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# Timing of Oral Cancer Diagnosis: Implications for Prognosis and Survival

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## 1. Introduction

Oral cancer has become a global health problem (Parkin, 2005; Gillison, 2007) and its increasing incidence and mortality rates are particularly relevant in certain parts of Europe (France, Hungary, Spain and Croatia), Brazil, and South-Eastern Asia (Sri Lanka, Pakistan, Bangladesh and India) (Warnakulasuriya, 2009). These geographical variations seem to reflect disparities in tobacco, areca nut and alcohol consumption (Warnakulasuriya, 2009). Worldwide, oral cancer has one of the lowest survival rates that remains unaltered despite recent therapeutic advances. Young adults seem to be growingly affected by tongue cancer in Brazil, several European countries and USA (Llewellyn, 2004). However, current reports describe a trend –more marked for tongue carcinomas– towards improved survival at each stage and at all ages but  $\geq 75$  years (Pulte, 2010).

Search for prognostic markers for oral cancer has been extensive and thorough with diverse results: age, gender, immunological or nutritional status, size and location of the tumour, disease stage, nodal status, oncogene expression, proliferation markers, or DNA content have been allocated independent prognostic value (Johnson, 1996); but tumour stage at diagnosis remains the most important prognostic maker for oral squamous cell carcinoma (Garzino-Demo, 2006). Unfortunately, almost half of the oral neoplasms are diagnosed at stages III or IV, with 5-year survival rates ranging from 20% to 50% depending upon tumour sites (Holmes, 2003; Brandizzi, 2005).

Early detection is widely recognised as the cornerstone to reduce diagnostic delay and, thus, to improve survival (De Faria, 2003; McDowell, 2006). However, this term (early detection) is not free from confusion as can be understood either as “a relative small tumour in size at the time of detection” or as “short time interval since cancer onset to diagnosis” (diagnostic delay) (van der Waal, 2011).

## 2. Early detection. Diagnosis of small-size oral carcinoma

Tumour size influences therapy and prognosis of oral cancer. Diagnosis of larger oral carcinomas has been linked to an increased risk of neck-node metastases and poor survival

(Woolgar, 1999). Lately, this variable (plain clinical or pathological tumour size) has been replaced by tumour thickness or depth of invasion as more significant prognostic factors (Gonzalez-Moles, 2002; O-charoenrat, 2003). Moreover, tumour thickness has proved independent predictive value for subclinical node metastases, local recurrence and survival (Po Wing Yuen, 2002). Accordingly, a critical thickness of 4 mm has been proposed, above which the risk for metastases is 4 times the risk of tumours with minor invasion depth (Ambrosch, 1995). Generally speaking, a small-size tumour should present a diameter inferior than 2 cm, less than 4 mm of invasion depth and usually asymptomatic (Woolgar, 2006). Thus, clinicians are recommended to be watchful on the signs of potentially malignant lesions or early stage cancers in all patients, but particularly on heavy smokers and alcohol consumers. These signs include indurations, bleeding, exophytic growths larger than 1 mm, chronic ulcerations with irregular, dirty or spotty appearance in lesions that do not disappear after the hypothetical causal agents have been removed, together with texture changes or granulation on the surface of the lesion. Moreover, keeping in mind that persistent erythroplastic lesions are the most frequent clinical presentation of early carcinomas (Mashberg, 1977; Mashberg, 1988; Bouquot, 1995) (Figure 1) along with erythro-leukoplastic (23%) and leukoplastic lesions (21%) may ease an early diagnosis of oral cancer (Mashberg, 1995).



Fig. 1. Erythroplastic oral squamous cell carcinoma.

