Departamento de Estomatología
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E ODONTOLOXÍA

Oral cancer: Factors related to late stage diagnosis. Impact of delay in diagnosis on survival.

Juan Manuel Seoane Romero

Santiago de Compostela, Septiembre de 2013

A mi familia, y en especial a mi hermano Javier

D. David Suárez Quintanilla, Catedrático de la Facultad de Medicina y Odontología de la Universidad de Santiago de Compostela,

D. Pablo Ignacio Varela Centelles, Profesor Asociado de la Facultad de Medicina y Odontología de la Universidad de Santiago de Compostela, y

D. Juan Manuel Seoane Lestón, Profesor Titular de la Facultad de Medicina y Odontología de la Universidad de Santiago de Compostela

HACEN CONSTAR:

Que el trabajo de investigación que presenta D. Juan Manuel Seoane Romero, con el título de "**Oral cancer: Factors related to late stage diagnosis. Impact of delay in diagnosis on survival.**", ha sido realizado bajo nuestra dirección, supervisando en todo momento su elaboración.

Que nuestro criterio reúne las características de rigor, originalidad y mérito suficientes para optar al grado de Doctor y ser elevado al superior juicio del Tribunal designado a tal efecto.

Para que así conste, a efectos de justificar los mencionados extremos ante los órganos competentes de la Universidad de Santiago de Compostela, a 3 de Septiembre de 2013.

Fdo. David Suárez Quintanilla	Fdo. Pablo I. Varela Centelles	Fdo. Juan M. Seoane Lestón

Fdo Juan M. Seoane Romero (doctorando)

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1. INTRODUCTION: TIMING OF ORAL CANCER DIAGNOSIS: IMPLICATIONS FOR PROGNOSIS AND SURVIVAL

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

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

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

1.1. Early detection. Diagnosis of small-size oral carcinoma

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

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

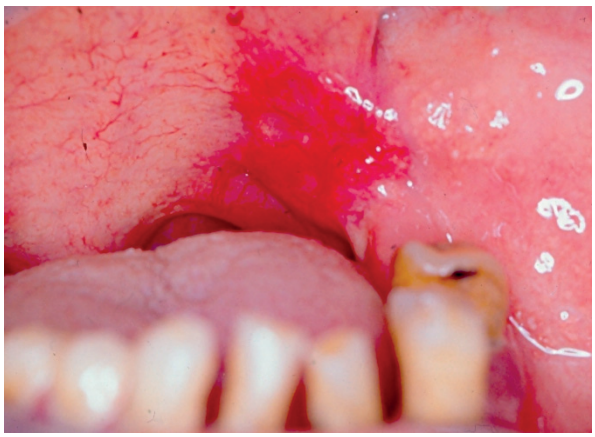

Fig. 1. Erythroplastic oral squamous cell carcinoma.

1.2. Diagnostic delay in oral cancer. Concept

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

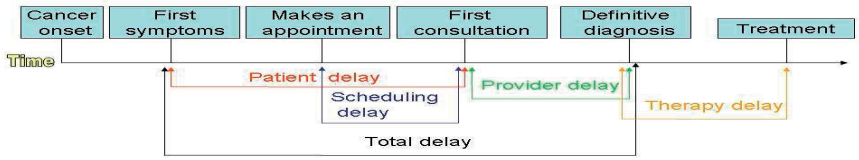

Fig. 2. Types of diagnostic delay in oral cancer.

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

opsy, and, finally for the pathologist to report the results back to the clinician (Gorsky, 1995).

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

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

1.3. Causes of oral cancer diagnostic delay

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

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

On the other hand, the accessibility (ability to obtain services based on oral health needs) can be limited by financial, structural and personal barriers (beliefs, language) and thus decisively conditioning the timing of oral cancer diagnosis (Seoane, 2010). Disparities in access to oral health services across Europe and USA are well known, particularly for low-income populations (uninsured, migrant, homeless, etc). Ethno regional differences have

also been identified in terms of incidence and mortality rates of oral cancer, which may result from the variation in the access to oral care but also from the different exposition to risk factors or from the limited resources in detection and prevention methods available to these individuals.

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

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

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

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

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

The most frequently studied variables (age, gender, and tobacco and alcohol intake) are not linked to late-stage diagnosis, as were not previously associated to professional or patient-related delays (Boing, 2010; Guggenheimer 1989). Neither precancerous lesions connected to the tumour seem to modify the spread of the disease at diagnosis, even when proliferative verrucous leu-

koplakia or the presence of mild to moderate epithelial dysplasia at the margins of a surgically removed oral squamous cell carcinoma carries a significant risk of local recurrence and modifies the prognosis of the disorder (Thomsom, 2007).

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

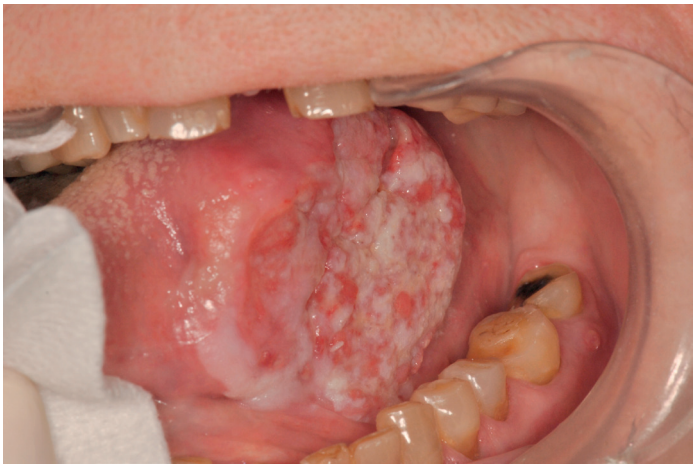

Fig. 3. Ulcerated-type tongue squamous cell carcinoma.

The site of the primary lesion has been also linked either to delayed diagnosis or diagnosis at advanced stages (Brouha, 2005): tongue, buccal mucosa and lip carcinomas seem to be diagnosed at earlier stages (Gorsky, 1995) than floor of the mouth and retromolar trigone neoplasms; whereas palate or gingival tumours showed contradictory results (Gorsky, 1995). Accordingly, the floor of the mouth, gingivae and retromolar trigone have recently been identified as independent prognostic factors for late-stage diagnosis, which may well be explained by the fact that patient's self-perception and self-exploration abilities are conditioned by the site of the tumour (Andersen, 1995); the presence of the gingivae within this group would be due to the association of gingival locations to advanced stage at diagnosis (late diagnosis) caused by the early invasion of the nearby bone (T4 primary tumour) (Seoane, 2006).

Late diagnosis of neoplasms, particularly in oral cancer, has been conventionally ascribed to delays in reaching a diagnosis, as patients at advanced

tumour stages are more likely to have experienced longer patient and professional delays than those diagnosed at earlier stages (Sargeran, 2009). Surprisingly, there is an evident lack of sound scientific evidence supporting this traditional association between diagnostic delay and disease extension (III-IV TNM stages) (Gomez, 2009; Gomez, 2010).

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

1.5. Relationships between diagnostic delay in primary oral cancer and disease extension.

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

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

The control of biases is a challenging issue for researchers in this field. The consideration of patient survival as the research outcome and the use of multivariate analysis to adjust for confounding factors (Wildt et al, 1995) meant an

improvement in the design of these studies but the sought association could not still be identified for oral cancer (Wildt et al , 1995) or for mixed samples of head and neck carcinomas (Gorsky & Dyan, 1995). Research designs were further improved by the combination of data collection methods to include prospective and retrospective data for reducing memory bias: McGurk et al (2005) gathered a sample of 613 cases over 40 years and failed to unveil a relationship between delay in diagnosis and tumour stage but they used an arbitrary time point of three months to distinguish between delayed and non-delayed cases in their mixed sample of head and neck cancers that, combined with a vague definition of diagnostic delay, compromise their conclusions.

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

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

There is no sound scientific evidence supporting an association between diagnostic delay in oral cancer, extension of the disease diagnosed at advancer stages (TNM III-IV) and lower survival rates. However, this fact is probably due to methodological flaws in the published reports to date (Allison, 1998a; Allison, 1998b; Allison, 1998c). These reports use different conceptions of diagnostic delay and are thus liable to misclassifications; use retrospective designs without strategies to diminishing patients' memory bias and often break down diagnostic delay classifications to groups with insufficient sample size. Moreover, the study of samples with heterogeneous cancer sites introduce confounding factors in the analysis, as the patient's self-perception and self-

exploration abilities depend on the site of the tumour (Allison et al, 1998a; Tromp et al., 2005; Wildt et al, 1995; O'Sullivan, 2001). For example, gingival locations are associated with advanced stages at diagnosis due to the early invasion of the adjacent bone tissue (T4 primary tumour) (Seoane et al., 2006) yet could present without time delay. Additional difficulties come from the type of data collected (e.g.: continuous variables (Wildt et al, 1995; Hollows et al 2000; Kumar et al, 2001; Kantola et al, 2002) versus categorical (Allison et al 1998b; Kerdpon et al 2001a), from the different sources of patient data (questionnaires, interviews, clinical records) and also from the already mentioned patient memory bias.

Different velocities of tumour growth may well also explain with some tumours remain small in size in spite of delay. Even though some studies related diagnostic delay and tumour stage (Brouha et al 2005), it is possible that the relationship between delay and advanced tumour stage is veiled by the fact that certain cancers remain silent during the initial stages and induce symptoms only when they reach and advanced phase (Scott, 2005). This being, tumour growth rate would act as a confounding factor in the relationship between diagnostic delay and tumour stage, since patients with aggressive tumours and poor prognosis do not usually present diagnostic delay, while tumours with low proliferation rates demonstrate good prognosis despite long diagnostic delays (Kaufman, 1980; Evans, 1982; Allison, 1998a).

A recent meta-analytical study has shown that diagnostic delay is broadly associated to more advanced stages in oropharyngeal cancers. This association resulted to be specially strong when the analysis was restricted to oral cancer (pooled RR, 1.47; 95% CI: 1.09-1.99) and when the delay was longer than one month (pooled RR, 1.69; 95%CI: 1.26-2.77) (Gomez et al 2009). The probability for delayed patients to present an advanced stage of oral cancer at diagnosis in this report was 25% higher than that of non-delayed patient. Nevertheless these data should be interpreted with caution since all 9 studies considered in the analysis were cross-sectional in nature, with retrospective designs and a potential for recall bias.

