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Non-Invasive Methods for Early Diagnosis of Oral Cancer

Manoela Garcia Dias da Conceição, Ana Cláudia Figueiró and Vera Lucia Luiza

Abstract

Oral cancer is a public health problem because of its high morbidity and mortality, and when not treated in a timely manner, it is significantly mutilating, causing damage to the physical and psychological aspects of patients and directly interfering with their quality of life. Several factors influence the early diagnosis of this pathology, including lack of self-care related to oral health, especially among people with prolonged use of dental prosthesis; delayed perception of the lesion; delayed search for professional assistance since the lesion is noticed by the patient; lack of information about oral cancer, its risk and protective factors, and oral lesions that may be suggestive of cancer; lack of health promotion and prevention activities aimed at oral cancer; and lack of training in oral cancer among oral health professionals. These factors must be tackled to promote the timely diagnosis of this pathology. The use of reliable noninvasive diagnosis methods is also important because they can be easily made available in low resource settings, increasing the coverage of people who are under risk of developing oral cancer.

Keywords: oral health, prevention, primary health care, secondary health care, oral cancer

1. Introduction

Oral health is part of general health and is essential to people's well-being. Good oral health implies being free from chronic orofacial pain, oral and pharyngeal cancer, soft tissue changes in the mouth, congenital disabilities, and other issues affecting the craniofacial complex [1].

Oral cancer (OC) is considered a public health problem because of its high mortality and morbidity rates. This problem also affects most people with low sociocultural level and who are alcoholics and smokers. However, there are other associated risk factors: chewing tobacco, use of a dental prosthesis, infection with human papilloma virus (HPV) type 16, nutritional deficiency, age, gender, poor oral hygiene, excess body fat, and chewing betel nut, among others [2, 3].

Data published by the International Agency for Research on Cancer (IARC) regarding cancer cases in general reported in 2012 about 14.1 million new cases, 8.2 million deaths within 5 years of diagnosis, and 32.6 million people living with cancer in the world. Of these, approximately 57% of new cases, 65% of deaths, and 48% of cases diagnosed in the last 5 years are in developing countries [4].

In 2018, new data were released, indicating an increase in new cases of cancer, with 18.1 million new cases and 9.6 million deaths [5]. The significant increase of this disease is clear, indicating the need for new plans for prevention and early diagnosis.

Regarding oral cancer, the highest rates have been observed in populations of Melanesia, Central-South Asia, Eastern and Western Europe, Africa, and Central America. Oral cancer is the sixth most common in the world, and most cases occur in India and Southeast Asia, according to the estimates for 2012 [6]. A change was seen in 2018 when oral cancer ranked in the 11th position among the most common cancers in the world. This type of cancer is quite common in Brazil, which has the third highest incidence in the world, behind only India and former Czechoslovakia [5].

Oral cancer is a condition that negatively interferes with the general and oral health of the individual. These oral problems cause pain and infection, leading to psychological and physical distress. It is important to note that such dental conditions express social exclusion. In general, they are associated with poor education, low income, unemployment, and difficulty in accessing care services [7]. Thus oral cancer patients represent a group of people that should receive differentiated attention because, besides cancer itself, they are highly susceptible to other ills [2]. When this disease affects individuals, they may have to face consequences such as facial mutilation. Also, they may render them unable to work, with severe damage to their quality of life. The disease may sometimes be lethal, mainly because of late diagnosis.

This pathology causes essential changes in the daily lives of the affected people, interfering with their body image, body functioning, and psychological, social, and family structure. The disease mostly affects the population in their working phase of life, causes indirect damage to the country. Late diagnosis is directly associated with shorter survival. However, if diagnosed early, it has a good prognosis and an average 5-year survival rate of 77.3% in stages I and II, but of 32.2% in stages III and IV [2].

Morbidity and mortality rates are high, with diagnosis in advanced phases in 65–85% of the cases, reducing the likelihood of cure [2, 8–11]. For most of these patients, palliative care is the only option available to achieve a better quality of life and control symptoms.