### 3. Diagnostic delay in oral cancer. Concept

The concept of diagnostic delay would comprise the time since first sign or symptom to definitive diagnosis. This fairly clear concept has been studied from different points of view with heterogeneous criteria (Allison, 1998a; Allison, 1998b; Allison, 1998c), resulting in categorisations that include: “patient delay”: the period between the patient first noticing a symptom and the first consultation with a health professional about the symptom; and “professional delay”: the period from patient’s first consultation with a clinician to the definitive pathological diagnosis”. This categorisation can be broken down further to include the “delay by patients”: time until consultation due to inaccessibility to the healthcare provider (Allison, 1998a; Allison, 1998b; Allison, 1998c; Onizawa, 2003) –which is not always due to the patients-. To overcome this ambiguity, the term “scheduling delay” (period between the patient making an appointment and actually seeing a healthcare professional) was introduced (Diz-Dios, 2005) (Figure 2).

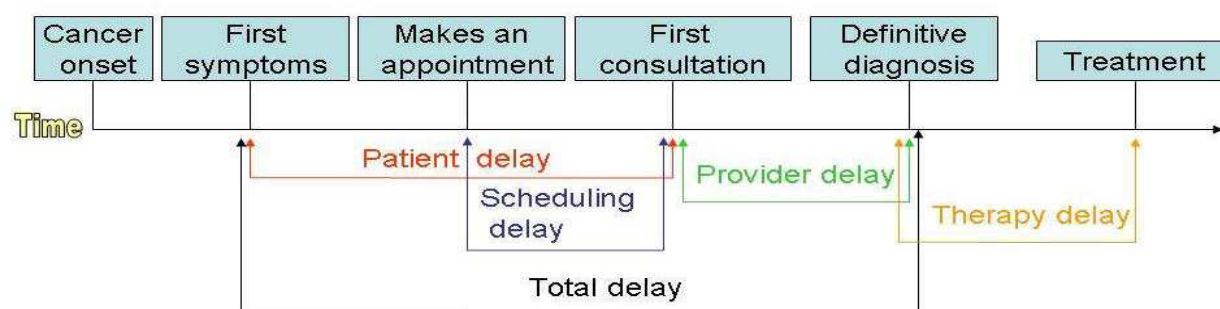


Fig. 2. Types of diagnostic delay in oral cancer.

Despite these efforts, to date there is no consensus on a time-point beyond which a cancer diagnosis can be considered delayed. Several research groups have used the mean or the median of the time distribution to categorise diagnostic delay (Andersen, 1995; Pitiphat, 2002; Carvalho, 2002; Gorsky, 1995), the latter being more frequent as it is not affected by the extreme values of distributions that usually show very wide ranges. Other authors choose an arbitrary time-point (more than thirty days) to discriminate between delayed and non-delayed cases (Allison, 1998a; Allison, 1998b; Allison, 1998c; Brouha, 2005), in order to allow time for the patient to identify the symptoms, seek consultation, for a follow up of 7-10 days and a second consultation and biopsy, and, finally for the pathologist to report the results back to the clinician (Gorsky, 1995).

Other criteria include a first stage: since the first symptom until the first contact with the clinician; a second stage: since the first visit until a referral letter is written; a third stage: since the patient gets the referral letter until the first consultation at a specialised service; and a 4<sup>th</sup> stage, since the first consultation to a specialist until a definitive diagnosis is reached (Onizawa, 2003). As can be inferred, this approach introduces some degree of complexity and limits the external validity of the studies performed under this scheme.

Regardless of the importance of this topic, it is somehow surprising the limited number of reports dealing with the influence of diagnostic delay in head and neck carcinomas retrievable from scientific databases, particularly when compared to melanoma or colorectal, breast, and bladder carcinomas.

#### 4. Causes of oral cancer diagnostic delay

The proportion of patients receiving a delayed definitive diagnosis of oral cancer remains high worldwide, with wide variations in the values reported: in Greece more than a half of oral cancer patients are diagnosed with delays longer than 3 weeks (Pitiphat, 2002), whereas Dutch and Spanish patients are diagnosed with an average delay of 1.5 months (Kowalsky, 1994; Seoane, 2006); series published from Canada, Italy, Denmark or Israel report medians of diagnostic delays ranging from 3 to four months (Allison, 1998a; Allison, 1998b; Allison, 1998c; Wildt, 1995; Gorsky, 1995).

