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Advanced Techniques In Oral Oncology: A Comprehensive Review

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Abstract
The most common type of oral cancer, oral squamous cell carcinoma (OSCC), is still a major global health concern. Due to delayed diagnoses, which are frequently caused by low public awareness and few screening alternatives, the five-year survival rate is still low. Modern methods in oral oncology have arisen to enhance patient outcomes and early identification, including as molecular and imaging diagnostics. This review showcases several cutting-edge diagnostic techniques, including flow cytometry, next-generation sequencing (NGS), chemiluminescence, toluidine blue, immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), and nano-diagnostics. By providing insights into tumor behaviour and enabling customized treatment approaches, these techniques advance our knowledge of the genetic and proteomic landscape of oral cancer. Combining these cutting-edge approaches with conventional diagnostics might greatly improve the accuracy of OSCC detection and risk assessment, despite drawbacks like false positives and expensive procedures. Improving patient care greatly depends on the creation of quick, non-invasive procedures and the investigation of genetic biomarkers. The present review highlights the need for continued research and training in oral oncology to maximize early diagnosis and intervention strategies.

Keywords: *Gene Expression, Immunohistochemistry, Polymerase Chain Reaction, Proteomics, Tumor Markers, Fluorescence In Situ Hybridization, Nanotechnology, Next- Generation Sequencing, Salivary Diagnostics*

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I. Introduction

Cancer is still a major global health concern, with oral cancer being one of the most common forms globally.[1] The World Health Organization (WHO) estimates that approximately 45% of identified cases result in death within five years.[2] Despite breakthroughs in treatment, oral cancer still has a significant fatality rate. While early discovery can raise survival rates to 80–90%, a late diagnosis has a considerable negative impact on prognosis. Advanced stage diagnoses are frequently the result of low public awareness and limited screening accessibility.[3] mouth squamous cell carcinoma (OSCC) is the most prevalent type of mouth cancer. It is caused by genetic abnormalities in squamous cells, which are frequently triggered by chromosomal alterations and epigenetic modifications. These changes lead to uncontrolled cell development. This genetic variability influences clinical outcomes and treatment responses, highlighting the need for better tumor classification and understanding of OSCC progression.[4]

Sample bias in multifocal lesions is one of the drawbacks of standard diagnostic procedures for oral cancer, which include tissue biopsy and routine inspections. As a result, non-invasive molecular diagnostic methods with higher sensitivity and specificity have been developed.[5] Saliva has proven to be a useful biomarker for detection as biomarkers are utilized more and more to predict treatment success. Advances in techniques like as optical coherence tomography (OCT) improve screening and surgical precision, while changes in biomarkers such as Bax, Bcl-2, mitochondrial DNA, and Ki-67 can help in the early identification of OSCC.[6,7]

The identification of genetic and proteomic anomalies in oral cancer is becoming more accurate thanks to molecular methods. Proteins in tissue can be identified by immunohistochemistry (IHC), and chromosomal abnormalities can be shown using fluorescence in situ hybridization (FISH).[8] Flow cytometry examines cell properties, while polymerase chain reaction (PCR) amplifies DNA sequences for the purpose of identifying mutations.[9] By analyzing genomic pathways, next-generation sequencing (NGS) improves our understanding of OSCC. Targeting cancer cells with biocompatible nanoparticles, nanotechnology shows great promise as well. Tumor heterogeneity assessment requires the ability to observe structural alterations in neoplastic tissues,

which is made possible by non- invasive imaging methods like the VELscope. Combining these strategies is crucial to improving patient outcomes for oral squamous cell carcinoma.[9]

II. Classification Of Advanced Techniques In Oral Oncology

In oral oncology, state-of-the-art diagnostic techniques are essential for improving patient outcomes and early diagnosis. Even while histopathology is still the most reliable method for identifying oral squamous cell carcinoma (OSCC), new developments in molecularand imaging technologies offer precise prognostic data and lessen the need for invasive procedures, enabling early detection and individualized treatment as is categorized in Table 1.[4,10]

