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.

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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 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 an 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 morbidity 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 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 the utility in clinical use [34]. Toluidine blue is 100% sensitive for oral malignancy, and its addition to oral examination may result in a 45% survival rate for two years when treated using a combination of surgery, radiation therapy and chemotherapy [27,30] and with increased morbidity and increased cost of care.

**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].
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 incongruous, 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 clinical 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
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 non-specific 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


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

<table>
<thead>
<tr>
<th>Extraoral examination</th>
<th>Perioral and intraoral examination</th>
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<tbody>
<tr>
<td>Visual inspection (face, head and neck)</td>
<td>Manual palpation</td>
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<tr>
<td>Asymmetry</td>
<td>Lymph nodes (periauricular, postauricular, submandibular, anterior–posterior deep cervical)</td>
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<tr>
<td>Swelling</td>
<td>Neck</td>
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<td>Discoloration</td>
<td>Labial mucosa and vestibule</td>
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<td>Ulceration</td>
<td>Buccal mucosa, sulcus, internal commissures</td>
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<td>Skin changes (crusts, fissuring, growth)</td>
<td>Gingiva and alveolar ridge</td>
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<td></td>
<td>Anterior tongue (dorsum, lateral, ventral)</td>
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<td>Base of tongue</td>
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<td>Floor of the mouth</td>
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<td></td>
<td>Hard and soft palate</td>
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<td></td>
<td>Retromolar trigone area</td>
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<td>Posterior pharyngeal wall</td>
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