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Review

Late stage diagnosis of oral cancer: Components and possible solutions

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SUMMARY

Stage of disease at the diagnosis of oral cancer is thought to be a significant factor in prognosis and outcome (International Agency for Research on Cancer/World Health Organization, 2014). Unfortunately, we continue to diagnose almost 2/3 of these cancers at advanced stages of disease despite the ongoing research for devices/methods to aid the clinicians in detection and accurate oral mucosal lesion diagnosis. This paper explores both the nature of oral cancer and the adjuncts available for detection, and presents the current issues in diagnostic delays of oral cancer detection.

Introduction

The International Agency for Research on Cancer and World Health Organization reported that 32.6 million people are living with cancer (within 5 years of diagnosis) worldwide, and over 14 million new cases of cancer and 8 million deaths due to cancer were observed in 2012 [1]. Approximately half of these were recorded in the less developed countries; however the regional variability in terms of mortality were 15% higher in more developed regions. These figures continue to alert the health-service planning officials, and require proper analyses of the data in order to provide appropriate measures to reduce these rates over time.

In the oral cavity, the most frequent malignancy is squamous cell carcinoma (SCC) which constitutes more than 90% of the malignancies [1–3]. SCC is considered a cancer with a poor prognosis, since the 5 year survival rate is reported as 50–63% [3–5].

Tobacco use and alcohol consumption are regarded as the primary risk factors for oral squamous cell carcinoma (OSCC) [2,3,6–10]. Even though Human papilloma virus (HPV) is now recognized as an independent risk factor particularly in oropharyngeal cancer [3,7,9], its role in oral cancer is still unclear [11]. Immunosuppression and family history represent underlying risk factors [12]. Also betel use, other chemicals, radiation, environmental and genetic factors are reported as relevant factors in oral carcinogenesis [8].

An additional at risk group includes immunosuppressed patients, whose tissue repair and immuno-surveillance may be decreased, and chemokine and cytokine-mediated oxidative DNA damage, increased cell turnover, and receptor up- and down-regulation have occurred [13]. Also, recipient homozygosity for HLA-DR and mismatching of the shared public epitope (67F–69T–70N–71T motif) are mentioned among the factors that contribute to cancer in immunosuppressed patients [14]. The clinical presentation of OSCC in these patients may be as erythematous and ulcerative lesions that may resemble cancer therapy induced mucositis [13].

Since OSCC is mostly observed on the lateral borders of the tongue, the floor of mouth, buccal mucosa, gingiva and soft palate [15,16], these regions should receive priority during an oral/dental exam. Clinically, patients may present with red/white or mixed lesions, white plaques, velvety red patches, ulcer with indurated raised margin, and exophytic or verrucous growth [3,15]. However, these lesions typically produce no prominent signs and discomfort until they progress. Some lesions may progress to a mucosal growth (mass) and ulceration; the patients may have lymph node involvement, discomfort, malodor, difficulty speaking, chewing and swallowing, and bleeding at the site of the lesion [3,4,15,16]. Additionally, OSCC lesions may arise without detectable pioneer lesions, and if they do, these preliminary lesions may look clinically innocuous and can be assumed benign in many cases.

Thus, thorough examination of the head and neck and soft and hard tissues within the oral cavity becomes important for detection of OSCC [17]. Examination must include complete head and

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neck examination, with detailed evaluation of cervical lymph nodes for location, size, mobility, texture and tenderness [17].

Even though oral cancers may be preceded by potentially detectable mucosal lesions [18–21], the utility of clinical oral examination (COE) for the detection of these potentially malignant disorders (PMDs) is not highly effective [18,22,23]. However, early detection of an oral mucosal lesion will facilitate diagnosis at early stage; a key step leading to necessary treatment [24–26], better treatment outcomes and lower cost of care [25,27,28], and decreased morbidity and mortality [24,27,29]. Early cancers (stage I and stage II) are highly curable (nearly 90% of people survive two years) using single modality therapy (surgery or radiation therapy) with less morbidity than advanced cancers (stage III and stage IV,) who have approximately a 45% survival rate for two years when treated using a combination of surgery, radiation therapy and chemotherapy [27,30] and with increased morbitity and increased cost of care.

Devices to assist in detection and promote diagnostic procedures include toluidine blue dye, exfoliative cytologic techniques, salivary diagnostics and optical imaging systems.

