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EMERGING TRENDS IN LIQUID-BASED CYTOLOGY FOR EARLY DIAGNOSIS OF ORAL CANCER AND ORAL LESIONS : ANARRATIVE REVIEW

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ABSTRACT

Cytology is a simple and cost-effective diagnostic method. Liquid-based cytology(LBC) is an advanced modification of conventional cytology, designed toenhance sample preparation for more accurate diagnosis. It has been extensively studied in cervical cytology, demonstrating high sensitivity, specificity, and improved sample quality. Additionally, LBC has been successfully adapted to study various oral lesions, proving to be a reliable alternative to conventional smears. This techniqueproduces a more representative sample, with reduced backgroundinterference, leading to quicker and more dependable screenings. Ratherthan being spread onto a glass slide and fixed, samples are placed in a vialwith a liquid preservative, which helps break up clots and remove debris. Theresulting cell pellet is then applied to a slide to create a thin monolayer ofcells, providing a clean background. LBC offers several advantages overtraditional methods. Thisarticle reviews the LBC technique and its application in diagnosing oraldiseases, particularly oral cancer and pre-cancer.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the sixth most common cancerglobally, with over 355,000 new cases reported annually and a high mortalityrate due to late-stage detection.[1] Despite advancements in surgical andtherapeutic modalities, the overall 5-year survival rate remains around 50%,unchanged for decades. Early detection significantly improves prognosis,emphasizing the need for efficient screening modalities.[2] Cytological screening, especially exfoliative cytology, offers a non-invasive,rapid, and economical approach for early diagnosis. However, conventionalcytology often suffers from sampling artifacts and poor smear quality. [3] Liquid-based cytology(LBC), a technological advancement first established incervicalcytology, addresses many of these limitations and is now gaining momentuminoral pathologyas an effective adjunctive screening tool that provides improved cell preservation, cleaner background, uniform cellular distribution, and enhanced morphological clarity, thereby increasing diagnostic accuracy and allowing the application of ancillary molecular and immunocytochemical techniques for early detection of potentially malignant and malignant oral lesions.[4]

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Epidemiology and Importance of Early Detection

Every year, oral cancer causes more than 177,000 deaths and about 355,000new cases worldwide. OSCC primarily affects the floor of the mouth, gingiva,and tongue and is primarily caused by squamous epithelium. Early diagnosisis essential because patients who receive a diagnosis early on havebetter quality of life and treatment outcomes than those who receive adiagnosis later. Unfortunately, because early lesions are asymptomatic andcurrent diagnostic procedures are limited, many cases are diagnosed inadvanced stages.[3]

Premalignant lesions like leukoplakia and erythroplakia are often theprecursors of oral cancer, which makes early

detection crucial. Asthese lesions develop from dysplasia to invasive carcinoma, thereis a crucial window for treatment. The asymptomatic natureof early disease and the limitations of routine visual-tactile examinations arethe main reasons why many oral cancers are diagnosed at advanced stages.If tailored for oral applications, cytological screening may beessential in filling this gap.[4]

What is Liquid-Based Cytology; Historical background

Dr. George N. Papanicolaou introduced cervical cytology in 1940. Cytologic screening lowers the incidence of invasive uterine cervix cancer, according to findings released by the Center of Cytology in Vancouver, British Columbia. Over the years, different studies conducted showed the Specificity of the standard pap smear test to be about 98-99%, however the Sensitivity ranges from 50-75%, or less.[3] The standard pap test has been found to have a number of drawbacks, such as insufficient cell transfer to the slide, uneven distribution of aberrant cells, masking inflammation, blood, and epithelial cell overlap.[5] To overcome these drawbacks, liquid-based cytology was developed in 1996 as a substitute for traditional Pap. In order to create a cell suspension in first-generation automated liquid-based cytology (LBC), the sample apparatus is rinsed into a fixative vial. This is used to create a monolayer of cells on a slide. These slides can be examined in lower time than Conventional smears & the residual sample can be used for ancillary testing(HPV).[6,7]In order to create a cell suspension in first-generation automated liquid-based cytology (LBC), the sample apparatus is rinsed into a fixative vial. This is used to create a monolayer of cells on a slide. These slides can be examined in lower time than Conventional smears & the residual sample can be used for ancillary testing(HPV).[6,7]

