Int. J. Oral Maxillofac. Surg. 2017; 46: 1–10
http://dx.doi.org/10.1016/j.ijom.2016.09.017, available online at http://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Systematic Review
Head and Neck Oncology

Key points and time intervals for early diagnosis in symptomatic oral cancer: a systematic review

P. Varela-Centelles[1,2], J. L. López-Cedrún[3], J. Fernández-Sanromán[4], J. M. Seoane-Romero[2], N. Santos de Melo[5], P. Álvarez-Nóvoa[2], I. Gómez[2], J. Seoane[2]

[1]Galician Health Service, EOXI Lugo, Cervo e Monforte, Lugo, Spain; [2]Stomatology Department, School of Medicine and Dentistry, University of Santiago de Compostela, Santiago de Compostela (A Coruña), Spain; [3]Service of Oral and Maxillofacial Surgery, Complexo Hospitalario Universitario de A Coruña, A Coruña, Spain; [4]Service of Oral and Maxillofacial Surgery, Povisa Hospital, Vigo (Pontevedra), Spain; [5]Departamento de Odontologia, Faculdade de Ciências da Saúde, Universidade de Brasília, Campus Universitário, Asa Norte, Brasília DF, Brazil

P. Varela-Centelles, J.L. López-Cedrún, J. Fernández-Sanromán, J.M. Seoane-Romero, N. Santos de Melo, P. Álvarez-Nóvoa, I. Gómez, J. Seoane: Key points and time intervals for early diagnosis in symptomatic oral cancer: a systematic review. Int. J. Oral Maxillofac. Surg. 2017; 46: 1–10.

Abstract. The aim of this study was to identify key points and time intervals in the patient pathway to the diagnosis of oral cancer, from the detection of a bodily change to the start of treatment. A systematic search of three databases was performed by two researchers independently. Articles reporting original data on patients with symptomatic primary oral or oropharyngeal squamous cell carcinoma that was pathologically confirmed were included. These articles had to include an outcome variable of 'diagnostic delay', 'time interval', or 'waiting time to diagnosis', or report time intervals from first symptom to treatment. Furthermore, the outcome variable had to have a clearly defined start point and end point, with the time measurement presented as a continuous or categorical variable. A total of 1175 reports were identified; 28 articles on oral cancer studies and 13 on oral and oropharyngeal cancer studies were finally included. These papers showed poor quality in terms of questionnaire validation, acknowledgement of biases influencing time-point measurements, and strategies for verification of patient self-reported data. They also showed great heterogeneity. The review findings allowed the definition of key points and time intervals within the Aarhus framework that may better suit the features of the diagnostic process of this neoplasm, particularly when assessing the impact of waiting time to diagnosis.

Key words: oral cancer; oral squamous cell carcinoma; oropharyngeal cancer; diagnostic delay; time intervals; Aarhus statement; Andersen model.

Accepted for publication 27 September 2016
Available online 15 October 2016

Oral and pharyngeal cancer (OPC), as a whole, is the sixth most common malignancy worldwide, with broad variations (up to 20-fold) in incidence.[1–4] Areas with the highest incidences include South Asia (Sri Lanka, India, Pakistan, and Taiwan), Eastern Europe (Hungary, Slovakia, and Slovenia), Latin America (Brazil, Uruguay, Puerto Rico, and Cuba), Southern Africa (Namibia, Botswana, and Mozambique), and certain regions in the Pacific (Melanesia and Papua New Guinea).[1,3,4] OPC is the most common cancer in certain countries (Malaysia and Sri Lanka), and two-thirds of these malignancies occur in developing countries.[2,5]

Regrettably, about half of oral cancers have already reached an advanced stage

(III or IV) when diagnosed, probably due to delays in diagnosis; this has an influence on survival rates (5-year survival 20–50% depending on the tumour site).[6–11] It has been suggested that if these malignancies were diagnosed and treated at an earlier stage, survival rates would exceed 80%.[10] However, the actual impact of the diagnostic and therapy delay on cancer outcomes is poorly defined,[12] to the point that some authors wonder ''Do diagnostic delays in cancer matter?''.[13] Regarding oral cancer, the answer is 'yes': the larger the diagnostic delay, the more advanced the stage at diagnosis,[9,14] with a longer interval from first symptom to referral for diagnosis being a risk factor for advanced stage and mortality from oral cancer.[14]

Furthermore, oropharyngeal and laryngeal cancers have reached the longest median patient intervals when compared to another 28 common and rarer cancers.[15] As a result of these findings, studies on the early detection and diagnostic delays in oral cancer are a priority for research on secondary and tertiary prevention,[2] as the early diagnosis of symptomatic cancer is considered to be central to the achievement of better outcomes.[16,17]

