

Diagnostic Delay in Oral Cancer: An Overview of Different Perspectives on a Public Health Problem

Pablo Álvarez-Nóvoa^{1*}, Juan M Seoane-Romero¹, Carmen López Silva², Miguel Anxo Losada-López³ and Pablo Varela-Centelles^{1, 2}

¹Stomatology Department, School of Medicine and Dentistry, University of Santiago de Compostela, Santiago de Compostela (A Coruña), Spain

²C.S. Praza do Ferrol, Primary Care Clinics, Galician Health Service, Lugo, Spain

³Hospital Lucus Augusti (HULA), Galician Health Service, Lugo, Spain

Abstract

Early diagnosis in oral cancer may have a major role in improving survival rates, allowing patients to take advantage of less aggressive treatments, mitigating the morbidity of the process. Definitive diagnosis of oral cancer is the result of a complex chain of related events. In an attempt to shorten this time period, many authors have developed different theoretical models for explaining the diagnostic process. The absence of a widely accepted framework and the heterogeneous approaches to this issue hamper research on this topic.

Public awareness about oral cancer is low, and patients frequently delay consultation with a healthcare professional despite having experienced some kind of symptoms for months. The design of the healthcare system has also a part in this play, as there are evidences supporting the idea that health policies modulate not only the diagnostic or treatment intervals, but also the patient's help-seeking period.

General medical and dental practitioners are in an excellent position for early diagnosis and prevention of oral cancer. Continuing education programmes have proved useful in increasing knowledge and favouring positive attitudes towards oral cancer amongst healthcare

providers. When asked about the main barriers for a correct diagnosis of oral cancer, clinicians usually demand further education, a better access to diagnostic resources, and complaint about tight working schedules. Thus, the aims of this narrative review have been to depict the components of the oral cancer diagnostic process, to describe the main agents involved, and also to identify feasible interventions with a potential to diminish these time intervals.

Keywords: Oral Cancer; Diagnostic Interval; Diagnostic Delay; Health Policies; Survival

***Corresponding Author:** Pablo Varela-Centelles, CS Praza do Ferrol. Praza do Ferrol 11, 27001 Lugo, Spain; Tel: +34.982. 245.46; E-mail: pvarelac@infomed.es

Introduction

Oral Cancer (OC) is a life-threatening, potentially disfiguring disease, causing functional disability, psychological alterations, and socioeconomic problems for patients and their relatives. Oral cavity is the most common location of head and neck primary malignant tumours. Even though it is an easy-to-explore anatomical area, almost 50% of oral cancers are diagnosed at stages III or IV [46], and mortality rates have been

linked to disease stage [41]: the five-year survival rate of patients diagnosed at stage I is estimated to be 80%, and falls down to 20% in those diagnosed at stage III and IV [42].

An ideal early diagnosis would take place during the carcinogenesis process, but current molecular biology techniques have not achieved this goal [18,11], and therefore early diagnosis at a cellular level and the identification of hypothetical diagnostic markers remain as an objective for the future.

Nowadays, suspicion of oral cancer is mostly based upon clinical findings and the actual characteristics of the disorder usually compromise the clinicians' degree of alert: being a low prevalence disease, a Health Care Professional (HCP) will rarely deal with this disorder -a General Dental Practitioner (GDP) might face no more than 10 OC patients and a General Physician (GP) would hardly witness more than one case during their working life [41, 24]. Besides, OC symptoms usually are non-specific and typically resemble minor or benign diseases [42, 41, 24, 19]. These circumstances may well result on a late diagnosis of an oral malignant lesion.

The difference between a late and an early diagnosis can be frequently mirrored in terms of disease stage which, in turn, conditions patients' survival. Therefore, the study of time lapses until OC diagnosis may unveil opportunities for interventions for shortening these time intervals, with a potential effect on survival to the disease.

OC diagnosis is a complex process affected by multiple factors, and many authors have proposed models for explaining this phenomenon [27, 2, 33]. These efforts have produced relevant pieces of research whose contribution to knowledge in this field is often limited by inconsistent definitions of time intervals and terms, as well as by a poor validity of the variables considered by different research groups. The publication of the Aarhus statement on cancer diagnostic delay [47] will presumably contribute to overcome these weaknesses.

A sound approach to the problem of diagnostic delay of oral cancer would require a detailed study of the existing theoretical framework together with an analysis of the parts played by the main actors in the process. Therefore, the aims of

this narrative review were to depict the components of the oral cancer diagnostic process, to describe the main agents involved, and also to identify feasible interventions with a potential to diminish these time intervals.

