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RESEARCH ARTICLE

ADVANCED DIAGNOSTIC AIDS IN ORAL PATHOLOGY

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Abstract

Oral cancers are one of the most common cancers worldwide today. They are usually neglected by the common population when compared to systemic cancers such as the lung cancer, colon cancer etc. However, they also may be extremely fatal if left untreated even at a very initial stage of the lesion. Early detection and treatment gives the best chance for its cure. The five-year survival rate of oral cancer still remains low and delayed diagnosis is suggested to be one of the major reasons. The detection and diagnosis are currently based on clinical examination, histopathological evaluation of the biopsy material and molecular methods. Several diagnostic aids have been developed over the years for early detection of oral cancer. The purpose of this article is to review the advanced available diagnostic adjuncts for the detection of oral cancer.

Introduction:-

Oral cancer, a universal malady, has become a stumbling block over the years due to its significant morbidity and mortality rates. The greater morbidity associated with this deadly disease is attributed to delay in its diagnosis / its presentation in advanced stage.Lack of awareness in the public of the various signs, symptoms and risk factors for oral cancer are all believed to be responsible for the diagnostic delay in a long venture (Stefano, 2009). [1]They are often difficult to diagnose by routine clinical examination.The pathology has extended its wings in the past few decades and has contributed greatly in understanding the pathogenesis of genetic disorders and in diagnosis of several undifferentiated malignant neoplasms. Molecular techniques are being used in clinical field. There are various techniques which are introduced in the field of pathology like brush cytology, velscope, confocal microscopy, tumor markers, microarray etc. New emerging technologies, including robotics, humanoid technology, lab-on-chip devices, nanodevices and patient 'smart' implants, will in the future offer unique opportunities for laboratories to develop..[2]

Review Of Literature:-

Several studies have been done in the past regarding the factors behind the diagnostic delay of Oral Cancers but early detection of it still remains disappointingly constant over recent decades. Oral Carcinoma can be a small problem in numerical terms, but it is considered as a highly lethal disease in world population (Binnie and Rankin, 1984).[3]

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They are often difficult to diagnose by routine clinical examination. Diagnosis of these diseases is mostly based on the microscopic study of cells and tissues (Richard et al., 2002).[4]Maryland, a District of Columbia has seventh highest overall mortality rate for oral cancer in the state, due to lack of information regarding educational materials and interventions for the public to promote oral cancer (Horowitz et al., 2002). [5]

In past three decades, the five-year survival rate has improved but still remains in the range of 53% to 60%. Most Oral cancer cases are not diagnosed until an advanced stage, which has been one of the major reasons for minimally improved survival rate over the years (Jemal et al., 2009; Yi-Shing, 2011).[6] Historically, the screening of patients with signs and symptoms of oral cancer and various precancerous lesions has usually been relied upon the conventional pattern, that is, oral examination (Lingen et al., 2008). [7]

Application of immunohistochemistry and other advanced molecular methods have proven to be a useful tool, laboratory diagnosis in oral cancer by the use of antigens and antibodies (Pettigrew, 1989).[8]

An early detection of these cancers helps in better and faster treatment for improving the prognosis to some extent and the available advanced diagnostic adjuncts aid as a helpful tool for the early diagnosis of oral cancer to the medical practitioners in treating patients suffering from it.[9]

Vital Tissue Staining – Toludine Blue Staining & Lugol's Iodine

Oral carcinoma in situ and early invasive oral carcinoma shows affinity for toluidine blue dye. Lugol's iodine and toluidine blue have been used together in the detection of early carcinomas and other oral lesions.[10]

Toluidine blue is an acidophilic meta chromatic dye which selectively stains acidic tissue components, thus staining DNA and RNA. As it binds to nucleic acids (DNA or RNA) , it helps in better visualization of high risk areas especially with rapid cell proliferation of OSCC and premalignant lesions (Pegah et al., 2012). [11]It stains mitochondrial DNA, cells with greater than normal DNA content or altered DNA seen in dysplastic and malignant cells. Lugol's solution is used for delineation of the malignant change which produces a brown black stain when the iodine reacts with the glycogen content. The use of toluidine blue and Lugol's iodine serves as a useful adjunct in the diagnosis of patients who are at risk and for selecting the site for biopsy with wide field cancers prior to treatment (Sujata and Ajit, 2006).[12]

However there are certain limitations for this diagnostic aids which lead to the further researches in the field of oral diagnosis.