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

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

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

1.6. Diagnostic delay and survival to oral cancer

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

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

affected more by the biology of the cancer (rapid tumour growth) than by a delayed diagnosis.

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

Table 2. Estudios que relacionan el retraso diagnóstico en CO y la supervivencia

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

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

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

1.7. Strategies to minimise diagnostic delay in oral cancer

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

1.7.1. Toluidine blue

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

1.7.2. Light-based detection systems.

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

1.7.2.1. ViziliteÒ (Zila Pharmaceuticals, Phoenix, AZ)

A number of cross-sectional studies assessed this chemiluminiscence device with high scores in sensitivity (100%), as every patient had previously visualized mucosal lesions, but low specificity values (0-14.2%) with high percentages of false positives. This device has proved a high capacity to emphasize certain visual features of the lesion, such as brightness and lesions limits (Epstein, 2009), but it does not aid in the identification of a premalignant or malignant oral lesion (Farah, 2007). A combination of Vizilite and toludine blue (ViziLite Plus) has been introduced to reduce the number of false positives but, although both specificity and predictive positive values improved, the scientific evidence on this combination published to date is scarce (Epstein, 2008).

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

1.7.2.2. Tissue fluorescence imaging

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

1.7.2.3. Tissue fluorescence spectroscopy

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

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

1.8. Oral cancer diagnosis at asymptomatic phases of the disease

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

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

Another potential bias affecting this kind of programmes would be the "lead-time bias", where survival to oral cancer may seem better when cases are diagnosed early but what actually happens is that cases are detected ear-

lier though patients do not live longer than would live if the neoplasm were diagnosed during the symptomatic period of the disease (van der Waal, 2011).

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

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

JUSTIFICATION

2. JUSTIFICATION

Oral cancer is considered to be one of the highest incidence rating cancers, ranking between the sixth and the eighth place in the mortality classification by cancer type on a global scale, probably because its final diagnosis is mainly obtained once the disease has already spread out (TNM III-IV).

Different studies have previously dealt with the influence of the time interval employed to establish a histological diagnosis on tumour stage at diagnosis. Recently our group has done a meta-analysis that seems to prove a clear association between tumour diagnostic delay and late-stage diagnosis of the disease. However, the information about the relationship between diagnostic delay in head and neck cancer is scarce and frequently ill-founded, particularly about oral cancer, and survival. It is also difficult to explain the lack of association or inverse association that has been observed by some authors when they have tried to relate a longer diagnosis delay with a higher mortality rate in this type of tumours. Nonetheless, the identification of the specific characteristics of the tumour and the clinical characteristics of the patients at high risk of late-stage diagnosis of oral cancer, may allow us to design strategies aimed at early diagnosis of these tumours and creating educational contents for future educational interventions for both high risk patients and professionals committed with the diagnosis of this disorder.

OBJECTIVES

3. OBJECTIVES

To create hypothesis that could explain the inconsistency of the association between diagnostic delay and survival to oral cancer.

To create a systematic review and meta-analysis to evaluate the relationship between diagnostic delay and survival to oral cancer.

To find out what are the clinical characteristics of the patient and the histopathological characteristics of the tumour that are associated with late stage diagnosis of the disease.

To find out what are the oral cancer preventive actitudes of the spanish dentists who particip in oral cancer continuos medical education programs.

BIOLOGICAL HYPOTHESIS:

Does tumour biological behaviour influence prognosis more than diagnostic delay in oral cancer?

4. BIOLOGICAL HYPOTHESIS: DOES TUMOUR BIOLOGICAL BEHAVIOUR INFLUENCE PROGNOSIS MORE THAN DIAGNOSTIC DELAY IN ORAL CANCER?

Abstract

Worldwide, oral cancer has one of the lowest survival rates (lethal disease for over 50% of cases diagnosed annually) and remains unaffected despite recent therapeutic advances.

Unfortunately, almost half of the oral cancers are diagnosed at stages III or IV, probably due to delays in reaching a definitive diagnosis. Many preventive approaches (secondary prevention) have been designed assuming the logical hypothesis that the longer the diagnostic delay, the more advanced the cancer and the worse the prognosis. However, a number of studies failed to prove this association or even found an inverse relationship.

We hypothesize that tumour's biological heterogeneity in terms of aggressiveness may explain shorter delays linked to advanced stages and bad prognosis. The assumption of this hypothesis would entail favouring oral cancer and precancer screening strategies at the preclinical stage of the disease, and therefore strategies of opportunistic screening for oral cancer and precancer on asymptomatic at risk population should be reinforced.

Keywords: mouth neoplasms, prognosis, delayed diagnosis, biological behaviour, squamous cell carcinoma.

Introduction

Oral cancer is a worldwide public health issue [1,2] whose incidence and mortality rates are steadily growing in Europe (eg: France, Hungary, Spain and Croatia), Brazil and South-Eastern Asia (Sri Lanka, Pakistan, Bangladesh and India) [3].

This neoplasm retains one of the lowest survival rate (lethal disease for over 50% of cases diagnosed annually) which remains unaffected despite recent therapeutic advances. This is particularly worrying as rising trends in oral cancer incidence are being reported for young and middle-age men from Brazil, India, certain areas of Europe and the USA [3,4].

Tumour stage at diagnosis remains the most important prognostic marker for oral squamous cell carcinoma [5]. Unfortunately, almost half of the oral cancers are diagnosed at stages III or IV with poor 5-year survival rates (20% to 50%) depending upon tumour sites, probably due to delays in reaching a diagnosis [6-9]. It has been suggested that if these malignancies were diagnosed and treated at earlier stages, survival rates would exceed 80% [10].

A number of researchers have revised the concept of diagnostic delay in head and neck cancer, however these investigations do not use homogeneous criteria [8,9,11], and comparative analyses are not always possible [8,9]. Nowadays, the concept of delay in diagnosis is often broken into two categories, namely patient delay –the period between the patient first noticing a symptom or sign and the first consultation to a healthcare professional concerning that symptom or sign [8,9,12,13] and provider/professional delay –the period from the patient's first consultation with a healthcare provider and the definitive pathological diagnosis [12,13]. The overall diagnostic delay (total delay) would elapse from the first symptom or sign until the definitive histological diagnosis [8,9,12,13].

It seems reasonable to assume that a cancer's stage at diagnosis is a function of the length of time it had been developing prior to diagnosis (logical hypothesis). Thus the longer the delay, the more advanced the disease would be and a worse prognosis should be expected [14]. However, many studies either failed to prove this association [15-23,25] or demonstrated an inverse relationship (shorter delays linked to more advanced stages) [19,22,24,25]. Although methodological flaws could partially explain this paradox, new hypotheses seem to be necessary in this field.

The hypothesis: Biological heterogeneity of oral carcinomas.

The inconsistencies observed in the association between longer delays in oral cancer diagnosis and worse outcome in terms of clinical stage and survival could be related to variability in the biological behaviour of these tumours. Differences in tumour aggressiveness would explain tumour's stage at diagnosis and patient survival better than the mere length of the diagnostic delay (Fig 1).

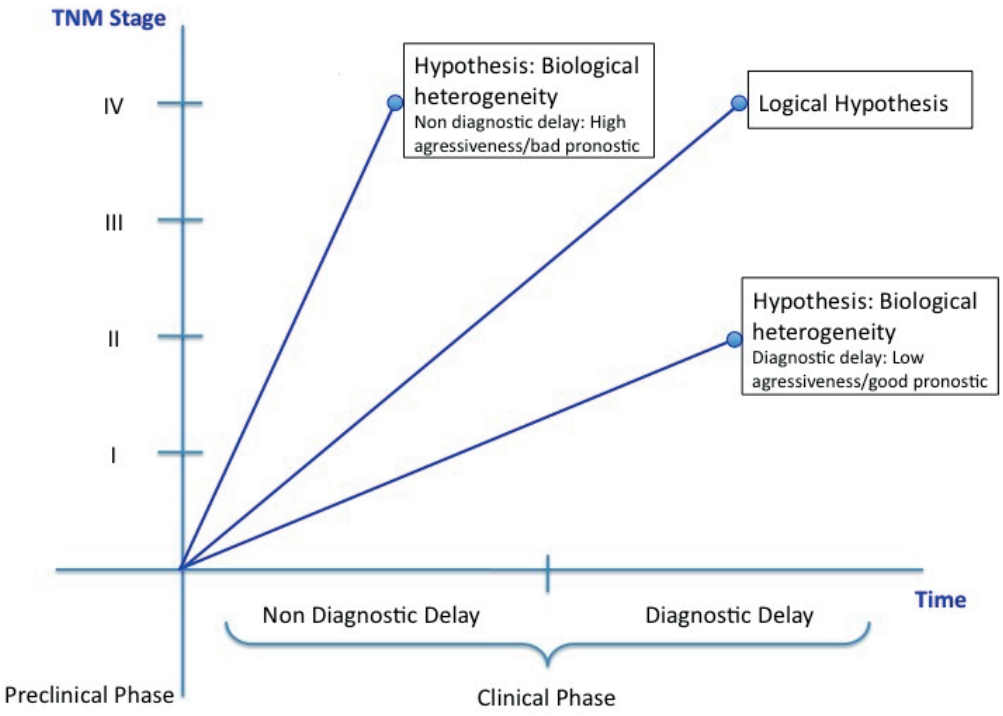

Fig. 1. Biological hypothesis of diagnostical delay in oral cancer

Supporting the hypothesis

Tumours of a single cancer type can appear to be similar but grow at very different rates and with different levels of aggressiveness [26]. Patients with fast-

growing tumours may be diagnosed relatively rapidly, but often an advanced stage has already been reached, given the nature of the disease [24]. Shorter patient and professional delays have been associated to advanced stage at diagnosis in some oral cancer series [19,22,24,25,27,28].

We have recently demonstrated, by means of a multivariate study, that when the analysis is adjusted for tumour stage at diagnosis (I-II vs., III-IV), proliferative activity arises as an independent prognostic factor for survival and diagnostic delay does not influence this outcome [29]. These results seem to suggest that survival to oral cancer is affected more by the rapid tumour growth of the cancer than by delays in the diagnosis.