Protective factors against this condition include general and specific measures. The adoption of healthy lifestyle habits, including adequate nutrition, physical exercise, and self-care, is part of the prevailing standards. In turn, specific practices include oral health care, routine inspection of the oral cavity, periodic dental evaluation, and cessation of smoking and alcoholism, and recent studies have shown the consumption green tea as a protective measure [12, 13].

Although oral cancer is easily detected, its diagnosis is late in most cases. It is possible to improve diagnosis through the use of health promotion and prevention measures and improved access to health services, to promote early diagnosis [7, 14, 15]. Diagnosis is followed by curative treatment, preventing mutilating and disabling sequelae.

The relevance of this disease and its early diagnosis should be considered for the possibility of curative treatment and promotion of the quality of life of patients. It is essential to know and recommend methods that act in favor of the early diagnosis of this pathology. It may mean identifying early malignant and even premalignant lesions, leading to the cure of these patients and rehabilitation to their social routine. It is equally important to act on factors that influence to late diagnosis of this pathology, through the planning of actions.

2. Factors related to late diagnosis of oral cancer

The problem of delayed diagnosis of OC is known worldwide, and each country or region has different strategies to address it. These factors are described in several studies [16, 17], showing that this is a global problem. Factors related to late diagnosis of OC concern the social determinants, health literacy, and characteristics of the health system:

1. Profile of the affected people concerning lifestyle habits: most people who develop OC were smokers and alcoholics and are in situations associated with other unhealthy lifestyles, such as poor diet and physical inactivity [2].

2. Lack of self-care in oral health: the most vulnerable populations, which are those with a low socioeconomic level, frequently have poor self-care due to their living conditions, especially in terms of oral health, besides other health problems. This problem directly interferes with their quality of life and interaction with peers. They also present a low search for health care, leading to the worsening of health problems and, in this case, late diagnosis of oral cancer [18].

3. Delayed perception of the lesion: due to poor self-care, most do not identify the presence of initial lesions in the oral cavity. Thus, injuries are only perceived when they cause discomfort, pain, bleeding, or other symptoms, and at that point, in most cases, the disease is already in an advanced stage [18].

4. Lack of information about oral cancer and its protective and risk factors: many campaigns for the dissemination of information on disease have been promoted, but specifically on oral cancer is still incipient. People asked to appear to not know about oral cancer, suspected lesions or risk, and protective factors, even patients who are undergoing treatment for this type of cancer [14, 19].

5. Lack of health promotion and prevention activities aimed at oral cancer: a few specific actions to promote and prevent this type of cancer are carried out. These actions are usually linked to other campaigns such as those focused on vaccination, smoking, and oral health in general [14].

6. Lack of training in oral cancer among oral health professionals and deficits in addressing this content in the curricula of undergraduate courses: oral health professionals are not routinely updated and trained on this content. Still, the approach during undergraduate training is deficient, producing professionals with little experience to approach patients with suspected lesions [14, 16].

7. Delayed search for professional assistance when the patient perceives the lesion: people usually notice the presence of the injury but do not seek a professional for confirmation. Often they refer to fear of confirming the diagnosis of the disease. This delay in seeking the diagnosis causes the lesion to continue growing, leading to late diagnosis [14].

8. Difficulties in accessing dental treatment: many people are unable to get adequate dental care due to the difficulty in accessing health services. In general, it is due to their vulnerable conditions or even because they do not seek health services [14].

Regarding oral cancer prevention and health promotion activities, it is essential to highlight the urgency of designing public policies for long-term health education actions. If education is not changed, concepts and habits will not change after short campaigns. That points out to the need for permanent education programs, since the best way to combat oral cancer is prevention, early diagnosis, and the attempt to eliminate risk factors. Health education through programs aimed at valuing periodic evaluations and the importance of examining the oral cavity are the significant weapons available to reduce the high incidence of oral cancer in the community [14].

