Global Oral Cancer Forum (Group 2)

Understanding gaps in the oral cancer continuum and developing strategies to improve outcomes

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Introduction

Oral cancer is a global health problem and statistical data from various regions, reported by Group 1 in the earlier session, confirms a rising incidence. Geographical variations in oral cancer incidence seem to reflect disparities in socioeconomic status of the global population (Johnson et al. 2011) and different lifestyles related to the use of tobacco, areca nut and alcohol consumption (Warnakulasuriya, 2009). Worldwide, oral cancer has one of the lowest overall 5-year survival rates, close to 50%; higher rates are reported from the US (63.2%; 2005-2011) (National Cancer Institute, 2015). Poor prognosis for people diagnosed with oral cancer has remained unaffected despite recent therapeutic advances (Chan et al., 2015). As discussed in the present paper, poor prognosis is largely attributable to cancers of the oral cavity and oropharynx being detected in advanced stages. Delays in diagnosis occur over various stages of a patient’s cancer journey.

Delays encountered in diagnosis have been attributed to the advancement of the stage of the disease at presentation to a specialist. In this session the authors aim to discuss gaps in our knowledge related to delays in diagnosis of oral cancer; to discuss barriers that remain for the early detection of this disease; and to bring to the attention of the forum examples of programs developed for professionals that have been established to overcome these delays. Organized Screening as a means of early detection is presented by Group 3 and as Group 6 has the task to address campaigns to improve public awareness: these will not be discussed here. From these global experiences we hope to make recommendations for future research to understand what we can do to recognize the disease earlier, and propose development goals to avoid diagnostic delays.

Does the stage of the disease influence survival?

Carefully conducted follow-up studies have highlighted several prognostic factors for oral cavity cancers. These include both patient and tumor factors, such as:

- Gender
In univariate studies most of these factors have shown significant associations. For example, Tromp et al (2005) suggest that a trend among men for drinking more than four alcoholic drinks per day has increased the risk of advanced stage disease significantly (OR = 2.67, \( P = 0.026 \)). However, when examined by multivariate analysis with due adjustments, the significance of the majority of these prognostic factors are attenuated, but the stage of the disease at diagnosis remains highly significant and is confirmed as an independent risk factor that influences survival. In a literature search of articles published since 2000 we found 16 studies— all with multivariate analysis – confirming advanced stage of oral cancer is associated with poor prognosis (Rodrigues et al, 2014; Rikardsen et al, 2014;Monteiro et al, 2014; Ling et al, 2013; Dissanayaka et al, 2012; Pruegsanusak et al, 2012; Jan et al, 2011; Liu et al, 2010; Kreppel et al, 2010; Mosleh-shirazi et al, 2008 ; Sargeran et al 2008 ;Lam et al, 2007 ; Aksu et al, 2006 ; Kademani et al, 2005; Sciubba 2001; Pericot et al, 2000). Despite major efforts to identify new predictive parameters and histological systems, the most recent Brazilian study by Rodrigues et al (2014) has shown that clinical stage is still the most reliable prognostic factor for patients with tongue cancer. These studies, which indicate positive associations of stage of disease with survival, are listed in Tables 1 A & B. Examples of studies indicating a direct association of the tumor stage with survival are illustrated in Figure 1. Oral cancer is often staged by the TNM system. Data from a US study (Table 2) shows a direct relationship between TNM stage of diagnosis and 5 - year survival (Sciubba, 2001). A recent study (Mücke et al, 2015) assessed how advanced a cancer is using other parameters- such as by measuring tumor volume - has shown that a large tumor volume was associated with a significantly poorer overall survival (\( P<0.001 \)).

In this article the authors argue that oral cancers have high death rates because the disease is often at an advanced stage before it is diagnosed, and major interventions
that reduce delays in diagnosis could contribute to improvement in disease-specific survival.

**Reasons for presentation in advanced stages**

Presentation at an advanced stage of the disease could occur either as a result of the biologically aggressive nature of a malignancy or due to delays encountered in the patients’ journey. Perhaps not much could be done by a clinician to interact against the aggressive nature of a particular cancer. The vital question that is important is: To what extent does delay in detection in primary care affect the stage of presentation, and thereby the outcome for patients with the disease? Some argue that it is still safe to leave this subject in a speculative limbo, without very much in the way of evidence. A meta-analysis has reported on total diagnostic delay in oral and oropharyngeal cancer based on 14 reported studies (Gomez et al., 2009). This analysis estimated that patients with delayed diagnosis had a higher probability of presenting with advanced stages of oral cancer compared with those without delayed diagnosis. This was particularly the case for those with a delay longer than 1 month (Gomez et al., 2009). In a further review, the relationship between diagnostic delay and stage at diagnosis varied in direction and magnitude, with no consistent positive association in any of the head and neck cancer sites (Goy et al., 2009). ‘Unnoticed’, or minor, symptoms may be responsible for the discrepancy reported in the literature between the stage of tumor and reported patient delay. Cleveland (2012), reviewing Gomez et al’s (2009) meta-analysis, concluded that based on the limited quality of the data, better evidence about the relationship between diagnostic delay and disease progression or disease outcomes is needed.

For this review we examined later studies that reported total delay from 9 countries since 2009. An updated data synthesis is listed in Table 3. Some improvement in diagnostic delay in noted in few studies eg. from Argentina, Finland, Spain and Italy.

**Delay in diagnosis during a patient’s cancer journey**

Delays that occur from the time a patient experiences his/her first symptom to the time of treatment can be conceptually divided into various stages, primarily based on who is responsible for this delay. Patient delay is defined as the time elapsed between symptom discovery and the first medical contact with a medical doctor or a
dentist concerning that symptom. Referral delay (also referred to as scheduling delay) is defined as the period between the first medical contact in a primary care setting with the general practitioner or dentist, and the next contact with the medical specialist. Medical specialist delay is defined as the period from the first contact with the medical specialist until definitive diagnosis. Based on the available resources in the healthcare system, further delays could occur from the time of confirmed diagnosis to the day the patient commences treatment (i.e. surgery). Total delay is defined as the period between symptom discovery and initiation of therapy. Gomez et al. (2010) and Guneri and Epstein (2014), in reviewing diagnostic delays, have produced schematic diagrams to assist understanding of these various stages of delay (Figures 2 A and B).

**Patient delay**

Goy et al.’s (2009) systematic review examined the evidence for an association between patient-related delay in presenting to a primary care facility and stage at diagnosis. The authors reviewed 10 eligible studies and findings indicated differing relationships between patient delay and stage. Patients’ recall bias may have affected these study results as inaccurate identification of the timing of symptom onset was likely to influence most of these studies. The most significant finding was reported by Brouha et al. (2005), who found that oral cancer patients who delayed more than 1 month in seeking care following symptom onset were twice as likely to have advanced-stage oral cavity cancer at diagnosis.

An integrative review on factors associated with patient delay and oral cancer was conducted by Noonan (2014) and this review included 16 studies reported between 2001 and 2010. His findings are represented in Table 4.

