Adjunctive aids for the detection of oral premalignancy

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ABSTRACT

Early detection of cancer greatly decreases the morbidity and mortality rates and thereby increases the 5-year survival rates. In developing countries like India where the disease is highly prevalent focus is mainly on decreasing the mortality rates which can be easily achieved by detection at an asymptomatic stage. Visual examination has been the standard screening method for screening oral cancer through several decades, and it is well known that conventional visual examination is limited to subjective interpretation and cannot be easily achieved in certain anatomical sites. As a solution to all these adjunctive techniques have emerged, and it has been widely used. An effort is made through this paper to review the most commonly used adjunctive aids for the detection of premalignancy and cancer.

KEY WORDS: Adjunctive aids, autoflourescence, chemiluminescence, oral squamous cell carcinoma, premalignancy, sensitivity, specificity

Cancer is the broad terminology given to a group of malignant lesions and conditions. As far as the head and neck region is considered 90% of the reported malignancies are oral squamous cell carcinoma (OSCC). OSCC takes the 12th position of the entire cancers reported worldwide and 3rd position of all cancers in India. There is also huge increase in the incidence rates of OSCC since the year 2012. OSCC is also considered to be one among the most debilitating and disfiguring of all cancers.
cancers. The WHO and International agency for research on cancer have stated that the incidence of cancer can be brought down to one-third of its original number by effective screening.[1]

Nevertheless, more than 60% of the newly diagnosed cases of OSCC are at terminal stage (III or IV),[6,8] which badly affects the 5-year survival rates. Research has been conducted in this aspect to find the factors affecting prevention and the reason behind the diagnostic delay of OSCC. The top factors attributed are a lack of awareness in the public as well as failure to recognize patients at high risk and the detection of early squamous cell carcinoma in the oral cavity by the clinicians.[8,9] All these factors emphasize on the need for early detection of OSCC.

It is now very evident that most cases of OSCC are preceded by some kind of precursor lesions such as leukoplakia and erythroplakia, it is also made clear that early detection and effective treatment for the premalignant lesion reduce the risk from progressing to a malignant lesion. OSCC affects the area which has got easy accessibility which favors the clinicians in arriving at an accurate diagnosis. Despite careful examination, small developing lesions often go unrecognized by clinicians.[10] To aid visual oral inspection in addition to normal light wide range of commercial adjunctive aids are available. All these adjunctive aids will of great use in detecting small lesion with a certain amount of dysplasia which appears normal under routine visual examination. Although there are several adjunctive tools available, their effectiveness remains a question mark. Clinicians may not be aware of the techniques involved with each aid and also its effectiveness, this paper aims to review all the adjunctive aids available.

**Adjunctive Techniques for Detection of Premaligancy**

**Vital tissue staining**

It is considered to be the simplest way to detect malignant and potentially malignant lesions. A chemical agent called dye is applied to the tissues so that a color change is brought as a result of some chemical reaction between the dye and abnormal tissue or the normal tissue and which helps in identifying the lesion and also its extent.

The various stains that have been in use are:

- **Toluidine blue (tolonium chloride)**
- **Lugols iodine solution**
- **Acetic acid.**

Toluidine blue (TB) is also known as tolonium chloride [Table 1]. Richart was the first person to use TB for the detection of carcinoma in situ of cervix in the year 1963.[11] TB is an acidophilic metachromatic dye of the thiazine group which selectively stains acidic tissue components such as sulfates, carboxylates, and phosphate radicals, thus staining DNA and RNA. TB stains dysplastic and anaplastic cells because of the increase in their nuclear content when compared to normal tissue.[12] In addition, dye penetration in malignant cells is facilitated by their wide intracellular canals.

To perform this test, have the patient first rinse his mouth with water and then swallow several sips of water. Aspirate excess saliva with suction and apply one percent acetic acid, a mucolytic agent, with a cotton applicator. If there is a large deposit of fibrin or debris in an ulcer, also remove this by suction. Next, place a small amount of one percent TB on the entire lesion as well as on some of the surrounding oral mucosa. Instruct the patient to rinse his mouth with water. Thus, washing away the excess TB. If the lesion is stained, the test is positive.

