Oral Cancer: Diagnostic Considerations

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ABSTRACT

Globally, oral cancer is among the top 10 most common cancers, and despite being largely preventable, the global incidence is still on the rise. The major risk factors for oral cancer in the Western world are tobacco and alcohol consumption, but in Nigeria, other risk factors like poverty, malnutrition, poor oral hygiene, kolanuts, immune suppression and chronic malaria may play a greater role. The overall prognosis for oral cancer is poor, with a 5-year survival rate of about 50%, although this is due to late presentation and delays in diagnosis. When diagnosed early, oral cancer is potentially curable, and the 5-year survival rate increases to over 80%. So, efforts should be geared towards prevention and early diagnosis. Biopsy for histopathologic examination is the gold standard for the diagnosis of oral cancer, but other methods that have been used for oral cancer screening include visual oral examination, vital staining, cytology, and light-based methods e.g. autofluorescence. In recent times, artificial intelligence and use of salivary biomarkers have shown promise in improving the early diagnosis of oral cancer.

Patient related factors play the major role in delaying the diagnosis of oral cancer, as patients often delay seeking professional advice for up to 6 months or more from when they first notice any oral symptom that may be linked to oral cancer. Public education, improvement in health-seeking behaviour, better healthcare facilities and use of adjunctive screening methods will help in reducing incidence of oral cancer as well as the associated morbidity and mortality

Keywords: Oral cancer, diagnosis, risk factors

INTRODUCTION

The term "oral cancer" refers to any malignant tumour affecting the lips or oral cavity, including the tongue, buccal mucosa, palate, floor of the mouth, alveolus and gingiva. (Omitola et al., 2017). It includes carcinomas, sarcomas and lymphomas, although the carcinomas are most frequent. (Okoh et al., 2015) Squamous cell carcinoma (SCC) accounts for up to 90% of oral cancers in most Caucasian studies (Bagan et al, 2010; Güneri and Epstein, 2014; Thomas et al, 2020). However, in Nigeria and other African countries, much lower figures have been reported. (Okoh et al., 2015)

Despite the fact that some cases of oral cancer can be prevented, (Groome et al., 2011) the global incidence is still on the rise, and it is currently ranked among the top 10 most common cancers worldwide. (Zhang et al., 2022)

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RISK FACTORS

In the Western world, the major risk factors are tobacco and alcohol consumption, with a lesser contribution from Human Papilloma Virus (HPV) infection, chemicals, radiation and genetic factors. (Güneri & Epstein, 2014) Many Nigerian studies have however failed to find significant associations

between oral cancer and usage of tobacco or alcohol (Oji & Chukwuneke, 2007; Oji & Chukwuneke, 2012; Lawal et al, 2013; Omitola et al, 2017). Other risk factors that have been proposed include poverty, malnutrition, poor oral hygiene, kolanuts, immune suppression, chronic malaria. (Oji & Chukwuneke, 2012; Lawal et al., 2013; Omitola et al., 2017) In particular, failure to consume fruits and vegetables regularly has been associated with an increased risk of developing oral cancer. (Lawal et al., 2013)

PROGNOSIS

The overall outlook for oral cancer is grim, with a 5-year survival rate of about 50%. (Bagan et al, 2010; Güneri and Epstein, 2014; Zhang et al, 2022) This is however due to the fact that most cases present late. (Bagan et al, 2010; Groome et al, 2011) When diagnosed early, oral cancer is potentially curable, (Sambandham et al, 2013; Güneri & Epstein, 2014) and with early presentation and appropriate treatment, the 5-year survival rate increases to over 80%. (Bagan et al, 2010; Su et al 2021) Besides the improvement in survival rates, early presentation has also been reported to reduce disease morbidity, as well as the emotional toll and financial burden of the impact of oral cancer on sufferers and their family. (Sambandham et al, 2013; Güneri & Epstein, 2014)

CLINICAL FEATURES

Oral cancer has a wide range of presentation. Early features include an unresolving red patch (erythroplakia), an unresolving white patch (leukoplakia), or a combined red/white patch (erythroleukoplakia). (Bagan et al, 2010) Among the late features are pain, swelling, non-healing ulcer, unexplained tooth mobility, weight loss, dysphagia and paraesthesia. (Bagan et al., 2010) Other features associated with oral cancer include oral malodour, bleeding at the site of the lesion and lymphadenopathy (Güneri Epstein, 2014)