Patient delay can largely be attributed to lack of public awareness of the signs and symptoms of disease and oral symptoms being rarely attributed to cancer and frequently interpreted as minor oral conditions (Scott et al., 2005). A qualitative study conducted in Scotland among young people who were later diagnosed with oral cancer outlines the reasons for postponing or barriers faced at a medical/dental consultation (Grant et al, 2010). Population studies in the UK have recorded an alarming lack of public awareness on oral cancer, that could be as low as 50%
Warnakulasuriya et al., 1999). Mouth Cancer Awareness Campaigns and social media interventions (discussed in Group 6) may need to be heightened at local and national levels to improve the public awareness of mouth cancer. Kerr et al. (2004) emphasise the need to develop and assess oral cancer education/awareness programs, specifically customized to the various dental-medical professionals/trainees and to populations at risk. The relevance and the magnitude of the observed effects of any awareness campaign require further study.

**Provider-related diagnostic delay**

There are a limited number of studies conducted in primary care investigating the interval to diagnosis (diagnostic delay). Diagnostic delay is traditionally measured by the number of days elapsed since the patient reports the first sign and/or symptom until a definitive diagnosis is reached. Many authors have used the mean or the median of the time distribution to categorize the diagnostic delay (Pitiphat et al., 2002; Onizawa et al., 2003; McGurk et al., 2005). The “Median time” lapsed is more frequently used because it is not affected by extreme values and the distributions usually have very wide ranges. Other authors choose an arbitrary time point (more than 30 days) to discriminate between delayed and non-delayed cases (Brouha et al., 2005; Tromp et al., 2005).

A recent Australian study has reported that delays in patients seeking advice have decreased compared to previous studies, while delays in professionals making a diagnosis have not improved considerably. (Kaing et al., 2015)

A recent meta-analysis (Seonne et al., 2015) has concluded that diagnostic delay is a moderate risk factor of mortality of head and neck cancer. Their investigation has revealed serious methodological limitations in the studies on oral cancer diagnostic delay. The authors recommended that the guidelines in the Aarhus Statement (Weller et al., 2012) should be used by researchers reporting on early cancer diagnosis to ensure standardized and uniform criteria, which would, in turn, permit interventions aimed at diminishing time intervals to treatment and improve the prognosis of the disease. The Aarhus statement, highlights that in the pathway of oral cancer patients it is strongly recommended to describe “key events” and “time intervals” instead of “diagnostic delay”.

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Logistic issues relating to the ‘measurement of delay’ cannot be easily resolved when transcribing data from patient records. Therefore, alternative ways of measuring delay must be found. Using data from the English National Audit of Cancer Diagnosis in Primary Care, Lyratzopoulos et al. (2013) found that the number of pre-referral consultations has construct validity as a measure of the primary care interval for a number of cancers. Among 18 common and rare cancers investigated by this group, oral and oropharyngeal cancers was also included in their analyses. In this audit, 21.9% of patients finally diagnosed with oral cancer had more than three consultations in primary care prior to referral. A correlation between pre-referral consultations and duration of primary care interval was intuitive, but evidence about this association is sparse in the literature. Point-of-care diagnostic technologies (that can be undertaken in primary care) can also have a part in reducing the number of consultations before referral, and such tests (discussed by Group 4) merit further development and evaluation.

Tumor aggressiveness may also play the role of a confounding factor in examining the association between delay and survival. Rapid progression of a malignancy could be affected by rapid proliferative activity of the tumor (e.g. biological aggressiveness) as well as by any delay in the diagnosis (Seone et al., 2010). The growth rate of a tumor varies enormously and there is little data in the recent literature since the work of Evans et al. (1982). Scott et al. (2005) observed that detecting a small cancer is only possible when the velocity of tumor growth is low and a proportion of tumors may be silent until advanced in stage. In other cancer sites, such as cervical, the results imply that in most cases stage at diagnosis is affected more by the biology of the cancer than by diagnostic delay. They also noted that a proportion of tumors may be silent until advanced in stage and evade a person noticing the change.

**Research in primary care related to professional diagnostic delay**

Professional delay in diagnosis of oral cancer has several definitions in the literature: the time elapsed since the first consultation to a healthcare professional until the first consultation to the treating professional (Allison et al., 1998), or until the appointment for treatment (Kowalski et al., 1994). It has also been defined as the time since first
consultation to the receipt of the referral letter at the specialized services (Scully et al., 1986; Schnelter, 1992; Hollows et al., 2000). However, the commonly accepted definition considers the time elapsed since the first consultation by a health professional until a definitive diagnosis is reached (Hollows et al., 2000; Wildt et al., 1995; Dimitroulis et al., 1992) or treatment is instituted. A number of definitions used by research groups and the grouping of the different time periods make comparisons difficult. This accounts for the reduced number of reviews addressing this issue. Data relating to how professional diagnostic delay leads to poor outcomes is meagre.

A study in Cordoba, Argentina, examined professional delayed encountered before arriving in 2 hospital centres (Morelatto et al. 2007). In a multivariate analysis the authors found that professional delay was the most related variable to the stage at the time of diagnosis (P>0.03). Detailed questioning revealed that eighty percent of the patients received some prescription medication by a health professional for cases later diagnosed to have oral cancer. 30% had received ploypharmacy, 26% mouthwashes and 20% received antibiotics or anti-inflammatory agents.

In study based on self completed questionnaires among patients diagnosed with oral cancer, Crossman et al. (2015) assessed the outcomes of the initial consultations with their GP. Their inquiry revealed that after consultation with a GP (n=109), 53% were referred to a specialist, 22% were referred for tests, 12% were told that their symptom was not serious, and 12% were treated for another condition (Crossman et al., 2015).

The following causes could be identified as causing professional diagnostic delay in primary care:

- Not practicing a full clinical examination (Warnakulasuriya & Johnson, 1999)
- Clinical signs of cancer being mistaken as signs of inflammatory disease (Onizawa et al., 2003)
- Low index of suspicion (Holland, 1982)
- Lack of familiarity and experience with the disease (Guggenheimer et al., 1989).
- Cancer symptoms, such as growths or ulcers, are not uncommon in the oral cavity and are equally indicative of benign disorders (Llewellyn et al, 2004)
- Comorbidity has also been suggested (Allison et al, 1998), as in these situations the clinicians tend to prioritize the stabilization of the existing disease before paying attention to new symptoms.

Two key studies from Finland and Canada provide strong evidence that delay in primary care could significantly affect the outcome.

In a study from Finland (Alho et al 2006), the action taken in the general practices at the initial visit of 221 patients later found to have cancer was analysed. Fifty-six percent (n=123) received referrals, 24% (53) follow-up appointments and 20% (45) neither (‘overlooked’). At 3 years, the risk of death was significantly higher among patients whose head and neck symptoms were overlooked (adjusted hazard ratio [HR] 1.89, 95% confidence interval [CI] 1.03–3.45). The excess risk associated with being overlooked, however, was confined to subjects with tongue or glottic tumors (HR 4.25, 95% CI 1.59–11.4).

The authors concluded that despite the rarity of patients with head and neck carcinoma in primary care, patients with symptoms of these diseases and especially with symptoms of tongue and glottic carcinomas should be initially referred for further care or follow-up. Their data confirmed that those overlooked by their primary care physician were at increased risk of death at 3 years compared with patients who were initially referred or followed up. These significant findings led to the authors’ conclusion that referral to a specialist or close follow-up should be considered for patients presenting to their primary care physician with symptoms of tongue and glottis cancer.