TB is effective in the identification of occult lesions and as a useful aid in delineating the surgical borders before excisional biopsy.[12–16] Current literature suggests that TB is good at sensitivity in detecting carcinomas, but comparatively poor sensitivity in detection of dysplasia. Furthermore, it is still not evident whether TB can identify epithelial abnormalities that cannot be seen with the naked eye. The main factor which prevents its usage as a primary screening modality is the high percentage of false positive results.[17,18] Shedd and Strong demonstrated that this test can detect squamous cell and epidermoid carcinoma as well as the usual benign oral lesions such as leukoplakia, lymphoid hyperplasia, lichen planus, and traumatic ulcerations. Myers has demonstrated that TB can also identify melanoma, fibrosarcoma, and lymphosarcoma in addition to epidermoid cancer.

Rosen et al.[19] have demonstrated that TB has a high sensitivity in its detection of malignant oral lesions; values vary from 84 to 100%. Studies have demonstrated a great variation in the specificity of staining by TB ranging from 44% to 100%. Warnakulasuriya and Johnson confirmed that OSCC could be detected with a sensitivity of 100% using a commercial rinse (orascan) containing TB as its active ingredient.[14]

Studies by Zhang et al.[20] say that toluidine blue not only detects lesions with high degree of cellular dysplasia but also will preferentially stains lesions with minimal or no dysplasia but with a high-risk clinical and molecular attributes.

According to Mashberg eradicating all the inflammatory factors, the number of false-positive results can be reduced and thereby increasing the specificity of staining. He also recommends re-evaluation and re-staining of false-positive lesions after 10–14 days, and in case of positive stain, the lesion should be considered as carcinoma.[21]

**Lugol’s iodine**

Lugol’s iodine was prepared by Jean Guillaume Auguste Lugol, a French physician, in 1829. He mixed a solution of potassium iodide and elemental iodine in distilled water and called it by the name Lugol’s iodine [Table 2].

To the suspective lesion where Lugols is to be used, a 2% acetic acid is applied followed by which Lugol’s iodine solution is applied. When the iodine solution is applied, healthy tissue will stain brown or brown-black. Despite the application of the staining Lugol’s iodine, abnormal cells will appear white...
Acetic acid is also prescribed as a mouth wash before the use of chemiluminescent devices for the detection of oral cancer.

Studies by Sankaranarayanan et al.\textsuperscript{[26]} investigated the efficacy of acetic acid in detecting cervical cancer in India and reported the sensitivity to be 78% and specificity 88%.

Blumenthal et al.\textsuperscript{[27]} compared the sensitivity and specificity of acetic acid and reported it had a sensitivity of 83.3% and specificity of 84.21%.

### Light-Based Detection Systems

#### Chemiluminescence

“Chemiluminescence” refers to the emission of light during a chemical reaction. In its simplest form, it can be represented as:

\[ A + B \rightarrow (I) \rightarrow \text{products + light} \]

Where (I) is a short-lived, intermediate compound. The compound ties to react with tert-buty1 alcohol to reach lower energy level by emitting visible light. The phenomena behind chemiluminescence are that the malignant cells have different absorption and reflection properties with respect to normal cells. Hence, normal mucosa appears blue, whereas abnormal mucosal areas reflect the light. This high reflecting property is due to higher nuclear/cytoplasmic ratio of epithelial cells.\textsuperscript{[28]}

There are many systems of chemiluminescence of which the two most widely used are the:

- Lumilinescent-based and
- The peroxyoxalate-based systems.

Speculite is based on the peroxyoxalate system of chemiluminescence. It produces a diffuse, blue-white. Chemiluminescent light source with peak outputs near 450, 540, and 580 nm wavelengths. The other commercially available product based on chemiluminescence is ViziLite system. The exact system which used in ViziLite is not revealed by the manufacturer, but it is believed to be based on peroxyoxalate system. The system comes in two flexible capsules: The outer one contains acetylsalicylic acid and the inner fragile one contains hydrogen peroxide. The construction of this system is in such a way that flexing the capsule ruptures the inner capsule and activates the chemical reaction. These chemicals react and emit blue-white light with a wavelength ranging between 430 and 580 nm\textsuperscript{[29]} for a period of 10 min. The kit comes with acetic acid solution which is used to clean the surface of the lesion for easy penetration of the light source. ViziLite system comes with TB and is now called ViziLite Plus. TB is said to enhance the properties of ViziLite.