ThinPrep and SurePath are two USFDA-approved LBC techniques from the first generation. Numerous studies have shown that these methods have a variety of advantages over traditional pap smears.[7] However, the cost of testing for these LBC approaches is considerable due to the need for an expensive automated instrument, which limits their creativity in developing countries. The majority of the instruments required by the first generation methods are eliminated by LiquiPrep, the second generation Liquid Based Cytology technology.[9] As a result, it provides a less expensive and easier way to screen for cervical cancer. A fixative fluid vial, a cleaning solution, and a cell base that serves as a membrane matrix to create a monolayer of cells make up the LiquiPrep system. This approach is appropriate for cervical cytology in underdeveloped countries because it is simple to prepare and has a higher detection rate than traditional pap.[8] Other inexpensive methods include Pap Spin (smear preparation based on cytospin), Turbitec (centrifugation onto a polylysine slide), cytoscreen (centrifuge-based), manual LBC, and semiautomated technology EziPrep, which filters blood and mucus from cervical specimens using a proprietary separator solution.[9] The samples are subsequently processed in the Nanocyt Neo processor that utilizes a filter-less technique to generate monolayered smears. The purpose of our study was to compare conventional Pap cervical cytology with this inexpensive liquid-based cytology approach.[5]Because it is easier to prepare and has a higher detection rate than traditional pap, this method is appropriate for cervical cytology in impoverished countries.[8] Pap Spin, Turbitec, cytoscreen, manual LBC, and semiautomated technology EziPrep are additional low-cost methods. EziPrep filters the blood and mucus from cervical specimens using a unique separator solution.[9] The samples are subsequently processed in the Nanocyt Neo processor that utilizes a filter-less technique to generate monolayered smears. The purpose of our study was to compare conventional Pap cervical cytology with this inexpensive liquid-based cytology approach.[5]

Principles and Techniques of Liquid-Based Cytology

LBC technique is in use since 1990s. Technically, the samples are collected using a brush-likedevice, and instead of making smears on slides, it is immersed into a vial of preservative fluid,usually with an alcoholic content, so that most of the sampled cells are retained.[3] Samples aretransported to the laboratory and are processed for removing obscuring material, mucus, and bloodwith a clearing solution and centrifuged by density gradient centrifugation for collecting cells. Thecentrifugation separates the cells according to their specific weight.[4] Granulocytes, erythrocytes,and debris that have a lower weight than the epithelial cells accumulate above the density gradientand are then discarded. Upon discarding the supernatant, the pellicle so formed is admixed with acellular base solution which is finally transferred to a clean slide to produce a thin monolayer ofcells with a clean background The collected sample can be processed by two methods.[5] In thedirect to vial method, the sample collected by the spatula is directly mixed into the liquid fixativeprovided for use in LBC. In the split sample technique, the sample collected is initially smearedonto the glass slide for use in conventional cytology and then placed in a preservative fluid for usein LBC. Instruments that are used for the collection of the sample are the plastic Ayre's spatula,cytobrush, cotton swab, and cytoprep instruments.[10]

The currently available products that use liquid-based methodology are ThinPrep, SurePath, Cytoscreen, and Labonard Easy Prep.[5]

THINPREP

ThinPrep, developed in 1996, was the first LBC technique to be approved by the FDA. It comes in two versions: semi-automated (T2000) and fully automated (T3000). While the T2000 machine processes slides one at a time, the T3000 machine may process up to 80 specimens every cycle. The transport fluid is called PreservCyt. After it has been fixed, each vial is placed individually in the ThinPrep Processor. There are three primary steps in the procedure.[1]

1. Dispersion: Produces a randomized cell solution by breaking up mucus and cell clumping.
2. Cell collection: Produces a negative pressure pulse that draws fluid through a filter and collects a
3. layer of cellular material.
4. Cell transfer: The cellular material from the filter is transferred to a glass slide, which is then put inside a fixative vial.