Groome et al (2011) reported a population-based study in Ontario, Canada, that examined factors associated with early versus late-stage oral cavity cancer diagnoses in a primary care setting. Their cohort study included all patients diagnosed with invasive squamous cell carcinomas of the anterior tongue and floor of mouth from 1991 to 2000. The principal data were collected through a province-wide chart review. They reported that both physician-related and system-related
delay were much less common than patient-related delay, but physician-related delay was associated with advanced stage disease \((P = 0.04)\). Overall, physician-related delay was documented in 14.3% and system-related delay in 1.6% of patients. Although only 35% of all patients had a regular dentist in this study, it is of interest to note that having a regular dentist and being followed up for a pre-cancerous lesion led to a better chance of an early diagnosis in the floor of the mouth.

**Delays in secondary care**

The increasing volume of patients arriving in secondary care facilities for the management of head and neck cancers can lead to longer waiting times for surgery following confirmation of the diagnosis. Delays take place within the context of a healthcare system that has waiting lists for operations and reduced manpower resources. This could theoretically lead to progression of the disease and undue psychological stress to the patients. A Dutch study (van Harten et al., 2014) investigated the effect of longer waiting times (after reaching a diagnosis) on disease outcome. Median waiting time for surgery following a confirmed diagnosis for patients with oral cavity cancers was 38 days (25-75% IQR 27-50.5), and 41 days for oropharyngeal cancers (25-75% IQR 30-54). The study did not reveal any adverse effects of longer waiting times, but the data was compounded by advanced cases being treated earlier to avoid further complication or inoperability had they waited any longer for treatment. The authors mentioned that this finding can be used cautiously to comfort patients who are anxious about delays they experience while awaiting surgery. However, a later study by the same authors on a larger cohort of Dutch patients \((n=13,140)\) with a median waiting time of 37 days for surgery or other therapies, showed that longer waiting time, was significantly related to a higher hazard of dying \((p<0.0001)\) (van Harten et al., 2015).

**Investigations on barriers that delay or affect early detection**

The role of the primary care practitioner as the first point of contact for patients with oral cancer has been increasingly highlighted (Fanaras and Warnakulasuriya, 2016). It is generally assumed that patients with symptoms directly or indirectly related to the oral cavity are likely to first visit their dentist for advice. However, many recent studies (Eadie et al., 2009; Crossman et al., 2015; Kaing et al., 2015) have pointed
out that patients with oral cavity cancers are being referred by family physicians more often than dentists. Vulnerable and high-risk groups, such as those from low socioeconomic backgrounds, smokers, those who consume alcohol heavily, or the elderly often have limited access to dental care. The awareness of general medical practitioners - especially in such cases - is crucial as these patient cohorts are more likely to visit their doctor first with symptomatic disease. New off-clinical counsellors (herbalists and pharmacy assistants) have also been identified as potential creators of patient diagnostic delay in oral cancer, raising the need for increasing oral cancer awareness amongst community pharmacists (Varela-Centelles et al., 2012)

A number of research methods have been used to record the response of both dentists and doctors in a primary care setting to examine barriers faced by them to either screen asymptomatic individuals or to examine their approach into complaints of likely malignant lesions.

A lack of understanding of the clinical presentation of disease and confidence on the part of health professionals has been suggested as a barrier for suspecting cancer and dealing promptly with an appropriate referral or arranging a follow-up visit. This particularly applies to general practitioners, for whom the availability of relevant clinical updates is limited. A large number of medical practitioners state that they have never received adequate training in the examination of the oral cavity and detection of oral cancer and as a result there is lack of confidence and knowledge of the risk factors and specific symptoms (Nicotera et al. 2004). The limited knowledge and exposure to disease of the oral cavity is a common theme in most European studies. Interestingly, the performed examinations for oral cancer and enquiry for risk factors, such as smoking and alcohol use, become more frequent with the increase in years of practising medicine.

Another barrier to performing routine screening has been shown to be the anxiety caused to the patients by a false-positive diagnosis or the need for further investigations (Noonan, 2014). However, annual oral cavity examinations could be life-saving (Kerr, 2000).
It is of interest to examine data from few studies reported in primary care. Wade et al (2010) used a questionnaire based on the Theory of Planned Behaviour (Ajzen, 1985) to determine the general practitioners’ intention to perform screening for oral cancer. The results were interesting as 97% of the participants claimed never to have had training on the examination and screening of malignancy of the oral cavity, and 68% stated they had no similar training for ear, nose and throat either. Scores for subjective norm and internal control beliefs showed that although they believed that screening for oral cancer was important and would have colleagues’ approval, but that low confidence would prevent them from performing an examination. External factors determining this behavior according to the same study were patient refusal, time limitation and lack of appropriate equipment.

Paudyal et al (2014), in a systematic review aimed at the acceptance of screening for oral cancer by the patients outside the primary dental care setting, reported that the majority of screening methods are entirely accepted by patients and that lack of acceptance of screening in a general practice setting is not a barrier itself. In fact, some studies showed that a large proportion (70%) of the patients would firstly consult their medical practitioner and then the dentist (Eadie et al., 2009). Where there was limited knowledge regarding oral cancer and screening methods on the patients’ part, which could cause anxiety and constitute a barrier to treatment, the provision of relevant information about the disease had a positive impact and made acceptance more likely (Paudyal et al. 2014).

A qualitative methodology was used by Brocklehurst et al (2010) in order to explore the general dental practitioners’ views on the issue of the opportunistic screening for oral cancer. Semi-structured interviews were used to determine the factors influencing the decision to screen and the screening process. Analysis of the data has shown a lack of diligence on the part of the participants, which was also demonstrated in earlier studies (Greenwood et al. 2001). Reported low incidence of malignant lesions by the dentists and lack of awareness of clinical guidelines have been identified as contributing factors. On the other hand, a lack of confidence was not recorded in this study. Years of practice and clinical experience constituted a factor providing the confidence to examine the oral cavity for malignancy. Patient
anxiety and awareness of the disease was also identified as a factor influencing screening and promoting referral for further assessment.

Macpherson et al (2003) conducted a survey among dentists and primary care doctors in Scotland, initially using a postal questionnaire and then semi-structured interviews for qualitative analysis. The majority of the medical practitioners (94%) indicated that they usually examine the mouth in response to complaint of pain or when there is a history of previous conditions of the oral cavity (81%). For 58% of the dentists, an examination for oral cancer was always included in routine dental checkups and 38% were screening only occasionally. A small proportion of primary care doctors (23%) felt ‘confident’ that an observed lesion required urgent referral, while the equivalent percentage for dentists and community dental officers was 48%. Although the majority of the doctors agreed that they had a significant role to play in oral cancer early diagnosis, 70% stated that the lack of training was a barrier to routine screening, with 37% declaring that they have never had any organized teaching on the subject. Lack of time was also identified by 47% of doctors as a contributing factor to limited screening of the oral cavity.

In order to help doctors and dentists in improving their skills in systematic examination of the oral cavity and neck, and to remind them of the signs to look for, recent attempts have been made to launch web-based learning tools, e.g. www.oralcancer.ldv.org http://learning.bmj.com/learning/module-intro/mouth-cancer-recognising-referring-early.html?moduleId=10015809&locale=en_GB. http://www.exodontia.info/files/BDA_2011._Early_Detection_of_Oral_Cancer._A_Ma nagement_Strategy.pdf
Strengths and weakness of available web resources and e learning platforms on oral cancer are reviewed by Varela-Centelles et al. (2015).