Vizilite

Vizilite is a non toxic chemiluminescent light. Today, vizilite Plus examination, in combination with the regular visual examinations, provides a comprehensive oral screening procedure for those patients who are at increased risk for oral cancer. Vizilite Plus technology helps in identifying soft tissue abnormalities which is shined inside the mouth. This shows glowing of abnormal tissue different from that of normal tissue thus making it more visible. The technique is painless and fast and can help in saving life. However, it cannot necessarily tell if they are potentially cancerous or not (Sujata and Ajit, 2006).[12]

To improve early detection of oral cancer, the use of a dilute acetic acid rinse and observation under a chemiluminescent light such as ViziLite is usually recommended (Oh and Laskin, 2007).[13]

Brush Cytology

Brush cytology (Oral CDX), developed in 1999 and has become popular in dental practice today. In the past decades, adjunctive technique has facilitates the early detection of oral premalignant and malignant lesions (OPML). In that context, Oral CDx is useful in the assessment of dysplastic changes in various suspected lesions especially in oral cancer (Patton et al., 2008).[14] As majority of oral cancers are squamous cell carcinomas,

Cytological study of oral cells is a relatively inexpensive, simple, noninvasive and also risk-free technique which is well accepted by the patient and medical practitioner today (Smaroula et al., 2009).[15] The oral cells can be obtained by the use of a cytobrush. With brush cytology, sensitivity for detecting oral epithelial dysplasia or Oral squamous cell carcinoma is high (Yi-Shing and John , 2011).[16]

But, the technique has attracted lots of controversies and more incidences of false negative results with this technique (Sujata and Ajit, 2006)[12] has been encountered so there is still need of more advanced diagnostics aids.

VEL scope

VEL scope is a hand-held device which was approved by Federation Dentaire Association for direct visualization of autofluorescence in the oral cavity. Only recently it was introduced in the market as a diagnostic adjunct for oral cancer detection. The VEL scope Vx is one of the most powerful tools available today for assisting in oral abnormalities especially oral cancer. The distinctive blue-spectrum light causes the soft tissues of the mouth to naturally fluoresce. The use of VEL scope Vx is a safe and simple technique and the entire examination can be done in about two minutes.

However, it is a relatively new device and so far only a limited number of studies have been done on its effectiveness as a diagnostic adjunct for oral cancer (Yi-Shing and John, 2011).[16]

***In Vivo* Confocal Microscopy**

Confocal microscopy is an imaging technique for various researches in cell biology with an advantage of optical sectioning and high resolution imaging. *In vivo* confocal images from the oral cavity show the characteristic features such as nuclear irregularity which is used to differentiate OSCC from normal oral mucosa.

However, further optimization of the instrument is still needed to rate it a promising non-invasive tool for the early detection of oral cancer (Yi-Shing and John, 2011)[16]

Saliva-based oral cancer diagnostics

The concept of saliva to diagnose OSCC is a latest concept. Oral fluid or the saliva is a noninvasive, accessible and highly efficient diagnostic medium today. The utility of salivary transcriptome diagnostics are helpful in the detection of oral cancer (Li et al., 2004). [17]

Promoter hypermethylation patterns of TSG p16, O6- methyl guanine-DNA methyltransferase, and death associated protein kinase are identified in the saliva of head and neck cancer patients and high salivary counts of Capnocytophaga gingivalis, Prevotella melaninogenica and Streptococcus mitis is found in patients with OSCC.

However, it is still difficult to support the suggestion that this could be a reliable diagnostic indicator (Crispian et al., 2008). [18]

Today, saliva testing for genetic patterns which are linked with oral cancer is gaining interest of research but still it has not been incorporated as a commercial product, but researchers are hopeful that this technology will be readily available in the market very soon (Tricia and Suzie, 2008). [19]

One of the factor behind oral cancer's such high mortality is failure in detecting it at an early early stages. The use of saliva for the detection of oral cancer has proved to be a historical goal that has to be reached to the population in the future for better and faster management stages. The use of saliva for the detection of oral cancer has proved to be a historical goal that has to be reached to the population in the future for better and faster management of OSCC (Wong, 2006).[20]