Toluidine blue staining

Toluidine blue (also known as tolonium chloride), has been used for more than 40 years to aid in detection and biopsy site selection of PMDs and to assess margins of SCC of the cervical and the oral mucosa [31,32]. When applied topically either as a rinse or by a swab, this metachromatic vital dye stains the tissues with rapid cell division (including in inflammatory, regenerative and neoplastic epithelial tissues and exposed connective tissue) and epithelial cells that harbor atypical DNA changes. Its binding has been associated with loss of tumor suppressor gene (TSG) loci on specific chromosomes that predict progression to cancer [33]. False positive results are primarily associated with inflammatory lesions and healing ulcers which also have high cellular metabolic rate. Thus, as is the case with all detection and diagnostic adjuncts and procedures, operator experience plays an important role with toluidine blue. Since inflammatory/ulcerative lesions may retain stain, two week follow up is suggested when possible in order to allow inflammatory lesions to resolve and to reduce a false positive interpretation. This is true for all clinical aids and adjuncts where differentiation from inflammatory from dysplastic and neoplastic changes represent a significant challenge for the technology employed. Professional training and experience affect the results of testing and therefore the utility in clinical use [34]. Toluidine blue is 100% sensitive for oral malignancy, and its addition to oral examination may result in reduction of over half of the false positive biopsies and alert the clinician to refer the patient to experienced providers for definitive diagnosis and treatment [7]. Toluidine blue has been recommended for use in high risk populations by experienced providers, but recommendations for use in other settings has not been defined [35–38].

Brush cytology

Dental practitioners may also use exfoliative cell collections in clinical settings to gather data for next steps in diagnosis. Brush cytology allows collection to the full thickness of mucosal epithelial tissue in order to examine the morphology of disaggregated cells under a light microscope [39]. Even though the sensitivity and specificity of cytology have been interrogated [38], being a minimally-invasive and well-tolerated method, its use has been advocated in clinical practice for patients where scalpel biopsy may not be possible, and for follow up of mucosal lesions with prior definitive diagnosis [2,38,40,41]. However, definitive diagnosis continues to require surgical tissue biopsy.

Optical diagnostics

Optical systems have been introduced to aid clinicians in oral mucosal lesion detection and to facilitate steps for diagnosis. The working principle of these systems is primarily based on the presence of abnormal metabolic or structural changes in optical properties of the tissues that occurs during the development of oral neoplasia. Fluorescent imaging is based on fluorophore concentrations, fluorescent collagen cross-links, tissue scattering characteristics, hemoglobin absorption properties, and tissue thickness [42–46]. Thus, when exposed to various forms of light or energy, mucosal tissues reveal different absorbance, reflectance and fluorescent profiles that may assist in detection of dysplastic/neoplastic tissue [47,48]. Various devices that utilize chemiluminescence [49–52], autofluorescence [42,46,48,51,53–58] and multispectral imaging [59,60] have been introduced in order to assist detection and determination to biopsy to facilitate diagnosis of PMD and OSCC with variable results. In general, the findings on imaging are impacted by the risk population involved and provider experience. As with other adjuncts, guidelines do not exist in general practitioner and "screening" settings.

Salivary biomarkers

Cancer biomarker detection coupled with exfoliative cytology and saliva biomarkers may provide non-invasive methods to detect PMD and OSCC. Biomarker 8-OHdG [61] salivary interleukin-6 (IL-6) [62–64], interleukin-8 (IL-8) [62–65], SAT (62,65), M2BP and S100P [62], vascular endothelial growth factor (VEGF) [63], miR-137 promoter methylation [66] were investigated in saliva of the patients with malignancy. Also, p53 protein immunoreactivity and angiogenesis [67,68] and MMP-1 SNP, rs5854 in biopsy specimens [69] have been examined to assess the malignant potential. No single molecular change has emerged and a panel of molecular measures for detection, diagnosis and predicting response to treatment and expecting outcomes of treatment are expected.

Delay in diagnosis and therapy

The potential of delay in diagnosis and delay in cancer therapy and impact upon cancer outcome is poorly defined, although the goal of "early detection and diagnosis of PMD and OSCC" continues. Still, we continue to identify OSCC at advanced stages with approximately two thirds of SCC diagnosed at stage III and IV.

It may be generally believed that patients with a short diagnostic delay have a preferable prognosis than those with a long diagnostic delay [70,71]. Even though the definition and the duration of "delay" is variable [1,74] and complex in nature [29] (Fig. 1). Diagnostic delay is commonly categorized as "patient delay" which is the period between the first detection of a sign/symptom and looking for health care for that [29,72–74]; and "professional delay" which is the duration from the first examination by a health care provider to the final histological diagnosis of the condition [24,29,72,73,75].

This process may also be explained in four steps: the onset of symptoms or signs to a visit to a health professional; from the initial visit to the patient referral; from receipt of the referral; and from the visit to the determination of definitive diagnosis [76]. The overall diagnostic delay would include this whole period and would be the result of the behaviors of both the patients and the professionals [29,75,77]. The final step is the duration from diagnosis to the initiation of the treatment [77–79].