Testing the hypothesis

It has been suggested that cancer biology may be more important than diagnostic delay. In order to test the feasibility of this hypothesis and to assess the impact of diagnostic delay on the course of oral squamous cell carcinomas, new studies with sound epidemiologic design to minimize the biases identified in the existing reports (selection, information, confounding, survival and lead-time biases) are needed [15-25]. It is mandatory to utilize standardised criteria for measuring the diagnostic delay and to develop protocols to mitigate recall bias [8,9]. The use of structured questionnaires at the primary care level and the participation of patient relatives could increase the quality of the information on diagnostic delay [8,27,28].

It seems advisable to conduct population-based studies with an important prospective component and an adequate sample size that consider exclusively incident oral cancer cases using patient survival as the main outcome. These studies should also account for potential confounding variables, such as age, gender, tumour site, co-morbidity and treatment –including also delay during the treatment phase- because it can influence outcomes [13]. A key point to assess oral cancer heterogeneity and its biological potential is the histological analysis of the whole tumour, otherwise there could exist a bias, particularly in large tumours. Future studies would benefit from a quantitative analysis approach (i.e.: analysis by flow cytometry of larger tumour samples), as this procedure permits the study of the fraction of proliferating tumour cells and the amount of fraction of spontaneous cell loss, which influence the tumour's growth rate [51]. Moreover, gene expression signatures generated from DNA microarray analysis have proved to be predictive biomarkers for clinical out-

come [52] and could be used to infer the clinical behaviour of the oral cancer and to adjust this way the actual weight of diagnostic delay on patient survival.

Discussion

Oral cancer main features (tumour size and nodal status) appear to correlate well with tumour growth chronology [31,32]. This paradigm focused research on the possibility that diagnostic delay contributed to the spread of the disease. Despite this theory could be confirmed for a number of tumours, no definitive conclusions could be drawn for oral cancer [8,9,33-39].

Theoretical tumour growth assumes no treatment and no cell lost, but cell loss increases when a tumour grows and outstrips its blood supply. Neoplasms typically grow progressively, but even within a single tumour type there are significant variations that lead to unpredictable differences in the pattern, speed of onset, and progression of patient symptoms that would definitively condition the moment of the diagnosis [26].

When dealing with delays in diagnosis, the beginning of the study has to be the recognition of the signs and symptoms by the patient. This fact is critically affected by his/her psychosocial characteristics, some of them able to predict diagnostic delay and advanced tumour stage at diagnosis [30]. Similar findings were reported from a case-control study demonstrating that the length of diagnostic delay was significantly greater in patients with advanced tumour stages (TNM stage IV) [16].

However, there is no sound scientific evidence supporting an association between diagnostic delay in oral cancer, disease extension at diagnosis, and lower survival rates [15-25]. This fact may well be partially due to methodological flaws in the published reports to date [8,9,36,40,41].

These reports use different conceptions of diagnostic delay and are thus liable to misclassifications, utilize retrospective designs without strategies to diminishing patient's memory bias and often break down diagnostic delay classifications into subgroups with small sample sizes. Studies involving tumours of different locations introduce confounding factors in the analysis, as the patient self-perception and self-exploration abilities depend on the site of the tumour [19,37,42]. For example, gingival locations are associated to advanced stages at diagnosis due to the early invasion of the adjacent bone tissue (T4 primary tumour), yet could present without time delay [38]. Additional difficulties come from the type of data collected (e.g.: continuous variables [19,27,30] *versus* categorical [41,43]), from the different sources of patient

data (questionnaires, interviews, clinical records) and also from the already mentioned patient memory bias.

Different velocities of tumour growth may well also explain why some tumours remain small in size in spite of delay. Even though some studies linked diagnostic delay and advanced tumour stage, it is possible that the relationship between delay and advanced tumour stage is veiled by the fact that certain cancers remain silent during the initial stages and induce symptoms only when they reach an advanced phase (silent tumour hypothesis) [7]. This being, the tumour growth rate would act as a confounding factor in the relationship between diagnostic delay and tumour stage since patients with aggressive tumours and poor prognosis do not usually present diagnostic delay, while tumours with low proliferation rates demonstrate good prognosis despite long diagnostic delays [44,45].

Despite the aforementioned, a recent meta-analytic study by our research group has shown that diagnostic delay is broadly associated to more advanced stages in oropharyngeal cancers. This association resulted to be especially strong when the analysis was restricted to oral cancer (pooled RR, 1.47; 95%CI: 1.09 – 1.99) and when the delay was longer than one month (pooled RR, 1.69 95%CI: 1.26 – 2.77) [9]. The probability for delayed patients to present an advanced-stage oral cancer at diagnosis in this report was 25% higher than that of a non-delayed patient. Nevertheless, these data should be interpreted with caution since all 9 studies considered in the meta-analysis were cross-sectional in nature, with retrospective designs and a potential for recall bias [9].

The number of studies focusing on the relationship between diagnostic delay and survival to oral cancer are scarce, and their results show substantial discrepancies: on the one hand the strength of the association did not reach signification [46], but on the other hand there seem to exist a strong relationship when referral delay is considered [27,47]. More specifically: when longer than a month, these delays worsen survival to oral and oropharyngeal cancer [47]. However, when tumour aggressiveness is considered, the role of diagnostic delay could not be demonstrated [29]. Moreover, confounding effects of lead-time bias could condition the association between diagnostic delay and survival to the tumour [26].

Reports on tongue cancer are particularly interesting [27,28] because the impact of diagnostic delays on survival are apparently unreasonable: shorter delays impaired survival. This paradoxical circumstance, where diagnostic delay, tumour stage and tumour prognosis are inversely related, has been previously described in endometrial, cervix, lung, colon, renal and urethral cancer,

and seems to suggest that stage at diagnosis and survival are strongly affected by the biological aggressiveness of the cancer [8, 26,48].

Oral cancer is a relatively proliferating tumour with proven heterogeneity in its biological behaviour. Specifically HPV negative, aneuploid and TP53-mutated tumours have shown less favourable prognoses [49]. Moreover, the expression of different oncogenic markers including , p16, p21, p27, MDM2, MGMT, EGFR, ERBB2, RARB, MYC, BCR-ABL1, RAS, CCND1, STAT-3, and VEGF, induce a more rapid clinical course [50] that considerably reduces the opportunities for a diagnosis at early stages of the disease. Alternatively, HPV positive oral cancers, mostly oropharyx, mainly wild-type TP-53 have demonstrated favourable prognosis [49].

Conclusion

Advanced tumour stages in oral cancer have been conventionally ascribed to delays in reaching a diagnosis. Surprisingly, there is a lack of sound scientific evidence supporting this traditional association between diagnostic delay and disease extension and survival. However, different oral cancer genetic profiles result on a wide variability in the biological behaviour of the tumour and may justify the hypothesis of the biological heterogeneity of diagnostic delay in oral cancer.

An important issue is the difficulty in comparing oral cancer subtypes with very different behaviours. Thus rapidly growing tumours –where the quickness in obtaining a diagnosis does not guarantee and early stage- have short periods for a potential screening, whereas slowly growing tumours permit a longer potential screening period. This circumstance should be taken into account when designing interventions aimed at reducing the duration of the diagnostic pathway.

In this sense, the corroboration of this hypothesis would imply favouring oral cancer and precancer screening strategies, and therefore opportunistic screening for oral cancer and precancer on asymptomatic, at-risk population should be reinforced.

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IMPACT OF DELAY IN DIAGNOSIS ON SURVIVAL TO HEAD AND NECK C ARCINOMAS: A META-ANALYSIS

5. IMPACT OF DELAY IN DIAGNOSIS ON SURVIVAL TO HEAD AND NECK CARCINOMAS: A META-ANALYSIS.

Abstract

Objective: To address the contradictory information on the role of delay in diagnosis in head and neck cancer survival.

Study Design: Systematic review and meta-analysis.

Search Strategy: Search on MEDLINE (1966 to March 2011), EMBASE (1980 to March 2011), and ISI proceedings (from inception to March 2011) The terms used were ("Head and neck cancers") *AND* ("delay" *OR* "prognostic" *OR* "survival") both in MeSH terms and free-text words. The reference lists of the retrieved articles were also revised manually to identify other potentially relevant papers. All searches were independently undertaken by two clinicians and one epidemiologist, and the results merged.

Setting: primary and specialized care levels.

Participants: Meta-analysis of data from papers on the subject published from 1966-2011.

Main outcome measures: Survival.

Methods: After search in Medline and other databases, we computed pooled Relative Risks (RR) and 95% Confidence Interval (95%CI) from the 10 studies retrieved.

Results: The estimate of the relative risk of mortality related to any diagnostic delay (either patient or professional delay) was 1.34 (95%CI 1.12-1.61). Referral delay was associated with a 3-fold increase of mortality. Total delay was marginally related with mortality (RR: 1.04, 95%CI: 1.01-1.07). By anatomic location, pharynx cancer shows the highest association (RR: 1.68, 95%CI: 1.22-2.31).

Conclusions: Diagnostic delay is a moderate risk factor of mortality from head and neck cancer. However, part of the effect observed may be due to residual confounding (confounding from unknown variables that is not eliminated by adjustment).

Keywords: meta-analysis, head and neck cancer, survival, diagnostic delay

Introduction

Head and neck cancer is ranked as the eighth leading cause of cancer death worldwide. [1-4] Several factors have been assessed as independent prognostic markers for head and neck cancer, but tumour stage at diagnosis is still recognised as the most important one.[3] Advanced stages are frequently associated with high mortality rates: the reported five-year survival rate for patients with localized disease is 82%, that of patients diagnosed with regional disease is 51% and that of patients with distant metastasis only 27.6%.[4] This poor five-year survival rate has remained unchanged for more than three decades.[3,4] Unfortunately, almost half of the head and neck cancers are diagnosed at advanced stages (III or IV), probably due to delays in reaching a diagnosis.[5,6]

Nowadays, diagnostic delay is most often categorised as (i) patient delay – the period between the patient first noticing a symptom and their first consultation with a health care professional concerning that symptom;[6,12,13] and (ii) provider/professional delay – the period elapsed between the patient's first consultation with a health care professional and the definitive pathological diagnosis. [6,12,13] The overall diagnostic delay (total delay) includes the period elapsed since the first symptom or sign until the definitive diagnosis.