Rancho mirage\textsuperscript{[29]} reported that combining chemiluminescence with TB increases the efficacy greatly. In a study conducted by Farah and McCullough\textsuperscript{[30]} in 55 patients with malignant and premalignant lesions, the accuracy of chemiluminescence was found to be 18.2%, but the sensitivity was 100% while the specificity was very low as 0–35%, whereas the study

### Table 1: Composition of toluidine blue

| Component          | Amount |
|--------------------|--------|
| Toluidine blue (g) | 1      |
| Acetic acid (cc)   | 10     |
| Distilled water (cc) | 86      |
| Absolute alcohol (cc) | 4.2  |

Mixing all the above ingredients, then the pH is adjusted to 4.5

### Table 2: Composition of Lugol’s iodine solution

| Component          | Amount |
|--------------------|--------|
| Iodine (g)         | 2      |
| Potassium iodide (g) | 4      |
| Distilled water (cc) | 100    |

or yellow. Lugol’s iodine solution produces a brown-black stain by reaction of the iodine with glycogen. It is believed that malignant epithelial cells will have decreased glycogen content when compared to normal cells; hence, the normal cells react with Lugol’s solution and take up a brown-black color, whereas the malignant cells remain white. Glycogen content is inversely related to the degree of keratosis, suggesting a role of glycogen in keratinization. Throughout the oral mucosa, the content of glycogen varies with the keratinization of the area of mucosa. This may limit use of Lugol’s iodine in keratinized lesions.

Lugol’s iodine in oral lesions demonstrates a high sensitivity although less than that of TB but greater specificity. Chaudhari et al.\textsuperscript{[22]} conducted a study with Lugol’s iodine and his results are indicative that the stain is highly effective as a screening tool for oral premalignancy and oral cancer. According to Umeda et al.\textsuperscript{[23]} and Kurita et al.\textsuperscript{[24]} Lugol’s iodine is of great use in deciding the margins for resection and thereby it is helpful in preventing local recurrence. In a study by Epstein et al.\textsuperscript{[25]} where he used both Lugols and toluidine blue for staining malignant and premalignant lesions, he concluded that this type of tissue stains can assist in delineating the extent. He also said that the use of TB as a single tissue stain is of value due to its sensitivity but is reduced in specificity due to the increase in percentage of false-positive results in benign lesions. In contrast, in the oral cavity, the use of Lugol’s iodine is less sensitive but is of greater specificity. Thus, the use of both tissue stains appears to be of great worth consideration. When either stain is positive, the sensitivity is highest, but specificity is reduced due to false-positive results when both tests are positive sensitivity is reduced but the specificity is greatest. The positive predictive value is greatest when both stains are positive.

#### Acetic acid

A composition of 3% to 5% acetic acid was initially used in the detection of cervical cancer since the anatomy of and the types of cancer in oral cavity and cervix is comparable acetic acid seems to be efficient in detecting carcinomas of the oral cavity. After a thorough cleaning and drying of the lesion, acetic acid should be applied with a piece of gauze for 60 s. A lesion with dysplastic changes will change its color to opaque white.

Acetic acid is said to have a higher specificity than TB but a lesser sensitivity. Since 5% acetic acid is easily available, and it is of lesser cost it earns an advantage over TB. Patients also well tolerate the application of acetic acid.
conducted by Ram and Siar\cite{31} in a group of 38 patients says that chemiluminescence has a sensitivity of 100%, specificity of 85.7%, and thus the accuracy to be 96.42%. Epstein et al., 2008;\cite{32} did a comparative study to evaluate the efficacy of visual examination, against chemiluminescence and TB and came to the conclusion that the chemiluminescent examination was of great use in delineating the margins in 61.8% of the cases.