Table 1: Diagnostic Techniques in Oral Oncology

Category	Techniques
1. Chair-side Investigations	Toluidine blueLugol's iodine Oral brush biopsy VELscope Chemiluminescence Light-based systems
2. Basic Diagnostic Techniques	Liquid-based cytologyHistopathology Enzyme-linked immunosorbent assay (ELISA)Immunohistochemistry (IHC) Flow cytometry Polymerase chain reaction (PCR)In-situ hybridization
3. Advanced Diagnostic Techniques	Microarrays Next-generation sequencing (NGS)Lab-on-chip Microfluidics-based techniquesNano-diagnostics Liquid biopsy 'Omics' technologies (e.g., genomics, proteomics)Synthetic biology

III. Chemiluminescence And Toluidine Blue In Oral CancerDetection

Chemiluminescence, known by the brand name ViziLite, is a diagnostic technique that facilitates the detection and monitoring of oral mucosal anomalies, particularly in high-risk oral cancer patients. This method uses a chemical reaction that produces very little heat to generatelight to identify lesions that might not be seen during a regular visual exam.[10] It makes use ofa light stick with a bluish-white light that has a wavelength between 430 and 580 nm. The retractor, flexible exterior capsule, and acetic acid in the system help to make keratinized lesions more visible against normal tissue, giving them an aceto-white appearance.[11] Chemiluminescence has a low specificity of 27.8% and a high sensitivity of about 77.3%, which leads to a significant percentage of false positives even though the process is quick andpainless.[12] Chemiluminescence can assist in identifying mucosal abnormalities but lacks reliability in differentiating benign, malignant, or potentially malignant lesions, as well as distinguishing between hyperplasia, dysplasia, and carcinoma.[13] Therefore, it is more suitableas an adjunctive diagnostic technique. Concerns have also been raised regarding the ViziLite system's practicality in clinical settings due to its high cost and single-use nature.[14] In contrast,toluidine blue, a metachromatic dye that binds to DNA, is a well-established method for identifying potentially cancerous lesions.[15] It demonstrates higher diagnostic accuracy for premalignant lesions, particularly ulcerated or erosive types, and can detect field cancerization. Compared to chemiluminescence, toluidine blue exhibits greater sensitivity (78% to 100%) and specificity (31% to 100%), making it a more reliable option for screening high-risk patientsand guiding treatment strategies.[16,17]

IV. Immunohistochemistry (IHC)

An important diagnostic method called immunohistochemistry (IHC) employs antibodies to find proteins in cells and tissues and provides information on protein-level gene expression. This technique is essential for identifying malignancies and improves upon traditional histological examination, particularly in cases of oral squamous cell carcinoma (OSCC).[18] Molecular biomarkers that offer prognostic information beyond clinical andhistological evaluations are revealed by IHC. Tumor-specific antibodies are chosen based on the expression of specific antigens, and a chromogen visualizes the antigen-antibody response,allowing the study of tumor histopathogenesis.[17] In OSCC, IHC detects biomarkers such as cell adhesion molecules, oncogenes, and tumor suppressor genes that are linked to tumor behaviour. IHC has a great deal of diagnostic utility, but it has drawbacks as well, like variable antigen expression and subjective result interpretation. The goal of standardized reporting rules such as the REMARK criterion is to improve biomarker study reliability. IHC-stained slide interpretation is largely dependent on the pathologist's experience, notwithstanding its benefits.[18,19]

V. Fluorescence In Situ Hybridization (FISH)

The sophisticated method known as fluorescence in situ hybridization (FISH) is used to identify and pinpoint DNA or RNA sequences inside of cells or tissues. This approach, a form of in situ hybridization (ISH),

has revolutionized molecular cytogenetics by enabling the viewing of genetic material in chromosomes and interphase nuclei, all while retaining the structural integrity of the tissue. FISH is especially helpful for detecting chromosomal abnormalities, such as translocations, duplications, and deletions, as well as aneuploidy, sinceit uses fluorescent markers to attach to specific nucleic acid sequences.[6]