Several research groups have assessed the role of diagnostic delay in the staging of the tumour, and by extension, in the survival from head and neck cancer. Heterogeneous criteria were used in this assessment. Different types of data were used (continuous [15] and categorical data[8,14]) and different sources of information on patient delay were collected (standard questionnaires, interviews, hospital records, etc.). This heterogeneity in the assessment, along with variations in tumour biology, may explain the absence of a consistent relationship between diagnostic delay and stage of the tumour in the literature.[3,5,6] While several research groups did not find sufficient evidence,[7-9] some others have recently described a significant relationship between advanced stages and diagnostic delay. [6,10,11] Despite these shortcomings, diagnostic delay has recently been recognised as an independent prognostic factor for survival to head and neck cancer. [3,7,11,15-17]

In view of this inconsistent data, we undertook a systematic review and meta-analysis to assess the relation between diagnostic delay and survival in head and neck cancer.

Material and methods

Literature search

We performed a systematic search on computerized databases including MEDLINE (1966 to March 2011), EMBASE (1980 to March 2011), and ISI proceedings (from inception to March 2011) for papers published in any language. The abstracts of the articles were screened to exclude irrelevant studies. The terms used were ("Head and neck cancers") *AND* ("delay" *OR* "prognostic" *OR* "survival") both in MeSH terms and free-text words. The reference lists of the retrieved articles were also revised manually to identify other potentially relevant papers. All searches were independently undertaken by two clinicians and one epidemiologist, and the results merged.

Studies were included if they fulfilled the following criteria:

(i). Presented original data from survival studies with a survival follow-up of at least 24 months, starting from the date of the histological diagnosis of a squamous cell carcinoma.

(ii). The sample was made of patients with head and neck cancer, excluding odontogenic, ear, skin and salivary glands tumours.

(iii). The exposure of interest in the study was *patient delay* (the time from the patient's first awareness of symptom or sign to the first consultation with a physician or dentist); or *professional delay* (PDI – presentation to diagnosis interval- the time from the patient's first consultation with a physician or a dentist to the date of final histological diagnosis); or *total diagnostic delay* (the sum of the patient and professional delay); or *referral delay* (difference between the date of first symptom and the date of the referral letter transferring the patient to the secondary care level).

Quality assessment

We assessed study quality by use of a five-point binary scale (yes/no) that we specifically developed for this study. The scale is based on the Newcastle-Ottawa scale[18] with modifications in view of standard guidelines.[19] Throughout this assessment, when the information on a specific item was not provided by the authors, we graded this item as "no". The quality scoring was indepen-

dently undertaken by two researchers (BT & JS). The first item assessed the source of the outcome date. One point was given if the date of death was ascertained through clinical history or death certificate and zero point if otherwise. The second item assessed the cause of death (one point if it was clearly due to the cancer diagnosed previously, including metastasis, and zero point if non-specific mortality was measured). The third item assessed the follow-up time (one point if follow-up was 4 years or more and zero if less than 4 years). The fourth item assessed the definition of delay. One point was given if inception was clearly defined and zero if not. The last item concerned adjustment for confounding factors. One point was given if the analysis was adjusted for sex, age and other factors and zero if not.

Statistical analysis

The study-specific adjusted log relative risks were weighted by the inverse of their variance to compute a pooled RR and its 95% CI. We computed both fixed-effects and random-effects pooled estimates. The fixed-effects model assumes that there is no between-study variance (i.e. that the results of the studies used in the meta-analysis are homogeneous and their variation is a result of sampling only). The random-effects model, by contrast, assumes that study results are heterogeneous. The random-effects model yields pooled results that are less precise (have wider CIs) but are closer to the true value in the event that heterogeneity exists. To quantify the heterogeneity, the proportion of the total variance due to between-study variance (the R_i statistic) was calculated.[20] For each analysis, we used random effects results whenever the test statistic for heterogeneity was significant, and fixed effects estimates otherwise. For each study, we estimated the relative risk of mortality for "any delay" by pooling the estimates of each category of delay presented by the authors of the study. When only one category of delay was presented, we used its estimate and included it in the category "any delay".

To assess publication bias visually, a funnel plot was used.[21] Because funnel plots have several limitations and represent only an informal way to detect publication bias,[20] the test suggested by Egger *et al.* was also applied.[22] All analyses were performed using the HEpiMA software, version 2.1.3 [23]

Results

A total of 1016 articles were accessed through the literature search strategy. Review of the titles, abstract, and in some cases the full text, excluded 1001 articles. We further excluded 7 studies due to either unclear or arbitrary definition of diagnostic delay,[24] or lack of information on any of the variables of interest.[24-30] We finally included 10 studies that were published in 8 different articles between 2001 and 2010 (Table 1 and figure 1). The period of data collection spanned between 1974 and 2002. The anatomic location of the tumours varied widely between studies: 2 studies presented data on tongue tumours, 3 on oral or oropharynx cancer, 2 on pharynx, 2 on larynx and 1 on glottis tumours. The sample size varied between 66 and 544 patients. All studies but one were carried out in European countries.[7,9,10,15,17,31-33] One article provided independent data for oral, pharynx and larynx cancers.[31] Five studies presented data on patient delay, five on professional delay, 2 on referral delay and 2 on total delay. One study presented data on professional delay that were clearly erroneous (point estimate of the relative risk out of the range of the confidence interval). [9] This erroneous estimate was not included in our meta-analysis. Distribution by tumor stage varied widely between studies: from 2% to 50% for TNM stage I and from 0% to 68% for TNM stage IV.

Table 2 lists the pooled effect estimates for all 10 studies and diverse subgroups. The random effects pooled estimate from all studies was 1.34 (95%CI 1.12-1.61) with substantial heterogeneity (Ri=0.95). Although patient and professional delays were associated with increased risk of mortality, both estimates did not reach statistical significance. Referral delay estimate, although based on 2 studies only, is associated with a statistically significant 3-fold increase of mortality. On the contrary, total delay is apparently not related with the outcome (pooled RR: 1.04, 95%CI: 1.01-1.07).

Although the funnel plot (figure 2) indicates a slight skewness to the right, the asymmetry test yielded a p-value of 0.83 indicating absence of asymmetry. Publication bias is then unlikely to occur with the data at hand.

By anatomic location, pharynx cancer shows the highest association between delay and mortality (Pooled RR: 1.68; 95%CI: 1.22-2.31, low heterogeneity).

To assess the possible confounding effect due to the stage of the tumor, we stratified our analysis into 2 subgroups: studies that included 60% or more of advanced stages (TNM III and IV) and studies with less than 60% of advanced stages. The pooled RR in the first group was 1.74 (95% CI: 1.30-2.33)

with no heterogeneity, and in the second group 1.19 (0.99-1.44) with considerable heterogeneity.

When we restricted the analysis to retrospective studies, we obtained a pooled estimate that showed an increase in the risk of about 60%. The risk increase for partially prospective studies was substantially lower.

The data of the studies included in this meta-analysis were collected either through questionnaires or by reviewing clinical records from primary care centers. The latter yielded a statistically significant pooled estimate of 1.77 (95% CI: 1.14-2.73).On the contrary, no increase in the risk was observed for those studies that collected the data through questionnaires.

Adjustment for potential confounding factors, such as sex, was not performed systematically in the studies retrieved. Those studies that adjusted for sex showed a minute increase in the risk of mortality that was non significant, unlike unadjusted studies the pooled estimate of which showed substantial risk increase.

After scoring the quality of the studies on a 5 point scale, we divided the studies in 2 groups: those that scored 4 or more points out of five and those which scored less. The high quality studies showed a pooled estimate of 1.77 (95% CI 1.14-2.75) while low quality studies showed no increase in the risk of mortality. Related to this issue, those studies which provided details on the source of mortality data yielded a higher risk increase than those with unknown data source.

Discussion

Globally, the results of this meta-analysis showed that diagnostic delay is moderately related to mortality of head and neck cancers. The association was stronger for referral delay and for pharynx cancer, a fact that may be due to the rapidity at which pharyngeal cancers metastasize. [11] In addition to the effect exerted by the stage of the tumour, part of the effect of delay on mortality may be caused by residual confounding, distortion due to incomplete adjustment for variables that could potentially distort the relation between delay and mortality. Sex is one of those variables. We observed that some of the studies included in our meta-analysis did not provide relative risk estimates adjusted for sex, and that the pooled effect for sex adjusted studies was much smaller than that of unadjusted studies.Also, the biological behaviour of the tumour may play the role of a confounding factor in the relation between diagnostic delay and survival, as patients with aggressive tumours and bad

prognosis do not usually present diagnostic delay whereas less aggressive tumours elicit good prognosis despite a long diagnostic delay.[14] Unfortunately, only one of the studies included in our review took the tumour proliferation activity into account.[33]

Other limitations of this systematic review and meta-analysis include the lack of consensus in the literature about the period beyond which the diagnosis of a head and neck cancer should be considered delayed: whilst some authors have used the mean or the median of the time distribution to describe and categorise the diagnostic delay,[14] the latter being more frequently used because it is not affected by extreme values and the distributions usually have very wide ranges, other authors divide diagnostic delay into arbitrary intervals [7,9,31,32] or define it as continuous variable without a specific time point.[15] Further, the large majority of the studies included in this meta-analysis were retrospective in nature. Their data are probably less accurate, due to the difficulties encountered by patients in remembering the exact date of the onset of symptoms. These data are prone to recall bias. In our study, we observed that the results from retrospective studies are overestimated. The reports from Finland [7,9,15,31] are probably less exposed to this bias, as primary care physicians recorded each visit on a specific sheet that included the reason for attendance, the diagnosis and the treatment given to the patient; and all new patients received at the tertiary care centres had to have a referral letter from their primary care physician.

