

Early diagnosis of oral cancer - A narrative review

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ABSTRACT

Oral cancer (OC) is a common malignancy in Asian countries. Early diagnosis is crucial because of its high mortality rate. Patients and physicians both contribute to the delay in oral cancer diagnosis. Improved knowledge of the disease, its risk factors and symptoms would have a positive influence upon the early diagnosis. Majority of the risk factors such as alcohol consumption, tobacco, betel nut, viral infections, chronic irritation and inflammation if identified timely can mostly avoid the cancer. Prevention and anticipation of diagnosis begin with identification of potentially malignant lesions of the oral mucosa and local conditions promoting chronic inflammation. Each lesion needs to be identified quickly and given the proper care. The clinical recognition and evaluation of oral mucosal lesions can detect up to 99% of oral cancers/ pre-malignancies. The World Health Organization states that a biopsy is required for any suspicious lesion that does not go away after two weeks of local causes of irritation have been identified and removed. Surgical biopsy is the gold standard for diagnosis of oral cancer. However oral brush biopsy, toluidine blue vital staining, auto-fluorescence imaging, and other non-invasive techniques have been created and researched to aid physicians in the diagnostic process. Currently, artificial intelligence is a key component in the early detection of oral malignancies. Present review was written to highlight various factors resulting in delayed diagnosis of oral cancer as well as to discuss different non-invasive techniques that can easily be used in early categorization of oral pre-malignant and malignant lesions.

Keywords: Oral cancer, Early diagnosis, Noninvasive techniques, Salivary biomarkers, Biopsy, Artificial intelligence.

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INTRODUCTION

The sixth most common cancer globally, after oropharyngeal malignancies, is an oral cancer [1]. An estimated 400,000 new instances of oral cancer are detected worldwide each year, with two thirds of those occurrences occurring in Asian nations like Bangladesh, Pakistan, Sri Lanka, Indonesia, and India [1,2]. It has one of the lowest rates of cancer survival in the entire globe. According to GLOBOCAN, in 2020, there were 377,713 newly diagnosed cases of lip and mouth cancer (264,211 male cases and 113,502 female cases), with a similar mortality rate of 177,757 (125,022 male cases and 52,735 female cases) [3]. Squamous cell carcinomas (OSCCs) account for about 90% of instances of oral malignancies; salivary minor gland tumors,

melanomas, and lymphomas are among the other oral cavity tumors that can occur [2,4]. Even while incidences of oral cancer in those under 40 are rising, the incidence of the disease rises with age and peaks in those over 60 [5].

Generally speaking, chewing betel quid, drinking alcohol, heavy tobacco use (including smokeless tobacco), and chronic inflammation are risk factors for oral cancer [5,6,7]. HPV-associated oral and oropharyngeal cancers (mostly HPV type 16) have become more common in recent years, mostly in younger individuals [6]. Actinic ultraviolet radiation (UV), primarily UV-B, also contributes to lip cancer [8]. Moreover, a deficiency in DNA repair pathways is linked to an elevated risk in hereditary disorders such as ataxia-telangiectasia, Fanconi's anemia, and xeroderma pigmentosum [7]. Many occurrences of oropharyngeal and oral cancer are discovered when the disease is already advanced, causing unnecessary morbidity and death [6,8,9]. In to raise the possibility of a successful result, it is crucial to diagnose promptly as possible, the lesions, even though they remain in the early phases. Low

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survival rates, an increased risk of treatment-related problems, and increased medical costs are linked to malignancies that are detected later or are more difficult to access [9-12].

IMPORTANCE OF EARLY DIAGNOSIS OF ORAL CANCER

Ninety-nine to ninety-four percent of oral cancers are attributed to oral cavity squamous cell carcinoma (SCC); nevertheless, other malignancies include metastatic tumors, soft and hard tissue sarcomas, and malignancies of the salivary glands [2,3]. Oral cancer survival rates are extremely low, at about 50% overall, and have not much improved in the past few decades despite advancements in treatment interventions [4,5]. It has long been known that a patient's clinical outcome can be improved by detecting oral cancers early on [13]. The best way to lessen mouth cancer-related death, morbidity, and disfigurement is to detect the disease early, while lesions are small or confined [9]. There are three different ways to use the term "early" in describing cancer: 1) early in the carcinogenesis process; 2) Early in the sense of being relatively tiny at the time of detection; and 3) Early in the sense of having a brief period of time—a short delay—between the onset of symptoms and the diagnosis. Oral cancer has a dismal prognosis; the total 5-year survival rate is as low as 40%. Nevertheless, if the illness is identified in phases I and II, the early stages of the disease, survival rates may exceed 80% [14]. In 50% of cases, mouth cancer is discovered at a later level (stages III and IV), because most people wait to seek medical assistance until they experience symptoms rather than exhibiting them at the outset [15]. In the event that lymphatic spread is already present, symptoms may include discomfort, bleeding, or a lump in the throat or tongue. The likelihood of developing an advanced stage of oral cancer is considerably increased when there is a more than month-long diagnostic delay [16]. Most of the time, the patient is mostly to blame for the delay in diagnosis; yet, an ineffective medical strategy can also cause the delay by failing to recognize the possibility of an oral cancer and failing to