The biopsy is undoubtedly the gold standard for the diagnosis of OC. However, there are several questions related to this method used in screening. It is an aggressive procedure, not readily accepted by people, especially when the lesion is asymptomatic and, even more so if it is proposed in oral health campaigns. The biopsy is limited by morbidity, once the procedure provokes another injury that may cause pain, bleeding, or other symptoms. Still, due to the resources required and the possibility of underdiagnosis, this method demands trained professionals to perform the procedure, trained pathologist, and facilities for the necessary reading of the exam. These characteristics mean a long time to receive the diagnosis, and patients experience discomfort caused by all the process [20].

Although the factors related to early detection of OC have different natures, it is noteworthy that, after all, the primary responsibility lies with the health system. For that, health service and program must organize its strategies according to the characteristics of the users.

Studies have been conducted to support measures aimed at solving the problem of late diagnosis, and the various approaches used to solve this problem are related to the factors abovementioned. In this text, we will address in particular the issue of noninvasive methods.

3. Prevention of oral cancer

Considering factors that interfere with the pathology diagnosis in question, the actions should be directed to them, to improve the care to the population.

Prevention and early diagnosis of oral cancer are critical. Equally important is the need for a differentiated look in this issue, given the characteristics of the affected population, the role of the dentist, the continuing training of oral health professionals, and the implementation of new strategies for early detection of this pathology [16, 21].

Actions related to the prevention of oral cancer and early diagnosis are foreseen within concepts widely worked in public health, which are health promotion and disease prevention. Health prevention requires firstly action based on knowledge of the natural history of the disease to prevent its progress [22]. Primary prevention is defined as a set of interventions to minimize the risk of specific ailments, reducing incidence and prevalence rates in the population and focusing on keeping individuals free from diseases.

Health promotion, on the other hand, is broader, as it refers to measures that act in the health disease process. Here, the intention is to modify the lifestyle and living conditions of the population, thus not working on a specific disease. Health promotion depends on the individuals, the community, and the sectors of society, health professionals, and oral health professionals [23].

Preventive measures may have a collective or individual approach. The collective approach includes interventions focused on health promotion. It means educational actions, periodic examinations of the most vulnerable people to the development of

oral cancer, integration of the oral health team into smoking control programs, and other actions related to control of oral cancer. Besides that is a systematic provision of information on reference sites to the population about the diagnostic examination of oral cancer. In turn, the individual approach includes early diagnosis, treatment, and rehabilitation [17, 18].

Some primary intervention and prevention measures would be ideal for reducing cancer, such as combating lifestyle, environmental, and occupational factors and investigating the genetic factors associated with some specific types of cancer [14]. Population screening is indicated as an important preventive measure. This process can favor the diagnosis of suspicious lesions, which are to be referred for differential diagnosis, making it possible to implement early intervention and increase the chance of cure [14, 24]. Studies indicate the relevance of the screening of this pathology in risk populations, such as smokers and alcoholics. And it is even more relevant given the delay in diagnosis. Although evidence from the use of the visual examination of the mouth on mortality rates is weak by OC, some authors

Risk factors for oral cancer	Primary and secondary prevention methods
Unhealthy lifestyle habits: tobacco and alcohol use, physical inactivity, nutritional deficiency, tobacco chewing, betel nut chewing, poor oral hygiene	Active performance of the dentist in care and prevention actions
Population characteristics: low sociocultural level, age, and gender	Training of the oral health team on oral cancer
HPV infection	Implementation of new early detection strategies, according to the population served
Prolonged use of dental prosthesis, especially in the absence of routine monitoring and evaluation by a professional	Individual and collective educational actions on healthy living habits
Lack of information about the disease, its risk factors and protection	Routine screening for early detection of cancer, especially among the most vulnerable to oral cancer
Lack of information to the population about health services and their flow when a suspected injury is diagnosed	Integration of the oral health team with smoking control programs and other actions related to oral cancer control
Lack of training of professionals working in care	Systematic information to the population on reference sites for oral cancer diagnostic examination
Lack of specific campaigns and information about oral cancer, its risk factors and protection	Fight against lifestyle, environmental, and occupational factors that may be related to oral cancer
	Investigation of genetic factors associated with some specific types of cancer for the risk group
	Tracking of this pathology in at-risk populations by the health team
	Offering opportunities for evaluation of oral lesions (active search—through home visits or specific campaigns)
	Follow-up of suspected cases, creating a reference service if necessary and establishing partnerships between universities and other organizations for prevention, diagnosis, treatment, and recovery
	Training of professionals working in the front line of health care