Further, key data to establish diagnostic delay, as perception of the symptoms and identification of the clinical signs, are clearly dependent on the specific location of the tumour and may explain the different magnitudes of association. Our results show a strong association between the existence of diagnostic delay and worse survival to pharyngeal carcinomas. It is remarkable that most of these pharyngeal cancers were diagnosed at very advanced stages of the disease (stage IV). [9,10,20]

On the contrary, the effect of diagnostic delay and mortality could not be proved for oral carcinomas, probably because 2 out of the 4 studies considered restricted their analysis to tongue tumours.[15,20] Existing reports on tongue cancer are particularly contradictory, as referral delays worsen survival, [15] but professional delays do not. [32] This paradoxical circumstance, where diagnostic delay, tumour stage and tumour prognosis are not related, was previously described in breast, cervix, lung, colon, renal and urethral cancer and seems to suggest that stage at diagnosis and survival are affected more by the biology of the cancer (rapid tumour growth) than by diagnostic delay. [34]

Although all three reports on larynx cancer show an effect of diagnostic delay and poor survival rates, the investigation that reported the weakest association did not include stage IV carcinomas in its study sample. [17] This fact may modify the final results by showing a weaker association than it actually exists for laryngeal carcinomas. Despite the fact that all reports on laryngeal cancer come from a specific geographical area (Finland and Denmark), it does not seem likely that it might compromise the generalisability of the results.

Conclusions

In view of the results obtained, we conclude that diagnostic delay is a moderate risk factor of mortality from head and neck cancer. However, we cannot rule out that, at least, part of the effect observed may be due to residual confounding (confounding from unknown variables that is not eliminated by adjustment). We consider that new studies assessing the prognostic impact of diagnostic delay are necessary. It is of paramount importance that optimal adjustment for confounding variables be carried out. These future investigations would also benefit from considering the biological features of the tumour and the delay in the treatment.

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Table 1. Summary of the 10 studies included in the meta-analysis

Study	Country	Period of data collection	Site of tumor	Sample size	Average delay (days)	TNM at diagnosis n (%)	Patient delay RR (95%CI)	Professional delay RR (95%CI)	Referral delay RR (95%CI)	Total delay RR (95%CI)	Any delay RR (95%CI)	Quality score
Kantola et al. (15)	Finland	1974-1994	Tongue	75	72 days (Referral delay) 21 days (Professional delay	I 9 (12%) II 22 (29.3%) III 33 (44%) IV 11 (14.7%)	-	-	6.3 (1.7-22.9)	-	6.3 (1.7-22.9)	3
Teppo et al. (31)	Finland	1986-1996	Tongue	62	42 days (median) (Patient delay) 21 days (median) (Professional delay)	I 8 (13%) II 22 (35%) III 25 (40%) IV 7 (11%)	0.58 (0.36-0.93)	1.07 (0.68-1.70)	-	-	0.79 (0.57-1.1)	4
Seoane et al. (33)	Spain	1997-2002	Oral	63	108 days (Total delay)	I 9 (14.3%) II 20 (31.7%) III 10 (15.9%) IV 24 (38.1%)	-	-	-	1.0 (0.9-1.1)	1.0 (0.9-1.1)	3
Sandoval et al. (32)	Spain	1996-1999	Oral and oropharynx	146	N.A.	I 15 (10.3%) II 30 (20.5%) III 35 (24%) IV 66 (45.2%)	-	-	2.1 (1.0-4.3)	-	2.1 (1.0-4.3)	4
Ho et al. (10)	USA	1994-2001	Oropharynx	87	106 days (Professional delay)	I 3 (3%) II 5 (6%) III 15(17%) IV 59 (68%)	-	1.09 (0.64-1.87)	-	-	1.09 (0.64-1.87)	1
Koivunen et al. (9)	Finland	1986-1996	Pharynx	84	108 (median) Total delay	I 3 (4%) II 17 (20%) III 16 (19%) IV 46 (55%)	2.5 (1.39-4.38)	Erroneous	-	-	2.5 (1.39-4.38)	4
Teppo et al. (31)	Finland	1986-1999	Pharynx	66	30 days (median) (Patient delay) 33 days (median) (Professional delay)	I 1 (2%) II 10 (15%) III 12 (18%) IV 41(62%)	3.33 (1.76-6.32)	0.24 (0.07-0.76)	-	-	1.79 (1.02-3.13)	4
Teppo et al. (31)	Finland	1986-1999	Larynx	93	60 days (median) (Patient delay) 63 days (Professional delay)	I 30 (45%) II 8 (12%) III 21 (32%) IV 7 (11%)	1.73 1.20-2.51	3.5 (1.8-6.9)	-	-	2.04 (1.47-2.82)	4
Teppo et al. (7)	Finland	1990-1995	Larynx	66	180 (median) (Total delay)	I 37 (40%) II 15 (16%) III 29 (31%) IV 12 (13%)	1.73 (0.48-6.21)	3.07 (1.20-7.88)	-	-	2.51 (1.17-5.36)	4
Hansen et al. (17)	Denmark	1995-1997	Glottis	544	108 days (1965-79) 100.5 days (1980-9) 115 days (1990-7)	I 270 (49.6%) II 204 (37.5%) III 70 (12.9%) IV 0 (0%)	-	-	-	1.04 (1.02-1.07)	1.04 (1.02-1.07)	3

N.A.: Not available

Table 2. Pooled relative risks (RR) and 95% confidence intervals (CI) of mortality due to delay in head and neck cancers*

Item	Number of studies	RR (95% CI) fixed effects	RR (95% CI) Random effects	Ri †	Q test p-value
Any delay (all studies)	10	1.05 (1.02-1.07)	1.34 (1.12-1.61)	0.95	0.00005
Patient delay	5	1.54 (1.21-1.94)	1.67 (0.88-3.19)	0.85	0.00005
Professional delay	5	1.34 (1.00-1.78)	1.32 (0.66-2.66)	0.82	0.0004
Referral delay	2	2.72 (1.45-5.09)	3.17 (1.12-9.00)	0.61	0.15
Total delay	2	1.04 (1.01-1.07)	1.04 (1.01-1.07)	0.00	0.44
Oral cancer	4	1.00 (0.92-1.10)	1.27 (0.81-1.98)	0.94	0.003
Pharynx cancer	3	1.68 (1.22-2.31)	1.69 (1.05-2.72)	0.55	0.11
Larynx cancer	3	1.05 (1.02-1.08)	1.64 (0.91-2.96)	1.00	0.00005
≥ 60% of stages III and IV	4	1.74 (1.30-2.33)	1.76 (1.21-2.54)	0.37	0.19
< 60% of stages III and IV	6	1.04 (1.01-1.07)	1.19 (0.99-1.44)	0.96	0.00001
Retrospective studies	8	1.09 (1.00-1.19)	1.57 (1.11-2.24)	0.92	0.00005
Partially prospective studies	2	1.04 (1.01-1.07)	1.34 (0.69-2.61)	1.00	0.05
Primary care centers	7	1.50 (1.25-1.79)	1.77 (1.14-2.73)	0.81	0.0001
Questionnaires	3	1.04 (1.01-1.07)	1.04 (0.95-1.13)	0.84	0.11
Population based studies	3	1.02 (0.92-1.11)	1.16 (0.82-1.65)	0.89	0.13
Hospital based studies	7	1.05 (1.02-1.08)	1.67 (1.14-2.44)	0.99	0.00005
Source of mortality data known	7	1.09 (1.00-1.19)	1.68 (1.13-2.49)	0.94	0.00005
Source of data unknown	3	1.04 (1.01-1.07)	1.17 (0.85-1.60)	0.99	0.15
Sex adjusted	7	1.04 (1.01-1.07)	1.16 (0.99-1.36)	0.94	0.0001
Sex non adjusted	3	2.77 (1.81-4.24)	2.77 (1.81-4.24)	0.00	0.42
Quality score < 4	4	1.04 (1.01-1.07)	1.04 (0.93-1.17)	0.89	0.04
Quality score ≥ 4	6	1.54 (1.28-1.86)	1.77 (1.14-2.75)	0.81	0.0002

* RR = Relative Risk; CI = confidence interval
† Proportion of total variance due to between-study variance

Figure 2. Study-specific and pooled relative risks from studies of diagnosis delay and head and neck cancer

