibroblasts (CAFs) make up the tumour microenvironment (TME), and they all interact with tumour cells to accelerate the spread of cancer.[13]

MULTIMODAL APPROACHES IN ORAL CANCER:

Multimodal approaches to oral cancer involve a combination of treatment strategies customized to the individual patient, aiming to improve treatment outcomes and reduce morbidity. These include surgery, radiation therapy, and chemotherapy, often used in conjunction depending on the stage and location of the tumor. Advanced cases may benefit from targeted therapies, such as EGFR inhibitors, and immunotherapy, which harnesses the body's immune system to fight cancer cells. In addition to these medical interventions, imaging modalities like MRI, CT, and PET scans are essential for accurate diagnosis, staging, and treatment planning. To enhance patient care and increase survival rate, multidisciplinary collaboration between oncologists, surgeons, radiologists, pathologists, and supportive care teams is essential. This may broadly classified into two categories. Multimodal Approaches to Oral Cancer Detection and Multimodal Treatment Approaches.

MULTIMODAL APPROACHES TO ORAL CANCER DETECTION

In order to improve patient outcomes, early detection of oral cancer is essential since it can result in less aggressive treatment and a far better probability of survival. Many cases are still diagnosed at very late stage, due to the lack of effective early screening programs and awareness and the asymptomatic nature of early lesions. This has prompted researchers and clinicians to focus on developing multimodal approaches for early diagnosis and screening.[14]

Conventional method of screening and diagnosis

It is based on clinical oral examination (COE). In COE, the doctor looks and feels for ulcers, lumps, lesions, and swollen lymph nodes using visual examination and palpation. It is difficult to diagnose oral cancer in its early stages due to the absence of symptoms and clinical manifestations that are commonly seen in the advanced stages, such as discomfort, ulceration, swelling, and induration (tissue hardening). These approaches are unable to detect the disease's deep spread and may yield inconsistent results.[15]

The GOLD STANDARD is the histological analysis of biopsied specimens from suspected tissues to get a conclusive diagnosis of oral cancer. For any lesion that remains in the oral mucosa for longer than three weeks, a biopsy is recommended. A biopsy is intrusive and unsuitable for routinely screening high-risk individuals. Processing time, interobserver and intraobserver variability, and sampling bias are further restrictions. These restrictions highlight how important it is to create supplemental diagnostic tools.[16]

Genomics based approaches

Both the screening of asymptomatic people and the diagnosis of symptomatic patients with oral cancer can be accomplished using genomic-based methods. Point mutations, gene amplification, fusion, deletion, insertion, and single nucleotide polymorphisms (SNPs) are the main DNA-based modifications that cause genetic changes. DNA can show characteristics peculiar to a tumour, including somatic mutations in the tumour suppressor and p53 genes, aberrant promoter methylation, microsatellite changes, the presence of

tumor-related viral DNA, and mitochondrial DNA mutations.[17]

Quantitative malignancy index diagnostic system (qMIDS)

The purpose of the qMIDS is to objectively evaluate the malignancy status of biopsy samples. The forkhead box M1 (FOXM1) oncogene expression is the basis for the digital index that qMIDS offers to evaluate the risk of squamous cell carcinoma (SCC). The transcription factor FOXM1 is a strong predictor of a bad outcome for cancer and is one of the most elevated oncogenes in 39 different forms of cancer. qMIDS has been helpful in differentiating between premalignant (high risk) oral dysplastic samples and benign (low risk) lesions such fibro-epithelial polyps or oral lichen planus.[18]

Biofluid diagnostics

It has been noted that people with cancer have different saliva and serum compositions, which suggests that biofluid diagnostics could be a useful screening technique. Easy accessibility, safe handling, easy storage, and non-clotting ability are benefits of saliva-based oral cancer diagnostics. Saliva is a biofluid that is typical of serum, and most of its constituents are obtained from serum via paracellular or transcellular pathways. Before malignant transformation, saliva can reveal molecular alterations due to its direct physical interaction with oral lesions. OSCC can be detected by identifying changes in the salivary proteome, transcriptome, metabolome, and microbiome. [19]

Salivary proteomics: The study of proteomics examines all protein isoforms and post-translational changes that are encoded by the cell's DNA under specific circumstances. While a cell's protein levels can vary significantly, its genome remains largely constant. Thus far, 17 elevated protein biomarkers have been found in proteomics investigations. Cyclin D1 thioredoxin, profilin 1, and interleukins 6, 8, and 1b were the most promising protein biomarkers. These target proteins might help clarify the disease's molecular process, which could have important clinical implications.[20]