identify and treat it in a timely manner [8–10]. The prognosis generally gets worse with increasing disease severity and decreased accessibility to the tumor site (the survival rate for lip cancer is higher than that of oropharyngeal cancer) [17]. The clinical and pathological stage remains the most important element influencing prognosis at diagnosis [18]. With the high death rate, early detection and diagnosis of oral cancer improves prognosis and survival rates and lowers treatment-related morbidity [19].

PITFALLS IN EARLY DIAGNOSIS OF ORAL CANCER

Both patients and medical professionals are to blame for the delay in mouth cancer detection. Overall delay, which encompasses scheduling, work-up, and treatment planning delays, varies across studies but often takes six months [3]. Overall delay is about split between the delays of the doctors and the patients, and it is partially caused by the public's and professionals' ignorance of oral cancer and in part because of obstacles within the medical system that can prevent people from obtaining medical and dental care.

Patients' Delay: There is little public knowledge of mouth cancer [14,17,19]. Fear of receiving a cancer diagnosis causes significant delays for a small number of patients, at least in developed nations, whereas most patients haven't even contemplated the potential for a cancerous condition if there is an oral lesion with symptoms [17]. This is especially valid for younger patients. [18,19]. Additional risks linked to patients' delays include excessive drinking and smoking, low socioeconomic status [20], not receiving regular dental treatment [11, 21], position on the tongue [22] and restricted access to primary health care for patients from low socioeconomic backgrounds.

Other factors/reasons patients may delay seeking medical attention for oral cancer, includes:

- **Cost:** Patients may not be able to afford the cost of medical care, including the cost of diagnosis and treatment.

- **Transportation:** Patients may not have reliable transportation to get to a doctor's office.
- **Language barrier:** Patients may have difficulty communicating with their doctor because of the language they speak other than Urdu or English.
- **Cultural factors:** Patients from certain cultures may be reluctant to seek medical attention, especially for cancer.

Patient delay for the timely detection of oral cancer can have a significant impact on survival rates. The earlier oral cancer is diagnosed, the sooner treatment can begin, and the better the chances of survival. Numerous actions can be taken to assist in avoiding patient delay, including:

- **Increase awareness of oral cancer:** People must be conscious of the symptoms and indicators of oral cancer, also the risk factors of the disease. Which may help them to seek medical attention sooner, if they notice any changes in their mouth.
- **Making it easier for people to get screened:** Oral cancer screening should be made more accessible to people, regardless of their ability to pay. This could involve expanding access to dental care, as well as providing financial assistance for screening.
- **Address the barriers to seeking care:** Many obstacles, including fear, embarrassment, and lack of transportation can keep people from getting treatment for oral cancer. These barriers need to be addressed in order to encourage people to seek care sooner.

Professional Delay: The amount of time that passes between the patient's initial appointment with a medical expert and the final pathological diagnosis is known as the professional delay [24]. It has been proposed that inadequate clinical examination, nonspecific clinical indicators, low index of suspicion, inexperience with the disease, and comorbidity are the reasons for professional delay [10,11,13,24]. According to Holmes *et al.*, following a standard oral examination, a general

dental office is more likely to send asymptomatic patients for a biopsy than a primary medical practice. Conversely, Kowalski *et al.* [12] found that before receiving a diagnosis, patients were three times probably visiting a primary care physician as opposed to a dentist. Individuals who smoke and drink and are at risk for oral malignancies are four to six times more likely to see a doctor than a dentist [23]. Research has highlighted the significance of a collaborative effort between family physicians and dentists in enhancing the probability of early identification of oral cancer. Therefore, a comprehensive assessment of the mouth cavity, head, and neck ought to be a component of every dental and medical checkup. In order to get a conclusive diagnosis as soon as possible, healthcare professionals may need to receive education to help them identify oral cancerous and precancerous tumors.

AWARENESS AMONG PATIENTS AND HEALTH CARE WORKERS

A deeper comprehension of the illness, its danger elements, as well as its symptoms might aid in the diagnosis process by making it easier to spot possible cancerous symptoms that could go unnoticed otherwise or not be adequately evaluated [8-12].