**Autofluorescence**

Malignant cells have altered the distribution of tissue fluorophores due to the structural changes in the epithelium and the adjoining stroma when such tissue is stimulated with a blue light of wavelength 400–460 nm, the tissue exhibits an altered autofluorescence when compared to the adjacent healthy tissue. This phenomenon is called autofluorescence. The normal oral mucosa appears pale green indicating good autofluorescence, whereas the abnormal tissue appears darker indicating a poor fluorescence. The most commonly used autofluorescence technology is the VELscope system.

**VELscope system**

The device is a handheld scope emitting blue light spectra of 400–460 nm wavelength. This emitted light is used to screen the mucosa for abnormalities.

Researchers who have investigated the effectiveness of the VELscope system have recommended VELscope for (i) delineating the border between malignant and healthy tissue, (ii) and identifying dysplastic/malignant lesions that appear normal to the naked eye under white light, (iii) to distinguish benign and dysplastic lesions.

In a study conducted by Poh et al.,\cite{33} he concluded that VELscope has 97% and 94% sensitivity and specificity, respectively, but the sample size was very small.

Kois and Truelove\cite{34} reported that VELscope has a sensitivity of 98% and specificity of 100%, and in one more study by Balevi\cite{35} said that it has the same sensitivity and specificity as per Kois and Truelove studies.

Other systems that are available are the Microlux-DL system and Orascoptic-DK system – both the systems use a light-emitting diode for emission of blue light spectra. The Orascoptic system comes with a mouth rinse containing acetic acid to enhance visualization.

**Autofluorescence imaging**

This technique uses laser, xenon light, or halogen lamp to radiate the suspected tissue, and it exhibits abnormal fluorescence on comparison with normal tissue. This device is capable of screening a wide area in a single shot. Ultraviolet (UV) to green edge of the spectrum is used as a source to radiate the tissue, the pattern of absorption and scattering are captured and recorded using a camera. The device consists of a light source attached to a handheld instrument for screening which is illuminated by the source, then visualized by notch filters which allow the passage of green and red autofluorescence. The images can be either visualized manually or can be captured using a camera and stored for future reference. Under fluorescence imaging, the healthy mucosa appears in shades of green against the dysplastic regions appearing dark.

Fryen et al.\cite{36} studied the efficacy of autofluorescence in detecting the cancerous lesions of the upper aerodigestive according to the results both premalignant and cancerous lesions greatly vary in their appearance when viewed with normal light and autofluorescence. He also concluded that even minute lesions which appeared normal under routine inspection were detectable.

According to Kulapaditharam and Boonkitticharoen\cite{37} that autofluorescence imaging shows a sensitivity from 68% to 93% and specificity from 70% to 79% for all head-neck lesions, and for the oral lesions, autofluorescence imaging had a sensitivity of 100% and a 73% specificity.

Betz et al.\cite{38} studies show that a low-intensity fluorescence of 375–440 nm is sufficient to identify the borders.

Paczona et al.\cite{39} recently investigated the use of autofluorescence videomicroscopy for diagnosis of head and neck squamous cell carcinoma. He concluded that the extensions of the lesion are better detected by autofluorescence imaging than white light endoscopy.

**Fluorescence spectroscopy**

Fluorescence spectroscopy is similar to visual autofluorescence, but with a slight modification [Figure 1]. Autofluorescence spectroscopy systems also consist of a light source usually in the near-UV to visible wavelength range, the light emitted is by the source is used to excite the tissues through a fiber. The spectrometer analyses the fluorescence produced by the tissues and the reflected light is filtered out. The fluorescence spectra produced by the tissues are recorded and also be saved by attaching the device to the computer, the computer carries out the spectral analysis. Thereby eliminates subjective interpretation errors. Fluorophores are responsible for the fluorescence produced by the tissue. The resultant spectra are also sensitive to the cellular components such as hemoglobin.