Table 1.
Summary of risk factors related to oral cancer and primary and secondary prevention methods.

suggest proceeding to the screening on individuals who are exposed to risk factors. For these people, it may result in an increased positive predictive factor [7].

The approach to OC should involve prevention and control measures, including routine screening for early detection; offer of opportunities for evaluation of oral lesions (active search—through home visits or specific campaigns); follow-up of suspected cases, creating a referral service if necessary; and establishing partnerships between universities and other organizations for prevention, diagnosis, treatment, and recovery [18].

Actions with this objective can be organized as primary prevention. They include activities geared at disseminating information to the population, intending to change unhealthy lifestyle habits to healthy ones and to reduce the prevalence and incidence rates. At this level, the emphasis is placed on drinking, smoking, diet, and exposure to sun and human papillomavirus (HPV) infection.

Secondary prevention, in turn, occurs through the identification of precancerous lesions. For correct identification, it is essential to train health-care professionals with an emphasis on assessing potentially malignant cell lesions/disorders (PMD) (DPM) [17].

Below in **Table 1** is a summary of the risk factors and prevention methods.

4. Noninvasive methods for diagnosis of OC

Easy-to-handle, noninvasive diagnostic methods are useful for identifying precancerous lesions. The following noninvasive methods are cited: toluidine blue testing, exfoliative cytology, autofluorescence, contact endoscopy, and in vivo microscopy. However, there is no scientific evidence that these methods are more effective than oral inspection and palpation. Thus, more extensive studies are needed to justify the widespread use of these methods in the population. However, studies have shown that these methods can be useful if used in people with risk factors and non-healing lesions, favoring a faster diagnosis [20, 25, 26].

The following noninvasive diagnostic methods should be used according to the possibilities and conditions of the context.

4.1 Toluidine blue test

Toluidine blue is a basic thiazine metachromatic dye that selectively marks acidic groups of tissue components (carboxylic radicals, sulfates, and phosphates), showing an affinity for nuclear DNA and cytoplasmic RNA, which fix the dye, becoming richly stained. The intensity of toluidine blue staining depends on the degree of involvement of the epithelial surface. In benign lesions, there is a faint coloration; in dysplasia and epithelial lesions and carcinomas, the coloration is more intense.

The application maneuver consists of drying and isolating the region to be examined from salivary contamination by grasping the site with the fingers and using gauze. Employing a flexible cotton swab, 1% acetic acid (acid solution) is applied to clean the lesion surface, remove the glycoprotein barrier of cells, and promote slight dehydration of the mucosa. After 1 minute, the AT dye is applied with the other side of the cotton swab, and after 1 minute, the excess is cleaned with 1% acetic acid again and washed with plenty of water.

The result is intended to highlight intensely stained areas compatible with areas of tissue degeneration. Indications: detection of epithelial dysplasias, in situ or early invasive carcinomas, delimitation of neoplastic epithelium margins, assessment of tumor recurrence after surgical or radiotherapy treatment, delimitation

of areas of cancer action, screening of oral lesions in population groups exposed to risk factors for oral cancer, and in intraoperative actions for marginal control of carcinomas.

It has the advantages of being painless, low-cost, and easy to apply, giving fast results, and having high sensitivity. As for disadvantages, it may generate false-positive or false-negative results and be of low and little specificity [10, 27].