Methods and Materials

We have carried out a narrative review of the scientific literature, using both international computerized repertoires (PubMed, EMBASE, Proceedings Web of Science and SciELO) and local databases (Catálogo de Bibliotecas del Sistema Universitario de Galicia / Catalogue of Libraries of the Galician University System).

The bibliographic search was undertaken during October-November 2014, considering the whole repertoires PubMed and SciELO, since 1980 in EMBASE, and since 1990 in Proceedings Web of Science (Conference Proceedings Citation Index-Science). The results were restricted to papers published in Spanish, Portuguese, French, Italian or English. The only exclusion criterion was the absence of relevant information for the objectives of this review.

The search strategy was ((“oral cancer” OR “oral squamous cell carcinoma”) AND (“diagnostic delay” OR “diagnosis” OR “time interval”) AND (“survival” OR “TNM stage” OR “quality of life” OR “prognosis”)). When the database architecture did not allow the use of this strategy, the search was fractioned in order to fulfil the conditions of the repertoire.

The publications were filtered by title and abstract contents. The selected documents were retrieved and divided into five non-mutually exclusive categories according to their main contents: Theoretical framework in diagnostic intervals research; Health system perspective; Patient perspective; GDPs' perspective; and GPs' perspective.

Results

Theoretical framework in Diagnostic intervals research

The absence of a widely accepted theoretical framework for research in this topic has resulted in a number of valuable, high-quality reports using such a wide range of study

variables and heterogeneous methodologies that hinder comparisons and progress in this field. In order to address this problem, several research groups have proposed models for describing the process between patient's first symptom, and search for help, to final diagnosis and the beginning of the treatment.

The first of these models, proposed by Shafer et al [27], considered only three determinants that affected the diagnostic interval: "appraisal delay", "illness delay" and "utilization delay". In this first attempt of describing the diagnostic interval, the factors that modulate patient response were described irregularly, and the process was considered a unidirectional one.

This three-stage model was modified in 1995 [2] to acknowledge the importance of the patients' behavioural response by including two additional stages: "appraisal delay", "illness delay", "behavioural delay", "scheduling delay" and "treatment delay". Psychological processes driving the patient through the model now play a major role, although they are not recognised as the sole determinants of interval duration. This model gained acceptance within the research community and somehow permitted the identification of further difficulties for research in oral cancer diagnostic delay: the absence of clear definitions or more specific time intervals, as well as a poor description of the processes taking place in each interval [33, 44]. "Illness delay" and "behavioural delay" have been particularly criticised: the former was considered difficult to distinguish from the appraisal delay, and the latter was pondered as a minor component with poor relevance for the model [44]. Scheduling delay has also been discussed; although its existence has been proven, it not only depends on patient's attitude [10].

"The model of pathways to treatment" [33] was published as an attempt to meet the objectives of promoting the early detection and treatment of the disease. It is a more complex and more complete model, which identifies not only the stages prior to the treatment of the disease, but also describes the processes and events taking place during this interval, as well as the factors determining the length of each interval. For the first time, the diagnostic route is not considered to be unidirectional or irreversible, highlighting the dynamism

of the diagnostic process, without determining a specific starting point.

It is important to mention its authors suggest abandoning the use of the term "delay", proposing the more accurate "time interval" to describe time periods between the milestones of the model. The "events" in this model are considered to be the key temporal moments towards diagnosis, defining the bounds between the "intervals". The duration of each period and the individual's response are modulated by a series of processes, resulting in the progression to the next event in the chain. The speed and direction an individual follows inside the chain is determined by a suite of factors encompassing the model.

In the year 2012, a consensus group presented the "Aahrus statement" [47], a document based on the models described in the literature, with the objective of providing recommendations for the definitions and methodological approaches that should be used in early diagnosis research. At the same time, a checklist aiming to facilitate the design of early diagnosis research works on cancer is proposed. After this publication, a new path is open for a more efficient and comparable research cancer diagnostic delay, although some adjustments may be needed in order to fit the specific characteristics of OC diagnosis.

The patients' perspective towards Oral Cancer

There are several reasons for a patient to seek healthcare, but the most commonly accepted one is the perception of a symptom at least two of three times a week [23]; nevertheless about 30% of patients wait more than three months before requesting medical care [34].