Improved Knowledge Among Patients: Patients' should adopt following measures:

- Patients' should consult dentist about risk factors (habitual user of smoked/ smokeless tobacco, betel quid or alcohol, chronic inflammation, family history of cancer and/or genetic diseases). If they have any of the factors that increase the risk of oral cancer, they should make sure to aware dentist/ professional workers about their increased risk. Professional workers can help to develop a plan for regular screening and early detection [25].
- Be aware of the indications and manifestations of oral cancer. The early signs and symptoms of oral cancer are often subtle and may not be noticeable. However, any changes in the mouth, such as red or white spots or ulcers that don't heal, should be taken seriously, swelling, sores or lumps in the mouth, changes in the way teeth fit together, pain, difficulty chewing or swallowing, unexplained

bleeding or discharge from the mouth, numbness or tingling in the mouth or sudden weight loss.

- Regular dental visits for checkups and cleanings. Dental checkups provide an opportunity for your dentist to look for any suspicious changes in your mouth.
- Any change in mouth should not be ignored [26].

Awareness Among Professional

Workers: Healthcare workers including dentists, doctors (family physicians), nurses and/or supporting staff should be aware of signs and symptoms for timely referral of patient to the concerned specialist [27].

Typical signs and symptoms: Using digital palpation and visual evaluation of the oral cavity, the clinical oral examination is the first step in the diagnostic procedure [13,25]. A comprehensive clinical examination of the mouth cavity can identify up to 99% of oral malignancies (Table-I). To get an early, conclusive diagnosis, the capacity to identify oral possibly malignant oral epithelial lesions (PMOELs) should be put into practice.

Oral disorders and diseases that can exist before the commencement of oral squamous cell carcinoma (OSCC) are known as potentially malignant oral epithelial lesions (PMOELs). These comprise a category of oral mucosal lesions that are clinically suspected like:

- **Leukoplakia:** This condition is classified as either clinically or histopathologic ally, but in 1978 the World Health Organization defined it white patch of the oral mucosa that cannot be wiped off [25].
- **Erythroplakia:** Less frequently occurring erythroplakia typically manifests as a red lesion with a velvety texture and a well-defined appearance [7, 28]. However, erythroleukoplakia, speckled erythroplakia, and leukoerythroplakia are conditions in which the lesion contains both red and white patches [8, 27].
- **Oral lichen planus:** Patients with lichen planus, an immunologically based chronic inflammatory illness, are mainly middle-aged [28], with a predisposition toward women between the ages of 30 and 60. [29].

- **Submucosal fibrosis:** An oral mucosal fibrotic lesion that is persistent is called submucosal fibrosis. It is most likely the manifestation of an overhealing wound in response to persistent chemical or mechanical assaults to the mucous membrane. Suspected lesions must be investigated more. According to the World Health Organization, the National Institute of Dental and Craniofacial Research, and recent research, any mucosal lesion that lasts for two weeks or more has to be evaluated, depending on the American Dental Association guideline, following the removal of any potential local irritants (damaged teeth, poorly fitted dental appliances, prosthetics, tooth plaque, etc.), tooth plaque, etc.), biopsies are required because the most reliable method for diagnosing OSCC is histological investigation[30-32]. A number of additional diagnostic auxiliary tools have been created to assist in overcoming the limitations of the traditional oral clinical examination. These techniques can help identify benign and possibly cancerous lesions, even though they are not as helpful as a biopsy [33]. A few of these are:
- **Oral Brush Biopsy:** A technique to examine the mouths of those who are most likely to develop mouth cancer is called an oral brush biopsy. Using this method, cells from the mouth's mucous membrane's deeper layers are harvested. The procedure involves minimal pain and bleeding [30].
- **Toluidine Blue Staining:** For the purpose of diagnosing Toluidine blue staining is a useful diagnostic tool for oral cavity cancer and pre-cancerous lesions which is straightforward, affordable, and non-invasive method [32]. Royal blue staining of dysplastic epithelium is caused by the cationic metachromatic dye toluidine blue. [34] Its administration is quite simple and quick: after applying 1% acetic acid to eliminate bacterial and salivary pellicle, the questionable lesion area is treated with a 1% aqueous solution for 30 seconds; the

staining pattern is subsequently assessed. [35] (Figure-4).