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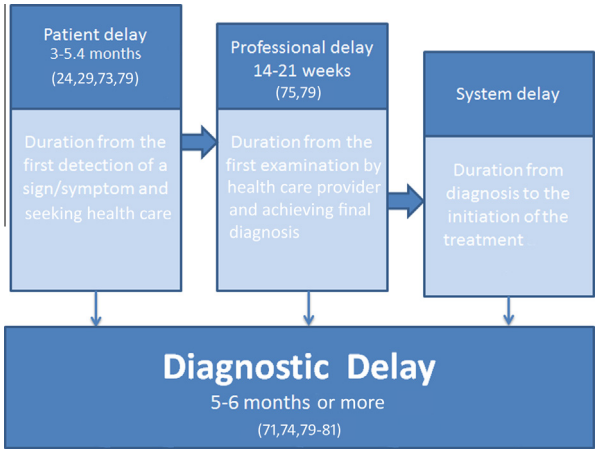

Fig. 1.

Patient delay

The diagnostic delay has been reported as five to six months, although this is highly variable [7,74,75,79–81]. Variability may be due to differences in tumor biology, and behavior, that may present as fluctuating tumor growth/progression time between patients and at different times in the tumor history. It is reported that patient delay constituted about 1.6–5.4 months of time [29,75,76,79,82].

Factors such as age, gender, socioeconomic status of the patients have been investigated in order to assess potential impact upon delay, with contradictory findings [21,29,76,82–88]. Patients who took traditional herbal medication before seeking professional consultation had a significant delay in diagnosis of OSCC [82,85]. Also worry, fear, denial and perception of social responsibilities have been attributed as the affective factors which may be associated with patient delay [29,82]. At the time of having symptoms, 13% of the patients thought they were caused by a potentially serious condition [85] while half of these patients thought it would get better by itself [71,84]. On the other hand, patients who had knowledge of oral cancer or who thought their lesion could be cancer were more likely to visit a health care provider [82].

Professional delay

Although the literature defines the onset of professional delay as the time from the patient's "initial presentation to a health care provider", the end points of this duration differ including time to referral to specialist, time to biopsy, or time to treatment [24]. Considering the recent trends in oral cancer epidemiology, dental practitioners have a higher probability of encountering patients with OSCC, even though only a proportion of OSCC patients consult with dentists [83], reflecting the patients' thought that "dentists are for teeth and gums" [83], which may cause delayed diagnosis. Dentists may also delay the process by providing limited oral examination and not identifying suspicious lesions in the presence of minimal signs or symptoms [76,77,83].

Diagnosis of an oral mucosal lesion requires identification of the potential abnormality, consideration of the finding that may represent significant pathology, that may lead to decision for tissue sampling, and accurate sampling of the most suspicious site. The adjuncts mentioned above may assist the clinician in this procedure. The biopsy tissue must be handled carefully during the biopsy procedure and processed in a manner such that minimal cell degeneration can occur, in order to provide a potentially diagnostic specimen to support an accurate diagnosis [89]. The pathologists' interpretation of the tissue submitted is also in itself a subjective step which is prone to inter- and intra-rater variability, and is based upon the skill and experience of the pathologist [90,91]. Finally, the histological and clinical findings must be evaluated for confirmation, and if congruous, diagnosis may be confirmed; if incongruous, repeating the test, using other tests, possibly obtaining additional consultation and patient follow up are needed.

Before initiating treatment for cancer, time is required for biopsy, additional tests and imaging, histological examination to reach to final diagnosis, tumor board review, treatment planning, and scheduling [24]. The cut-off points at which the delays significantly worsen the prognosis have been estimated at 3 months for patient delay and 6 months for professional delay [73]. Others have reported professional delay to vary between 5 and 21 weeks [29,75,78].

Oral cancer patients may present to a health care provider when sufficient symptoms or signs develop in the oral and maxillofacial region, or an abnormality may be identified upon routine clinic visit [74,76,82]. The primary care provider or referred provider may determine the need for biopsy which can then lead to diagnosis. The primary care provider should include a history of risk factors and potential signs and symptoms, followed by extraoral and intraoral examination in routine daily practice [24,68,80,92] (Table 1). However, dental and medical practitioners may not easily discriminate malignant lesions due to the low incidence of oral malignancies among general population, and the nonspecific appearance and potentially insidious nature of the lesions [68,71], especially in young and low risk patients [71,75]. In such instances, they should refer the patients in any case of suspicion [80,92] to reduce the delay in diagnosis [71,76]. Additionally, after evaluating the patients' concerns and conditions, it is the responsibility of the referring clinician to determine whether the patient needs urgent referral [10,70,75,80].

Approximately 18% of dental practitioners preferred to recommend antibiotic therapy, whereas 13% thought that if any further investigation or treatment was necessary, then referral to a specialist is indicated [75]. This points to the key importance of recognition of abnormality; as without this, no further action would be taken.