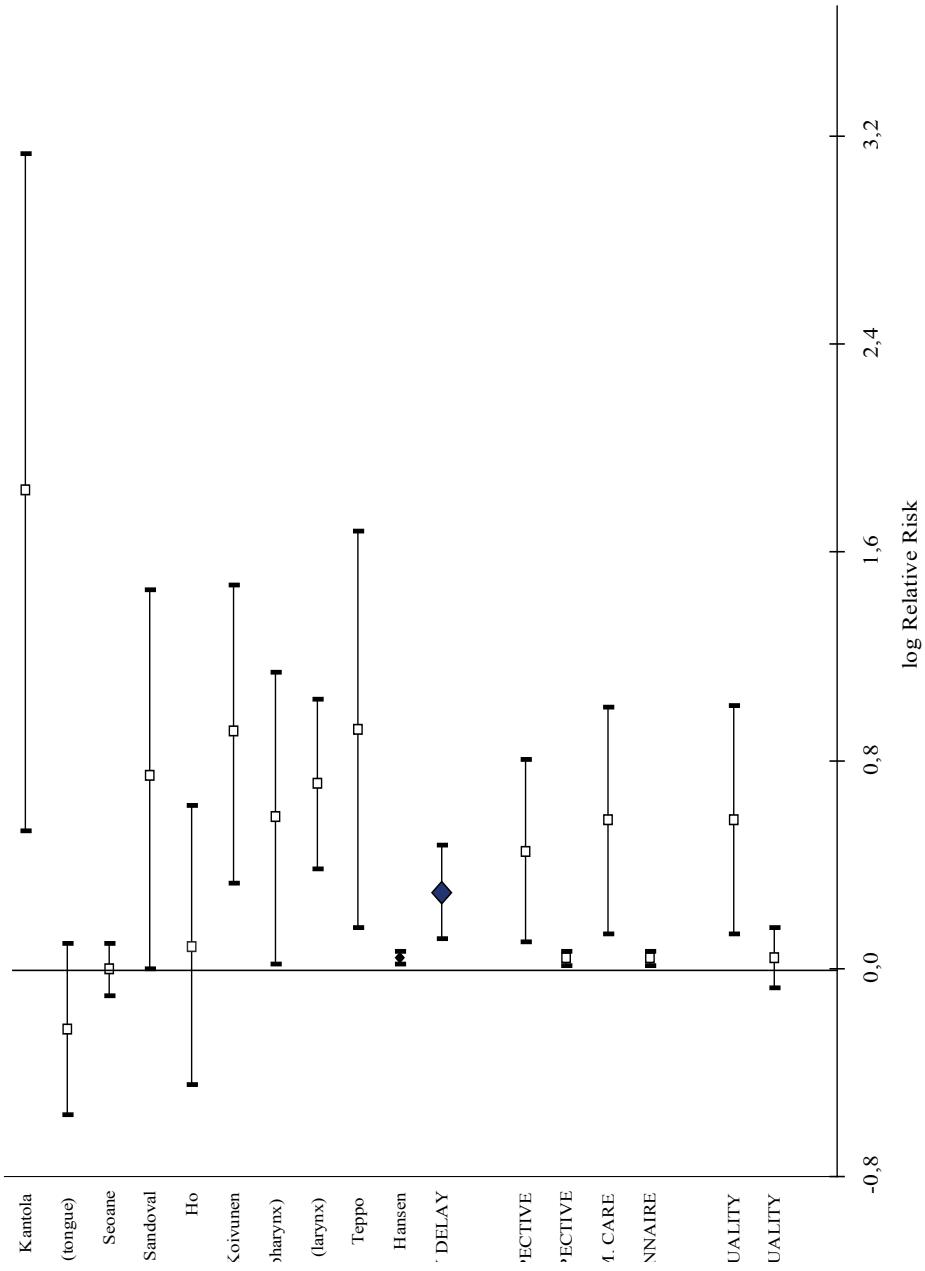
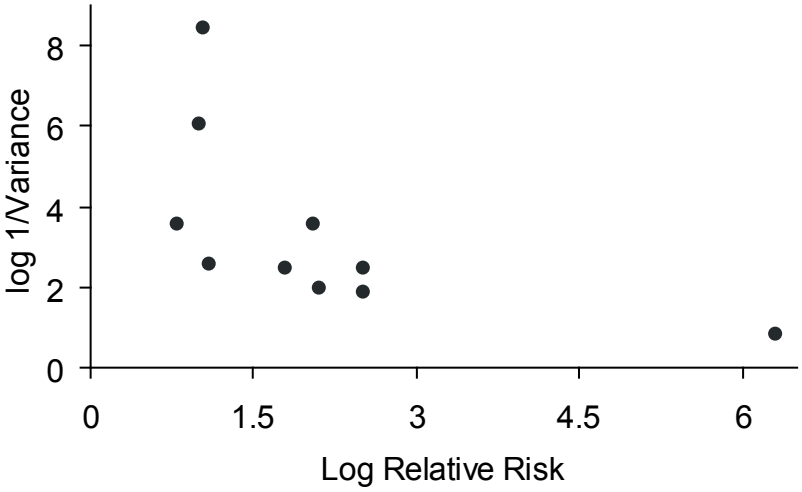


Figure 2. Funnel plot of Relative Risk vs. log Inverse Variance of Relative Risk for any delay.



FACTORS RELATED TO LATE STAGE DIAGNOSIS OF ORAL SQUAMOUS CELL CARCINOMA

6. FACTORS RELATED TO LATE STAGE DIAGNOSIS OF ORAL SQUAMOUS CELL CARCINOMA.

Abstract

Aims: To identify factors related to advanced-stage diagnosis of oral cancer to disclose high-risk groups and facilitate early detection strategies.

Study design: An ambispective cohort study on 88 consecutive patients treated from January 1998 to December 2003. Inclusion criteria: pathological diagnosis of OSCC (primary tumour) at any oral site and suffering from a tumour at any TNM stage. Variables considered: age, gender, smoking history, alcohol usage, tumour site, macroscopic pattern of the lesion, co-existing precancerous lesion, degree of differentiation, diagnostic delay and TNM stage.

Results: A total of 88 patients (mean age 60±11.3; 65.9% males) entered the study. Most patients (54.5%) suffered no delayed diagnosis and 45.5% of the carcinomas were diagnosed at early stages (I-II). The most frequent clinical lesions were ulcers (70.5%). Most cases were well- and moderately-differentiated (91%). Univariate analyses revealed strong associations between advanced stages and moderate-poor differentiation (OR=4.2; 95%CI=1.6-10.9) or tumour site (floor of the mouth (OR=3.6; 95%CI=1.2-11.1); gingivae (OR=8.8; 95%CI=2.0-38.2); and retromolar trigone (OR=8.8; 95%CI=1.5-49.1)).

Regression analysis recognised the site of the tumour and the degree of differentiation as significantly associated to high risk of late-stage diagnosis.

Conclusions: Screening programmes designed to detect asymptomatic oral cancers should be prioritized. Educational interventions on the population and on the professionals should include a sound knowledge of the disease presentation, specifically on sites like floor of the mouth, gingivae and retromolar trigone. More studies are needed in order to analyse the part of tumour biology on the extension of the disease at the time of diagnosis.

Key words: oral cancer, advanced-stage, diagnosis, cohort study.

Introduction

Survival rates for oral cancer are very poor (around 50% overall), and no remarkable improvements have occurred in recent decades despite advances in therapeutic interventions (1). Variables like age, co-morbidity, immunological or nutritional status, size and location of the tumour, nodal status, oncogene expression, proliferation markers, or DNA content have been assessed as independent prognostic markers for oral cancer (2), but stage at diagnosis remains as the most important prognostic indicator for oral and oropharyngeal squamous cell cancers (SCCs) in such a way that advanced stages are frequently associated with high mortality rates (3-5).

Advances in therapy and standards of care are likely to have played a role in the moderate increase of survival trends, particularly for females and tongue cancer (6,7).

Detecting oral cancer at an early stage is believed to be the most effective means of reducing rates of death, morbidity and disfigurement from this disease (1), but progression in this field is slow: late-stage presentation is commonplace despite the existing evidence supporting that visual and tactile exploration may ease detection of oral cancer at early stages (8-10). Evidence also suggests that an oral examination of high risk individuals may be a cost-effective screening strategy (11).

An important number of studies have assessed the determinants for diagnostic delay (*period elapsed since the first sign or symptom until definitive diagnosis*) despite its controversial part in oral cancer (12-14), but the reports aimed at identifying predictors for diagnosis at advanced stages are very scarce though tumour stage is directly related to mortality by oral cancer.

This study was designed to analyse the hypothetical factors related to diagnosis of oral cancer at advances stages (III-IV) in order to identify high-risk groups for late-stage diagnosis and facilitate early detection strategies.

Material and methods

An ambispective cohort study was designed to analyse those factors related to late-stage oral cancer diagnosis. The study sample was made of 88 patients treated at the Oral and Maxillofacial Surgery Service of the CHUAC from January 1998 to December 2003 that met the following inclusion criteria: pathological diagnosis of OSCC (primary tumour) at any oral site and suffering from a tumour at any TNM stage.

The primary sites of oral cancer were: buccal mucosa (n=5), upper and lower gingiva (n=15), hard palate (n=2), tongue (n=32), floor of the mouth (n=24) and retromolar trigone (n=10).

The variables considered included age, gender, smoking history, alcohol usage, tumour site, macroscopic pattern of the lesion (ulcerated, exophytic or mixed), co-existing precancerous lesion, and degree of differentiation.

The time interval from the self-reported date when oral cancer signs and/or symptoms were first noted by the patient to the date of definitive pathological diagnosis was defined as the total diagnostic delay. In order to limit the recall bias inherent to this kind of studies, delay data collected from the patient was also validated by those obtained from close relatives. In both situations, identical structured interviews were undertaken for all cases. The median of total diagnostic times has been used as a cut-off point to distinguish between delayed and non-delayed cases in a more objective way.

TNM stage was considered as the dependent variable (early = tumour-node-metastasis [TNM] stage I or II; advanced = TNM stage III or IV). Early stages include a variety of tumour sizes (<4 cm) without invasion of adjacent structures, and no lymph node or distant metastases. Advanced stages include tumours invading adjacent structures, e.g., through cortical bone, into deep (extrinsic) muscle of tongue, maxillary sinus, and skin, or a more advanced node status than early stages' or display distant metastases (15).

Statistical analysis

Data were entered on the PASW statics18 statistical package and the sample characterized by the variables of interest. A descriptive study was conducted where quantitative variables were expressed as mean ± standard deviation; and qualitative ones as absolute frequency and percentage.

Means were compared using the Student's t test after assessing their normality with the Kolmogorov-Smirnov test. Those variables that are clinically relevant or were significantly related to advanced TNM-stage after univariate analysis (simple logistic regression) were included in a multivariate model (multiple logistic regression). The significance level chosen for all tests was $p<0.05$.

Results

A total of 88 patients (mean age 60±11.3), mostly males (65.9%) entered the study. The most frequent tumour sites were tongue (36.4%), floor of the mouth (27.3%) and gingivae (17%).

The median for the interval between the first sign/symptom to pathological diagnosis was 45 days, and most patients (54.5%) suffered no delayed diagnosis. A 45.5% of the oral carcinomas were diagnosed at early stages (I-II). The most frequent clinical lesions were ulcers (70.5%), being the cancer associated to a precancerous lesion in a 16.5% of the cases.

Most cases were well- and moderately-differentiated (91%) (Table 1).

Univariate analyses revealed that age (OR=1.0; 95%CI=0.9-1.0), smoking habit (OR=1.4; 95%CI=0.5-3.9), alcohol usage (OR=1.0; 95%CI=0.4-2.6), co-existence of a precancerous lesion (OR=0.6; 95%CI=0.2-2.1) and the clinical presentation (ulcerated/mixed) of the oral carcinoma (OR=2.7; 95%CI=0.7-9.9) were neither significantly associated to diagnosis at advanced-stages, nor to TNM-advanced stage (OR=0.7; 95%CI=0.3-1.6).

On the other hand, male gender was identified as a risk factor for late TNM stage at diagnosis (OR=3.8; 95%CI=1.4-9.6). Strong associations between advanced stages and moderate-poor differentiation (OR=4.2; 95%CI=1.6-10.9) or tumour site (floor of the mouth (OR=3.6; 95%CI=1.2-11.1); gingivae (OR=8.8; 95%CI=2.0-38.2); and retromolar trigone (OR=8.8; 95%CI=1.5-49.1)) have also been identified by univariate analysis (Table 2)

Regression analysis excluded "gender" from the multivariate model, remaining tumour site and degree of differentiation significantly associated to high risk of late-stage diagnosis (Table 3).

