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REVIEW ARTICLE

LIGHT AT THE END OF TUNNEL- AN INNOVATIVE WAY OF BIOPSY MAPPING

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Abstract

Oral cancer is a crucial global health issue with high morbidity and mortality rate. Oral cancer is preceded by clinically conspicuous oral potentially malignant disorders (OPMDs) and microscopically apparent altered epithelial changes known as oral epithelial dysplasia (OED). The current gold standard in the detection of precancer lesions and conditions is a biopsy. Even an experienced clinician finds it difficult to locate an appropriate biopsy site. To overcome this, a non-invasive, low-cost, portable device known as the 'Active Biopsy Guidance System' (ABGS) has been developed. It is a software that combined multimodal optical imaging and microscopic imaging with real-time projection of cancer risk maps onto the field of view. ABGS, appropriately locate the biopsy site and improve the diagnostic precision. In this review, we attempt to demonstrate a biopsy guidance system, a versatile, quantitative precise tool in biopsy site selection.

Introduction:-

Oral cavity carcinoma remains a major cause of morbidity and mortality in patients with head and neck cancer. The survival for oral cavity carcinoma is 60%, but it can differ from 10% to 82% depending on the stage of the carcinoma, age of the patient, race, comorbidity, and location in the oral cavity.[1] The OPMDs, term together used for oral premalignant lesions and conditions. The most commonly found OPMDis leukoplakia but others including oral lichen planus, and oral submucosal fibrosis, may also be seen.[2]Oralcancer is preceded by clinically conspicuous oral potentially malignant disorders (OPMDs) and microscopically apparent altered epithelial changes known as oral epithelial dysplasia (OED).[7]Pindborg in 1977 defined dysplasia as "A lesion in which part of the thickness of epithelium is replaced by the cells showing a varying degree of cellular atypia".[3]

Despite the recent advances in diagnosis and therapeutic approaches, the 5- year survival rate of oral cancer patients is less than 50% over the last 50 years due to the main two reasons:[4]

1. The majority of oral cancer patients (60%) are presented at advanced stages (stage III and stage IV);
2. Oral cancer has the highest risk for the development of a second primary tumor ('field cancerization phenomenon') of any cancer.[4]

Improving the early detection and treatment of oral cancer and its precursors extends the best opportunity to decrease the incidence and mortality of oral cancer. The standard method for oral cancer screening is aconventional oral examination and palpation. The visualization methods in addition to standard oral examination are now commercially available including toluidine dye, brush cytology, and ViziLite. [4]

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A variety of autofluorescence (AF) imaging has been increasingly used non-invasively to identify neoplastic lesions**.**The diagnostic potential of autofluorescence (AF) lies in the ability to delineate the alteration in tissue morphology and biochemistry that occur during malignant progression. Autofluorescence properties of oral tissue vary based on the anatomic site within the oral cavity and pathological diagnosis.[5]When the tissue is illuminated in the UV visible region, fluorophores (NADH and FAD in epithelial layers, collagen, and elastin crosslinks in stroma) absorb the portions of photons and emit lower energy photons which can be detected as fluorescence. Neoplastic lesions areassociated with loss of blue-green autofluorescence in comparison with normal tissue. The current AF-based approaches rely on subjective interpretation.[6]Inflammatory lesions are associated with loss of stromal fluorescence which may limit the specificity of AF- based cancer detection.

The application of digital imaging processing to AF imaging of oral tissue, emerging as a promising technology to aid clinicians in objective detection of oral neoplastic lesions. AF imaging coupled with objective image analysis is considered a non-invasive tool for cancer detection with 95.9% sensitivity and 96.2% specificity in the training set, and 100% sensitivity and 91.4% sensitivity in the validation set.[6]

The surface area imaged in InVivo microscopy is limited by the small field of view. To provide large area assessment, FDA-approved Widefield fluorescence (WF) imaging system. The WF imaging system captures AF signals of neoplastic tissues, which shows an increased red-to-green(R/G) Fluorescence intensity ratio in neoplasia compared to inflammation and normal mucosa. In vivo, assessment of mucosal tissue with Non-linear optical microscopy(NLOM) revealed subsurfacecytologic(nuclear pleomorphism) and architectural (remodeling of extracellular matrix) atypia in histologically confirmed neoplastic tissue with 94% sensitivity and 97% specificity.[7]A variety of techniques has been combined with multimodal imaging including, non-linear optical microscopy, optical coherence tomography, reflectance confocal microscopy, and fluorescence microscopy. This combination of approaches suffers many challenges including; ensuring accurate registration between widefield and microscopic images, real-time image analysis, and precise location of the biopsy site. [8]