- **Autofluorescence Imaging:** Although oral cancer is still mostly diagnosed through clinical examination with white light, autofluorescence imaging can provide extra information regarding the type of lesion, aiding in the diagnosis and identifying lesions that require biopsy [36]. The idea that cancer and dysplasia alter the mucosa's fluorescence serves as justification for the application of autofluorescence imaging. Normal mucosa typically exhibits light-green fluorescence; however, the illness results in a reduction of green fluorescence, which darkens the mucosa [32]; this is because the components that trigger autofluorescence in healthy tissues are not distributed uniformly in healthy tissues [36] (Figure-V)
- **Salivary Biomarkers for Point-of-Care Testing:** Through molecular research, over 100 biomarkers, including human saliva has been discovered to contain viruses, cytokines (IL-1b, IL-8, TNF- α), protein receptors (CD44) [37] and DNA and RNA markers that are overexpressed in a carcinogenic process [38]. These markers act as indications of pathological processes and carcinogenesis [39]. Patients may take some of these techniques well since they are affordable, simple, and non-invasive point-of-care testing approaches.
- **Artificial Intelligence:** From patient screening to therapy, artificial intelligence is starting to have a significant influence on oncological workflow by increasing diagnostic precision [40-42]. The use of radiomics, a computational method that aids in diagnosis and essentially entails the conversion using imaging data to find unique characteristics that are invisible to the naked eye, has been increasing recently. These novel imaging features could have therapeutic, prognostic, and diagnostic applications [43]. Applications of white light imaging (WLI) and autofluorescence imaging (AFI) were

merged in digital devices equipped with an external light emitting diode (LED) system by Song *et al.* and Uthoff *et al.* Compared to the separate use of the applications, the authors were able to achieve superior validation of the pictures for the differentiation of non-suspicious lesions (normal and variants of normal) and suspicious lesions (malignant and premalignant) by utilizing this technique with transfer learning (VGG-CNNM) [40-44].

Table-I: A few more common clinical signs and symptoms of cancer of the oral mucosa; in the early period that can be totally asymptomatic but evident as a visible aberration of the normal texture and surface of the mucosal lining.

1. Persistent mouth sores and/or pain
2. Localized modifications of appearance of the oral mucosa
3. Alteration in consistency of oral mucosa
4. Raised patch or plaque in the oral mucosa
5. Persistent lump or growth in the oral mucosa
6. Localized bleeding area in the oral mucosa



Figure-I: Female, 72 years—verrucous leukoplakia in the right buccal surface. (Dental College-HITEC IMS, Taxila).



Figure-II: Male, 61 years—erythroplastic area in the posterior hard palate, revealed severe dysplasia and in-situ carcinoma in the histopathologic examination. (Dental College-HITEC IMS, Taxila).

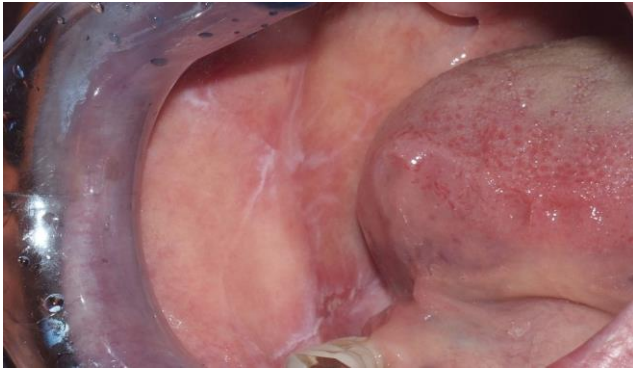


Figure-III: Male, 52 years—white reticular striae on the right cheek mucosa in a patient with oral lichen planus histopathologically confirmed. (Dental College-HITEC IMS, Taxila).

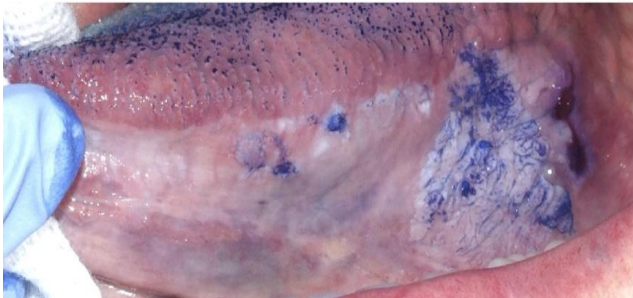


Figure-IV: Male, 72 years—wide corrugated leukoplakia of the left border of the tongue; the application of toluidine blue staining revealed several foci of suspected epithelial dysplasia or cancer. (Cuocolo, et al. 2022).

CONCLUSION

The management of this physically and mentally debilitating disorder depends on early identification of oral cancer and prompt intervention. This is only possible by reducing both patients' delay and doctors' delay by improving oral cancer awareness among the general population and medical professionals should be on the lookout for lesions with an unclear cause. The availability of innovative point-of-care diagnostics as well as a number of diagnostic tools and visual screening devices can help clinicians better characterize any problematic lesion that identify the possibility of cancerous transformation utilizing salivary biomarkers. While surgical biopsies and

histology are still regarded as the "gold standard," objective clinical examination should also involve supplementary procedures. In addition, by identifying intricate patterns, artificial intelligence presents fantastic chances for task automation.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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AUTHOR CONTRIBUTION

Azka Haroon: Conception of study, manuscript writing, revising critically for important intellectual content, final approval of the draft version, agree to be accountable for all aspects of the work

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