Other factors affecting delay
Social and cultural factors
Disadvantaged groups are more likely to be diagnosed with advanced disease or worsened cancer-related outcomes (Wade et al., 2004). In whatever way we measure deprivation – by education, income or occupation - people in lower social classes are at a higher risk of developing oral cancer (Conway et al., 2008). Inevitably, they also present late in health care settings: a study among patients under 45 years of age from South East England confirmed that patients of a lower social class were more likely to delay presentation to a healthcare setting (Llewellyn et al., 2004). Even controlling for Socio Economic Status [SES], minority and medically-underserved groups tend to present with late stage disease and consequently suffer higher morbidity and mortality rates than other groups (Freeman, 2004). The 5-year survival rates for oral cavity, pharynx and other head and neck cancers are significantly lower for male African Americans than Caucasians. Shavers et al. (2003) suggested that differential rates of early detection may contribute to racial differences in survival and mortality from cancers of the oral cavity and pharynx. Patients who took traditional herbal medication before seeking professional consultation had a significant delay in diagnosis (Tromp et al., 2005).

Evidence from other fields of oncology suggests that patient delay behavior may be influenced by holding negative attitudes toward seeking medical help, and holding negative beliefs about the consequences of the cancer. In patients reporting lifestyle stress in the period prior to diagnosis, the risk of delay could be higher (Llewellyn et al., 2004). (Table 4)

In a national population-based survey of adults in the UK (Robb et al., 2009) most widely endorsed barriers to seeking the first consultation was:

- Difficulty in making an appointment
- Not wanting to waste doctor’s time
- Worry about what the doctor might find

In addition to providing education, during public awareness we should consider empowering the public to seek medical advice as well as strengthen support at primary care by improving access.
Assessment of Oral Cancer Risk

Measuring risk for oral cancer has not received much attention. Regrettably, prediction of cancer risk is a minor component of oral health risk appraisals.

As most people have not even heard of oral cancer, perception of individual oral cancer risk is also poor (Warnakulasuriya et al., 1998). The Harvard Cancer Risk Index offers a simple estimation of personal risk of cancer for a number of major and common cancers (Colditz et al., 2000). It offers the potential for tailored health promotion messages to at-risk populations and also serves as a guide to general practitioners and dentists to screen or monitor the oral cavity of high-risk subjects whenever they present in a healthcare setting with other comorbidities.

A private insurance company (Denplan) in the UK has developed a risk assessment system for oral diseases (DEPPA) including an oral cancer risk assessment for patients registered in their Private Health System. Recently the program recorded 60,000 assessments by 700 dentists registered to use DEPPA. The key informers used are:

- Smoking and smokeless tobacco use
- Alcohol intake above safe limits (synergistically with smoking)
- Age and gender
- History of previous oral cancer

Based on above assessments, a score of 1-5 is assigned to patients at registration and follow up. In January 2016, for example, 2587 patients were assessed using DEPPA (average age was 56 years) and 10% were recorded to have several or many risk indicators (Score of 4 or 5) [Personal information Drs Mike Busby and Henry Clover].

However, among young persons [arbitrarily set at under 45 years of age], approximately 25% of those who develop oral cancer may not have had any risk factors (Llewellyn et al., 2001), calling into question whether a high risk
assessment may significantly disadvantage this age group. Although oral cancer among under 45-year-olds is still relatively rare, a review has shown that oral cancer cannot be discounted in patients of any age who report no history of tobacco or alcohol use (Llewellyn et al., 2001).

**Access to care**

There is lack of adequate healthcare coverage available to many persons living in less developed countries to seek medical opinion when faced with minor /initial mouth cancer symptoms. There are, of course, countries in the developing world, such Cuba, Chile and Sri Lanka, which should be considered as exemptions which provide universal access to free care. Elsewhere, even when it’s available it is often inequitable and unaffordable. Socioeconomic inequalities and poor access to care are not exclusive to low income countries. Long-term trends (based on US SEER data) in oral and pharyngeal cancer (OPC) incidence, mortality and survival show significant differences among U.S. blacks and whites. Five-year relative survival rates for patients diagnosed during the period 1995-2001 were higher for whites than for blacks and lowest for black males (Morse and Kerr, 2006). The US healthcare system has been very fragmented and uncoordinated, resulting in delays of diagnosis and treatment. With the passage of the Affordable Care Act (ACA) there are provisions within the Accountable Care Organization’s (ACO) framework that may help address some of these delays. ACOs will benefit as they implement changes in their health systems to reduce costs and improve quality of care. There is an opportunity for the Global Oral Cancer Forum (GOCF) to present a value proposition to the ACOs that early detection and diagnosis, of oral and oropharyngeal cancer can do both; improve morbidity associated with these malignancies and reduce costs.

A number of organizations, such as the International Association of Dental research (IADR) through Global Oral Health Inequalities: the Research Agenda (GOHIRA have created awareness of the role of socioeconomic inequality in access to care both within and between countries and have proposed new research and mobilization of resources to be equably allocated to public health
programs (Williams, 2014).

Some reported interventions to improve early detection

NICE (UK) Guidelines

Considering that survival rates in oral cancer patients had not improved for decades the UK Department of Health (DoH), through the National Institute for Health and Clinical Excellence (NICE) developed guidelines for the detection and referral of head and neck cancers. These were set out in 2004 and recently revised. The objective was to reduce any diagnostic delays that could occur in primary care. These guidelines allowed all patients who met the DoH’s criteria for urgent (2-week) referral to be referred directly to the designated oral and maxillofacial unit at a local hospital or an oral medicine unit in a teaching dental hospital in the UK. The 2005 NICE guidelines for urgent referral in England and SIGN guidelines for Scotland (http://sign.ac.uk/pdf/sign90.pdf) are collectively given below:

- Ulceration of oral mucosa persisting for more than 3 weeks
- Oral swellings persisting for more than 3 weeks
- All red or red and white patches of the oral mucosa
- Dysphagia persisting for more than 3 weeks
- Unexplained tooth mobility not associated with periodontal disease
- Unresolved neck masses for more than 3 weeks.

Use of the 2-week waiting referral scheme in the UK was expected to provide rapid access to secondary care facilities to confirm the diagnosis of suspected cancer. NICE considered any referral criterion on the basis of a very low likelihood of cancer and this 2005 guidance led to high proportion of false-positive referrals under the 2-week wait system. An audit of 100 urgently referred cases to a secondary care facility suggested that only 6% were subsequently confirmed with a cancer following specialist investigations (Singh & Warnakulasuriya, 2006).

The revised NICE guideline (2016) includes only the first three symptoms of the previous list, and the system suggests that red or white patches consistent with
leukoplakia or erythroplakia should be referred by GPs, but such patients are first reviewed by a dentist prior to referral. This is so that dentists can exclude benign disease such as geographic tongue and candida infection, which form a significant proportion of false-positive referrals. Whether the revised guidelines will improve the sensitivity of case detection remains to be seen.

Even persistent oral ulcers and erosions fail to arouse suspicion as this is a final common manifestation, sometimes clinically indistinguishable, of a diverse spectrum of conditions ranging from traumatic lesions, infectious diseases, systemic and local immune-mediated conditions though a neoplastic ulcer need to considered on the top of the list of the differential diagnosis drawn by a clinician. Compilato et al. (2009) have, therefore, drawn up a guideline distinguishing simple, complex and destroying (S-C-D system) ulcerations, as each requires different diagnostic evaluations and referral priorities.