A reprocessing procedure that uses 10% glacial acetic acid in

CytoLyt to wash tissues obtained using the ThinPrep Pap test has been authorized by the FDA. This test is authorized for use in molecular testing by the FDA. Commercially available LBC kits include ADR Madeplus, Biopro, Procer, and SurePrep.[1]

SUREPATH (CYTORICH LBC)

This method was created in 1999 and is the second LBC method that the FDA has approved. A plastic collection device is used to gather the sample, and the head of the device is separated and placed in the collection vial with the transport fluid (CytoRich). The cell suspension is subjected to a density gradient centrifugation procedure after the vials are vortexed. An AutoCytePrep "robot" that can process 48 samples at once is loaded with the centrifuge tubes. After re-suspending the cell pellet, an aliquot is moved to a settling chamber that is placed on a microscope slide. A thin layer of cells is formed on the slide by allowing the cells to settle under gravity. After the extra fluid and cells are eliminated, the slide is automatically stained. Reverting to the initial cell pellet and creating a new slide with a larger aliquot of suspension is an option if the preparation is deemed insufficient or unsatisfactory. The FDA has not authorized this method for HPV testing.[1]

CYTOSCREEN

Sample preparation is done by hand. The transport fluid is called CYTeasy, and the sample collection apparatus is called Cytoprep. After vortexing the samples, a photometric reading is obtained to determine the sample's cellularity. After centrifuging an aliquot of the sample onto a glass slide, standard laboratory techniques are used to stain it.[1]

LABONARD EASY PREP

Cytoprep brushes are used for sample collection and Cytoscreen is used for fixation in this manual sample preparation method. A glass slide with absorbent paper that has been punched to create a 250 mm hole is connected to a separation chamber that holds an aliquot of the sample fluid. A clamping unit consists of eight chambers. During sedimentation, the absorbent paper gently removes the fluid, leaving a thin, dry layer of cells, while the plastic chamber holds the cell suspension in place. Slides are stained using standard laboratory techniques after the cells settle in a thin layer on the slide.[1]

Imaging system

Slides can now be interpreted using computer-guided imaging systems. These systems increase the effectiveness and efficiency of cancer screening by fusing imaging technology with human interpretation skills. A cytopathologist examines the 22 fields of interest that the ThinPrep Imaging System (TIS) imager finds to contain aberrant cells.[5] The BD FocalPoint Slide Profiler (previously known as the AutoPap Primary Screening System) and the BD FocalPoint GS Imaging System are the other two imaging systems created by SurePath Pap. When compared to manual screening techniques, clinical trial data for the BD FocalPoint GS Imaging System and the ThinPrep Imaging System demonstrated improved disease detection. These LBC methods that are sold commercially all require a lot of resources.[8]

Innovations and Emerging Trends in LBC

The development of more flexible testing at points of care, the expansion of molecular diagnostics and personalized medicine, and the incorporation of cutting-edge technologies like artificial intelligence (AI) are the main forces behind the growth of innovations and trends in liquid cytology (LBCs). [4] [8]

1. Computer-Assisted Imaging

ThinPrep Imaging System (TIS) and **FocalPoint GS** automate slide

improve diagnostic accuracy and automate slidescreening. improves reproducibility in identifying aberrant cells.

2. Cost-Effective Modifications

Centrifuged LBC (CLBC): produces high-quality smears by using straightforward centrifugation methods with ethanol and acetic acid.

Shandon Papspin LBC: showed 100% specificity, 96% sensitivity, and just 1.4% insufficient smears.