DNA Ploidy & Quantification of nuclear DNA content

DNA ploidy is the measurement of nuclear DNA content that provide a measurement of gross genetic damage. If the chromosomes are not uniformly distributed to the daughter cells during mitosis or if some parts of chromosomes become detached, the chromosomal segregation becomes unbalanced and aneuploidy is seen which is commonly observed in many cancers. DNA image cytometry shows high sensitivity and serves as a non-invasive method for cancer (Crispian et al., 2008).[18]

Pre-malignant lesions such as oral leukoplakias, the nuclear DNA distribution patterns can be analyzed by flow-cytometry, showing different rates of dysplasia, however the quantity of specimens should be more for the examination (Grässel-Pietrusky et al., 1982)[21]

Even cytology with DNA-cytometry has emerged as a highly sensitive and non-invasive method for the early diagnosis of oral epithelial neoplasia and hence in oral cancer (Maraki et al., 2004).[22]

Tumor Markers & Bio Markers

Tumor markers may be present in blood circulation, body cavity fluids, cell membranes and cell cytoplasm when released by cancer cells or produced by the host in response to cancerous substances. They are used in identification of a cancerous growth (Sujata Satoskar and Ajit Dinakar, 2006).[12]Tumour Suppressor Genes, oncogenes, cell proliferation markers, angiogenic markers and cell adhesion molecules are some of the potential tools which help in prediction for the prognosis of patients with OSCC.[22]

According to a study, use of cytokeratin markers are also used in detecting OSCC by the help of analyzing the altered keratin expression in the oral site especially the buccal mucosa (Vaidya et al., 1989).[23]

PCR-Based diagnostic aids

The polymerase chain reaction (PCR) is a scientific technique in molecular biology which can be used in the diagnosis and study of infectious diseases and malignancies associated with micro organisms. PCR helps in the study of cancer and provide clearer understanding of the pathogenesis of neoplasia. PCR can be used to detect mutations in cancer-associated oncogenes (e.g., K-ras, Nras), tumor suppressor genes (e.g., p53, p16) etc. and aids as an important detection tool (Richard et al., 2001). [24]

PCR technique has increased the range and sensitivity of diagnostic procedures but still with a major drawback, as contamination and amplification artefacts may give rise to difficulties in the interpretation of the desired results (O'Leary et al., 1997)[25]

With the introduction of polymerase chain reaction (PCR), reverse transcriptase PCR (RT-PCR) and other molecular techniques, the diagnosis and prognosis of other lesions such as chronic myelogenous leukemia has also been useful (Glassman,1998)[26]

However according to some studies it has been stated that due to the high cost effective side of this technique this is not being able to be widely used in daily diagnostic routines.

Auto fluorescence Spectroscopy

Auto fluorescence spectroscopy has emerged as a promising tool for oral cancer detection. The system consists of a small optical fiber which produces various excitation wavelengths and a spectrograph which receives and records on a computer and analyzes it with the help of software, the spectra of reflected fluorescence from the tissue. [27]

However, the technique is controversial and often found with unclear results. Overall, it seems to be very accurate for distinguishing lesions especially malignant tumors from healthy oral mucosa, with a high sensitivity and specificity (Stefano Fedele, 2009).[28] It is a non-invasive aid in the detection of various alterations in the structural and chemical compositions of cells indicating the presence of a diseased tissue. It can be useful in guiding the clinician in identifying the optimal location for biopsy (Sujata Satoskar and Ajit Dinakar, 2006). [12]

According to a study, on using violet excitation light, camera-based autofluorescence photodetection technique has presented as a highly promising tool for the diagnosis of oral malignancies (Betz et al., 1999)[29]

Fluorescence Photography

Fluorescence photography is non-invasive, rapid, simple and reproducible method in detection of oral cancer. Fluorescence positivity can show enlargement of carcinomas and progression of the disease. The system is usually used in the diagnosis of squamous cell carcinoma. However, biopsies are still necessary (Sujata and Ajit, 2006)[12].