Undoubtedly, there are potential factors responsible for late diagnosis of oral cancer: on the one hand, psychosocial factors related to the patient may well condition the perception of the cancer symptoms by the individual and lead him/her to erroneous behavioural responses that may adversely affect his/her demands and access to care. This may explain why the use of traditional herbal medication before visiting a healthcare professional is recognised as a significant independent predictor for patient delay in Thailand (Kerdpon, 2001a; Kerdpon, 2001b).

On the other hand, the accessibility (ability to obtain services based on oral health needs) can be limited by financial, structural and personal barriers (beliefs, language) and thus decisively conditioning the timing of oral cancer diagnosis (Seoane, 2010). Disparities in access to oral health services across Europe and USA are well known, particularly for low-income populations (uninsured, migrant, homeless, etc). Ethno-regional differences have also been identified in terms of incidence and mortality rates of oral cancer, which may result from the variation in the access to oral care but also from the different exposition to risk factors or from the limited resources in detection and prevention methods available to these individuals.

The causes of diagnostic delay related to the clinician are particularly interesting, and can be basically due to not to practice a full clinical examination (Bruun, 1976), the presence of unspecific or banal clinical signs (Bruun, 1976), low index of suspicion and lack of familiarity and experience with the disease (Guggenheimer, 1989). Co-morbidity has also been suggested (Allison, 1998a; Allison, 1998b; Allison, 1998c), as clinicians in these situations tend to focus their attention on the existing disorders.

Lack of oral cancer knowledge has also been described to influence delays in referral and treatment (Colella, 2008; Seoane 2010), and this situation has been detected internationally as a worrying lack of knowledge on diagnostic procedures, main locations of oral cancer (Alonge, 2003) and on leuko- or erythroplakia-like carcinomas as primary oral cancer lesions, as well as on the effects of vegetable intake on the incidence of oral cancer. Conversely, facts like squamous cell carcinoma being the most common histopathological type of oral cancer, criteria for referral of patients with suspicious lesions, that early detection improves the 5-year survival rate and that tobacco and alcohol are risk factors for oral cancer (Seoane 2010) are well known by the healthcare professionals.

In short, diagnostic delay is a complex concept conditioned by tumour biology, patient behaviour, clinician awareness and attitudes, as well as by the healthcare system performance.



## 5. Other factors related to late stage diagnosis of oral squamous cell carcinoma

Although recognition of predictors for advanced-stage diagnosis could permit the implementation of strategies for increasing the number of oral carcinomas diagnosed at an early stage, there is no much information on this issue.

The most frequently studied variables (age, gender, and tobacco and alcohol intake) are not linked to late-stage diagnosis, as were not previously associated to professional or patient-related delays (Boing, 2010; Guggenheimer 1989). Neither precancerous lesions connected to the tumour seem to modify the spread of the disease at diagnosis, even when proliferative verrucous leukoplakia or the presence of mild to moderate epithelial dysplasia at the margins of a surgically removed oral squamous cell carcinoma carries a significant risk of local recurrence and modifies the prognosis of the disorder (Thomsom, 2007).

Ulcerated-type oral squamous cell carcinomas are usually diagnosed at stages III or IV (Jaulerry, 1985) (Figure 3). Although the predictive value of the clinical appearance of the primary lesion remains controversial, it is accepted that ulcerated lesions imply poorer survival rates (Jaulerry, 1985).



Fig. 3. Ulcerated-type tongue squamous cell carcinoma.

The site of the primary lesion has been also linked either to delayed diagnosis or diagnosis at advanced stages (Brouha, 2005): tongue, buccal mucosa and lip carcinomas seem to be diagnosed at earlier stages (Gorsky, 1995) than floor of the mouth and retromolar trigone

neoplasms; whereas palate or gingival tumours showed contradictory results (Gorsky, 1995). Accordingly, the floor of the mouth, gingivae and retromolar trigone have recently been identified as independent prognostic factors for late-stage diagnosis, which may well be explained by the fact that patients' self-perception and self-exploration abilities are conditioned by the site of the tumour (Andersen, 1995); the presence of the gingivae within this group would be due to the association of gingival locations to advanced stage at diagnosis (late diagnosis) caused by the early invasion of the nearby bone (T4 primary tumour) (Seoane, 2006).