The UK was the first European country to establish national guidelines to facilitate prompt referral of a suspected malignancy from primary to secondary care. The availability of a government-funded National Health Service provides the cornerstone for such a scheme and for an integrated care pathway. Countries with similar health systems could attempt to reproduce the NICE referral guidelines to measure their effectiveness. Based on the UK system, the Spanish Dental Council has introduced a similar scheme to their dentists.

**Spanish Oral Cancer Campaign**

At a cost of €30,000 euros per year, the Spanish Dental Council has involved 2000-3000 dentists per year (10% of Spain’s dental practitioners) in a national campaign to promote early detection and prevention of oral cancer over the past 5 years. A clinical guide on referral of malignancy suspected lesions (http://www.canceroral.es/) was prepared, dentists attended a 4-hour course on early oral cancer diagnosis, and received a free copy of a book on oral cancer. When evaluated among 440 participating dentists, the intervention appears to have improved the dentists’ knowledge, confirming the importance of this campaign (Seoane-Lestón et al., 2010). Free oral screening was delivered over a 2-week period at volunteer private
dental clinics by 1700 dentists. An urgent pathway (similar to the UK) for the referral of patients with suspicious lesions to maxillofacial surgery services was established, but this has had an unbalanced impact in different regions. Furthermore, the Spanish Dental Council found it difficult to persuade the public authority to actively participate in this campaign.

**Early Intervention in Oral Cancer in Portugal: The PIPCO program**

In January 2014, a new initiative called Early Intervention in Oral Cancer (Projeto de Intervenção Precoce de Cancro Oral; PIPCO) was officially approved in Portugal, developed under the framework of the National Program of Oral Health Promotion, and has been driven by the Portuguese Ministry of Health and the General Dental Council. The program underpins easier access to primary care, more investigation for oral symptoms and faster referral that could reduce the proportion of people diagnosed with oral cancer at a later date.

As most of dental care is provided by dentists in private clinics, the aim of the program is to involve private dentists in the oral cancer diagnostic process. The main novelty of the Portuguese program is the combination of public and private resources, and a joint doctor-dentist referral pathway for high-risk cases. The program also benefits from the government underpinning payment for procedures performed by private dentists enrolled on the project.

At the inception of the Project, all interested dentists working in Portugal were invited to attend a 7-hour theoretical course on differential diagnosis of oral cancer and to undertake a 1-hour evaluation of their knowledge on this topic and further calibration on biopsy techniques. A total of 240 dentists were then selected based on the test results and on geographical criteria (to achieve an appropriate distribution of professionals involved across the country), to act as oral cancer diagnosticians. This represented one selected dentist of 35 potential candidates each to provide care for approximately 43,750 potential patients. The design of the study allows patients visiting the family physician in the first instance (public health system) to be referred to his/her dentist. The dentist is required to perform a screen and a differential diagnosis at this visit (will receive a payment of $16 for the dentist check) and if
something suspicious is detected, he/she will perform a biopsy ($53). Biopsy will be reported at the hospital laboratory (public health system) and the dentist will inform the patient of the biopsy results and provide a referral to the nearest hospital for further assessment.

From March to December 2014 (10 months), a total of 2,412 patients were referred to dentists involved in this program for differential diagnosis. Biopsy samples were taken in 320; 14 cases were confirmed as positive for oral cancer (0.5% of all patients referred to a dentist by his/her GP and 4% of biopsies performed).

The Portuguese program is at an early stage for further evaluation, but represents efforts by the government to enter a public-private partnership in an attempt to develop a care pathway that will reduce diagnostic delays and combat difficulties to access for care for high risk patients who may otherwise not visit a dentist. The Portuguese program, if it proven successful in the coming years, could be implemented in other countries with a particular focus on populations with low health awareness and/or literacy, and taking into account its cost-effective approach for affordable interventions in private clinics.

**United States**

**State of Maryland**

From early 2000 the State of Maryland in the US took a concerted effort to launch a state-wide Comprehensive Oral Cancer Control Plan (Maybury, 2011). Over a 12 year period oral cancer examinations increased from a disturbingly low 20 percent to 40 percent of the population. The Maryland model not only included dentists but other health professionals as well, including dental hygienists, physicians, physician’s assistants and nurse practitioners. An early goal was to develop skills to deliver diagnostic services in primary care and to address racial disparities in oral cancer incidence. The Maryland model has demonstrated that a multi-sectorial approach to provide education to the public and improving the skills of health professionals can create substantial changes in the outcomes of oral cancer in a state-wide population (Alfano, 2012). The steps taken by Marylanders may serve as a model for other US states.
Detroit, Michigan

A social marketing campaign was launched in 2005-2007 to address excess risk of oral cancer in Detroit tri-county area, Michigan. According to the 1998-2002 Surveillance Epidemiology and End Results data, rate of oral and pharyngeal cancer (“oral cancer”) incidence among black males living in the Detroit tri-county area (Macomb, Oakland, and Wayne) was one of the highest in the United States (US) (25.7 per 100,000 persons) (Kolker, 2007). The Detroit Oral Cancer Prevention Project, launched a multifaceted social marketing campaigns and community outreach programs that primarily targeted black males living in the Detroit tri-county area. During the campaign, 42 billboards, 1,327 radio advertisements screened during 2 popular radio programs and 2 newspaper advertisements, were used to increase awareness of high risk of oral cancer and promote free screening at a clinic run by the project. In a community outreach intervention, 3 health educators led 242 education sessions across 89 organizations. 1,020 adults were screened and 78 were referred for further examinations (Ismail, 2012; Jedele, 2012). Dentists and physicians in the area reported increased interest in oral cancer screening by their patients. The authors’ data suggested that the campaign was more likely to be associated with a decreasing trend of oral cancer incidence in the intervention counties but caution should be taken in evaluating multiple factors that contribute to the reduced oral cancer incidence rates and mortality because factors other than the intervention may affect incidence and mortality rates such as reduced use of tobacco products and advances in treating oral cancer. This study however, highlights a potential impact of concerted efforts to improve the oral cancer awareness in the high-risk communities.

South America
Retraining dentists in Argentina to reduce delays in diagnosis

Considering that the healthcare system for caring for oral cancer care in Argentina is not coordinated systematically, in 1998 Oral Medicine academics introduced a data gathering program that later led to a novel intervention.

Analysis of clinical data corresponding to 274 oral cancer (OSCC) patients diagnosed and followed up for 5 years at the Oral Medicine Department of the
School of Dentistry of the University of Buenos Aires (FOUBA) (Brandizzi et al., 2008), showed that 5-year survival rate was only 38%, and that the localizations with worse prognosis were the floor of the mouth and tongue, with 19 and 27% 5-year survival rate respectively. Morelatto et al (2007) in Córdoba province, Argentina, further showed a 30-day professional delay in diagnosis in 68% of patients diagnosed at stages I and II and 54% of patients diagnosed at stages III and IV. Interestingly, professional delay was significantly longer in early stage cases. A previous study involving an online survey conducted in alumni of the University of Buenos Aires showed that only 30% of dentists routinely examine the oral mucosa.

In view of the above findings several strategies were implemented at different levels: At the graduate teaching level, students were required to begin mandatory oral examination of every patient by examining the tongue, especially the border of the tongue. This strategy was adopted to try and change the habitual approach of dentists. The second approach was to retrain the practicing dentists to undertake routine screening and discuss their cases with regional specialists via tele-medicine. More than 520 general dentists from different provinces throughout the country received training including theory and practice work in seminar-based courses and through an online hospital network. The training aimed to calibrate dentists to detect potentially malignant disorders and oral cancer. Community specialists were appointed to take appropriate photographs of suspicious oral lesions detected in their region. These images were transmitted via e-mail in order for those in charge of the region to establish presumptive diagnosis and mark the biopsy site/sites on the photographic image. Difficult cases were analyzed and discussed by all the regional heads.