Preparing the slide, hybridizing fluorescent probes with the target DNA or RNA, and seeing the outcomes under a fluorescence microscope are the three primary processes in FISH. Usually, the probes are complementary DNA sequences that attach to certain regions of interest. Combining FISH with immunocytochemistry allows for the simultaneous study of gene activity at the DNA, RNA, and protein levels, which is one of the main benefits of the technique. This feature offers a more thorough understanding of the cellular and molecular mechanisms underlying illnesses such as cancer.[6,20] The method is particularly useful in the field of cytogenetics, since it helps identify flag chromosomes and chromosomal rearrangements, both of which are essential for the diagnosis of genetic diseases and tumors.[7]The examination of non-dividing cells is made possible by the great sensitivity of FISH, whichdetects chromosomal aberrations in both metaphase and interphase nuclei. One drawback of FISH, despite its great efficacy, is that its reagents are only good for a single test because ofphotobleaching, a process that causes fluorescent dyes to fade over time.[6,20]

VI. Gel Electrophoresis And Blotting Techniques

Gel electrophoresis is a crucial technique for separating charged molecules like DNA, RNA, and proteins based on size and charge. By applying an electric current to a gel matrix, smaller fragments migrate further than larger ones. Agarose gel electrophoresis is particularlycommon for DNA fragment separation, often utilized in cloning and PCR product analysis.[6] In DNA damage analysis, the comet assay, or single-cell gel electrophoresis (SCGE), quantifiesDNA damage in individual cells by creating a comet-like appearance, where damaged DNA forms a tail. This assay is sensitive for detecting single-strand and double-strand breaks, making it vital in genotoxicity testing.[21] For protein analysis, one-dimensional sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) separates proteins by molecular weight, while two-dimensional gel electrophoresis (2D-PAGE) combines isoelectricpoint and molecular weight for higher resolution, essential in proteomics research.[22] Blotting techniques like Southern, Northern, and Western blotting are crucial for confirming specific biomolecules' presence by transferring molecules from a gel to a membrane for detection.[6]

VII. Polymerase Chain Reaction (Pcr) And Reverse Transcriptase Pcr(Rt-Pcr)

PCR is a crucial molecular technique for amplifying DNA, widely used in diagnosing infectious diseases and cancer. It identifies mutations in oncogenes and tumor suppressor genes, enhancing understanding of cancer pathology. The technique amplifies a specific DNAsequence through cycles of denaturation, primer annealing, and DNA polymerization, resultingin billions of copies of the target DNA. This process employs heat-stable DNA polymerase, such as Taq, to withstand repeated thermal cycles.[6,17,23] RT-PCR, a variant of PCR, amplifiesRNA by first converting it into complementary DNA (cDNA) using reverse transcriptase. This method is vital for studying gene expression and diagnosing RNA-based viruses. RT-PCR closely follows the PCR process but starts with RNA, producing cDNA for amplification. It can be conducted as a one-step or two-step process, with the latter offering enhanced accuracyand cDNA storage.[6,24]. RT-PCR has proven effective in detecting disseminated cancer cells after incisional biopsy in oral squamous cell carcinoma patients, aiding in monitoring disease progression and recurrence. Both PCR and RT-PCR deliver rapid, sensitive, and specific amplification of nucleic acids, supporting applications in clinical diagnostics and gene expression profiling. However, they require careful handling to avoid contamination and ensureaccuracy, particularly when detecting viral RNA or identifying tumor biomarkers.[6,24] Limitations include the need for prior sequence knowledge and sensitivity to temperature fluctuations during amplification. Additionally, established protocols for in situ PCR enhancethe specificity and sensitivity of these techniques.[24,25]