To overcome the above challenges, a prototype system entitled “Active Biopsy Guidance System” can be considered a beneficial aid to clinicians. Active Biopsy Guidance System(ABGS) is an integration of multimodal imaging, microscopic imaging, and real-time projection of cancer risk maps onto the oral mucosa. ABGS is a non-invasive tool, to evaluatethe large area for biopsy guidance, provide results immediately at the point of care, and objectively locatean appropriate site within those lesions.

The features highlighted in ABGS are:
1. Widefield fluorescence images are acquired to provide a large field of view (FOV);
2. A cancer risk map is generated and converted to a heat map that delineates suspicious regions according to thered-to-green (R/G Ratio) fluorescence ratio;
3. High-resolution micro-endoscopic (HRME) images highlight the nuclear morphology;
4. Biopsy guidance maps generation.

Materials and Method:-

Instrumentation

Figure (1a) Equipment required for biopsy map generation and projection:

It consists of two subsystems:

1. The camera and projector are connected to the laptop through articulating arm.

Camera and projector for white light (WL) and AF image acquisition, laptop, and projector for image analysis and projection of cancer risk maps respectively.

2. Microscope with fiber optic probe to image nuclear morphology

The camera can acquire white light (WL) images with cool white illumination light emitting diode (LED) and AF images with the illumination of 405nm LED.Illumination for the microscopic component is provided by a 460nm LED. A microscope is designed to image oral tissue following topical application of 0.01% of proflavine, a topical fluorescent contrast medium to stain the nucleus. After application of topical contrast medium, the probe is placed in gentle contact with oral mucosa, to delineate the distribution of shape and size of epithelial nuclei.[8]

Procedure:-

The entire procedure of ABGS divided into four main steps

Step 1: Widefield imaging

A live video feed from a widefield camera is displayed at the beginning of the imaging session. The user then adjusts the articulating arm until the lesion is in focus. The user will press the button to acquire white light (WL) and AF image pair. When a satisfactory image frame is achieved, the user will save one WL and two AF images. The AF image is then displayed on the computer, user outlines the mucosal site to exclude non-mucosal sites such as gloves, teeth, and cheek retractors. Outlined image is again projected onto the oral mucosa.[8]

Step 2: Cancer risk map generation and projection:

The clinicians then outline the clinically most suspicious region within the lesions. Meanwhile, WL and AF images are processed.First,the pixel intensity values of the red and green channels of the AF image are calculated. Using this value, the red-to-green (R/G Ratio) fluorescence ratio is calculated.[8]The region of normal mucosa is defined as a 65*65pixel square of mucosa with the lowest R/G ratio.The pixel with an R/G ratio below the threshold is excluded and the pixel with an R/G ratio above the threshold is converted into a heat map to generate a cancer risk map. [8] [9]

Step 3: Multimodal imaging

After the cancer risk map projection, the clinician applies 0.01% proflavine agent to the oral mucosa with a cotton tip applicator, and the probe is directed towards the area highlighted as a high risk for cancer. Simultaneously, the widefield camera tracks the position of the probe with the help of colored dental ligatures attached to the distal tip of the imaging probe. The image analysis algorithm calculated the number of abnormal nuclei/mm^2. The diagnostic score is assigned at the location of the probe in each widefield frame. The microscopic image is analyzed and a high-resolution mosaic is generated. Immediately after image acquisition, the microscopic image undergoes initial quality control (QC) and is sent to multitask task network (MTN) for diagnostic scoring.[8] [9]