METHODS OF DIAGNOSIS

1. Visual Oral Examination (VOE)

It is also called Comprehensive Oral Examination. It involves a thorough and methodical examination of the oral cavity under adequate illumination to detect any abnormality. Despite the emergence of various devices for oral cancer detection, a VOE is the most cost-effective method for population-based screening for oral cancer. However, it is subjective, and depends heavily on the experience of the clinician; it requires training and calibration. During VOE, particular attention should be paid to high-risk sites such as the floor of the mouth, lateral borders of the tongue and soft palate. (Bagan et al, 2010; Güneri & Epstein, 2014)

2. Vital staining

Vital staining techniques involve the use of dyes to stain human tissues in vivo, and the most commonly used dyes are toluidine blue and Lugol's iodine. Toluidine blue preferentially stains dysplastic or malignant cells because of increased DNA content. It has a high sensitivity of over 90%, but relatively low specificity (≈67%). (Güneri and Epstein, 2014; Chaurasia et al., 2021). Lugol's iodine on the other hand stains normal oral mucosa brownish, whereas dysplastic or malignant oral mucosa either picks up no stain or appears pale compared to the surrounding normal tissues. It has a sensitivity of ≈87% and a specificity of ≈84%. (Chaurasia et al., 2021) In an attempt to harness the sensitivity of toluidine blue and the specificity of Lugol's iodine, a combination of both dyes has been used. However, significant improvement in outcomes were not achieved. (Chaurasia et al., 2021)

3. Cytology

This involves the microscopic examination of disaggregated cells of the oral mucosa, for detection of morphological changes typical of dysplastic or malignant cells. The cells can be obtained through different means such as scraping, imprinting, aspiration or brushing. The Oral CDx brush is a minimally invasive brush biopsy technique that has become very popular for obtaining oral epithelial cells for cytology because it able to collect a complete transepithelial sample. (Güneri & Epstein, 2014) Cytology has a high degree of specificity for oral cancer (≈ 90%), and is particularly useful for screening high risk populations, but as a diagnostic tool, it is inferior to histology.

4. Light-based methods

a. Autofluorescence

Autofluorescence is a phenomenon which refers to when light of a particular wavelength interacts with cells, causing excitation and re-emission of light of different wavelengths. Human tissues contain naturally occurring fluorophores such as collagen and keratin, which exhibit autofluorescence (Su et al, 2021) VELScope® is a handheld device that emits blue light (400 nm and 460 nm wavelengths), and is able to screen for alterations in oral mucosal autofluorescence. (Chaurasia et al., 2021) Normal oral mucosa produces green autofluorescent light, while abnormal oral mucosal absorbs the light and appears dark. A wide range of sensitivity (22% to 74%) and specificity (8% to 96%) has been reported with this method. (Chaurasia et al., 2021)

b. Chemiluminesence

Chemiluminescence is the emission of light as the result of a chemical reaction. ViziLite® Blue oral examination kit is a handheld chemiluminescence-based device used as an adjunctive tool for visual examination of oral mucosal lesions. The kit consists of a retractor and a capsule containing some chemical products. When the capsule is bent, the chemical products react, producing a bluish-white light, which is used for examination of the oral mucosa. (Sambandham et al., 2013; Chaurasia et al., 2021) With this method, abnormal oral mucosa appears white, whereas normal oral mucosa appears light blue. This method has a relatively high sensitivity (77% - 90%) but very low specificity (27% - 30%). (Sambandham et al., 2013)

c. Multispectral Fluorescence- and Reflectance

Identafi® is probe-like device designed for multispectral screening of oral potentially malignant disorders and oral cancer. It uses three light sources: white light, violet light, and green-amber light which can be used sequentially during an oral mucosal examination. The white light provides an optimal view for a VOE of the oral mucosa, while the violet light excites endogenous fluorophores, enhancing the fluorescence of normal tissues; this results in a dark appearance when a suspicious oral lesion is present. The green-amber light excites haemoglobin molecules in the blood, which allows the visualization of diffuse or dilated vasculature through reflectance spectroscopy, and is used mainly to distinguish benign from malignant oral lesions, which are more likely to have abnormal vascular structures. (Chaurasia et al., 2021)

5. Artificial intelligence

Artificial intelligence (AI) refers to the ability for machines to mimic intelligent human behaviour. Machine learning (ML) on the other hand is a subset of AI in which computer systems are able to automatically learn from experience without explicit programming. (Rashidi et al., 2019) Machine learning refers to a set of tools for making inferences and predictions from data. Essentially, machine learning learns patterns from existing data and applies it to new data. In traditional ML, a model can be trained to learn a function by mapping certain input variables (e.g. risk factors for oral cancer) from the training data into an output (e.g. development of oral cancer). (Rashidi et al., 2019) Subsequently, the model is able to predict the development of oral cancer from the risk factors.