This kind of tissue fluorescence can also be induced by a laser-induced phenomenon. 5-aminolaevulinic acid (5-ALA) applied topically or systemically enhances the intensity of the fluorescent spectra. 5-ALA is precursor of protoporphyrin IX (PpIX), this technique is called the photodynamic diagnosis. This photodynamic diagnosis is said to have a high sensitivity but limited specificity in the detection of OSCC. False-positive results are especially problematic in patients who have had prior radiotherapy. Photodynamic diagnosis is thus not suitable for diagnosing recurrent lesions or second tumors in patients who have undergone radiation treatment. Even low levels of glucose can influence production of PpIX, and thus patients must fast...
during the 4 h necessary for examination which may require strict patient management. Considering the often limited compliance among higher-risk patients, this may be difficult to ensure.

Kolli et al.\(^{[40]}\) used a different combination of excitation wavelengths ranging between 200 and 450 nm, he used the emission and excitation wavelength ratio, and he stated that there is a significant difference in the autofluorescence pattern of healthy and cancerous tissue. Gillenwater et al.\(^{[41]}\) used excitation of wavelengths 337, 365, 410 nm, and he reported that autofluorescence spectroscopy has a sensitivity of 82% and specificity of 100% in diagnosing oral cancers. Majumder et al.\(^{[42]}\) used an excitation wavelength of 337 nm, and he claimed that autofluorescence spectroscopy has a higher sensitivity of 86% than the previous studies.

**Biopsies**

**Brush biopsy**

Brush biopsy is done with a circular bristled brush, which is designed in such a way that it could sample all epithelial layers including the superficial layer of the lamina propria of the connective tissue. The brush has a flat surface on one side and a circular edge on the other side with a handle for applying pressure to the sample; thereby it is able to produce a sample of the entire thickness of the epithelium [Figure 2].

To obtain a sample, the brush must be moistened with the patient’s saliva and applied to the surface of the lesion. The procedure is said to be painless, so anesthetic agent may not be required. In case sampling is done for a lesion which is previously tender then an anesthetic can be used, but a topical agent is not advised since it may cause distortion of epithelial cell morphology of the sample. Once a proper contact is achieved between the lesion, and the brush moderate pressure is applied, and the brush is rotated until there is pinpoint bleeding, indicating the entry into the lamina propria and thus obtaining a transepithelial biopsy. The sample is then transferred to a glass slide by distributing the obtained material evenly over the glass surface. Then, the steps of fixation and staining follow.

The computerized analysis of brush biopsies has been introduced since 1999 for the evaluation of oral lesions. The brush technique and method of preparing the slide are similar.
to the manual brush biopsy. However, the prepared slide is scanned by an automated computer-driven microscope system, and a specially designed software is used to analyze the scanned slides. Any abnormality in cell morphology which is suggestive of dysplasia and carcinoma of the oral epithelium are analyzed, and the images of abnormal cells identified by the computer. The images of the abnormal cells are displayed on monitor, which are visually assessed and interpreted by the pathologist, who renders a final diagnosis.

Studies by Christian[46] concluded that the sensitivity of the OralCDx technique to detect dysplasia and OSCC was 92.3% and the specificity was 94.3%. The positive likelihood ratio was 16.2 and the negative likelihood ratio was 0.08. The study by Scubba[46] of 945 OralCDx biopsies reported a sensitivity of 96% and a specificity of 90% to detect cases of dysplasia or squamous cell carcinoma (OSCC). Svirsky et al.,[46] 2002, conducted a study in 298 patients and he compared the results of eighty patients who had undergone both brush cytology and a scalpel biopsy, according to him, the brush technique had a sensitivity of 92% and a specificity of 94%. A retrospective study by Poate et al.,[46] reported that the brush biopsy has a sensitivity of 71%, specificity of 32%, and a positive predictive value of 44%. Scheifele et al.,[47] performed a study using brush biopsy of 90 oral lesions with a clinical diagnosis of leukoplakia, lichen planus, or squamous cell carcinoma showed that the brush biopsy has a sensitivity of 92.3% and specificity of 94.3%.

**Conclusion**

At present, the knowledge of these adjunctive aids among the clinicians is very low, and these aids are only directed to help experienced clinicians. Moreover, the impact of these aids on patient survival and recurrence of the disease is not yet been established. Therefore, future research is recommended with a large sample size on a long time basis.

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**Conflicts of interest**

There are no conflicts of interest.

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