System delay

It should be recognized that the term "patient delay" may not be solely the result of the patients' actions, but "system factors" such as accessibility, availability, and cost may be responsible as well [29,70,72,81,86]. The scheduling delay may be the result of the barriers in the health care system, resource availability and broad issues of health care economics [70]. Problems with access to healthcare professionals [29,84,86], and the lack of availability of specific treatment [70] were seen as barriers to seeking help. In India and developing countries, it is estimated that only 40% of the patients with advanced oral cancer had access to primary health care services [86]. Barriers in national health care systems vary, but should be thoughtfully addressed to improve access to diagnostic and treatment services.

The oral cavity has a complex anatomy and represents a difficult area for self examination when compared to that of breast/skin examination. However, patient delay may be reduced by recognition of symptoms and signs (early clinical manifestations) and by educational interventions, especially in the risk groups for oral cancer [72,74,79]. Engagement of media (internet, television advertisements and programs, radio, newspaper and magazines, posters, leaflets, electronic communications) for raising oral cancer awareness in the society has been suggested [72,74,83,84]. Even though its' impact is still questioned [29], educational means to inform the people within high risk groups about SCC is advocated with the goal of potentially reducing patient delay [87]. Additionally, developing appropriate initiatives to increase knowledge among dental and medical practitioners both at undergraduate

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Table 1
The components of the recommended clinical examination for oral cancer [68].

Extraoral examination		Perioral and intraoral examination	
Visual inspection (face, head and neck)	Manual palpation	Visual inspection and manual palpation	Visual inspection for color, texture, surface anomaly
Asymmetry	Lymph nodes (periauricular, postauricular, submandibular, anterior–posterior deep cervical)	Lips	Palatine tonsils
Swelling	Neck	Labial mucosa and vestibule	Posterior pharyngeal wall
Discoloration		Buccal mucosa, sulcus, internal commisures	
Ulceration		Gingiva and alveolar ridge	
Skin changes (crusts, fissuring, growth)		Anterior tongue (dorsum, lateral, ventral)	
		Base of tongue	
		Floor of the mouth	
		Hard and soft palate	
		Retromolar trigone area	

and professional level by continuing education is needed to reduce professional delay [27,71,72,83]. Systems to promote expert referral should be developed, and be known in the health care community [72,77]. Promotion of access to expertise in order to achieve proper diagnosis and therapy is needed, particularly for financially challenged people [83]. Expert resources should be available without delay to support steps to achieve diagnosis, staging, and management [80]. When referral is considered, learning how to access to the appropriate expertise in the community would help to facilitate diagnosis and management [93]. Dental professionals should seek every opportunity to enhance their knowledge and clinical practice skills by attending to postgraduate courses, using adjunct methods to improve the detection and diagnostic accuracy, and to consult with the experts with appropriate training and clinical skills.

In conclusion, the issues related to OSCC are of high importance due to the changing epidemiology and the increasing numbers of cases seen, including the patients with no history of tobacco or alcohol abuse and/or the previous identified risk factors, and those with immunosuppression. Precursor lesions (PMDs) either may have innocuous appearance or may be asymptomatic or minimally symptomatic, but if the abnormality is not appreciated, no next steps in diagnosis can be made. Detection of abnormality is clearly critical in patient and provider evaluation: the key challenge is differentiating PMD and OSCC from variations of normal and from benign and inflammatory lesions. Unfortunately, even though current adjuncts provide some additional information, they are challenged to identify/differentiate PMDs and OSCC from inflammatory analogues. Definitive diagnosis depends on diagnostic procedures such as detection of tissue change, decision to biopsy, biopsy site selection, quality of the tissue submitted, laboratory procedure and pathologist's skill and interpretation. Consequently, each step in patient presentation and professional decision making may be responsible for delay, and the often asymptomatic or nonspecific findings also increase the risk in delay.

All educational methods to improve the knowledge of the clinicians and to raise public awareness with respect to OSCC should be employed. Additionally, system barriers shall be meticulously analyzed and appropriate solutions shall be discussed within related officials in order to find ways to decrease the delays in OSCC diagnosis and to be able to detect these lesions in earlier stages. Definitive diagnosis is currently based on interpretation of histologic appearance, although special stains are increasingly influencing the diagnosis. Future molecular testing is expected to allow pathologic diagnosis with less reliance on interpretation of histologic criteria and findings may guide treatment. However the first step in OSCC diagnosis depends on recognition of potential abnormality and steps that will lead to diagnosis.

Conflict of interest

The authors have no conflict of interest.