Salivary transcriptomics: Potential biomarkers such as differentially expressed transcripts are found in OSCC patients saliva samples. OSCC patients' saliva samples exhibit elevated levels of some RNA biomarkers, including DUSP1, HA3, OAZ1, S100P, SAT, IL6, IL8, and IL1B. Researchers have looked into the clinical utility of salivary microRNAs (miRNAs) as oral cancer diagnostic indicators. Tumour initiation and oral cancer malignancy modulation are mediated by dysregulated miRNAs.[21]

Serum Diagnostics: Several investigators have found blood plasma and serum biomarkers may have diagnostic value. It can be used both as a screening as well as a diagnostic tool for cancer detection. Chang *et al* proposed two core-fucosylated glycoproteins in blood plasma—apolipoprotein A-IV and LRG1, as potential serum diagnostics (biomarkers) in oral cancer detection. But the exact spatial location of lesions cannot be identified with this technique.[22]

Vital Staining

Vital staining is the process of highlighting and staining aberrant tissue areas with a dye, such as toluidine blue (TB) or tolonium chloride. TB is a blue metachromatic dye that attaches itself to nucleic acids. Compared to normal cells, dysplastic and anaplastic cells have a larger nucleic acid content. TB helps detect any mucosal abnormalities by staining diseased cells more than normal ones. Although the stated diagnostic effectiveness of TB staining varies, it is still regarded as a valuable addition to COE. It is advised that a biopsy be considered for any lesion that has a positive TB stain.[23]

Brush biopsy

Brush biopsy is a common non-invasive method of evaluating lesions. For the brush biopsy, trans-epithelial cell samples are taken from questionable areas that uses exfoliative cytology method. For patients with several lesions who have never had oral cancer and who would not consent to frequent scalpel biopsies, it is imperative. Brush biopsies have the benefits of being easy to use, non-invasive, and reasonably priced. They are useful for both detecting symptomatic instances and screening asymptomatic patients. A scalpel biopsy is usually advised when atypical and positive results are found.[24]

Chemiluminescence

Chemiluminescence is the release of visible light after a chemical reaction. A high nucleus-to-cytoplasm ratio causes dysplastic and cancerous cells with aberrant nuclei to reflect this light. Normal epithelium appears darker, but abnormal squamous epithelium tissue appears aceto-white. One technique for screening asymptomatic people is Vizilite. This technique will not distinguish benign, inflammatory, potentially malignant disorders and cancerous conditions.[25]

Tissue autofluorescence

Exposure to UV-visible light can stimulate native fluorophores in the oral epithelium and submucosa, resulting in tissue fluorescence. Changes in their fluorescence and concentration are brought on by carcinogenesis. The analysis of tissue autofluorescence has been done using spectroscopy and autofluorescence imaging. A commercial tool called VEL scope employs tissue autofluorescence to screen for oral precancerous lesions by observing how light interacts with the epithelium and connective tissue to alter their structure and metabolism. This technique lack specificity.[26]

Computed Tomography

Computed Tomography (CT) is used to diagnose oral cancer by assessing the degree of bone invasion, retromolar trigone extension, and buccal space infiltration. The accuracy of CT in identifying bone degradation and staging cancer has been demonstrated by numerous investigations. The soft tissues in the oral cavity cannot be adequately described by CT, and image artefacts from metallic dental fillings make diagnosis more difficult.[27]

Magnetic Resonance Imaging (MRI)

MRI offers fine-grained pictures of the body and outperforms CT in terms of tumour contrast and soft tissue distinction. Patients with symptoms of oral cancer may be diagnosed using MRI. It works well for determining tumour sites, assessing tumour thickness, and staging for malignancy. Combining CT and MRI improves lymph node staging compared to traditional oral examination (64% sensitivity, 87% specificity). MRI is useful for pre-operative planning, although its usefulness for early detection is not well established.[28]

Positron Emission Tomography (PET)

PET is a type of functional imaging that measures the metabolic activity of tissues. Patients with symptoms may be diagnosed with PET. PET has been compared to CT and MRI in terms of its diagnostic effectiveness in detecting primary tumours. Compared to 75% sensitivity and 79% specificity achieved with CT and MRI, PET employing FDG (FDG-PET) has been shown to reach 80% sensitivity and 86% specificity. Even though PET-CT and PET-MRI combined have better diagnostic capabilities, CT and MRI examination is still the primary method. These methods have been found to be unsuccessful for identifying the disease in its early stages, despite the fact that they aid in the identification of metastases and the direction of treatment.[29]

Ultrasound

Ultrasound's real-time capabilities, versatility, adaptability, reproducibility, and safety make it a popular clinical tool for evaluating head and neck cancer. Comparing

ultrasound systems to the other imaging modalities mentioned above, they are likewise reasonably priced. Patients who are hypersensitive to contrast agents or have metallic implants may undergo it. The thickness and defining borders of oral tumours are measured by ultrasound imaging, which can be used to guide surgical resection margins and predict the likelihood of metastatic phases of the illness.[30]