4.2 Exfoliative cytology

It can be defined as the morphological and morphometric study of desquamated cells of the mucosa, mainly suprabasal cells, through optical microscopy. It consists in the examination of cells from various parts of the body to determine the cause or nature of the disease that affects them.

There are reports of numerous methods for collection of these cells in the literature. Conventional exfoliative cytology and liquid-based exfoliative cytology are two of the most disseminated among them.

Collecting the material in exfoliative cytology involves scraping the surface of the lesion with a spatula or brush, which is then smeared over the glass slide, and the material is fixed to the slide using 95% alcohol or 1:1 alcohol/ether solution.

Exfoliation cytology in liquid media has been developed in recent years as a method that could replace the conventional exfoliative cytology proposed by Papanicolaou. Collection by this method is done using a brushing device with soft bristles arranged in a conical shape, which is then dipped in a methanol-based preservative liquid contained in a hermetically sealed tube. Such liquid has the function of preserving the cellular structure, the proteins, and principally the genetic material. The liquid undergoes a centrifugation or homogenization process, which helps to shrink some artifacts, and it is then filtered. The residual material in the filters is put in blades by contact imprinting. Debris, red blood cells, and mucus pass through the filter pores, which retain the epithelial cells to be analyzed.

It has the advantages of being painless, harmless, noninvasive, and low-cost. As for disadvantages, it does not have the same efficacy as biopsy concerning identifying the type of lesion, but it is beneficial when the biopsy is not possible [20, 28, 29].

4.3 Fluorescence/autofluorescence

Optical fluorescence can be used as an aid to oral clinical examination. It allows, by autofluorescence, the detection of numerous changes in the oral cavity that could go unnoticed by the dentist or even be difficult to perceive with the visual method alone.

The oral fluorescence system allows the observation of changes in dental hard tissues such as stains, dental plaque and calculus, incipient lesions, and marginal infiltrations and facilitates the differentiation between restorative materials such as composite resin and ceramic.

In soft tissues, it is possible to detect potentially malignant lesions and tumoral lesions. Therefore, the optical fluorescence system allows the simple, noninvasive, and real-time diagnosis and identification of structures and alterations in the oral cavity, revealing lesions that would not be easily detected with conventional illumination.

As advantages, this method is highly sensitive to cancer and dysplasia, allows the evaluation of large areas of the oral mucosa during a consultation, and is noninvasive and painless. However, it has the disadvantage of false-positive results [20].

4.4 Contact endoscopy

It is also known as contact microstomatoscopy. It consists of the contact of the endoscope lens with the mucosa, the vermilion, and or the lesion.

It has the advantages of being painless and providing a fast diagnosis. However, a study by showed that the difficulties encountered about the device and the anatomical structures examined (lip and oral cavity) were related to the contact of the lens surface, fine tremors, and the sliding of the device; these difficulties varied according to topography. The quality depended on the site of the lesion, the extent of the ulceration, the volume of crusts, prior cleaning of the site, patient collaboration, the presence of more or less saliva, the mobility of the examined structure, and the support for the device [28, 30].

4.5 In vivo microscopy

High-resolution microendoscopy, optical coherence tomography, confocal reflectance microscopy, and multiphoton imaging are considered in this classification. These methods allow practitioners to see many of the same microscopic features used for histopathological evaluation at the consultation.

Each technology measures different optical properties of the tissue and offers various features in parameters such as image depth, resolution, visual field, and acquisition time. Their development is at an early stage. We cite Raman spectroscopy as a promising technique for cancer diagnosis. This device is an analytical noninvasive technique that provides information about the molecular structure of the investigated sample, considering that the molecular structures of proteins and lipids differ between normal and neoplastic tissues.

The advantage of these technologies is their accuracy, but the high cost of acquisition is a significant disadvantage [20, 31].