VIII. Flow Cytometry

Flow cytometry is a laser-based technique that detects and measures the physical and chemical characteristics of cells or particles in a fluid mixture. Its popularity stems from the ability to rapidly analyze multiple cell characteristics, including size, granularity, and fluorescence intensity. A flow cytometer consists of three main systems: fluidics, optics, and electronics. The fluidics system transports particles to the laser beam, with a sample injected into a sheath fluid, ensuring the sample core interacts with the laser beam. The optics system includes excitation optics to focus the laser beam and collection optics that direct emitted light to detectors. Photomultiplier tubes (PMTs) and photodiodes convert light signals into electrical signals for processing, while the electronics system converts these signals into digital data foranalysis. Different types of flow cytometers include traditional flow cytometers, acoustic focusing cytometers, cell sorters, and imaging flow cytometers. Research indicates that DNA ploidy patterns and DNA indices correlate better with malignancy grade in oral carcinomas than histologic differentiation.[26] Aneuploid tumors demonstrate more

aggressive growth, suggesting that DNA content analysis can assist in tumor diagnosis and prognosis, providing critical insights into tumor characteristics and behaviour.[17,26,27] From the first devices that employed mercury arc lamps to the most recent systems that use coherent, monochromatic laser beams, flow cytometers have come a long way. The flow cell is essential because it enables interaction between the laser beam and cells, producing fluorescent light signals that are dispersed and can be amplified for detection. Dichroic mirrors and filters are used to gather light scattering and fluorescence, and high-resolution DNA flow cytometry is used to identify DNA aneuploidy in human lesions, suggesting the progression of oral carcinogenesis. Despite its limitations, DNA ploidy analysis is nevertheless useful for determining the prognosis of head and neck malignancies and has applications in virology, immunology, and oncology.[27,28]

IX. Microarray Technology

DNA microarrays, sometimes referred to as DNA chips or biochips, are grid-shaped solid supports, usually composed of silicon or glass, with each dot representing a single gene.They can examine thousands of genes' expression at once. Glass is used in modern arrays because of its exceptional qualities, which enable small sample volumes and low light sensitivity. Labeled with fluorescent dyes, isolated mRNAs or amplified cDNAs are hybridizedwith the DNA array in microarray investigations. A laser excites the dyes, washing away non-specific hybrids and producing a digital image that is converted into numerical data. Similar expression profiles across samples can be used to identify shared regulatory mechanisms, andnew developments point to the possibility of using salivary transcriptome diagnostics as a means of identifying cancer biomarkers.[28,29] There are two types of nucleic acid microarrays: *oligonucleotide- and cDNA-based*. Whereas oligonucleotide arrays use short DNA sequences for enhanced specificity, with many probes representing each gene, cDNA arrays amplify cDNAs and place them onto a solid platform. The technique involves fluorescently tagged target samples and a scanner for detection. RNA extraction, labeling mRNA retrotranscribed to cDNA, hybridization, scanning for fluorescence intensity, and using specialist software to process digital images are the stages involved in cDNA-based microarrays. Applications include finding SNPs, gene mutations, and biomarkers for oral squamous cell carcinoma, as well as for drug discovery, diagnostics, and gene expression profiling. Benefits include real- time data for thousands of genes; drawbacks include expensive and difficult data analysis.[28,29]

X. Next Generation Sequencing (NGS)

Next Generation Sequencing (NGS), introduced in 2005, revolutionizes rapid sequencing of entire human genomes in hours. This technology enables simultaneous sequencing of thousands to millions of DNA molecules, significantly reducing cost-per-base and analysis time. NGS also facilitates the exploration of both coding and non-coding RNAs by generating complementary DNA strands from RNA samples.[17] NGS platforms monitor nucleotide additions to spatially arranged DNA templates, employing various template generation and interrogation techniques. Despite its clinical promise, challenges remain in simplifying sample preparation, reducing costs, and addressing ethical concerns related to whole-genome information. As genomic variations linked to diseases are identified, the utilityof whole-genome sequencing for simultaneous diagnoses is expected to increase.[6] NGS is categorized into four generations: the first generation is represented by Sanger sequencing, thesecond includes techniques like pyrosequencing and reversible terminator chemistry, the third encompasses single-molecule fluorescent sequencing and nanopore sequencing, and the fourth aims for direct genomic analysis within cells. By allowing nucleotide-by-nucleotide reading, NGS enhances throughput, enabling a range of applications including DNA sequencing and whole-genome characterization. Commercial systems like Illumina and Ion Torrent have advanced the understanding of genetic alterations in diseases such as oral squamous cell carcinoma (OSCC),[30] yet challenges persist, particularly with data management and shorter read lengths, which complicate de novo genome assembly. Despite these limitations, NGS offers significant potential in personalized medicine and molecular diagnostics.[31]