References

[1] International Agency for Research on Cancer/World Health Organization. <http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx> (accessed 24.03.2014).
[2] Lambert R, Sauvaget C, de Camargo Cancela M, Sankaranarayanan R. Epidemiology of cancer from the oral cavity and oropharynx. Eur J Gastroenterol Hepatol 2011;23:633–41.
[3] Messadi DV. Diagnostic aids for detection of oral precancerous conditions. Int J Oral Sci 2013;5:59–65.
[4] Adami GR, Adami AJ. Looking in the mouth for noninvasive gene expression-based methods to detect oral, oropharyngeal, and systemic cancer. ISRN Oncol 2012;2012:931301.
[5] Mehrotra R, Sharma N, Umudum H, Ceyhan K, Rezanko T. The role of cytopathology in diagnosing HPV induced oropharyngeal lesions. Diagn Cytopathol 2012;40:839–43.
[6] Gupta B, Ariyawardana A, Johnson NW. Oral cancer in India continues in epidemic proportions: evidence base and policy initiatives. Int Dent J 2013;63:12–25.
[7] Epstein JB, Silverman Jr S, Epstein JD, Lonky SA, Bride MA. Analysis of oral lesion biopsies identified and evaluated by visual examination, chemiluminescence and toluidine blue. Oral Oncol 2008;44:538–44.
[8] Scully C, Petti S. Overview of cancer for the healthcare team: aetiopathogenesis and early diagnosis. Oral Oncol 2010;46:402–6.
[9] Cleveland JL, Junger ML, Saraiya M, Markowitz LE, Dunne EF, Epstein JB. The connection between human papillomavirus and oropharyngeal squamous cell carcinomas in the United States: implications for dentistry. J Am Dent Assoc 2011;142:915–24.
[10] Mighell AJ, Gallagher JE. Oral cancer – improving early detection and promoting prevention. Are you up to date? Br Dent J 2012;213:297–9.
[11] Lingen MW, Xiao W, Schmitt A, Jiang B, Pickard R, Kreinbrink P, et al. Low etiologic fraction for high-risk human papillomavirus in oral cavity squamous cell carcinomas. Oral Oncol 2013;49:1–8.
[12] Radoï L, Paget-Bailly S, Guida F, et al. Family history of cancer, personal history of medical conditions and risk of oral cavity cancer in France: the ICARE study. BMC Cancer 2013;13:560.
[13] Shah AT, Wu E, Wein RO. Oral squamous cell carcinoma in post-transplant patients. Am J Otolaryngol 2013;34:176–9.
[14] Nolan A, Girdler NM, Seymour RA, Thomason JM. The prevalence of dysplasia and malignant lip lesions in transplant patients. J Oral Pathol Med 2012;41:113–8.
[15] International Agency for Research on Cancer (IARC). <www.iarc.fr/en/publications/pdfs-online/pat-gen/bb9/bb9-chap4.pdf>. (accessed 08.03.2014).
[16] Bagan J, Sarrion G, Jimenez Y. Oral cancer: clinical features. Oral Oncol 2010;46:414–7.
[17] Li L, Fukumoto M, Liu D. Prognostic significance of p53 immunoexpression in the survival of oral squamous cell carcinoma patients treated with surgery and neoadjuvant chemotherapy. Oncol Lett 2013;6:1611–5.
[18] Huber MA, Bsoul SA, Terezhalmy GT. Acetic acid wash and chemiluminescent illumination as an adjunct to conventional oral soft tissue examination for the detection of dysplasia: a pilot study. Quintessence Int 2004;35:378–84.
[19] Seoane J, Warnakulasuriya S, Varela-Centelles P, Esparza G, Dios PD. Oral cancer: experiences and diagnostic abilities elicited by dentists in Northwestern Spain. Oral Dis 2006;12:487–92.
[20] Morse DE, Psoter WJ, Cuadrado L, et al. A deficit in biopsying potentially premalignant oral lesions in Puerto Rico. Cancer Detect Prev 2009;32:424–30.