Photoacoustic Imaging (PAI)

PAI is a relatively new imaging technique that combines ultrasound and light. For the purpose of identifying and differentiating between the various stages of carcinogenesis, PAI and ultrasound imaging may offer complementing structural and functional data. To evaluate this new technology in screening and diagnosis, more research is needed.[31]

Optic Coherence Tomography (OCT)

OCT is an interferometric imaging technique that may produce structural pictures of targeted tissues with a depth of up to 3 mm and a high resolution (10–20 μm). In the early detection, diagnosis, and treatment of oral cancer, it is a new and promising technology. It is an effective technique for precisely analysing the structure of oral tissues in real time. Since it can produce high-resolution images without requiring tissue removal or biopsy, this imaging modality is advantageous as a supplement to conventional diagnostic techniques.[32]

Artificial Intelligence (AI)

Excessive workload, complicated activities, and exhaustion can all negatively impact the results of cancer detection done by humans. Within the field of artificial intelligence (AI), machine learning (ML) involves teaching computers to detect patterns in training datasets, or historical data. These patterns can then be applied to the testing dataset, or current sample, to precisely discover patterns in massive, complicated, and noisy historical data. It is now possible to detect malignancies in the liver, breast, lung, brain, and skin with recent advances in machine learning. Comparing ML to traditional or alternative methods, it has also been demonstrated that ML improves the prediction of cancer susceptibility, recurrence, and death by 15% to 25%. It might soon prove to be an effective screening and diagnostic tool to help detect oral cancer.[33]

MULTIMODAL APPROACHES TO ORAL CANCER TREATMENT

An evaluation of each patient with an oral cancer diagnosis is necessary to create a suitable, customised, and ideal treatment strategy. According to the Union for International Cancer Control, the TNM system is the primary technique for cancer staging. In this system, the tumor's size (T), potential metastases to neighbouring lymph nodes (N), and metastases to other body parts (M) are all described. To precisely define the tumor's clinical stage, specialists can add specific numbers (ranging from 0 to 4) or "X" if the tumour cannot be measured. The disease site, stage, and pathology findings all affect the choice of treatment. First, whether curative or palliative, the treatment provided should be decided by a multidisciplinary team of medical professionals. If the illness is surgically resectable and limited to the main site with potential cervical nodes, curative treatment is selected. When the disease has moved to remote locations or is medically unresectable involving important structures, palliative treatment is a possibility. The three primary treatment options for oral cancer are chemotherapy, radiation therapy, and surgery. For patients who present with early-stage (Stage I or II) disease, single-modality treatment with either surgery or radiation therapy is typically advised. Patients with locally or regionally advanced illness are advised to get multimodal treatment.[34]

Surgery

Surgery is the primary modality for oral cancer treatment. The main goal of surgical treatment is the complete resection of the

tumor with an adequate margin, which can be used as a prognostic factor for patients and influence further therapy. A surgical margin of <1 mm are considered positive, 1–5 mm close, and >5 mm clear/adequate. The status of the margin should be investigated using intraoperative frozen section, fluorescence molecular imaging, or narrow band imaging during surgery**.** [35]

Radiotherapy

For patients with stage III or IV disease, insufficient margins, and penetration into bone or lymphovascular and perineural regions, adjuvant postoperative radiation is advised. According to studies, radiation therapy has a significant rate of locoregional control and can be used as an alternative curative strategy when surgery is not appropriate. The primary treatment may be directed towards radiotherapy due to patient-related considerations such as comorbid conditions, advanced age, or the patient's refusal of surgery because of the possibility of postoperative facial abnormalities and difficulty speaking, eating, and swallowing.[36]

External beam radiation therapy (EBRT): Through EBRT, high-energy radiation is delivered to the tumour site from an outside source. Methods such as volumetric modulated arc therapy (VMAT) and intensity-modulated radiation therapy (IMRT) provide accurate tumour targeting while preserving nearby healthy tissues. By lowering adverse symptoms including mucositis and xerostomia (dry mouth), these developments have improved patients' overall quality of life.[37]

Brachytherapy: In brachytherapy, a radioactive source is positioned inside or close to the tumour. With this method, the tumour can get high doses of radiation while the surrounding tissues are exposed to the least amount possible. It is useful for small, localised tumours or as a supplement to treat recurrent disease.[38]

Chemotherapy

Chemotherapy is frequently used in conjunction with other treatments, particularly for oral cancer that has spread or become advanced. It can be used as palliative therapy, adjuvant therapy or neoadjuvant therapy to reduce tumour size before surgery.[39]