Current knowledge on patient symptoms appraisal processes is insufficient [23, 34], and therefore further development of models explaining both the "appraisal interval" and the "help-seeking interval" (as defined in "The model of pathways to treatment") are needed. In this sense, the Social Cognitive Theory describes how an individual categorises experiences that he/she considers as threatening for his/her own wellbeing by comparing with previous experiences [15]. Consequently, the

chances for seeking help are related to the individual perception of a circumstance as a menace for the person's welfare [33].

The most frequent interpretation patients find for a cancer-related symptom includes ulceration, physical trauma, dental problem, etc. without considering oral cancer as a feasible explanation for their symptoms [34, 26, 1], but this initial warning sign can be reinterpreted because of its persistence, or as a consequence of new information or knowledge that can explicate either the symptoms or their variation in time [34].

For the sake of reducing patient-related intervals, it is worth mentioning that oral cancer is one of the least known malignancies among lay public [45, 48] and that patients' attitude depends largely on knowledge of the disease, often leading to misunderstanding of the symptoms [34,6,21] and resulting in undesirable diagnostic delays.

Health policies and Oral Cancer

The organisation of the healthcare system and access characteristics influence not only the pathways followed to diagnosis and treatment and the duration of these stages, but also the way a person seeks medical advice. Therefore, health policies have to be considered when studying diagnostic delay. This is particularly relevant for health systems based upon the "double gate-keeping" scheme: primary care units act as the entrance to the system (first gate-keeper). If a patient reaches secondary care, the specialist acts as the second gate-keeper, deciding whether the patient requires additional treatments or diagnostic tests [3].

While some countries have developed effective strategies for diminishing the diagnostic interval for patients with symptoms suspicious of cancer [25,20,4], some others restrict their fast tracks for the most common cancers, and oral cancer is not usually included in these strategies [5].

General dentists' attitude towards Oral Cancer

Dentists should be the key HCPs in the different levels of oral cancer prevention, particularly in early diagnosis, in order to minimize the diagnostic interval.

Oral cancer screening programmes have not proved to be cost-effective but in those areas with high prevalence of the disease [29, 39, 30]. As a consequence, opportunistic screening gains importance and underlines the role of the Dental Profession in secondary prevention of OC by incorporating this type of intervention in dentists' daily practice [32, 36, 28, 40, 14]. Despite its simplicity and affordability (the clinical examination takes no more than two minutes), a large proportion of dentists do not conduct routine oral cancer explorations yet [13].

The need for continuous education and development of HCPs is out of question, and the issue of oral cancer is not an exception [22]. Dentists' knowledge and training on this topic seem to be low [35, 9, 8, 7] although some differences between countries have been reported. These dissimilarities can be partially explained by the different prevalence of the disease by geographical regions.

Effective secondary prevention requires a dentist being able to identify the main mucosal alterations related to oral cancer, besides knowing how to act when they are found. In this sense, GDPs seem to be aware of the importance of white and/or red lesions (these to a lesser extent), and about non-healing ulcerations once the apparent causal factors have been removed [28, 40].

Regarding dentists' confidence about handling OC patients, there seems to be a relationship between confidence level and years in practice and OC continuous education experiences [28]. This degree of awareness turns into action for 40% to 70% of dentists, who report to undertake routine complete OC exploration for their patients [36, 38, 38]. Both knowledge and attitudes seem to improve after the attendance to continuing education courses [36, 28, 38], and these interventions are welcomed by clinicians [8, 7].

General practitioners perspective towards Oral Cancer

Primary care physicians share with GDPs a major role in OC diagnosis as many patients would firstly present to their GP complaining about an oral problem; this phenomenon has

been attributed to the high cost of dental attention or to previous negative experiences [7, 43].

Although GPs agree they should have a role in early oral cancer detection [18], they feel limited because of insufficient training in this field, inadequate equipment, and tight working schedules [7, 17, 43, 12]. Moreover, their knowledge about OC risk factors seems to be lower than GPs', giving more importance to tobacco consumption over alcohol abuse, and being less capable to recognise red or mixed precancerous lesions [7, 17, 12].

Discussion

Research on diagnostic intervals encompasses a variety of fields of knowledge which positively affect the aim of identifying global goals to diminish its length. Thus, a comprehensive analysis of the diagnostic delay phenomenon would be better approached from a multidisciplinary point of view by incorporating scientists with different backgrounds to research groups.