After ten years of the program, the cases referred to the Oral Medicine Department at the FOUBA were evaluated and compared to the data obtained during the 10 years before implementing the project. In the second decade, 5-year survival rate rose by 24%, increasing from 38% before the program to 62% after implementation of the oral cancer prevention program described here. This statistically significant change was more evident in tongue cancer survival rates, which increased from 27% in the first period to 55% in the second. In addition, the number of cases diagnosed at advanced stages of the disease (3 and 4) decreased from 66.3% to 50.7%.
Based on the results obtained with the project in Argentina, the International Association for Dental Research (IADR) supported the implementation of an oral cancer prevention program in Latin America, Through their Regional Development Program. The program is currently underway in Venezuela, Panama, Colombia, Peru, Uruguay, Chile, Paraguay and Argentina

**Consequences of delayed diagnosis**

The authors have thus far focused on the issues of poor prognosis and increased morbidity resulting in poor quality of life for oral cancer survivors that could be directly attributable to delays in diagnosis in either primary or secondary care. As a result of delays, the increased cost burden of treating advanced cancers also requires due consideration (Jacobson *et al.*, 2012)

Despite the rising incidence of oral cancer and particularly oropharyngeal cancers (OC/OP) and the potential for disability and disfigurement that may result from treatment, published research on the direct and indirect cost burden of oral cancer is limited. It may be hypothesized that early detection of cancers may diminish the cost of care for individuals and employers, thus providing additional impetus for more effective preventive efforts.

In the United States, an analysis of commercially-insured individuals revealed that the average medical costs of OC/OP cancers in the first year after diagnosis was $79,151, which is significantly higher than the cost to treat other cancers ($31,559-$65,123) (Lawless, 2009; Short *et al.*, 2011). Furthermore, individuals who received surgery, radiation and chemotherapy (ie cases detected in advanced stages) averaged $153,892 during the first year after diagnosis. These medical costs are approximately twice any other reported cancer costs. These results are not surprising given the multiple modalities of treatment driven by the significant number of late or later stage diagnoses. Further, the average number of missed days of work for those individuals who survived and were not disabled was 48.3 days compared to other cancers at 44 days of missed work. Lastly, 52% of OC/OP cancer patients who survived were permanently disabled and unable to return to work (Taylor, et al 2004). Therefore, delays in detection and diagnosis have a significant burden on individuals as well as society.
Improving early diagnosis in primary care

The current standard for oral cancer detection in primary care in most countries is by visual examination supplemented by palpation. Clinical skill building among primary care practitioners should therefore be considered as a part of life-long learning.

As shown in a US study that pre and post tested knowledge on oral cancer, continuing education courses have a positive influence on participants' oral cancer attitudes, knowledge, and behavior. Life long learning potentially could make a difference, particularly on the earlier detection of asymptomatic lesions (Silverman et al., 2010).

In most situations diagnostic and adjunctive diagnostic tests are essential elements of healthcare delivery to confirm clinical findings of a suspicious mucosal abnormality. These tests are designed to inform and guide decisions that influence the course of illness and costs. Since the early 2000, a number of adjunctive diagnostic and screening tests for oral squamous cell carcinoma have been introduced. These diagnostic tests are presented and discussed in detail by Group 4 at the Forum.

Clinical and economic value for diagnostic tests can be established through the following evaluation criteria:

- Feasibility (technical) of the dental office to produce consistent results
- Diagnostic accuracy as defined by sensitivity (false positive), specificity (false negative) and positive and negative predictive values
- Impact on diagnostic and therapeutic thinking and behavior of the dentist
- Impact on patient outcomes (improved outcomes)
- Impact on society (cost-effectiveness).

In the US, with the FDA approval of many commercial products, the field of diagnostic testing is shifting the location of where this testing is conducted. With today’s technology, there is a move away from central laboratory facilities to point-of-care locations, such as outpatient treatment facilities and even
home-based tests. Home pregnancy tests and glucose monitoring are but two examples of this shift. The extension to the dental office is within our grasp. The OncAlert product, discussed in Group 4, represents a point of care technology for oral cancer. These technologies have enhanced costs in the short term, but could pay off in the future because of their potential to detect cancers early.

In countries that lack a national health service, the commercial sector is central to research, development and testing of diagnostic aids, and their input and vision in partnership with governmental and academic organizations will be essential for formulating solutions to early detection of cancer.

Conclusions

Every year half a million people are diagnosed with oral and oropharyngeal cancer worldwide. On average 50% of them die with or of the disease within the first 5 years of diagnosis. Diagnostic delay in the detection of oral and oropharyngeal cancers is common. The data presented by our group has significant implications for future oral cancer policy and planning cancer services. Clearly, late detections pose a major public health challenge in most countries in the world. Some methodological issues when researching referral delays in primary care need to be considered. We urge the Forum to reflect on the overarching question on how to improve death rates from oral cancer.

Although it is not known whether patient delay is a result of a lack of knowledge with regard to oral cancer signs and symptoms, public education is still paramount in raising people's awareness of oral cancer from an early age. To achieve this goal, targeted education campaigns through media to alert the public about the warning signs of oral cancer are needed. To reduce scheduling delays, medical and dental school training about this disease must be improved. Opportunistic oral cavity examinations with follow-up of suspicious lesions must be promoted to reduce the burden of disease.
In addition, stronger evidence on the impact of delay on disease control could be achieved through better measurement of delay duration. More detailed studies relating delay to disease outcomes are needed. Views of patients and caregivers are of critical importance for understanding any gaps in primary healthcare delivery. Such evidence would underscore the need for programs to educate high-risk persons and primary care providers about the importance of prompt referral in the presence of symptoms, and may also provide a stronger argument than is currently available for opportunistic screening of high-risk persons for oral cancer whenever possible.

The study of patients' visits to primary care facilities prior to a cancer diagnosis can identify determinants and populations at risk of a delayed diagnosis. Development of early detection guidelines will help to configure optimal diagnostic assessment programs. Evidence-based guidelines with standards of care that suit local settings are fundamental for improving the quality of care delivered when a person presents to a GP or a dentist with a suspicious sign or symptom that needs an urgent referral.

**Acknowledgements**: We thank Dr Luis Monteiro (Oporto- Portugal) for conducting a literature search on the stage of oral cancer and prognosis.

**References**


Cleveland JL, Thornton-Evans G. Total Diagnostic Delay in Oral Cancer may be Related to Advanced Disease Stage at Diagnosis. Journal Of Evidence-Based Dental Practice 2012 Jun;12(2):84-6.


Wade et al., cáncer disparities by race, ethnicity and socioeconomic status. CA J Cancer Clin 2004; 54: 78-98.