Late diagnosis of neoplasms, particularly in oral cancer, has been conventionally ascribed to delays in reaching a diagnosis, as patients at advanced tumour stages are more likely to have experienced longer patient and professional delays than those diagnosed at earlier stages (Sargeran, 2009). Surprisingly, there is an evident lack of sound scientific evidence supporting this traditional association between diagnostic delay and disease extension (III-IV TNM stages) (Gomez, 2009; Gomez, 2010).

The biological behaviour of the tumour has also been investigated as an hypothetical predictor for a late-stage diagnosis, with positive results, as poorly differentiation of a tumour (biologically more aggressive) proved to be an independent risk factor for diagnosis at stages III and IV, which may suggest that the TNM stage of a tumour when diagnosed could be affected more by the biology of the cancer (degree of differentiation) than by a delay in the diagnosis.

## **6. Relationships between diagnostic delay in primary oral cancer and disease extension**

Tumour size and nodal status seem to correlate well with tumour growth chronology in oral cancer (Spiro, 1986; Brown, 1989; Parker, 1996). This paradigm led to investigations on the feasibility that diagnostic delay contributes to the spread of the disease. Despite this theory could be proved for certain tumours (Erwenne, 1989; Porta, 1991; Faccione, 1993), no definitive conclusions could be drawn for oral cancer, where disagreements between the groups who discard an association (Allison et al, 1998; Kantola et al, 2001; Kerdpon et al, 2001b) and those who endorse it (O'Sullivan, 2001; Brouha et al, 2005b, Gomez et al., 2009) are evident.

The paper by Guggenheimer et al (1989) was one of the first in considering this hypothetical relationship in a mixed sample of 149 oral and pharyngeal cancers and failed to identify an association even after considering patient and professional delays separately. From then on, this has been a common conclusion in the literature (Jovanovic et al, 1992; Amir et al, 1999; Hollows et al, 2000; Kerdpon et al, 2001a; Kerdpon et al 2001b) until 1994, when Kowalski et al. significantly related professional delay and tumour stage, but not between overall delay and spread of the disease, which may suggest the relevance of memory bias in this particular type of research.

The control of biases is a challenging issue for researchers in this field. The consideration of patient survival as the research outcome and the use of multivariate analysis to adjust for confounding factors (Wildt et al, 1995) meant an improvement in the design of these studies but the sought association could not still be identified for oral cancer (Wildt et al, 1995) or for mixed samples of head and neck carcinomas (Gorsky & Dyan, 1995). Research

designs were further improved by the combination of data collection methods to include prospective and retrospective data for reducing memory bias: McGurk et al (2005) gathered a sample of 613 cases over 40 years and failed to unveil a relationship between delay in diagnosis and tumour stage but they used an arbitrary time point of three months to distinguish between delayed and non-delayed cases in their mixed sample of head and neck cancers that, combined with a vague definition of diagnostic delay, compromise their conclusions.

The composition of the study sample may be relevant, since Scott et al (2005) found no relationship between diagnostic delay and tumour stage, but discovered a trend in this direction for certain oral sites. Carvalho et al (2002) somehow confirmed this trend in their series of 676 head and neck squamous cell carcinomas when observed that laryngeal and hypopharyngeal cancers were more prone to be diagnosed at advanced stages than lip, oral and oropharyngeal neoplasms. Additional light in this course was provided by Allison et al (1998c) who demonstrated that patients with upper aerodigestive tract carcinomas with professional delays longer than 1 month had an increased risk to be diagnosed at late stage.

When dealing with diagnostic delay, the beginning of any study is, unavoidably, the recognition of the signs and symptoms by the patient, and this recognition is undoubtedly affected by his/her psychosocial characteristics. The first group in considering these variables was that of Kumar et al (2001) who identified a significant relationship between overall diagnostic delay and tumour stage in their sample of 79 patients. Similar findings were reported by Pitiphat et al (2002) from a case-control study, demonstrating that the length of diagnostic delay was significantly greater in patients with advanced tumour stages (TNM stage IV).