Indubitably, the heterogeneous methodologies and definitions used in the literature limit researchers' efforts to attain clear and comparable conclusions. In this sense, the Aarhus statement [47] provides a series of definitions, time intervals and methodological recommendations to be used in early cancer diagnosis research. The use of this theoretical framework in future investigations will definitely contribute to progress in this field.

Investigations on diagnostic delay are frequently compromised by circumstances which are difficult to control, such as patients' memory bias or the biological characteristics of the tumour [37] as the most evident examples to be kept in mind.

Patients' disease patterns determine the reaction towards a symptom and this reaction is modulated by the individual knowledge about a particular health problem. Hence, lack of knowledge may well lead to an incorrect response.

Knowledge about OC is reported to be low worldwide, as only 56% in a sample of Britons had heard of oral cancer [45], and just 25% of Americans were able to identify a sign of

oral cancer [13]. Despite OC awareness is reported to have improved in recent years [48], the same investigation describes a worrying lack of concern about both the signs of OC and the relationship between alcohol consumption and oral cancer. Despite educational interventions have been widely used to increase OC awareness, the materials used for this purpose are frequently insufficient in quantity and quality, usually difficult to read, and hard to comprehend by the average public.

Some countries like Denmark [16, 20] or the UK [25] have already established specific health policies for patients with a suspicion of cancer. The Danish scheme has resulted in significant reduction of the diagnostic interval and preparation for the treatment by 41 % during the 2002-2010 period [16]. Other countries, such as Spain, do not have fast tracks for oral cancer, although specific lines of action for early diagnosis in breast, cervix and colorectal cancer exist. An extension of these schemes to oral cancer and the use of clearly defined referral guidelines may have an impact on survival to this neoplasm [35].

Both dentists and physicians need to be aware of their own individual importance in managing oral cancer. Continuing education programmes offer the possibility of updating and improving knowledge and attitudes towards oral cancer. Seoane-Lestón J et al. [36] assessed the impact of a four-hour educational course about different aspects of oral cancer amongst Spanish dentists, finding a significant improvement in oral cancer knowledge. As this kind of courses are appreciated by both physician and dentists [7], they could be considered a useful tool for increasing OC awareness among primary care HCPs. Bearing in mind that physicians retrieve important amounts of information -up to 80% of their needs- informally on the Internet [31], online resources should also be taken into account when planning interventions for reducing gaps of knowledge amongst HCPs. Another barriers for OC diagnosis recognised by physicians include insufficient time and lack of resources for performing an adequate oral exploration for their patients [43].

Diagnostic delay is the result of the interaction of many agents and circumstances, such as psychosocial factors, gaps of

knowledge, health policies, or even HCPs attitudes. As these issues vary in different geographical areas and environments, specific local information is needed in order to design effective interventions for diminishing OC diagnostic intervals. The use of a common theoretical framework for these investigations would permit the identification of areas of improvement and the exchange of information about successful experiences in this field.

Acknowledgements

This investigation was funded by the Ramón Domínguez

Research Foundation: “Convocatoria de Axudas á Investigación Biomédica 2014”.

The authors declare no conflict of interest.