Discussion

The current recommendations to screen for oral cancer at every routine check-up is not practical and has not produced the intended results. Selective opportunistic screening may be a more realistic and effective solution. Detection of oral and oropharyngeal SCCs during a non-symptom-driven examination has proved an association to lower stage at diagnosis, in the same way as patients with a regular primary care dentist are significantly more likely to be diagnosed at early stages (4, 16).

Unfortunately, about a 60% of cancers are identified late (stages III or IV) with survival rates ranging from 10% to 40% after 5 years (17, 18). Up to a

54.5% of the patients in this series were diagnosed at late stages, and recognition of predictors for advanced-stage diagnosis could permit the development of strategies aimed at improving this percentage.

Age, gender, and tobacco and alcohol consumption did not behaved as variables linked to late-stage diagnosis; as were not previously associated to professional or patient-related diagnostic delays (19, 20). The existence of precancerous lesions associated to the tumour did not seem to modify the extension of the disease at the moment of diagnosis, despite that proliferative verrucous leukoplakia or the presence of mild or moderate epithelial dysplasia at the margins of a surgically removed OSCC carries a significant risk of local recurrence and modifying prognosis (21).

Ulcerated-type OSCC were diagnosed mostly (up to a 60%) at stages III-IV, but this association did not reach statistical signification. Moreover, the predictive value for survival of the lesion clinical appearance is controversial, although it is accepted that ulcerated lesions imply poorer survival rates (22).

Previous reports have described the association between primary tumour site and delayed diagnosis or diagnosis at advanced stages (23): tongue, buccal mucosa and lip have been recognised as locations that favour early-stage diagnosis (18), whereas the floor of the mouth and the retromolar trigone have been linked to diagnosis at advanced stages; locations like palate or gingivae showed contradictory results (18, 24). Our data show that the floor of the mouth, gingivae and retromolar trigone behaved as an independent prognostic factor for late stage at diagnosis. These findings may well be explained by the fact that patient's self-perception and self-exploration abilities depend on the site of the tumour (25), and also because gingival locations are associated to advanced stages at diagnosis (late diagnosis) due to the early invasion of the adjacent tissue (T4 primary tumour) (26).

Advanced-stage diagnosis in oral cancer has traditionally been attributed to delays in reaching a diagnosis, as patients at advance tumour stages are more likely to have longer patient and professional delays than those at early stages (27). However, the lack of sound scientific evidence supporting the existence of an association between diagnostic delay, extent of the disease (III-IV TNM stages) and lower survival rates is evident (12-14). This fact is probably related to a series of limitations and methodological flaws identified in the published reports to date, mainly related to heterogeneity in both the definition and measurement of diagnostic delay, the retrospective nature of these studies and also to a memory bias of the patients (12,13).

In this study, diagnostic delay was not significantly linked to advanced stage at diagnosis; thus the quickness in obtaining a diagnosis does note guar-

antee an early-stage tumour, although delay in the diagnosis of a neoplasm is universally considered unacceptable.

On the other hand, poor differentiation of the tumour (biologically more aggressive) behaved as an independent risk factor for diagnosis at stages III-IV. The tumour growth rate may play the role of a confounding factor in the relationship between diagnostic delay and disease-stage or survival, as patients with aggressive tumours and bad prognosis do not usually present diagnostic delay whereas tumours with low proliferation rates elicit good prognosis despite long diagnostic delays (28). Unfortunately, the evidence on tumour proliferation activity that could corroborate this hypothesis is scarce.

This paradoxical circumstance has previously been described in breast, cervix, lung, colon, renal, and urethral cancers and seems to suggest that stage at diagnosis is affected more by the biology of the cancer (rapid tumour growth) than by diagnostic delay (28,29). These results seem to suggest that the stage of oral cancer at the time of diagnosis is affected more by the biology of the cancer (degree of differentiation) than by diagnostic delay.

Taking into account that early diagnosis is a foremost step for reducing cancer mortality, it is concluded that the efforts aimed at early diagnosis or oral cancer should be prioritized towards screening programmes designed to detect the disease during its asymptomatic phases. Educational interventions on the population, particularly focused on risk groups (self-exploration) and on the professionals (clinician's index of suspicion) should include a sound knowledge of the disease presentation, specifically on sites like floor of the mouth, gingivae and retromolar trigone. More studies are needed in order to analyse the part of tumour biology on the extension of the disease at the time of diagnosis.

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Table 1. Description of the sample (n=88).

Variables	Mean	SD	Minimum-Maximum
Age	60.3	11.3	38.8 88,1
	n	%	95% CI
Gender			
Female	30	34.1	23.6-44.5
Male	58	65.9	55.4-76.3
Smoking			
Non-Smoker	22	27.2	16.8-37.4
Former-Smoker	16	19.7	10.4-29.0
Current-Smoker	43	53.0	41.6-64.5
Alcohol usage			
Non drinker	51	65.4	54.1-76.5
Drinker	27	34.6	23.4-45.8
Tumour site			
Tongue	32	36.4	25.7-46.9
Floor of the mouth	24	27.3	17.3-37.1
Gingivae	15	17.0	8.6-25.4
Buccal Mucosa	5	5.7	1.8-12.7
Retromolar trigone	10	11.4	4.1-18.5
Hard palate	2	2.3	0.2-7.9
TNM Stage			
Stage I	10	11.4	4.1-18.5
Stage II	30	34.1	23.6-44.5
Stage III	14	15.9	7.6-24.1
Stage IV	34	38.6	27.8-49.3
Tumour size			
T_1	12	13.6	5.8-21.3
T_2	43	48.9	37.8-59.8
T_3	10	11.4	4.1-18.5
T_4	23	26.1	16.3-35.8
Neck node status			
Negative (N_0)	61	69.3	59.1-79.5
Positive($N_{1,2,3}$)	27	30.7	20.4-40.8
Macroscopic features			
Exophytic	12	15.3	6.7-24.0
Mixed	11	14.1	5.7-22.4
Ulcerated	55	70.5	59.7-81.2
Degree of differentiation			
Well	29	33.0	22.8-43.8
Moderate	51	58.0	47.6-69.5
Poor	7	8.0	1.7-14.3

Table 2. Patient characteristics distribution according to TNM-stage at diagnosis. Simple logistic regression analysis.

Variables	Early stage (I-II) n=40 (45.5%)	Advanced stage (III-IV) n=48(54.5%)	p-value	Odds Ratio (95%CI)
Age (yrs)				
Mean ±SD	59.4±11.0	61.1± 11.6	0.5	1.0 (0.9-1.0)
Gender				
Female	20 (66.7)	10 (33.3)		1.0 (Referent)
Male	20 (34.5)	38 (65.5)	0.005	3.8 (1.4-9.6)
Tobacco use				
Non-smoker	11 (50.0)	11 (50.0)		1.0 (Referent)
Smoker	24 (40.7)	35 (59.3)	0.4	1.4 (0.5-3.9)
Alcohol Use				
Non-drinker	12 (44.4)	15 (55.6)		1.0 (Referent)
Drinker	22 (43.1)	29 (56.9)	0.9	1.0 (0.4-2.6)
Associated precancerous lesion				
No	28 (43.1)	37 (56.9)		1.0(Referent)
Yes	7 (53.8)	6 (46.2)	0.5	0.6 (0.2-2.1)
Macroscopic features				
Exophytic	8 (66.7)	4 (33.3)		(Referent)
Mixed+Ulcerated	28 (42.4)	38 (57.6)	0.1	2.7 (0.7-9.9)
Location				
Tongue	22 (68.8)	10 (31.1)		(Referent)
Floor of the mouth	9 (37.5)	15 (62.5)	0.02	3.6 (1.2-11.1)
Gingivae	3 (20.0)	12 (80.0)	0.004	8.8 (2.0-38.2)
Buccal mucosa	3 (60.0)	2 (40.0)	0.7	1.4 (0.2-10.1)
Retromolar trigone	2 (20.0)	8 (80.0)	0.01	8.8 (1.5-49.1)
Hard palate	1 (50.0)	1 (50.0)	0.6	2.2 (0.1-38.8)
Diagnostic delay				
No	20 (41.7)	28 (58.3)		1.0(Referent)
Yes	20 (50.0)	20 (50.0)	0.4	0.7 (0.3-1.6)
Degree of differentiation				
Well	20 (69.0)	9 (31.0)		(Referent)
Moderate	19 (37.3)	32 (62.7)	0.008	3.7 (1.4-9.8)
Poor	1 (14.3)	6 (85.7)	0.02	13.3 (1.3-127.5)

Table 3. Multiple logistic regression analysis of the association between advanced staged and patients/tumours characteristics.

Characteristics	B	S.E.	Wald	p-value	Odds Ratio (95%CI)
Constant	-2.88	0.7	14.4	0.000	0.056
Gender					
Female					
Male	0.98	0.58	2.82	0.09	2.6 (0.8-8.4)
Location of the tumour					
Tongue					
Floor of the mouth	1.57	0.71	4.8	0.028	4.8 (1.1-19.5)
Other	2.37	0.68	11.9	0.001	10.7 (2.8-41.3)
Degree of differentiation					
Well					
Moderate	1.32	0.58	5.2	0.022	3.7 (1.2-11.7)
Poor	4.11	1.30	9.9	0.002	61.1 (4.7-786.7)

CONTINUING DENTAL EDUCATION THROUGH SCIENTIFIC JOURNALS: PREVENTIVE ATTITUDES OF GENERAL DENTAL PRACTITIONERS (GDPS) IN ORAL CANCER

7. CONTINUING DENTAL EDUCATION THROUGH SCIENTIFIC JOURNALS: PREVENTIVE ATTITUDES OF GENERAL DENTAL PRACTITIONERS (GDPS) IN ORAL CANCER

Summary

Little is known on educational strategies in cancer control. Continuing Medical Education (CME) has a large impact on oral cancer attitudes, knowledge, and behavior. Reading scientific journals is a key component of CME. The objective of this study was to assess preventive and clinical attitudes of the participants in an educative intervention in oral cancer based on scientific journals.