Step 4: Biopsy guidance map generation

The MTN performs two main functions, semantic segmentation and classification of the nucleus. In semantic segmentation, the pixels in the image are categorized into three groups nuclear, keratin, and background. Quadrant with a high % of keratin is excluded from the generation of the diagnostic score. Based on the MTN score each nucleus is classified into normal or abnormal and the number of nuclei per unit area is calculated.[8]The normalized R/G intensity ratio at each high-resolution micro-endoscopic image(HRME) is combined with the number of abnormal nuclei/$mm^2$for classification as benign or moderate dysplasia-cancer, using (47.1*normalized ratio of RG ratio)+(number of abnormal nuclei/mm^2)=273.7 as a linear decision threshold.[9] The location of any pixel with exceeded threshold is overlaid and saved as an image and projected onto the oral cavity.This updated threshold was used prospectively in the multimodal imaging system, which classifies “dysplasia or cancer” if the threshold exceeded the value 273.7 and as “benign” otherwise.[9]

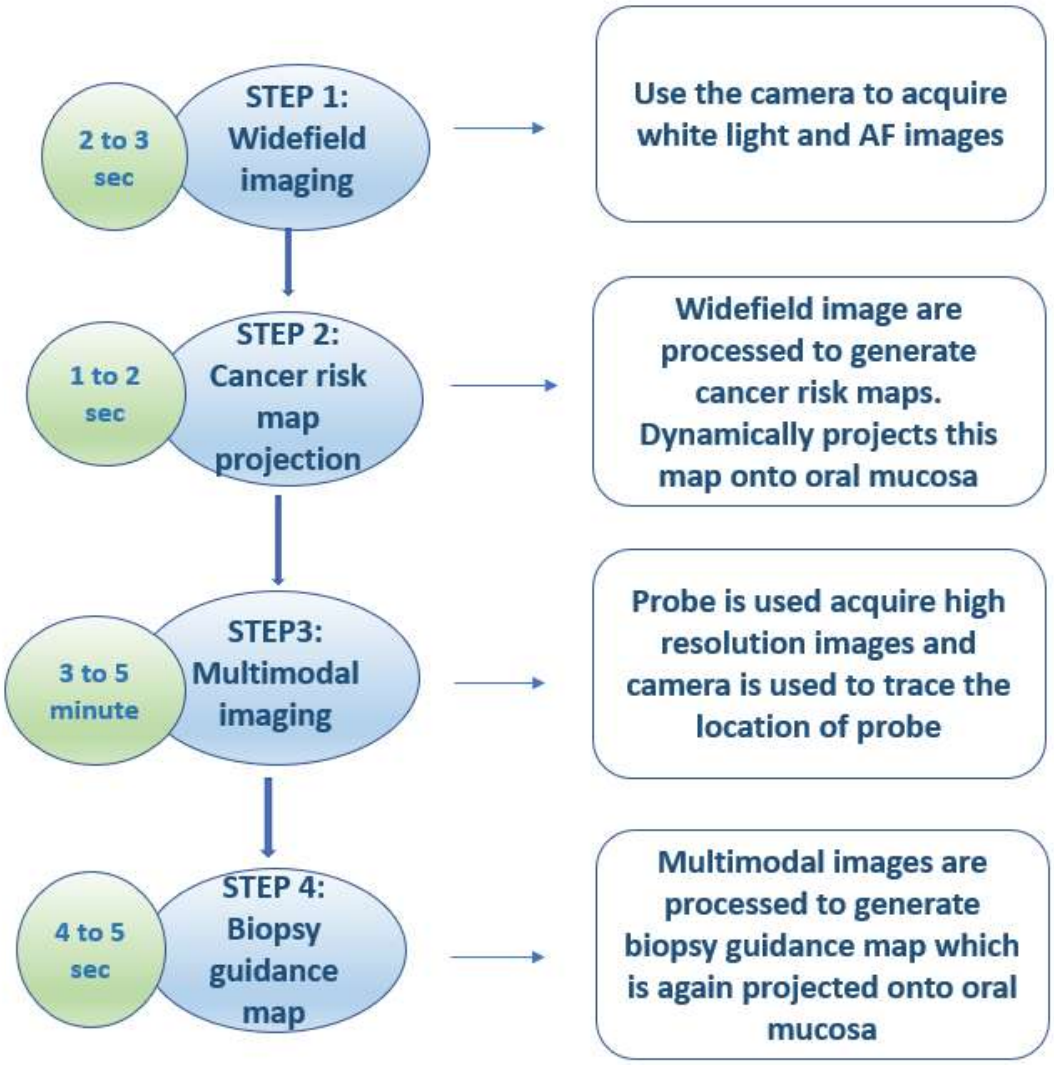

Fig 1:- Imaging workflow of ABGS.