There is no sound scientific evidence supporting an association between diagnostic delay in oral cancer, extension of the disease diagnosed at advanced stages (TNM III-IV) and lower survival rates. However, this fact is probably due to methodological flaws in the published reports to date (Allison, 1998a; Allison, 1998b; Allison, 1998c). These reports use different conceptions of diagnostic delay and are thus liable to misclassifications; use retrospective designs without strategies to diminishing patients' memory bias and often break down diagnostic delay classifications to groups with insufficient sample size. Moreover, the study of samples with heterogeneous cancer sites introduce confounding factors in the analysis, as the patient's self-perception and self-exploration abilities depend on the site of the tumour (Allison et al, 1998a; Tromp et al, 2005; Wildt et al, 1995; O'Sullivan, 2001). For example, gingival locations are associated with advanced stages at diagnosis due to the early invasion of the adjacent bone tissue (T4 primary tumour) (Seoane et al., 2006) yet could present without time delay. Additional difficulties come from the type of data collected (e.g.: continuous variables (Wildt et al, 1995; Hollows et al 2000; Kumar et al, 2001; Kantola et al, 2002) versus categorical (Allison et al 1998b; Kerdpon et al 2001a), from the different sources of patient data (questionnaires, interviews, clinical records) and also from the already mentioned patient memory bias.

Different velocities of tumour growth may well also explain why some tumours remain small in size in spite of delay. Even though some studies related diagnostic delay and tumour stage (Brouha et al 2005), it is possible that the relationship between delay and advanced tumour stage is veiled by the fact that certain cancers remain silent during the initial stages and induce symptoms only when they reach an advanced phase (Scott, 2005).



This being, tumour growth rate would act as a confounding factor in the relationship between diagnostic delay and tumour stage, since patients with aggressive tumours and poor prognosis do not usually present diagnostic delay, while tumours with low proliferation rates demonstrate good prognosis despite long diagnostic delays (Kaufman, 1980; Evans, 1982; Allison, 1998a).

A recent meta-analytical study has shown that diagnostic delay is broadly associated to more advanced stages in oropharyngeal cancers. This association resulted to be specially strong when the analysis was restricted to oral cancer (pooled RR, 1.47; 95% CI: 1.09-1.99) and when the delay was longer than one month (pooled RR, 1-69; 95%CI: 1.26-2.77) (Gomez et al 2009). The probability for delayed patients to present an advanced stage of oral cancer at diagnosis in this report was 25% higher than that of non-delayed patient. Nevertheless these data should be interpreted with caution since all 9 studies considered in the analysis were cross-sectional in nature, with retrospective designs and a potential for recall bias.

Study	Tumour site	Age-range (years)	Gender M/F	Delay Non-advanced/Advanced	OR (95%CI)
Guggenheimer, 1989	Oral & OPH	NS	NS	54/19	0.5 (0.2-1.2)
Gorsky,1995	Oral & OPH	10-99	363/180	259/1323	1.0 (0.5-2.1)
Allison, 1998	Oral & Pharynx	34-91	134/54	67/84	3.0 (1.8-4.8)
Kerdpon, 2000	Oral	32-93	117/44	42/78	1.7 (1.0-2.9)
Kantola, 2001	Tongue	26-85	34/41	6/20	3.4 (1.0-11.7)
Pitiphat, 2002	Oral & Pharynx	26-91	65/40	38/15	0.8 (0.3-2.3)
Carvalho, 2002	Oral & OPH	15-82	363/54	78/224	0.8 (0.5-1.4)
Onizawa, 2003	Oral	33-96	100/52	41/32	0.7 (0.3-1.4)
Scott, 2004	Oral	22-89	157/88	48/59	1.3 (0.8-2.2)

NS: not stated; OPH: Oropharynx; M: male; F: female; OR: odds ratio; CI: confidence interval

Table 1. Association between diagnostic delay and advanced disease stage for oropharyngeal carcinomas.