G.A. Colditz, K.A. Atwood, K. Emmons, R.R. Monson, W.C. Willett, D. Trichopoulos & D.J. Hunter, for the Risk Index Working Group, Harvard Center for Cancer


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*Fig 1.* Kaplan Meier curves illustrating survival in relation to stage of disease in 7 studies published from 2005-2015 from various countries.
Rikardesen et al., 2014 – Northern Norway

Monteiro et al., 2014 Oporto, Portugal

Ling et al 2013, Xingjiang, China

Dissanayaka et al., 2012, Sri Lanka

Jan et al., 2011, Taichung, Taiwan

Kreppel et al., 2010 Cologne, Germany
Figs 2 A and B. Types /Stages of diagnostic delay in oral cancer (Gomez et al., 2008; Guneri & Epstein, 2014)
Tables 1 A and B: Association of stage of disease and Survival
Factors not found to be significant

- age, gender, race, tumor site, positive margins

Factors significant with survival

- TSCC
  - stage, treatment type, loco-regional recurrence, tumour grade, perineural permeation
  - tumor invasion depth, perineural invasion, resection margin, treatment, stage

- OOSCC
  - stage, treatment, recurrence
  - sex, age, neck surgery

- OC
  - age, gender, alcohol consumption, smoking history
  - age, gender, smoking habits, diagnostic delay

- OSCC
  - stage, treatment, recurrence
  - systemic recurrence, tumour size, T stage, N stage, systemic recurrence, tumour size

- HNC
  - age, gender, treatment, stage, differentiation, treatment failure
  - age, gender, smoking, alcohol habits, margin status, lymphatic invasion
  - gender, age, residence, smoking habits, subsite

- BCSC
  - stage, differentiation, treatment failure
  - age, tumour differentiation, primary site, smoking, pT status

- OSCS
  - stage, pattern of invasion, excision margins

- HNC
  - stage, treatment, differentiation, age > 50 years

- OSCS
  - surgical margins, cervical nodal metastasis, stage

- OSCS
  - surgical margins, cervical nodal metastasis, stage

- OSCS
  - surgical margins, cervical nodal metastasis, stage, smoking, smoking history

- TSCC, tongue squamous cell carcinoma; OSCC, oral squamous cell carcinoma; HNC, head and neck cancer; OC, oral cancer; OSCS, oral and oropharynx squamous cell carcinoma; DSS, disease-specific survival; DFS, disease-free survival; OS, overall survival; CDSS, cumulative disease-specific survival; NR, not referred.

Table 2 – Five year survival rates in Oral Squamous Cell Carcinomas

<table>
<thead>
<tr>
<th>Stage</th>
<th>TMN classification</th>
<th>5-Year survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1N0M0 (primary tumour less than 2cm)</td>
<td>85</td>
</tr>
<tr>
<td>II</td>
<td>T2N0M0 (primary tumour between 2 and 4 cm)</td>
<td>66</td>
</tr>
</tbody>
</table>
### Table 3. Reports on total diagnostic delay of oral cancer. An international perspective.