References

1. Al-Dakka I (2010). Public awareness of oral **cáncer** and associated risk factors is low. *Evid Based Dent* 11(4):107-7.
2. Andersen BL, Cacioppo JT (1995). Delay in seeking a cancer diagnosis: delay stages and psychophysiological comparison processes. *Br J Soc Psychol* 34(1): 33–52.
3. Andersen RS, Vedsted P, Olesen F, Flemming B, Sødengaard J (2011). Does the organizational structure of health care systems influence care-seeking decisions? A qualitative analysis of Danish cancer patients’ reflections on care-seeking. *Scand J Prim Health Care* 29(3):144–9.
4. Baughan P, O’Neill B, Fletcher E (2009). Auditing the diagnosis of cancer in primary care: the experience in Scotland. *Br J Cancer* 101 Suppl 2:S87–91.
5. Borràs JM, Colomer C, Soria P, López R (2010). Priorities for cancer control in Spain. *Ann Oncol* 21 Suppl 3:iii111–14.
6. Brouha XD, Tromp DM, Hordijk GJ, Winnubst JA, de Leeuw JR (2005). Oral and pharyngeal cancer: Analysis of patient delay at different tumor stages. *Head Neck* 27(11):939–45.
7. Carter LM, Ogden GR (2007). Oral cancer awareness of general medical and general dental practitioners. *Br Dent J* 203(5):E10; discussion 248–9.
8. Clovis JB, Horowitz AM, Poel DH (2002) Oral and pharyngeal cancer: practices and opinions of dentists in British Columbia and Nova Scotia. *J Can Dent Assoc* 68(7):421–5.
9. Colella G, Gaeta GM, Moscariello A, Angelillo IF (2008). Oral cancer and dentists: Knowledge, attitudes, and practices in Italy. *Oral Oncol* 44(4):393–9.
10. Diz Dios P, Padrón González N, Seoane Lestón J, Tomás Carmona I, Limeres Posse J, Varela-Centelles P (2005). “Scheduling delay” in oral cancer diagnosis: A new protagonist. *Oral Oncol* 41(2):142–6.
11. Friedrich RE (2010). Delay in diagnosis and referral patterns of 646 patients with oral and maxillofacial cancer: a report from a single institution in Hamburg, Germany. *Anticancer Res* 30(5):1833–6.
12. Greenwood M, Lowry RJ (2001). Primary care clinicians’ knowledge of oral cancer: a study of dentists and doctors in the North East of England. *Br Dent J* 191(9):510–2.
13. Horowitz AM (2001). Perform a death-defying act: the 90-second oral cancer examination. *J Am Dent Assoc* 32(supplement):36s–40s.
14. Horowitz AM, Drury TF, Canto MT (2000). Practices of Maryland dentists: oral cancer prevention and early detection--baseline data from 1995. *Oral Dis* 6(5):282–8.
15. Leventhal H, Brissette I, Leventhal EA. 2003. The common-sense model of self-regulation of health and illness. In: Cameron LD, Leventhal H (eds), *The Self-Regulation of Health and Illness Behaviour*, pp. 42–65. Routledge, New York.
16. Lyhne NM, Christensen A, Alanin MC, Bruun MT, Jung TH et al. (2012). Waiting times for diagnosis and treatment of head and neck cancer in Denmark in 2010 compared to 1992 and 2002. *Eur J Cancer* 49:1627–1633.

17. Macpherson LM, McCann MF, Gibson J, Binnie VI, Stephen KW (2003). The role of primary healthcare professionals in oral cancer prevention and detection. *Br Dent J* 195(5):277–81; discussion 263.
18. Mydlarz WK, Hennessey PF, Califano JA (2010). Advances and perspectives in the molecular diagnosis of head and neck cancer. *Expert Opin Med Diagn* 4:53–65.
19. Neal RD (2009). Do diagnostic delays in cancer matter? *Br J Cancer* 101 Suppl 2:S9–S12.
20. Olesen F, Hansen RP, Vedsted P (2009). Delay in diagnosis: the experience in Denmark. *Br J Cancer* 101 Suppl 2:S5–8.
21. Panzarella V, Pizzo G, Calvino F, Compilato D, Colella G, Campisi G (2013). Diagnostic delay in oral squamous cell carcinoma: the role of cognitive and psychological variables. *Int J Oral Sci* 6(1):39–45.
22. Pentenero M, Chiecchio A, Gandolfo S (2014). Impact of academic and continuing education on oral cancer knowledge, attitude and practice among dentists in north-western Italy. *J Cancer Educ* 29(1):151–7.
23. Petrie KJ, Weinman J (2003). More focus needed on symptom appraisal. *J Psychosom Res* 54(5):401–3.
24. Pitchers M, Martin C (2006). Delay in referral of oropharyngeal squamous cell carcinoma to secondary care correlates with a more advanced stage at presentation, and is associated with poorer survival. *Br J Cancer* 94(7):955–8.
25. Richards MA (2009). The National Awareness and Early Diagnosis Initiative in England: assembling the evidence. *Br J Cancer* 101 Suppl 2:S1–4.
26. Rogers SN, Vedpathak SV, Lowe D (2011). Reasons for delayed presentation in oral and oropharyngeal cancer: the patients perspective. *Br J Oral Maxillofac Surg* 49(5):349–53.
27. Safer MA, Tharps QJ, Jackson TC, Leventhal H (1979). Determinants of three stages of delay in seeking care at a medical clinic. *Med Care*, 17(1):11–29.
28. Saleh A, Kong YH, Vengu N, Badrubeen H, Zain RB, Cheong SC (2014). Dentists' perception of the role they play in early detection of oral cancer. *Asian Pac J Cancer Prev* 15(1):229–37.
29. Sankaranarayanan R, Ramadas K, Thomas G, Muwonge R, Thara S, Mathew B, Rajan B (2005). Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. *Lancet* 365(9475):1927–33.
30. Sankaranarayanan R, Ramadas K, Thara S, Muwonge R, Thomas G, Anju G, Mathew B (2013). Long term effect of visual screening on oral cancer incidence and mortality in a randomized trial in Kerala, India. *Oral Oncol* 49(4):314–21.
31. Schmidt T (2013). Informal education of medical doctors on the Internet. *Stud Health Technol Inform* 190:92–4.
32. Sciubba JJ (2001). Oral cancer and its detection. History-taking and the diagnostic phase of management. *J Am Dent Assoc* 132 Suppl:12S–18S.
33. Scott SE, Walter FM, Webster A, Sutton S, Emery J (2013). The model of pathways to treatment: conceptualization and integration with existing theory. *Br J Health Psychol* 18(1):45–65.
34. Scott SE, McGurk M, Grunfeld EA (2007). The process of symptom appraisal: Cognitive and emotional responses to detecting potentially malignant oral symptoms. *J Psychosom Res* 62(6):621–30.
35. Seoane J, Corral-Lizana C, González-Mosquera A, Cerero R, Esparza G, Sanz-Cuesta T, Varela-Centelles P (2011). The use of clinical guidelines for referral of patients with lesions suspicious for oral cancer may ease early diagnosis and improve education of healthcare professionals. *Med Oral Patol Oral Cir Bucal* 16(7):e864–9.
36. Seoane-Lestón J, Velo-Noya J, Warnakulasuriya S, Varela-Centelles P, González-Mosquera A, Villa-Vigil MA, Rodríguez-Lozano F, Diz-Dios P (2010). Knowledge of oral cancer and preventive attitudes of