## 7. Diagnostic delay and survival to oral cancer

The number of studies focusing on the relationship between diagnostic delay and survival to oral cancer are scarce (Table 2), and their results show substantial discrepancies: on the one hand the strength of the association did not reach signification (Ho, 2004), but on the other hand there seems to exist a strong relationship when referral delay is considered (Kantola, 2001; Sandoval, 2009), more specifically: when longer than month, these delays worsen survival to oral and oropharyngeal cancer (Sandoval. 2009), however when tumour aggressiveness is considered, the role of diagnostic delay could not be demonstrated (Seoane, 2010).

Reports on tongue cancer are particularly paradoxical, as referral delays worsen survival, but professional delay behaves as a protective prognostic factor with shorter delays showing a trend towards impaired survival (Kantola, 2001; Teppo 2008). The impact of delays on survival was apparently unreasonable, as shorter delays impaired survival. This paradoxical circumstance, where diagnostic delay, tumour stage and tumour prognosis are inversely related, has been previously described in breast, cervix, lung, colon, renal and urethral cancer and seems to suggest that stage at diagnosis and survival are affected more by the biology of the cancer (rapid tumour growth) than by a delayed diagnosis.

These conclusions demand more studies assessing the impact of diagnostic delay on the course of oral squamous cell carcinomas with sound epidemiologic design (prospective), standardised criteria for diagnostic delay and protocols to minimise recall bias. These future investigations would also benefit from considering in their statistical analyses the biological features of the tumour and treatment delays.

Author	Country	Data collection	Tumor Site	SS	TNM n (%)	P D RR (95% CI)	Prof D RR (95% CI)	Ref D RR (95% CI)	T D RR (95% CI)
Kantola	Finland	1974-1994	Tongue	75	I 9 (12%) II 22 (29.3%) III 33 (44%) IV 11 (14.7%)	-	-	6.3 (1.7-22.9)	-
Teppo	Finland	1986-1996	Tongue	62	I 8 (13%) II 22 (35%) III 25 (40%) IV 7 (11%)	0.58 (0.36-0.93)	1.07 (0.68-1.70)	-	-
Seoane	Spain	1997-2002	Oral	63	I 9 (14.3%) II 20 (31.7%) III 10 (15.9%) IV 24 (38.1%)	-	-	-	1.0 (0.9-1.1)
Sandoval	Spain	1996-1999	Oral & OPH	146	I 15 (10.3%) II 30 (20.5%) III 35 (24%) IV 66 (45.2%)	-	-	2.1 (1.0-4.3)	-

SS: sample size; PD: patient delay; Prof D: professional delay; Ref D: referral delay; TD: Total Delay; RR: relative risk; OPH: oropharyngeal

Table 2. Reports on the association between diagnostic delay in oral cancer an survival.

This is important, as the clarification of this hypothetical relationship between diagnostic delay and survival to oral cancer may condition early oral cancer detection strategies either by strengthening programmes for diminishing diagnostic delay or favouring oral cancer and precancer screening strategies.

## **8. Strategies to minimise diagnostic delay in oral cancer**

A delay when dealing with oral cancer diagnosis is unacceptable. Despite the quickness in obtaining a diagnosis does not ensure an early-stage tumour, it is essential for reducing cancer mortality (Horowitz, 1995). Specific educational interventions on the population, focused on risk groups (self-exploration) and on the clinicians (index of suspicion) are needed to achieve this goal. These interventions should provide sound knowledge of the disease presentation and competences for visual/tactile diagnosis. Additional improvements to ease accessibility to health care and the implementation of clear referral schemes for patients with suspicious lesions would also contribute to this purpose. An example of these schemes would be the “Two weeks wait”, rolled out in December 2000 in the United Kingdom for referral of head and neck cancer patients from primary care to specialised centres (Department of Health, 2000). The audit of this programme showed a high proportion of non-malignant lesions being referred through the fast-track system, highlighting a low sensitivity among the general practitioners and stressing need for better visual detector guidelines. This assessment stressed the need for the primary care clinician to know which kind of cases should be sent to the specialist (all suspicious lesions and all suspicious borderline lesions). As it is difficult to detect oral cancer lesions at early stage, several ancillary diagnostic tests have been developed to improve diagnostic performance, such as toluidine blue staining, chemiluminescence and autofluorescence (Trullenque -Eriksson, 2009).