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[21] Panzarella V, Pizzo G, Calvino F, Compilato D, Colella G, Campisi G. Diagnostic delay in oral squamous cell carcinoma: the role of cognitive and psychological variables. Int J Oral Sci 2013. http://dx.doi.org/10.1038/ijos.2013.88.
[22] Kerr AR, Sirois DA, Epstein JB. Clinical evaluation of chemiluminescent lighting: an adjunct for oral mucosal examinations. J Clin Dent 2006;17:59–63.
[23] Farah CS, McCullough MJ. A pilot case control study on the efficacy of acetic acid wash and chemiluminescent illumination (ViziLite) in the visualisation of oral mucosal white lesions. Oral Oncol 2007;43:820–4.
[24] Stefanuto P, Doucet JC, Robertson C. Delays in treatment of oral cancer: a review of the current literature. Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:424–9.
[25] Epstein JD, Knight TK, Epstein JB, Bride MA, Nichol MB. Cost of care for early- and late-stage oral and pharyngeal cancer in the California Medicaid population. Head Neck 2008;30:178–86.
[26] Downer MC, Evans AW, Hughes Hallet CM, Jullien JA, Speight PM, Zakrzewska JM. Evaluation of screening for oral cancer and precancer in a company headquarters. Community Dent Oral Epidemiol 1995;23:84–8.
[27] Scully C, Kirby J. Statement on mouth cancer diagnosis and prevention. Br Dent J 2014;216:37–8.
[28] Jacobson JJ, Epstein JB, Eichmiller FC, et al. The cost burden of oral, oral pharyngeal, and salivary gland cancers in three groups: commercial insurance, medicare, and medicaid. Head Neck Oncol 2012;4:15.
[29] Allison P, Franco E, Black M, Feine J. The role of professional diagnostic delays in the prognosis of upper aerodigestive tract carcinoma. Oral Oncol 1998;34:147–53.
[30] Harrison LB, Sessions RB, Hong WK, editors. Head and neck cancer: a multidisciplinary approach. Philadelphia (PA): Lippincott, William & Wilkins; 2009. <http://www.cancer.gov/cancertopics/pdq/treatment/lip-and-oral-cavity/HealthProfessional> (accessed on 07.03.2014).
[31] Mashberg A. Final evaluation of tolonium chloride rinse for screening of high-risk patients with asymptomatic squamous carcinoma. J Am Dent Assoc 1983;106:319–23.
[32] Onofre MA, Sposto MR, Navarro CM. Reliability of toluidine blue application in the detection of oral epithelial dysplasia and in situ and invasive squamous cell carcinomas. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;91:535–40.
[33] Epstein JB, Zhang L, Poh C, Nakamura H, Berean K, Rosin M. Increased allelic loss in toluidine blue-positive oral premalignant lesions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;95:45–50.
[34] Cancela-Rodríguez P, Cerero-Lapiedra R, Esparza-Gómez G, Llamas-Martínez S, Warnakulasuriya S. The use of toluidine blue in the detection of pre-malignant and malignant oral lesions. J Oral Pathol Med 2011;40:300–4.
[35] Güneri P, Epstein JB, Ergün S, Boyacioğlu H. Toluidine blue color perception in identification of oral mucosal lesions. Clin Oral Investig 2011;15:337–45.
[36] Güneri P, Epstein JB, Kaya A, Veral A, Kazandı A, Boyacioglu H. The utility of toluidine blue staining and brush cytology as adjuncts in clinical examination of suspicious oral mucosal lesions. Int J Oral Maxillofac Surg 2011;40:155–61.
[37] Ujaoney S, Motwani MB, Degwekar S, et al. Evaluation of chemiluminescence, toluidine blue and histopathology for detection of high risk oral precancerous lesions: a cross-sectional study. BMC Clin Pathol 2012;12:6.
[38] Rethman MP, Carpenter W, Cohen EE, et al. American Dental Association Council on Scientific Affairs Expert Panel on Screening for Oral Squamous Cell Carcinomas. Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas. J Am Dent Assoc 2010;141:509–20.
[39] Bloching M, Hofmann A, Lautenschläger C, Berghaus A, Grummt T. Exfoliative cytology of normal buccal mucosa to predict the relative risk of cancer in the upper aerodigestive tract using the MN-assay. Oral Oncol 2000;36:550–5.
[40] Huang MF, Chang YC, Liao PS, Huang TH, Tsay CH, Chou MY. Loss of heterozygosity of p53 gene of oral cancer detected by exfoliative cytology. Oral Oncol 1999;35:296–301.
[41] Sciubba JJ. Improving detection of precancerous and cancerous oral lesions. Computer-assisted analysis of the oral brush biopsy U.S. Collaborative OralCDx Study Group. J Am Dent Assoc 1999;130:1445–57.
[42] Poh CF, Zhang L, Anderson DW, et al. Fluorescence visualization detection of field alterations in tumor margins of oral cancer patients. Clin Cancer Res 2006;12:6716–22.
[43] Schwarz RA, Gao W, Redden Weber C, et al. Noninvasive Evaluation of oral lesions using depth-sensitive optical spectroscopy. Cancer 2009;115:1669–79.
[44] Fedele S. Diagnostic aids in the screening of oral cancer. Head Neck Oncol 2009;1:5.
[45] Pavlova I, Williams M, El-Naggar A, Richards-Kortum R, Gillenwater A. Understanding the biological basis of autofluorescence imaging for oral cancer detection: high-resolution fluorescence microscopy in viable tissue. Clin Cancer Res 2008;14:2396–404.
[46] Poh CF, MacAulay CE, Zhang L, Rosin MP. Tracing the "at-risk" oral mucosa field with autofluorescence: steps toward clinical impact. Cancer Prev Res (Phila) 2009;2:401–14.
[47] Swinson B, Jerjes W, El-Maaytah M, Norris P, Hopper C. Optical techniques in diagnosis of head and neck malignancy. Oral Oncol 2006;42:221–8.
[48] Patton LL, Epstein JB, Kerr AR. Adjunctive techniques for oral cancer examination and lesion diagnosis: a systematic review of the literature. J Am Dent Assoc 2008;139:896–905.
[49] Ram S, Siar CH. Chemiluminescence as a diagnostic aid in the detection of oral cancer and potentially malignant epithelial lesions. Int J Oral Maxillofac Surg 2005;34:521–7.