3. Advanced Sampling Devices

Orcellex Brushes: Designed for oral use, they increase cellular yield to more than 55,000 cells per sample and gather deeper epithelial cells. False-negative rates are greatly impacted by sampling technique; poortools result in insufficient samples.

4. **Future Prospects**

Emerging research focuses on:

Combining molecular diagnostics with **integration** (e.gDNA methylation, microRNA examination). **Standardization** of LBC oral usage procedures. automated cell classification using **AI-powered image analysis**. increased accessibility in developing countries through inexpensive manual LBC adaptations. These developments can increase LBC's **dependability and reach** in a variety of clinical contexts.

Clinical Applications and Uses

LBC was better at seeing hyphaes and/or pseudohyphaes, and it has also been used to diagnose infectious diseases.[9] Although LBC is technically better than CEC, it was not found to be a reliable way to identify oral candidiasis. Studies of salivary gland tissues revealed similar results: extracellular and stromal elements were similar in LBC and CS smears, background matrix material quality was low, and chondromyxoid matrix was better visible on CS.[6] LBC was helpful for preoperative salivary gland tumor diagnosis by immunocytochemical staining, and its sensitivity, specificity, positive predictive value, and negative predictive value for diagnosing salivary gland lesions were all 100% when compared to CS. LBC has shown a sensitivity of 95.6% and a specificity of 84.9% when used to evaluate traumatic, inflammatory, or benign hyperplastic oral lesions as well as OPMDs and malignant lesions.[7,11]

LBC is beneficial in:

1. Screening populations at high risk (e.g. The g. tobacco users)

2. Assessing suspicious lesions in both general and specialty dentistry settings

3. Tracking recurrence in patients with OSCC who have already received treatment

4. Complementing histopathological diagnosis in borderline cases (LBC should be used as an adjunct, especially in cases where malignancy is clinically suspected, despite its advantages)

5. Better cell morphology and staining, less blood and mucus artifact, enhanced cellular preservation, and the ability to perform molecular testing on leftover material are all advantages over conventional cytology.[9,10]

Limitations and Diagnostic Pitfalls

It has been suggested that LBC artifacts are declining. On the other hand, it has also been suggested that LBC lacks some cytomorphological alterations, which can prevent incorrect diagnoses. Salivary gland lesions like pleomorphic adenoma may be misdiagnosed due to variations in the quantity and kind of background matrix.[7,8] Similarly, some artifacts are unique to LBC, and understanding these artifacts is essential to preventing misdiagnosis. In order to avoid misdiagnoses, the author emphasizes the importance of being aware of these artifacts. Even though these decreases in mucus, erythrocytes, and inflammatory cells are thought to be advantageous in cervical pathology, these elements may be crucial in the diagnosis of specific oral lesions in oral smears.[9]

False negatives are common in superficially differentiated SCCs andkeratinized lesions. **False positives** can arise from inflammatory or necrotic changes. The lesion site, equipment quality, and operator skill all affect technique sensitivity. Therefore, histopathological biopsy remains the gold standard, especially when cytological results are ambiguous or contradict clinical findings.[11]

CONCLUSION

LBC is a quick, non-invasive, comparatively painless procedure that has only been reported to cause mild discomfort. The test's sensitivity is said to increase with training, and it does require more sophisticated laboratory equipment and skilled personnel. Nonetheless, the technique's overall cost might be advantageous since it prevents repeat studies brought on by insufficient sampling, especially in developing nations. LBC is used to assess pre-malignant and malignant lesions, detect glandular lesions, assess suspected infections like herpes, candidiasis, illnesses brought on by different strains of the human papillomavirus (HPV), Chlamydia trachomatis, and Neisseria gonorrhoea, as well as for molecular-based diagnosis and research. Nowadays, the majority of laboratories in the West have switched to liquid-based cytology, which has improved detection, reduced the number of subpar samples, and more.

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