### **8.1 Toluidine blue**

Tolonium chloride (toluidine blue) has been assessed as diagnostic aid for diagnosis of oral malignant and premalignant lesions by a number of studies (Epstein, 2007; Epstein, 2008; Epstein, 2009). These results were studied from a meta-analytical perspective in 1989, revealing sensitivities ranging from 93.5% to 97.8% and specificities from 73.3% to 92.9% (Rosenberg, 1989), this good performance of the product was somehow spoiled by the serious methodological limitations observed in some of the original reports. A more recent report by Lingen (2008) described sensitivities for the detection of oral cancer ranging from 0.78 to 1.00, and specificities of 0.31 to 1.00. A comprehensive analysis of the current evidence suggest that toluidine blue is good at detecting carcinomas, but its sensitivity in detecting dysplasia is significantly lower (Epstein, 2008; Lingen, 2009).

### **8.2 Light-based detection systems**

These systems are based upon the structural and metabolic changes the oral mucosa undergoes during the carcinogenesis process. These phenomena induce different absorbance and refractance profiles when exposed to different sources of light or energy (Epstein, 2009).

#### **8.2.1 Vizilite® (Zila Pharmaceuticals, Phoenix, AZ)**

A number of cross-sectional studies assessed this chemiluminescence device with high scores in sensitivity (100%), as every patient had previously visualized mucosal lesions, but

low specificity values (0-14.2%) with high percentages of false positives. This device has proved a high capacity to emphasize certain visual features of the lesion, such as brightness and lesions limits (Epstein, 2009), but it does not aid in the identification of a premalignant or malignant oral lesion (Farah, 2007). A combination of Vizilite and toluidine blue (ViziLite Plus) has been introduced to reduce the number of false positives but, although both specificity and predictive positive values improved, the scientific evidence on this combination published to date is scarce (Epstein, 2008).

A different system based on the same principles of ViziLite (Microlux/DL, Danbury, USA) has been designed, which illuminates the lesion with a diffused light from a light-emitting diode. When assessed prospectively, it showed a sensitivity of 77.8% and a specificity of 70.7% (McIntosh, 2009). Some reports point that chemoluminescence could be useful to identify lesions hidden to incandescent light sources, but no evidence supports this theory.

### **8.2.2 Tissue fluorescence imaging**

The VELscope® system (Visually Enhanced Lesion Scope; LED Dental Inc., White Rock, USA) uses autofluorescence technology to detect the loss of fluorescence in visible and non-visible oral lesions. Its sensitivity ranged from 97 to 100%, and proved useful to establish safer surgical margins in tumour excision (Huber, 2009), but no methodologically sound studies back the usefulness of this system as ancillary diagnostic tool when dealing with malignant or premalignant lesions in lower-risk, primary care patients (Lingen, 2008; Epstein, 2009).

### **8.2.3 Tissue fluorescence spectroscopy**

This system produces various excitation wavelengths that are received by a spectrograph and recorded on a computer (Fedele, 2009). Its main advantage is the elimination of the subjective interpretation of the changes in the fluorescence of the tissues, but its main indication is limited to the exploration of previously visually-diagnosed small lesions. This device has shown a high sensitivity and specificity to differentiate healthy mucosa from malignant oral lesions (De Veld, 2005).

Regardless of these promising technologies, the path until these systems enhance visual detection beyond what is achieved through conventional visual and tactile examinations is still to be covered.

## **9. Oral cancer diagnosis at asymptomatic phases of the disease**

The studies on diagnostic delay consider only the symptomatic stage of the disease, which represents a minor part of the disease natural history. The equivocal relationship between diagnostic delay and certain outcomes of interest, like tumour stage and survival to the disease, suggest the need to prioritise the early diagnosis of oral cancer through screening programmes aimed at detecting the disease during its asymptomatic phases, as there is evidence demonstrating that oral visual inspection is satisfactorily sensitive to detect oral precancers and that can improve oral cancer stage at diagnosis. Moreover, community-based screening on these bases may thus decrease oral cancer specific mortality amongst people who use tobacco, alcohol or both (Kujan, 2006).