Deep Learning (DL) is a subset of ML that mimics the human brain's ability to process data and identify images and objects, and to process languages. (Iqbal et al., 2021) Deep learning models are different from traditional ML models; they are more suitable for large volumes of text and images, and require a lot more training data. From simple analysis of a clinical photograph, a DL model is able to categorize it into normal (no lesion), benign or malignant. (Tanriver et al., 2021) A two-stage deep learning model for oral cancer screening was proposed by Tanriver et al. which enabled automated detection and classification of various oral lesions. (Tanriver et al., 2021)

6. Histopathology (considerations for biopsy)

Biopsy of the representative tissues with subsequent histopathological examination is the gold standard for the diagnosis of oral cancer. (Chaurasia et al., 2021) Important questions to ask during the consideration for biopsy include when to biopsy, who should perform biopsy, what should be biopsied and where should be biopsied? Regarding the when, it is important to perform biopsy as soon as possible following detection of a clinically suspicious lesion. To limit professional delays, it is preferable for the Maxillofacial surgeon who will eventually treat the patient to perform the biopsy. It is important to biopsy any ulcer, red patch or white patch which cannot be diagnosed clinically, and fails to resolve after 2 weeks of conservative treatment, as well as all excised oral tissues and any periradicular swelling seen following a tooth extraction. In a study by Omoregie et al. two cases of Burkitt's lymphoma were diagnosed through examination of periradicular biopsies. (Omoregie et al., 2008) Preferred areas for biopsy include red areas, mixed red/white areas and nodular areas. It is important to avoid necrotic areas, because they are usually non-representative.

7. Saliva based cancer diagnostics (biomarkers)

Several biomarkers have been detected in the saliva of individuals with oral cancer, serving as non-invasive means of detecting oral cancer. Such biomarkers include interleukin-6 (IL-6), interleukin-8 (IL-8), S-100 protein, vascular endothelial growth factor (VEGF), p53 protein and matrix metalloproteinase 1 (MMP-1). (Cheng et al., 2014; Güneri & Epstein, 2014; Chaurasia et al., 2021) Biomarkers are often used as a panel, as no single biomarker can reliably be used in isolation to detect oral cancer.

BARRIERS TO EARLY DIAGNOSIS

Delay in diagnosis of oral cancer includes both patient-related factors (patient delay) and practitioner-related factors (professional delay). Patient delay refers to the interval between the first detection of a sign/symptom that may be

indicative of oral cancer and eventual presentation to a healthcare professional. (Gómez et al., 2010) Reasons for such delay include ignorance, fear, religious/cultural beliefs and poverty/lack of finance. Patient delay plays a greater role in diagnostic delay, (Thomas et al, 2020) as patients often delay seeking professional advice for periods ranging from 5 to 6 months or even more from when they first notice any oral symptom that could be linked to oral cancer. (Güneri & Epstein, 2014)
Professional delay on the other hand refers to the interval between the first examination by a healthcare professional and the final histological diagnosis of the condition. (Gómez et al, 2010) Reasons for this include low index of suspicion of some clinicians, inadequate biopsy specimen, long turnaround time for histopathology, delay in referral to the Maxillofacial Surgeon and lack of specialized equipment and/or personnel. (Güneri & Epstein, 2014)

REMEDIES TO LATE DIAGNOSIS OF ORAL CANCER

The overall diagnostic delay can be shortened through the following measures: identification and follow-up of high-risk individuals, oral health education of the public and primary healthcare workers on the early recognition of features that may be linked to oral cancer, improvement in the health-seeking behaviour individuals, prompt investigation and early referral to a specialist. (Agarwal et al, 2011; Güneri & Epstein, 2014) Other measures include improvement in availability and affordability of healthcare facilities, as well as an increase in the number of specialist healthcare personnel. (Agarwal et al., 2011)

CONCLUSION

Although oral cancer is largely preventable, the global incidence is still on the rise. The prognosis for oral cancer is poor when detected late, so emphasis should be on prevention and early diagnosis. Education of the public, improvement in health-seeking behaviour, improved availability and affordability of healthcare facilities and use of adjunctive screening methods will help in reducing incidence of the disease as well as the associated morbidity and mortality.

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Conflicts of interest
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