According to the latest NCCN Guidelines, adjuvant chemotherapy is advised when postoperative adverse pathologic features like entra-nodal extension, positive or close margins, pT3 or pT4 primary, pN2 or pN3 nodal disease, nodal disease in levels IV or V, perineural invasion, or vascular or lymphatic invasion are noted.[40]

Commonly used agents include carboplatin, cisplatin, and 5-fluorouracil (5-FU). These medications disrupt cellular division and DNA replication, but systemic toxicity and resistance restrict their usage.[41]

Targeted therapy

The treatment of oral cancer has seen a promising development with targeted medicines. The possibility for more potent and less harmful treatments is presented by these therapies, which directly target biological pathways implicated in the development of cancer.[42]

EGFR is often overexpressed in OSCC, and it is a crucial therapeutic target. Tyrosine kinase inhibitors like gefitinib and erlotinib and monoclonal antibodies like cetuximab block EGFR signalling, which is essential for the growth and survival of tumour cells.[43]

Studies are investigating targeted treatments against a number of pathways, including angiogenesis and the PI3K/AKT/mTOR pathway. The goal of agents targeting these pathways is to stop the growth and spread of tumours. For example, the anti-VEGF monoclonal antibody bevacizumab reduces the tumor's blood supply by blocking angiogenesis.[44]

Immunotherapy

Immunotherapy is a new method of treating oral cancer that uses the body's immune system to combat cancerous cells.[45]

Nivolumab and pembrolizumab, two programmed death-1 (PD-1) inhibitors, have been authorised in recent years to treat patients with oral cancer who exhibit the following traits: recurrent or metastatic squamous cell carcinoma and development of the illness after six months of platinum-containing treatment.[46,47]

Based on how immune cells are distributed, the tumour immune microenvironment can be classified as either "hot" or "cold." Immune cells are dispersed in an immunologically "hot" tumour, but not in a "cold" tumour.[48] When it comes to "hot" tumours, immune checkpoint inhibitors work best when used alone. “Cold” tumors require other therapies, like chemotherapy, to recruit the immune cells to the tumor tissue making immunotherapy effective.[49]

Pembrolizumab + docetaxel and pembrolizumab + lenvatinib are two novel immunotherapy and chemotherapy combinations that have been evaluated and shown encouraging results with few side effects in the treatment of oral cancer.[50]

Novel drug delivery systems

Drug delivery systems and nanotechnology advancements have improved the capacity to deliver therapeutic medicines to tumour sites more efficiently, lowering systemic toxicity and enhancing treatment success.[51]

It is possible to create nanoparticles to deliver specialised imaging agents, targeted medicines, or chemotherapeutic drugs to cancer cells. By limiting exposure to healthy tissues, this tailored administration maximises medication concentration at the tumour location. Additionally, combination therapies where several drugs are administered at once are possible with nanoparticle-based systems.[52]

Oral cancer cells that overexpress EGFR can receive chemotherapeutic drugs specifically from nanoparticles coated with ligands that bind to EGFR.[53] Drugs can now be released locally and precisely at the tumour site with innovations like hydrogels and biodegradable polymers. These technologies decrease the frequency of drug administration and increase therapeutic efficacy.[54]

Gene Therapy

A state-of-the-art method for treating or preventing disease is gene therapy, which aims to fix genetic flaws or alter the expression of particular genes. Gene therapy has the potential to improve treatment efficacy for oral cancer by focussing on the underlying genetic pathways causing the disease to progress.

With the use of gene editing technologies like CRISPR-Cas9, precise genome modifications are possible, potentially leading to the introduction of therapeutic genes into cancer cells or the correction of genetic abnormalities linked to oral cancer.[55]

The restoration of tumour suppressor genes, which are frequently inactivated in oral cancer, is another use of gene editing. It may be possible to restore normal cell growth control and increase the sensitivity of cancer cells to other treatments by reintroducing functional copies of genes like p53 or RB1.[56]

Future Direction

Integration of emerging therapies (or) multimodal approaches is the future of oral cancer treatment. More investigations combining novel drugs and emerging technologies will make the future of cancer treatment in a more personalized approach. Global collaborations and data sharing across genetic backgrounds may help researchers speed up the development of new cancer therapies. Future treatment is more patient centred which may improve the quality of life by minimizing the toxicity.

CONCLUSION

Multimodal approaches in oral cancer is an advancement in oral oncology with increased survival, thus improving the quality of life. Combination of surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, and gene therapy along with AI based diagnostics; health care provider can plan better treatment profile for each patient in a unique way. While challenges

remain particularly in minimizing long-term treatment effects the ongoing evolution of personalized, multidisciplinary care continues to offer promising outcomes. Further research and global collaboration may be vital in refining these approaches for ensuring high quality care for cancer patients.

Declaration by Authors

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