4.6 Tumor biomarkers

Tumor biomarkers are substances found in blood, urine, or other body fluids and tissues that may be in increased amounts when a particular type of cancer is present. These biomarkers are used for diagnostic elucidation through serology and histological methods. They are cellular, structural, and biochemical components that can be quantitatively measured by biochemical, immunological, and molecular methods in body fluids and tissues associated with neoplasms and possibly the organs where cancer originates.

At present, no marker is used for cancer detection in the general population, only for people who are in the risk group for certain types of cancer. In this case, biomarkers can help to diagnose the disease in early stages.

Research on the diagnosis of saliva using nanotechnology and molecular technologies to detect oral squamous cell carcinoma (OSCC) is currently being expanded. Collecting saliva for this assessment is a secure, noninvasive method, which is considered advantageous.

Diagnosing saliva using nanotechnology and molecular technologies to detect OSCC has become an attractive field of study. New cancer-related proteins have been reported, as well as potent biomarkers for early diagnosis, further facilitating the application of quantification in proteomics for carcinogenesis research. Identifying transcripts and pathways that change at early stages of carcinogenesis provides potentially useful information for early diagnosis and prevention strategies.

At the beginning of the research on this method, the hope was that all cancers could be detected at an early stage, preventing the death of millions of people. But only a few markers can detect cancer at an early stage. The disadvantages of this method are most people have a small amount of these markers that prevents detection, the levels of these markers tend to increase when the disease progresses, some cancer patients may never have high levels of markers, and even in the presence of elevated levels, they do not always indicate cancer, as they may be related to other disorders [6, 32–36].

4.7 Oral inspection and palpation

The main areas examined for oral cancer are the face, neck, lips, nostrils, and oral cavity. Before the screening, the patient should remove all removable dental appliances and devices to leave the entire area exposed. The patient must be seated or lying down, and the dentist must look for signs of asymmetry, edema, swelling, staining, ulceration, or other abnormalities.

To examine the inside of the mouth, the practitioner will use good lighting and a mirror to see clearly; he will also use a tongue depressor to immobilize the organ and look at the back of the mouth. After or during the visual examination, the dentist will palpate the head, face, around the jaw, under the chin, and the oral cavity. The aim is to detect unusual lumps or masses. Another sign of a potential problem is immobility in some regularly moving tissue.

The advantages are the fast, painless, low-cost characteristics of the method, and the disadvantage is that it relies heavily on the examiner's skills and knowledge. Conventional oral examination (COE) alone is insufficient for risk stratification. COE is generally useful for identifying lesions but not for subsequent clinical follow-up for treatment planning [20].

Despite the importance of the methods described above as adjuvants in the process of diagnosis of suspected lesions, the biopsy is considered the gold standard for definitive diagnosis [20].

All of these methods have their advantages and disadvantages and can be used in care to facilitate diagnosis. These noninvasive alternatives are not much disseminated in health services, and visual inspection under white light and palpation by a physician or dentist remain as the gold standard for screening of oral cancer. This procedure, however, has the limitation of being dependent on the examiner's experience; this limitation underlies the development of more objective diagnostic techniques.

Despite the scarcity of evidence about the abovementioned noninvasive methods as the diagnosis of a lesion front line, they can be useful in several situations. For instance, in cases where the biopsy is not a reasonable procedure, either for cost or complexity, most of these methods can make a difference.

They used to be inexpensive, can be performed by less specialized professionals, are generally handled with lighter technology, and are more easily implemented in less resourceful regions and within primary health care [25, 26]. In these situations, the aim is to replace noninvasive techniques where a biopsy cannot be performed promptly. More, it can facilitate the screening of lesions in apparently healthy people, with or without risk factors for cancer, since it is a recommended noninvasive method that makes it possible to differentiate malignant to benign lesions. Despite the several possibilities of diagnostic methods, the rates still indicate that patients are diagnosed in advanced stages of cancer [25, 26, 37].