However, it has to be born in mind that these kind of approaches can also be affected by biases, like the so-called “length-time bias”, where the possibility to detect aggressive oral carcinomas by screening is low due to the fact that the period until symptoms arise is short. On the other hand, less aggressive tumours with longer periods until symptoms are easier to detect by screening; this phenomena may make think that an early diagnosis improves prognosis, when what actually happens in that this approach detects mostly tumours biologically less aggressive (van der Waal, 2011).

Another potential bias affecting this kind of programmes would be the “lead-time bias”, where survival to oral cancer may seem better when cases are diagnosed early but what actually happens is that cases are detected earlier though patients do not live longer than would live if the neoplasm were diagnosed during the symptomatic period of the disease (van der Waal, 2011).

A different approach would be the case-search: the patient is explored searching for subclinical disease. This procedure is not so demanding but in any situation, the screening test should be easy, safe, reproducible and valid, as well as accepted by the population and by the healthcare workers involved, and should also assess risks, nuisances and costs. In areas with low prevalence of oral cancer, screening programmes result in a reduced detection rate. However, opportunistic high-risk screening (involves offering patients a screen when they attend a clinic for some other, unrelated reason), particularly in general dental practice, may be cost-effective (Conway, 2006). This screening may be more effectively targeted to younger age groups, chiefly 40-60 years old (Conway, 2006). Moreover, new educational strategies are needed to identify populations at particular risk; younger people (Farshadpour, 2007) and non-smoking and non-drinking oral cancer patients (females, old at disease presentation). Thus, the range of ages for systematic oral examination should be broaden.

Opportunistic screening by general dentists includes a systematic review of the oral mucosa during regular dental care. About 83%-86% of European and American GDPs declared to perform a systematic exploration of oral soft tissues to rule out oral cancer. Despite this fact, their ability to make a correct positive detection of oral cancer (sensitivity) remains low, as reported scores varied from 0.4 to 1.0. The specificity ranged from 0.31 to 0.92; these low values would mean that patients with oral carcinomas would not be adequately referred for the decisive diagnosis and treatment (Downer, 2006). Despite that, selective opportunistic screening may be a realistic and effective solution, as detections of oral and oropharyngeal squamous cell carcinomas during a non-symptom-driven examination has demonstrated to be related to lower stages at diagnosis although there is insufficient evidence to determine whether screening by visual and tactile examination in asymptomatic patients alters disease-specific mortality (Downer, 2006). Of course, it has to be kept in mind that “insufficient evidence” only means that there are no methodologically sound studies available to support a given technique or approach.

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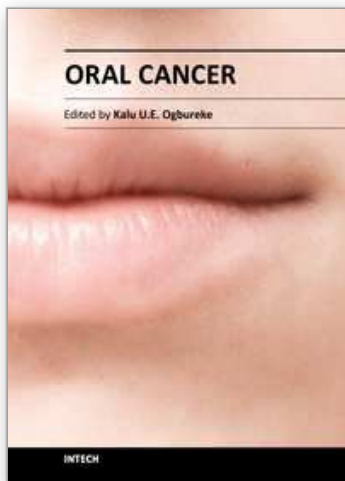
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## **Oral Cancer**

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Oral cancer is a significant public health challenge globally. Although the oral cavity is easily accessible, early diagnosis remains slow compared to the enhanced detection of cancers of the breast, colon, prostate, and melanoma. As a result, the mortality rate from oral cancer for the past four decades has remained high at over 50% in spite of advances in treatment modalities. This contrasts with considerable decrease in mortality rates for cancers of the breast, colon, prostate, and melanoma during the same period. This book attempts to provide a reference-friendly update on the etiologic/risk factors, current clinical diagnostic tools, management philosophies, molecular biomarkers, and progression indicators of oral cancer.

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