Although the term 'cancer diagnostic delay' has proven to be inconsistent and inaccurate, and also to bear strong legal implications,[16] it has taken root in the scientific literature in the last 75 years.[18] During this period it has been impossible to reach a consensus on a time-point beyond which a cancer diagnosis should be considered as delayed.[8,14] Different definitions have been suggested to this end, using heterogeneous criteria (mean or median time distribution,[19–22] or arbitrary time points[9]), which has severely hampered comparisons among studies. Moreover, the rare usage of conceptual frameworks in these investigations has often led to excessively simplistic approaches to the problem, considering only patient delay, professional delay, and health system delay, even assuming the existence of overlaps between these time periods.[9,12]

In an attempt to simplify the design and monitoring of interventions aimed at reducing the time to diagnosis in symptomatic cancer, the use of different conceptual frameworks has been recommended. Amongst the most robust of these frameworks are the 'general model of total patient delay' (Anderson model), which comprises five delay stages between the detection of an unexplained sign(s) or symptom(s) and the beginning of treatment for the illness,[19] and the 'model of pathways to treatment' (the Aarhus statement), a refined version of the former consisting of a description of events, processes, intervals, and contributing factors involved in the path towards symptomatic cancer diagnosis.[16,23] However, no reports dealing with this topic in regard to oral cancer with a systematic approach could be identified. Thus, the present study was designed to identify key points and time intervals in the patient pathway to the diagnosis for symptomatic oral cancer, from the detection of a bodily change to the definitive treatment.

Methods

A study protocol was designed for the study, which included a document search and data retrieval. The resulting systematic search followed a narrative synthesis of the literature guided by the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[24] The search was undertaken in June 2015 (updated in January 2016) in the MEDLINE, Embase (from 1980), and Proceedings Web of Science (Conference Proceedings Citation Index—Science since 1990) databases, according to the following strategy: ((oral cancer OR oral squamous cell carcinoma OR oropharyngeal cancer) AND (diagnostic delay OR time interval)), using both medical subject headings (MeSH) and free text terms. The search strategy (MEDLINE) was as follows: #1 delayed diagnosis [MeSH Terms]; #2 diagnostic delay; #3 patient delay; #4 professional delay; #5 doctor delay; #6 provider delay; #7 total delay; #8 time interval; #9 waiting time to diagnosis; #10 treatment delay; #11 pathways to treatment; #12 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11); #13 mouth neoplasm; #14 oral cancer [MeSH Terms]; #15 oropharyngeal cancer [MeSH Terms]; #16 (#13 or #14 or #15); #17 (#12 and #16).

The sources identified were deemed relevant if they met the following criteria: (1) reported original data, without restrictions in terms of study design; (2) included only patients with symptomatic primary, pathologically confirmed, oral or oropharyngeal squamous cell carcinoma; (3) the outcome variable was 'diagnostic delay' or 'time interval' or 'waiting time to diagnosis', or the reference reported one or several time intervals in the patient pathway from first symptom to treatment[16,23,25]; (4) the outcome variable was clearly defined by a start and an end point, and the time lapse measurement was presented as a continuous or categorical variable.

Data collection and extraction

Two researchers (PVC and JMSR) extracted the data in an unblinded manner, but independently, and entered it into a custom-made form following a standardized procedure. Disagreements were resolved by a third researcher who was blinded to the study hypothesis. Inter-observer concordance for the two categories was calculated by means of Epidat 3.1 statistical software (Programa para Análisis Epidemiológico de Datos Tabulados, Xunta de Galicia, Santiago de Compostela, Spain).

Quality assessment

The Aarhus checklist for research in early cancer diagnosis was used as a framework for assessing the quality of the selected sources.[16] This list includes 20 items, seven related to definitions of time-points and intervals (date of first symptom, date of first presentation to healthcare, date of referral, and date of diagnosis) and 13 related to measurements (three general, eight for studies using questionnaires and/or interviews with patients and/or healthcare providers, and two for studies using primary case-note audit and database analyses).

Again, two researchers assessed the reports independently and a third researcher was called on in the case of disagreement, and the score sheet was discussed until a consensus was reached. The presence of biases related to systematic reviews, such as publication bias, time lag bias, and outcome-reporting bias, was also considered by directly contacting the corresponding authors of the papers included in this systematic review by e-mail.[26]

Results

A total of 1175 potentially eligible reports were identified; 1085 of these were discarded after assessing both the titles and abstracts, because they were not related to 'diagnostic delay' or 'time intervals' ($\kappa = 0.83$). Another 49 articles did not meet the inclusion criteria (Fig. 1). Finally, 28 papers reporting on oral cancer studies and 13 reporting studies on cancers of closely related sites (oral and oropharyngeal cancers) were included ($\kappa = 0.75$). Information from these articles is summarized in Tables 1 and 2.[27–39,7,40–66]

The selected studies were mostly observational in nature, retrospective and hospital-based, and were performed mainly in Europe and America (>70%). A total 6087 patients with symptomatic cancer