<table>
<thead>
<tr>
<th>Report</th>
<th>Country</th>
<th>Location</th>
<th>Patients</th>
<th>Median of Total Delay*</th>
<th>Total Delay* &gt;3 months</th>
<th>Range of Total Delay*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elwood et al 1985</td>
<td>Canada</td>
<td>Mouth</td>
<td>134</td>
<td>3 mo.†</td>
<td>64% (&gt;2 mo.) ‡</td>
<td>N.A.</td>
</tr>
<tr>
<td>Jovanovic et al 1992</td>
<td>Holland</td>
<td>Mouth</td>
<td>50</td>
<td>46 days</td>
<td>N.A.</td>
<td>14-724 days</td>
</tr>
<tr>
<td>Kowalski et al 1994</td>
<td>Brazil</td>
<td>Mouth &amp; oropharynx</td>
<td>336</td>
<td>N.A.</td>
<td>57.4%</td>
<td>N.A.</td>
</tr>
<tr>
<td>Gorsky et al 1995</td>
<td>Israel</td>
<td>Mouth &amp; oropharynx</td>
<td>543</td>
<td>4 mo. (lip cancer)</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>Wildt et al 1995</td>
<td>Denmark</td>
<td>Mouth</td>
<td>167</td>
<td>4 mo.</td>
<td>N.A.</td>
<td>19-783 days</td>
</tr>
<tr>
<td>Allison et al 1998</td>
<td>Canada</td>
<td>Upper aerodigestive tract</td>
<td>188</td>
<td>N.A.</td>
<td>58.5% ‡</td>
<td>N.A.</td>
</tr>
<tr>
<td>Kerdpon et al 2001</td>
<td>Thailand</td>
<td>Mouth &amp; lip</td>
<td>161</td>
<td>141.8 days (mean)</td>
<td>20% †</td>
<td>0-1085 days</td>
</tr>
<tr>
<td>Pitiphat et al 2002</td>
<td>Greece</td>
<td>Mouth &amp; pharynx</td>
<td>105</td>
<td>30 days</td>
<td>52% † (&gt;3 weeks)</td>
<td>0-170 days</td>
</tr>
<tr>
<td>Carvalho et al 2002</td>
<td>Brazil</td>
<td>Lip, mouth, oropharynx</td>
<td>417</td>
<td>N.A.</td>
<td>27.57% (&gt;2 mo.)</td>
<td>N.A.</td>
</tr>
<tr>
<td>Onizawa et al 2003</td>
<td>Japan</td>
<td>Mouth</td>
<td>152</td>
<td>2.7 mo.</td>
<td>N.A.</td>
<td>0.4-63 mo.</td>
</tr>
<tr>
<td>McGurk et al 2005</td>
<td>UK</td>
<td>H &amp; N</td>
<td>613</td>
<td>3 mo.</td>
<td>51.22%</td>
<td>N.A.</td>
</tr>
<tr>
<td>Tromp et al 2005</td>
<td>Holland</td>
<td>H &amp; N</td>
<td>306</td>
<td>N.A.</td>
<td>78.4%</td>
<td>N.A.</td>
</tr>
<tr>
<td>Scott et al 2005</td>
<td>UK</td>
<td>Mouth</td>
<td>245</td>
<td>3 mo.</td>
<td>44%</td>
<td>0-36 mo.</td>
</tr>
<tr>
<td>Brouha et al 2007</td>
<td>Holland</td>
<td>H &amp; N</td>
<td>306</td>
<td>14 days ‡</td>
<td>N.A.</td>
<td>0-570 days †</td>
</tr>
<tr>
<td>Morelatto et al 2007</td>
<td>Argentina</td>
<td>Mouth</td>
<td>70</td>
<td>68.8 days m†</td>
<td>61% (&gt;1 mo.)</td>
<td>N.A.</td>
</tr>
<tr>
<td>Peacock et al 2008</td>
<td>USA</td>
<td>Mouth</td>
<td>50</td>
<td>205 days (mean)</td>
<td>N.A.</td>
<td>52-786 days</td>
</tr>
<tr>
<td>Teppo et al 2008</td>
<td>Finland</td>
<td>Tongue</td>
<td>62</td>
<td>1.4 mo. †</td>
<td>32% †</td>
<td>0.1-18 mo. ‡</td>
</tr>
<tr>
<td>Gao and Guo 2009</td>
<td>China</td>
<td>Mouth</td>
<td>102</td>
<td>7 weeks ‡</td>
<td>N.A.</td>
<td>1-367 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author &amp; publication year</th>
<th>Focus</th>
<th>Design</th>
<th>Sample</th>
<th>Findings: Factors associated with patient delay and oral cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerdpon and Sriplung, 2001</td>
<td>To investigate the factors related to patient and professional delay in diagnosis of oral cancer</td>
<td>Quantitative Structured questionnaire</td>
<td>n = 161</td>
<td>Prolonged patient delay associated with the use of traditional herbal medicine. No significant association between any other variables investigated (sex, age, marital status, religion, area of residence etc)</td>
</tr>
<tr>
<td>Kumar et al., 2001</td>
<td>To analyse the psychosocial factors related to delay in presentation of oral cancer patients</td>
<td>Quantitative Questionnaire</td>
<td>n = 79</td>
<td>Ill-fated to have cancer (fate) Cancer a curse Non-availability of transport trivial ulcers in mouth (symptom interpretation) Socioeconomic status was associated (univariate analysis) with patient delay in India Belief that prolonged treatment renders the family stressful</td>
</tr>
<tr>
<td>Pitiphat et al., 2002</td>
<td>To identify factors associated with delay in the diagnosis of oral cancer</td>
<td>Explorative Quantitative Structured Questionnaire</td>
<td>n = 105</td>
<td>Non smokers/Former Smokers have a significantly higher risk of delay than current smokers (no association with the quantity consumed) No association between delay and alcohol use No association between age, gender and education with delay. Strong association between sexually transmitted disease and delay in diagnosis</td>
</tr>
<tr>
<td>Onizawa et al., 2003</td>
<td>To analyze factors contributing to delay in the diagnosis of oral cancer</td>
<td>Quantitative Retrospective case study analyses</td>
<td>n = 152</td>
<td>There was no significant association between delay and gender, age, past history of malignant disease, number of family members living in the same house, daily medication, employment, tobacco use or alcohol consumption</td>
</tr>
<tr>
<td>Study</td>
<td>Research Question</td>
<td>Design/Methodology</td>
<td>Sample Size</td>
<td>Findings</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Llewellyn et al., 2004</td>
<td>To investigate factors predictive of patient delay among younger patients with oral cancer</td>
<td>Qualitative Interview</td>
<td>n = 53</td>
<td>Risk of delay was higher in patients with no further education Significant stress in the period prior to diagnosis lower amounts of tobacco smoked per day Patients of lower social class more likely to delay</td>
</tr>
<tr>
<td>Tromp et al., 2004</td>
<td>To investigate the association between patient delay and the psychological factors in patients with head and neck cancer</td>
<td>Mixed Methods Questionnaire Interview</td>
<td>n = 277</td>
<td>Age (over 65) Living alone Gender and education not related Negatively related to optimism, health hardiness and overall defensive functioning Positively related to avoidance coping. Excessive drinking</td>
</tr>
<tr>
<td>Brouha et al., 2005</td>
<td>To examine which factors are related to patient delay in patients with pharyngeal and oral cancer</td>
<td>Retrospective Mixed Methods Design Interview and Questionnaire</td>
<td>N = 134</td>
<td>Marital status, living situation, education and income not associated with patient delay. Smoking and drinking not related. Psychosocial variables Symptom presentation was a factor for delay e.g. pain with no visible lesion, longer delay Symptom interpretation Misattribution of symptoms (dental problems or infection) Lack of knowledge (no idea what the cause could be) Reasons to postpone (thought the symptom was harmless; didn't bother them, ignored symptom, didn't go to doctor often, were anxious).</td>
</tr>
<tr>
<td>Rozniatowski et al., 2005</td>
<td>To examine the psychosocial factors involved in delayed consultation by patients with head and neck cancer</td>
<td>Mixed Methods Semi-structured interview Clinician administered questionnaire Self-administered questionnaire</td>
<td>n = 100</td>
<td>Living alone (social factors) (65% for more than 1 month and 43% for more than 3 months)</td>
</tr>
<tr>
<td>Scott et al., 2006</td>
<td>To explore patients' initial experiences and reactions to developing symptoms of oral cancer</td>
<td>Qualitative exploratory study In-depth semi-structured interviews</td>
<td>n = 17 (before treatment)</td>
<td>Psychosocial Variables Process of symptom interpretation Unconcerned about symptoms Knowledge of oral cancer Beliefs regarding the symptom (not attributed to cancer (failure to attribute symptoms to cancer is a predictor of patient delay), minor oral conditions), Coping responses (self medication, changing the way they ate) Patients social responsibilities (competing life events) (barrier to seeking help)</td>
</tr>
<tr>
<td>Scott et al., 2007</td>
<td>To produce a theory guided investigation of the specific cognitive and emotional reactions to the self-discovery of potentially malignant oral symptoms</td>
<td>Qualitative Exploratory Study Semi-structured interviews</td>
<td>n = 57</td>
<td>Attributing the symptoms to transient, minor conditions that cause no need for emotional distress Symptom interpretation/reinterpretation Symptom beliefs Emotional responses e.g. lack of concern</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Title</td>
<td>Methodology</td>
<td>Sample Size</td>
<td>Findings</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------</td>
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<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Rogers et al., 2007</td>
<td>Exploring the relationship between deprivation and patient delay in presentation and treatment of oral cancer</td>
<td>Retrospective quantitative case note review</td>
<td>( n = 559 )</td>
<td>Primary health professional, patient age, gender, marital status and deprivation showed no obvious correlation with patient delay. High alcohol consumption implicated as a factor in patient delay, also an association with smoking.</td>
</tr>
<tr>
<td>Scott et al., 2008</td>
<td>Factors associated with patient delay for potentially malignant oral cancer symptoms</td>
<td>Cross sectional Quantitative Questionnaire (psychosocial and patient delay)</td>
<td>( n = 80 )</td>
<td>Minor condition, Lack of knowledge, Lower perceived ability to receive help (socioeconomic status), Competing life events, Higher levels of deprivation. 3 variables that were independent predictors of patient delay (average severity of life events in the 'patient delay period; knowledge of oral cancer; perceived behavioural control.) Misattribution (relating the sore mouth to a current stress in their lives rather than relating it to cancer).</td>
</tr>
<tr>
<td>Scott et al., 2009</td>
<td>Exploring the reasons for patient delay in seeking treatment following self-discovery of potentially malignant oral cancer symptoms</td>
<td>Qualitative Exploratory Study Semi-structured interviews</td>
<td>( n = 57 )</td>
<td>Beliefs regarding the oral symptom (Initial interpretation as minor, self correcting condition; self treatment), Factors relating to the circumstance (Competing responsibilities) Emotions.</td>
</tr>
<tr>
<td>Gao and Guo, 2009</td>
<td>To analyse the possible factors involved in patient delay</td>
<td>A prospective quantitative approach Self-designed questionnaire</td>
<td>( n = 102 )</td>
<td>Gender and age was not associated with patient delay.</td>
</tr>
<tr>
<td>Grant et al., 2010</td>
<td>Explores the reasons for patient delay in younger patients seeking treatment from a GP or a dentist</td>
<td>Qualitative Exploratory Study Semi-structured interviews</td>
<td>( n = 15 ) (&lt;45 yrs old)</td>
<td>Low awareness, Self treatment, Watchful waiting, Interpretation of symptoms (no pain, small, didn't bother them, minor condition).</td>
</tr>
<tr>
<td>Rogers et al., 2010</td>
<td>Exploring the reasons for delayed presentation in oral and oropharyngeal cancer from the patients perspective</td>
<td>Cross Sectional Mixed Methods Short survey Telephone Interview</td>
<td>( n = 71 ) (44 of whom were interviewed)</td>
<td>Misinterpretation of symptoms (minor/trivial, staying the same initially, probably would get better by itself, self medication), Low awareness (little thought as to whether it might be cancer).</td>
</tr>
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