[50] Epstein JB, Gorsky M, Lonky S, Silverman Jr S, Epstein JD, Bride M. The efficacy of oral lumenoscopy (ViziLite) in visualizing oral mucosal lesions. Spec Care Dent 2006;26:171–4.
[51] Mehrotra R, Singh M, Thomas S, et al. A cross-sectional study evaluating chemiluminescence and autofluorescence in the detection of clinically innocuous precancerous and cancerous oral lesions. J Am Dent Assoc 2010;141:151–6.
[52] Rajmohan M, Rao UK, Joshua E, Rajasekaran ST, Kannan R. Assessment of oral mucosa in normal, precancer and cancer using chemiluminescent illumination, toluidine blue supravital staining and oral exfoliative cytology. J Oral Maxillofac Pathol 2012;16:325–9.
[53] De Veld DC, Witjes MJ, Sterenborg HJ, Roodenburg JL. The status of in vivo autofluorescence spectroscopy and imaging for oral oncology. Oral oncol 2005;41:117–31.
[54] Awan KH, Morgan PR, Warnakulasuriya S. Evaluation of an autofluorescence based imaging system (VELscope™) in the detection of oral potentially malignant disorders and benign keratoses. Oral Oncol 2011;47:274–7.
[55] Scheer M, Neugebauer J, Derman A, Fuss J, Drebber U, Zoeller JE. Autofluorescence imaging of potentially malignant mucosa lesions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:568–77.
[56] Farah CS, McIntosh L, Georgiou A, McCullough MJ. Efficacy of tissue autofluorescence imaging (VELScope) in the visualization of oral mucosal lesions. Head Neck 2012;34:856–62.
[57] McNamara KK, Martin BD, Evans EW, Kalmar JR. The role of direct visual fluorescent examination (VELscope) in routine screening for potentially malignant oral mucosal lesions. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114:636–43.
[58] Rana M, Zapf A, Kuehle M, Gellrich NC, Eckardt AM. Clinical evaluation of an autofluorescence diagnostic device for oral cancer detection: a prospective randomized diagnostic study. Eur J Cancer Prev 2012;21:460–6.
[59] Lane P, Follen M, MacAulay C. Has fluorescence spectroscopy come of age? A case series of oral precancers and cancers using white light, fluorescent light at 405 nm, and reflected light at 545 nm using the Trimira Identafi 3000. Gend Med 2012;9(1 Suppl):S25–35.
[60] Bhatia N, Lalla Y, Vu AN, Farah CS. Advances in optical adjunctive AIDS for visualisation and detection of oral malignant and potentially malignant lesions. Int J Dent 2013;2013:194029.
[61] Agha-Hosseini F, Mirzaii-Dizgah I, Farmanbar N, Abdollahi M. Oxidative stress status and DNA damage in saliva of human subjects with oral lichen planus and oral squamous cell carcinoma. J Oral Pathol Med 2012;41:736–40.
[62] Brinkmann O, Kastratovic DA, Dimitrijevic MV, et al. Oral squamous cell carcinoma detection by salivary biomarkers in a Serbian population. Oral Oncol 2011;47:51–5.
[63] Malhotra R, Patel V, Chikkaveeraiah BV, et al. Ultrasensitive detection of cancer biomarkers in the clinic by use of a nanostructured microfluidic array. Anal Chem 2012;84:6249–55.
[64] Cheng YS, Rees T, Wright J. A review of research on salivary biomarkers for oral cancer detection. Clin Transl Med 2014;3:3.
[65] Elashoff D, Zhou H, Reiss J, et al. Prevalidation of salivary biomarkers for oral cancer detection. Cancer Epidemiol Biomarkers Prev 2012;21:664–72.
[66] Langevin SM, Stone RA, Bunker CH, Grandis JR, Sobol RW, Taioli E. MicroRNA-137 promoter methylation in oral rinses from patients with squamous cell carcinoma of the head and neck is associated with gender and body mass index. Carcinogenesis 2010;31:864–70.
[67] Abbas NF, Labib El-Sharkawy S, Abbas EA, Abdel Monem El-Shaer M. Immunohistochemical study of p53 and angiogenesis in benign and preneoplastic oral lesions and oral squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:385–90.
[68] Li L, Morse DE, Katz RV. What constitutes a proper routine oral cancer examination for patients at low risk? Findings from a Delphi survey. Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:e379–86.
[69] Erdei E, Luo L, Sheng H, et al. Cytokines and tumor metastasis gene variants in oral cancer and precancer in Puerto Rico. PLoS ONE 2013;8:e79187.
[70] D'Souza G, Dempsey A. The role of HPV in head and neck cancer and review of the HPV vaccine. Prev Med 2011;53(Suppl 1):S5–S11.
[71] van der Waal I. Are we able to reduce the mortality and morbidity of oral cancer; some considerations. Med Oral Patol Oral Cir Bucal 2013;18:e33–7.
[72] Gómez I, Warnakulasuriya S, Varela-Centelles PI, et al. Is early diagnosis of oral cancer a feasible objective? Who is to blame for diagnostic delay? Oral Dis 2010;16:333–42.
[73] Teppo H, Alho OP. Relative importance of diagnostic delays in different head and neck cancers. Clin Otolaryngol 2008;33:325–30.
[74] Friedrich RE. Delay in diagnosis and referral patterns of 646 patients with oral and maxillofacial cancer: a report from a single institution in Hamburg, Germany. Anticancer Res 2010;30:1833–6.
[75] Yu T, Wood RE, Tenenbaum HC. Delays in diagnosis of head and neck cancers. J Can Dent Assoc 2008;74:61.
[76] Onizawa K, Nishihara K, Yamagata K, Yusa H, Yanagawa T, Yoshida H. Factors associated with diagnostic delay of oral squamous cell carcinoma. Oral Oncol 2003;39:781–8.
[77] Morelatto RA, Herrera MC, Fernández EN, Corball AG, López de Blanc SA. Diagnostic delay of oral squamous cell carcinoma in two diagnosis centers in Córdoba Argentina. J Oral Pathol Med 2007;36:405–8.
[78] Brouha XD, Tromp DM, Koole R, Hordijk GJ, Winnubst JA, de Leeuw JR. Professional delay in head and neck cancer patients: analysis of the diagnostic pathway. Oral Oncol 2007;43:551–6.