- Spanish dentists. Primary effects of a pilot educational intervention. *Med Oral Patol Oral Cir Bucal* 15(3):e422–6.
37. Seoane-Romero JM, Varela-Centelles P, Diz-Dios P, Ramos-Barbosa I, Fernández Feijoo J, Seoane J (2012) Does tumour biological behaviour influence prognosis more than diagnostic delay in oral cancer? *Journal of Cancer Research Updates* 1(1):22-27.
38. Silverman S Jr, Kerr AR, Epstein JB (2010). Oral and pharyngeal cancer control and early detection. *J Cancer Educ* 25(3):279–281.
39. Subramanian S, Sankaranarayanan R, Bapat B, Somanathan T, Thomas G, Mathew B, Vinoda J, Ramadas K (2009). Cost-effectiveness of oral cancer screening: results from a cluster randomized controlled trial in India. *Bull World Health Organ* 87(3):200–206.
40. Vijay Kumar KV, Suresan V (2012) Knowledge, attitude and screening practices of general dentists concerning oral cancer in Bangalore city. *Indian J Cancer*, 49(1):33–8.
41. van der Waal I (2013). Are we able to reduce the mortality and morbidity of oral cancer; some considerations. *Med Oral Patol Oral Cir Bucal* 18(1):e33–7.
42. van der Waal I, de Bree R, Brakenhoff R, Coebergh JW (2011). Early diagnosis in primary oral cancer: is it possible? *Med Oral Patol Oral Cir Bucal* 16(3):e300-5.
43. Wade J, Smith H, Hankins M, Llewellyn C (2010). Conducting oral examinations for cancer in general practice: what are the barriers? *Fam pract* 27(1):77–84.
44. Walter F, Webster A, Scott S, Emery J (2012). The Andersen Model of Total Patient Delay: a systematic review of its application in cancer diagnosis. *J Health Serv Res Policy* 17(2):110–8.
45. Warnakulasuriya KA, Harris CK, Scarrott DM, Walt R, Gelbier S, Peters TJ, Johnson NW (1999). An alarming lack of public awareness towards oral cancer. *Br Dent J* 187(6):319–22.
46. Warnakulasuriya S (2009). Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol* 45(4-5):309–16.
47. Weller D, Vedsted P, Rubin G, Walter FM, Emery J et al. (2012). The Aarhus statement: improving design and reporting of studies on early cancer diagnosis. *Br J Cancer* 106(7):1262–7.
48. West R, Alkhatib MN, McNeill A, Bedi R (2006). Awareness of mouth cancer in Great Britain. *Br Dent J* 200(3): 167–9, discussion 151.