Discussion:-

Conventional oral examination is the standard method for oral cancer screening, although its sensitivity is limited by several factors. To date, various approaches have been proposed including toluidine blue, brush cytology,and chemiluminescent light source. Toluidine is a vital dyethat has been used in the oral cavity to improve the visibility of lesions during visual examination. The sensitivity of toluidine blue ranged from 38 to 98%, while the specificity ranged from 9 to 93%. TheViziLightis a disposable chemiluminescent light source that illuminates tissue with blue light. The authors noted that the ViziLight examination could not discriminate between benign or inflammatory and premalignantor malignant lesions.[4] Recently several studies have shown that AF imaging may improve the ability of clinicians to differentiate normal oral tissue from neoplastic tissue. One very well-known example of AF -based oral cancer screening is VELscope. The VELscope directly visualizes the loss of fluorescence and differentiates neoplastic from non-neoplastic oral mucosa. Benign lesions such as inflammation are also associated with loss of stromal autofluorescence, which may limit the diagnostic specificity in low-risk populations. VELscope and other AF-based imaging devices rely on qualitative observation to detect and delineate loss of fluorescence, and performance depends on subjective visual recognition skills.[4] [6]

Although multimodal imaging and supporting software tools have progressed considerably in recent years, clinicians must observe the results on a computer screen and conclude where to perform a biopsy by mentally translating the

target location from the screen to the patient's mouth. This translation process presents a level of difficulty in precisely identifying the best biopsy location.

The application of digital image processing techniques to AF imaging of oral tissue provides the ability to objectively identify and delineate the peripheral extent of neoplastic lesions in the oral cavity. High-resolution imaging of oral tissue can visualize morphological and architectural changes at the cellular level including nuclear size, shape, and density associated with oral cancer. The combination of widefield AF imaging and high-resolution imaging may yield the best sensitivity and specificity for the detection of oral neoplasia.[6]

One example of the above-combined approach is Active Biopsy Guidance System (ABGS).ABGS is a low-cost, portable, multi-imaging platform that helps the clinician to identify suspicious lesions at an early stage in real-time. ABGS involves four main steps including: (1) first the clinician uses a widefield camera to take white light and AF pictures of the patient's oral cavity. (2) Clinician then outlined the mucosal site onto the AF images to exclude the non-mucosal site to generate cancer risk maps. (3) In the third step flexible probe is used to highlight the high-risk suspicious lesion to acquire high-resolution microscopic images. This imaging step takes less than 5 minutes. (4) In the final steps the system analyzed the multimodal images and computes the biopsy guidance maps. ABGS improves the clinician's ability to differentiate OPMDs from clinically similar benign lesions such as chronic inflammations, so the chances of false positive results are less compared to AF- based imaging alone. [7] [8]

Near-infrared fluorescence imaging is a surgical guidance approach in sentinel lymph node resection, this surgical guidance combines the results of imaging into a digital overlay and this digital overlay is displayed on the computer monitor to the clinician. Then clinician mentally relies on that information back onto the patient and this will increase the chances of misregistration.

One key benefit of ABGS is that it can physically project diagnostic information onto the field of view. On comparing to digital overlays, physical projection of diagnostic information offers real-time actionable guidance without the risk of misregistration during the mental transfer from the display to the patient. The ABGS is designed in a way to balance the consumer-grade electrical and optical components to minimize cost and increase reproducibility. A combination of widefield AF imaging, microscopic imaging, and real-time projection of cancer risk maps will increase the specificity compared to AF imaging alone.[8]

Conclusion:-

The integration of widefield AF imaging, microscopic imaging, and real-time projection of cancer risk maps provide direct visible guidance to identify early lesions andlocate appropriate sites for biopsy. It offers a versatile, quantitative, and precise tool to translate multimodal imaging into real-time actionable guidance to improve patient incomes.

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