XI. Nano Diagnostics

Nanotechnology is transforming cancer detection and treatment, providing notable advantages over traditional imaging contrast agents. Nanoparticles, which range from 1 to 100nm in size, are easier to synthesize, more biocompatible, and capable of specifically targeting surface molecules. This enables enhanced image resolution and contrast, particularly through surface plasmon resonances at near-infrared wavelengths, which is beneficial for detecting andmonitoring OSCC. Researchers can assess dental diseases such as dental caries and oral cancerat the nanoscale by analyzing the morphological and biochemical properties of dental surfaces and fluids. Advanced applications include optical coherence tomography (OCT), magnetic resonance imaging (MRI), and surface-enhanced Raman spectroscopy (SERS), all of which improve diagnostic sensitivity and specificit. Despite these advancements, challenges such as nanoparticle stability, penetration depth, and procedure complexity remain. Nevertheless, nano-based diagnostics present real-time, cost-effective solutions

for oral cancer diagnosis, facilitating molecular targeted imaging and improved treatment monitoring.[17,31]

XII. Immunofluorescence

Immunofluorescence is a technique that detects specific antigens using antibodies. First described in 1942 and refined by Coons in 1950, it utilizes fluorescent dyes to visualize antigen-antibody interactions under ultraviolet light. In direct immunofluorescence, a fluorochrome-labeled antibody binds directly to the antigen, providing quick results but requiring specific antibodies for each pathogen. Indirect immunofluorescence uses an unlabeled primary antibody and a labeled secondary antibody, amplifying the fluorescence signal. This method is crucial in diagnosing autoimmune disorders and visualizing cellular structures. Despite challenges like photobleaching, immunofluorescence remains vital for diagnosing conditions such as pemphigus vulgaris and lupus erythematosus.[8,32]

XIII. Autofluorescence And Velscope

Early diagnosis of oral mucosal illnesses and potentially malignant conditions is critical for improving patient outcomes. The British Columbia Cancer Agency collaborated with VELscope to develop a tool that visualizes tissue fluorescence to detect alterations in oral mucosal tissues. It helps detect early metabolic changes by producing blue light (400–460 nm),which causes normal mucosa to glow green and abnormal regions to look darker.[32,33] The efficiency of autofluorescence is associated with cellular alterations that accompany neoplastic transformation, exposing variations in the cross-linking of collagen and elastin. However, the VELscope has a sensitivity of 62.8% and specificity of 62.2% for diagnosing lesions.[34,35] Dueto its low specificity, biopsies may be required for confirmation in cases when false positives occur. Future developments in genetic markers and technology might improve specificity, although interpretation is still arbitrary and differs between physicians.[33, 34]

XIV. Conclusion

Recent advancements in oral cancer screening techniques have focused on developingfaster and more effective diagnostic methods. Understanding the genomic, proteomic, and epigenetic changes involved in carcinogenesis is essential for clinicians treating oral mucosal diseases. Molecular diagnostics, despite their limitations, show promise as standard care tests and provide valuable insights through translational studies. Combining clinical examinations, histopathology, and molecular diagnostics can improve risk stratification for oral squamous cell carcinoma (OSCC) and mitigate the disease's impact. Various adjunctive diagnostic methods, such as exfoliative cytology, vital staining, chemiluminescent techniques, and saliva- based tests, support traditional examinations. Optical imaging technologies enable rapid, non- invasive detection of precancerous lesions, reducing the need for biopsies and allowing for real-time evaluations of treatment effectiveness. As molecular research progresses, it will enhance the understanding of biomarkers as crucial diagnostic and prognostic tools, ultimatelyimproving patient management and outcomes. Training clinicians to identify precancerous stages is essential in preventing the advancement of oral cancer.

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