According to a study, fluorescence photography has shown as a useful tool for the diagnosis of oral cancer, especially in patients with squamous cell carcinoma (Onizawa et al., 1996).[30]

In Situ Hybridization

In situ hybridization (ISH) combines molecular biological techniques with histological and cytological analysis of gene expression. RNA and DNA can be readily localized in specific cells with this method. ISH has been useful as a

research tool, and recent studies have used this technique in the diagnostic pathology laboratory and in microbiology for the tissue localization in infectious agents.[31]

Other recent developments in the applications of ISH involve in situ polymerase chain reaction (PCR) and in situ reverse transcription (RT)-PCR, which can be used to detect very low levels of nucleic acids in tissues by taking advantage of the powerful amplification capacity of PCR. In situ PCR will contribute significantly to progress in this field because of the marked increase in the sensitivity of this method.[32]

IDENTAFI 3000

This technology is a combination of anatomical imaging with fluorescence, fiber optics and confocal microscopy to map and delineate precisely the lesion in the area being screened. It is small in size and easy accessibility to all tissues in the oral cavity. The mechanism is similar to veloscope and also detect changes in angiogenesis with green amber light illumination.[33]

Microarray

The pattern of gene expression vary in normal tissue and its malignant counterpart, which can be assessed by Tissue microarray technique. RNA from malignant lesion and from a control tissue are extracted, and cDNA are prepared by reverse transcription. These reverse transcription reactions incorporate different fluorescent dyes so that cDNA from the tumor and from the control tissue can be distinguished by their fluorescence emission spectra. These cDNAs are mixed and then hybridized to the microarray. A relative increase in expression of a particular gene in a tumor sample leads to an increase in binding of labeled tumorderived cDNA to the spot in the array that is complementary to the gene of interest. DNA microarrays are being used to detect single nucleotide polymorphisms (snps) of human genome.[34]

Future of diagnostic techniques

LAB ON CHIP-

Lab-on-chip or micro-total-analysis systems (TAS) also known as Microfluid technology .It is the adaptation, miniaturization, integration and automation of analytical laboratory procedures into a single device or "chip". Microfluidics is often regarded as the chemistry or biotechnology equivalent of the silicon integrated silicon chip that has revolutionized electronics, computers and communications. Microfluidics are by definition suited for handling living cells (whose typical diameter is a few micrometers) in a three-dimensional, biologically relevant environment. This microfluidic chip accepts saliva sample, can be operated by minimally trained personnel, and can provide a diagnostic answer in an automated and timely fashion. The detection of oral pre-cancer (dysplastic) and cancer cells within the chip will take advantage of membrane-associated cell proteins that are singularly expressed on cell cancer cells.[35]

Nuclear magnetic resonance microscopy

This advanced diagnostic technique allows the pathologist to look into the pattern of cell in tissue and facilitates examination of cells for the presence or absence or mutation of genes that control growth and function and will facilitate examination of specific marker of disease. This will allow non invasive 3D visualization of single in cell in living tissue. New innovation will be cellular metabolo imaging cytonmr.[36]

Clinical Microbiology

Microbiology and infectious disease will rely on lab on chip devices, including automated DNA, RNA and protein/ peptide extraction chips coupled to organism identification chips and sequencing chips giving real time analysis of patient specimens.[37]

Cyogenetics

The use of interphase cytogenetic fine gene locus mapping and locus specific sequencing of novel disease loci in patient with specific monitoring of locus specific changes following the treatment.[38]

Other advanced oral diagnostic aids

. Multi -Spectral Digital Microscope.
.Time -Resolved Laser -Induced Fluorescence Spectroscopy.
.Diffuse Reflectance Spectroscopy .
.Terahertz Imaging.

.Hyperspectral Imaging.
.Confocal Laser Endomicroscopy.
.Quantun Dots and Nano Particles.
.Bionano -chip Sensor.

Conclusion:-

Oral pathologist has its uniqueness in itself as they can be a clinical specialist, researcher, academician or entrepreneur. In the branch of histopathology, the prediction for future is that of diagnostic macroscopic and microscopy which will develop alongside molecular pathology, rather than as a substitute. Keeping in mind, the prime importance of early diagnosis and prompt treatment of PMLs and OSCCS, the role played by these advanced and futuristic diagnostic clinical techniques is better understood.

Advanced diagnostic clinical techniques offer a patient centric, non-invasive and simple adjunctive method to aid in the accurate determination and apt diagnosis of suspicious oral lesions.

In the near future, these advanced diagnostic clinical aids show promising results and with the help of new age techniques like Trimodal spectroscopy, Hyper spectral Imaging etc., the morbidity and mortality of patients can be reduced with one goal in mind, the well-being of our patients. There is still much to be done as far as patient management and accuracy of diagnostic methods is concerned, which will enable the society as a whole to be more productive and healthier.

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