These adjuvant diagnostic methods may help dentists better evaluate lesions suggestive of oral cancer before a definitive biopsy. The existing adjuvants such as

Method	Indication	Advantage	Disadvantage
Toluidine blue test	Diagnosis and surgical approach to various mucosal tumors	Painless, low-cost, easy application, fast result, and high sensitivity	It can generate false-positive or false-negative results, being of low specificity
Exfoliative cytology	Initial assessment of incipient lesions and follow-up of areas that underwent previous surgical resection	Painless, harmless, noninvasive, inexpensive	It does not have the same efficacy as biopsy in the identification of the type of lesion; however it is very useful when biopsy is not possible. It can generate false-positive or false-negative results
Fluorescence/autofluorescence	Adjuvant method in oral clinical examination for detection of cellular disorders	High sensitivity for cancer and dysplasia, ability to evaluate large areas of the oral mucosa at the moment of consultation, noninvasive, painless	It can generate false-positive results
Contact endoscopy	A colposcope with optical magnification of up to 40 times is applied to help diagnose oral cavity lesions	Painless, fast diagnosis	Difficulties in relation to the device and the anatomical structures examined (lip and oral cavity) related to the contact of the lens surface, fine tremors, and slippage of the device
In vivo microscopy	Histopathological evaluation of suspected lesions at the moment of consultation	High precision	High cost
Tumor biomarkers	Diagnostic elucidation, tumor recurrence evaluation, or follow-up of treatment progress	Early detection, noninvasive	It can generate false-positive or false-negative results

Method	Indication	Advantage	Disadvantage
Oral inspection and palpation	Identification of lesions, monitoring of oral health of the individual, screening of suspicious lesions for oral cancer	Fast, painless, and low-cost	It depends on the examiner's skill and knowledge

Table 2.
Noninvasive methods for diagnosis of oral cancer.

toluidine blue, acetowhitening, and autofluorescence imaging are not much specific and, therefore, generally not recommended. Recently, new in vivo microscopy technologies such as high-resolution microendoscopy, optical coherence tomography, reflectance confocal microscopy, and multiphoton imaging have shown to offer promising improvements and more accurate diagnosis of these lesions and are not invasive procedures. The advantages of these technologies are that they allow the visualization of the microscopic characteristics used for histopathological evaluation at the moment of consultation, making the diagnosis faster, besides being painful or uncomfortable to patients [20].

Other measures discussed are those related to the reorganization of health services, screening of risk groups, and awareness campaigns. These measures are used in many countries around the world, but the problem of late diagnosis is still a worldwide reality [38, 39].

New strategies to approach the population and to identify suspicious lesions are paramount in the dissemination of information and for the increase of early diagnosed cases. The cooperation of primary health-care teams and not only of oral health professionals is essential for the fight against late diagnosis. Because other sectors of the health area often assist the population and can identify the risk, and even suspicious lesions, they also should be able to refer patients to the oral health sector. Thus, with all professionals working together in primary health care, identifying risk factors and suspicious lesions, and referring to the responsible sector, this collaborative work may bring a great positive gain for the population [14, 38].

Below in a **Table 2** is a summary of the methods discussed above.

4.8 Considerations

Considering the real problem of oral cancer worldwide, actions aimed at reducing the negative impact on society should be carried out with planning to achieve excellence of care to the population.

Some factors lead to late diagnosis of oral cancer. Thus, such elements must be identified in each population so that health professionals can act to interfere with these factors, leading to better care for the community. Knowing population profile to be assisted is required, as much to identify factors that interfere with the diagnosis of the pathology as in the action planning.

Although the biopsy is considered as the gold standard for definitive diagnosis, there are some constraints for your full application. This method is invasive and expensive, the results may take some days to be disclosed, and it requires specialized training, thus limiting its use for screening. Therefore, noninvasive methods are valuable, becoming more suitable in specific contexts.

Nomenclature

OC	oral cancer
HPV	human papilloma virus
IARC	International Agency for Research on Cancer
MPD	malignant cell lesions/disorders
COE	conventional oral examination

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