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[79] Peacock ZS, Pogrel MA, Schmidt BL. Exploring the reasons for delay in treatment of oral cancer. J Am Dent Assoc 2008;139:1346–52.
[80] McLeod NM, Saeed NR, Ali EA. Oral cancer: delays in referral and diagnosis persist. Br Dent J 2005;198:681–4.
[81] Scott SE, Grunfeld EA, McGurk M. Patient's delay in oral cancer: a systematic review. Community Dent Oral Epidemiol 2006;34:337–43.
[82] Tromp DM, Brouha XD, Hordijk GJ, Winnubst JA, de Leeuw JR. Patient factors associated with delay in primary care among patients with head and neck carcinoma: a case-series analysis. Fam Pract 2005;22:554–9.
[83] Kerdpon D, Sriplung H. Factors related to delay in diagnosis of oral squamous cell carcinoma in southern Thailand. Oral Oncol 2001;37:127–31.
[84] Rogers SN, Pabla R, McSorley A, Lowe D, Brown JS, Vaughan ED. An assessment of deprivation as a factor in the delays in presentation, diagnosis and treatment in patients with oral and oropharyngeal squamous cell carcinoma. Oral Oncol 2007;43:648–55.
[85] Rogers SN, Vedpathak SV, Lowe D. Reasons for delayed presentation in oral and oropharyngeal cancer: the patients perspective. Br J Oral Maxillofac Surg 2011;49:349–53.
[86] Agarwal AK, Sethi A, Sareen D, Dhingra S. Treatment delay in oral and oropharyngeal cancer in our population: the role of socio-economic factors and health-seeking behaviour. Indian J Otolaryngol Head Neck Surg 2011;63:145–50.
[87] Seoane-Romero JM, Vázquez-Mahía I, Seoane J, Varela-Centelles P, Tomás I, López-Cedrún JL. Factors related to late stage diagnosis of oral squamous cell carcinoma. Med Oral Patol Oral Cir Bucal 2012;17:e35–40.
[88] Noonan B. Understanding the reasons why patients delay seeking treatment for oral cancer symptoms from a primary health care professional: an integrative literature review. Eur J Oncol Nurs 2014;18:118–24.
[89] Rastogi V, Puri N, Arora S, Kaur G, Yadav L, Sharma R. Artefacts: a diagnostic dilemma – a review. J Clin Diagn Res 2013;7:2408–13.
[90] Fischer DJ, Epstein JB, Morton TH, Schwartz SM. Interobserver reliability in the histopathologic diagnosis of oral pre-malignant and malignant lesions. J Oral Pathol Med 2004;33:65–70.
[91] Fischer DJ, Epstein JB, Morton Jr TH, Schwartz SM. Reliability of histologic diagnosis of clinically normal intraoral tissue adjacent to clinically suspicious lesions in former upper aerodigestive tract cancer patients. Oral Oncol 2005;41:489–96.
[92] Brocklehurst PR, Baker SR, Speight PM. Factors which determine the referral of potentially malignant disorders by primary care dentists. J Dent 2010;38:569–78.
[93] Epstein JB, Guneri P, Barasch A. Appropriate and necessary oral care for people with cancer: guidance to obtain the right treatment at the right time. Support Care Cancer Mar 28, 2014; doi 10.10076.s00520-014-2228-x PMID 24676676 [Epub ahead of print].

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