The study consisted of a cross-sectional study performed on online users of the Spanish Board of Dentists and Stomatologists, using an anonymous, self-applied questionnaire. We asked 791 General Dental Practitioners (GDPs) to participate in the study. The large majority claimed that they deliver tobacco-cessation counseling (93.6%), as well as advice on alcohol consumption (66.6%) while advice on vegetable intake was less frequently provided (42.4%).

Alcohol intake advice, routine mucosa exploration and biopsy performance on lesions suspicious of malignancy are preventive attitudes related to training. Compared with those who did not benefit from CME courses or did so only once, the GDP's who received 4 or more CME courses show a doubling in the odds of giving alcohol advice to their patients, a ten-fold increased odds of performing mucosa check on a routine basis and are 3.5 times as likely to take biopsies of suspicious lesions. A longer experience as a GDP does not increase the probability of adopting preventive attitudes.

In addition to the presentation of the results of our study, we also discuss in a less specific fashion the usefulness of other preventive measures in oral cancer

introduction

Oral and pharyngeal cancer represent the sixth leading cancer in the world and rank in the top three cancers in high incident areas.1 Furthermore, oral cancer with a worldwide incidence of 3.8 cases per 100,000 person-years and a mortality rate of 1.9 cases per 100,000 person-years, accounts for 1.68% of all cancer deaths, based on data reported by the International Agency for Research Cancer (IARC, WHO, 2010).2 This disorder is the seventh most prevalent malignancy in Europe (IARC, WHO, 2004).1,3 Survival remains unaffected despite recent therapeutic advances,1-4 mainly due to delay in the diagnosis.4,5 However, if these malignancies were diagnosed and treated at early stages survival rates would probably exceed 80% .5

Professional diagnostic delay is strongly related to tumor stage at the time of diagnosis.6 Determinants of professional diagnostic delay include lack of knowledge on oral cancer, lack of experience in the disease, absence of full clinical examination and presence of co-morbidity.7,8

Dentists play a critical role in the early diagnosis of oral cancer5. Several authors have identified specific training in medical graduates and dental students as a key issue to reduce the burden of oral cancer through effective cancer control strategies. These strategies include advice on reducing tobacco consumption, promotion of healthier diet and lifestyle and, most importantly, early detection through screening examinations and adequate follow-up.9-16 It is then of paramount importance to develop appropriate initiatives to increase knowledge and favor preventive attitudes both at university and professional level, using Continuing Medical Education (CME) in the latter.17

CME courses exert a positive influence on oral cancer attitudes, knowledge, and behavior of the attendees, which is a key issue in oral cancer control.5,18 Reading scientific journals is a key component of the CME.19-22 In this regard, dental professional organizations in the USA (American Dental Association) and Europe (British Dental Association) have implemented CME initiatives aimed at providing training on new treatments, last research advances and business practices, using their newsletters or journals. However, we are not aware of any oral cancer-related CME effort using scientific journals aimed at GDPs.

The Spanish Board of Dentists and Stomatologists (SBDE, in Spanish: COE) has recently carried out a pilot experience in continuous education in oral cancer by means of scientific journals. The objective of this study was to assess preventive and clinical attitudes related to oral cancer among GDPs.

Methods

We carried out a cross-sectional study between January and December 2009 among GDPs affiliated with the SBDE (affiliation is compulsory for dental practice) who accessed an online Continuous Education program based on the journal of the Board (RCOE: Revista del Consejo de Odontólogos y Estomatólogos), a journal that is distributed to or freely accessed every trimester by the 25000 members of the Board.

As a special collaboration with our study, RCOE published in April 2009 a monograph on oral cancer, written by a panel of experts, which focused on early detection of lesions suspicious of malignancy.23 A customized platform was designed to host an anonymous and confidential self-administered questionnaire designed for our study, as well as an online exam on the content of the monograph that had to be submitted to the accreditation board in order to pass the CME course.

The questionnaire was a modified version of previous survey instruments.14-15 To ensure feasibility, we carried out a pilot study among a small sample of the participants. The questions were broadly grouped into three sections: GDPs profiling questions (demography and practice), questions on preventive attitudes towards oral cancer, and specific questions about clinical practice oriented towards early detection (systematic examination of the oral cavity and biopsy of suspicious oral lesions).

Ethical approval was granted by the Bioethical Committee of the University of Santiago de Compostela.

Statistical analysis

Statistical analysis was performed using SPSS+ 11.0 statistical package (Chicago, IL, USA). To determine which factors were related to preventive attitudes, we used a multiple logistic regression analysis to obtain odds ratios (OR) and their 95% Confidence Intervals (95%CI). The outcome is one of the following preventive attitudes: anti-tobacco advice, alcohol advice, fruit intake advice, routine mucosa check or biopsy performance, and the exposure variables are those related to training, such as the number of CME courses or the amount of professional experience. The estimates were adjusted by age, sex and the rest of the exposure variables. Hence, each of our OR estimates is free of potential confounding due to personal variables or to other variables related to training.

Results

Our study population was formed by 791 GDPs with a mean age of 35 ± 9.6 years, mostly females (61.7%), more than one-third of whom had 10 years or more of practice. About one-fourth of the participants acknowledged that their only postgraduate training on oral cancer was reading the monographic issue of the newsletter used in this study, while 36.3% had attended more than two courses on oral malignancies. Table 1 summarizes the distribution of key variables in the study population. The large majority (93.6%) delivers anti-tobacco advice to their patients and two-thirds advise their patients to reduce alcohol intake. However, only 42% recommend their patients to have an adequate intake of fruit and vegetables. As for routine clinical attitude, 90.3% check their patients' oral mucosa but only 29% perform biopsy on suspicious oral lesions.

From multivariate analysis (Table 2) we observe that no variable is significantly related to anti-tobacco advice delivery. This means that advice is given independently of the background or training of the GDPs. We also observe that recommendations on fruit intake are significantly more frequent among older GDP's, but no other factor, especially those in connection with training, is related to this preventive attitude. Alcohol intake advice, routine mucosa exploration and biopsy performance on lesions suspicious of malignancy are preventive attitudes related to training factors. Compared to those who did not benefit from CME courses or did so only once, the GDP's who received 4 or more CME courses show a doubling in the odds of giving alcohol advice to their patients, a ten-fold increased odds of performing mucosa check on a routine basis. They are 3.5 times as likely to take biopsies of suspicious lesions and twice as likely to give alcohol advice to their patients. Also, those who received 2 to 3 CME courses double their odds of performing mucosa check. Having received specific oral cancer courses increases by 50% the likelihood of performing biopsies when indicated. Finally, a longer experience as a GDP (measured by years of practice in the field) does not seem to increase the probability of adopting preventive attitudes. On the contrary, experienced doctors are less likely to take biopsies. However, older GDP's do perform more biopsies on suspicious lesions.

Discussion

Whereas continuous dental education is compulsory in the USA, this requirement is not uniform in European countries, where, in general, it is considered as a moral duty for the dentist. Nowadays several countries including Austria, Cyprus, Estonia, Finland, The Netherlands, Norway, Sweden and Spain maintain a voluntary scheme for their CME system.24 Therefore, the results of our study cannot compare directly to those countries where CME is mandatory for dentists.

Our results show that CME courses are useful to increase GDP's preventive attitudes, especially those related to clinical practice (routine mucosa exploration and biopsy performance). Specific courses are useful to increase biopsy taking but do not seem to improve other preventive attitudes. The paradoxical association between the decrease in mucosal exam and biopsy taking as years in practice increase, could well be explained by the fact that less experienced GDPs (<10 years) have benefited from improved continuous education schemes and have received undergraduate training entirely at dental schools. Similar findings have been reported from Italy, where the school of graduation (dental school vs. medical school) seems to influence these preventive practices. 18

Our study is limited by the fact that it is a cross-sectional study based on a convenience sample. In particular, the main disadvantage of this design is that it does not allow for proper causal inference as exposure and outcome are measured at the same time and temporality is not firmly established. However, this type of studies has proved useful for health services management to improve clinical practice and to identify educational problems. There is potential for selection bias in our data due the absence of randomization of the participants. However, the population of our study is representative of the Spanish general population of GDP's as far as it concerns age, years of professional experience, geographic distribution and preventive attitudes towards oral cancer.15

Confounding by other variable cannot explain our results. We have adjusted our results by those factors that may be related with the outcome and with the main exposure (preventive attitudes and training). The relative risk estimates are robust to this adjustment. However, as in any observational study, we cannot rule out the presence of residual confounding due to unknown or unmeasured variables.

Prevention frequently offers the most cost-effective strategy for cancer control.29,30 Despite the fact that advice on smoking cessation, alcohol in-

take moderation and healthy eating is an essential and ethical part of the dentist's role, several gaps in knowledge were described previously. 31

Regarding smoking, previous studies show a significant reduction in the risk of oral cancer among quitters, which approximates that of never smokers approximately 10 years after cessation.32 Our results show that a high proportion of GDPs report using their position to advice patients on tobacco cessation. A similar proportion was reported in the UK .33

Alcohol consumption is considered excessive when it exceeds an average of one (for females) or two (for males) drinks per day.34 Recommendations to reduce alcohol intake have the potentiality of reducing the incidence of oral cancer and oral premalignant lesions in non-smokers and smokers alike. However, only two-thirds of our population advised on alcohol consumption. Contrary to earlier impressions, it has been shown that patients do accept alcohol screening and alcohol counseling by the dentist. 35

Regardless of the existence of studies that support the beneficial effects of high intake of vegetables and fruits on the risk of developing cancers of the oral cavity and on reducing recurrences and mortality (overall and specific),36 the lower consumption of fruits and vegetables constitutes the less known risk factor for oral cancer both in Europe and the USA,9-16 as confirmed by our results, with only 42.4% of the participants providing dietary recommendations (5 serves per day) to prevent this disease.

Educational aspects

Reading scientific journals is an accepted method of continuous scientific training. There is now a growing awareness of the need of any clinician to devote a certain amount of time to this activity.25,26,27

Some authors have shown that clinicians favor enrolment in educational courses over reading activities to achieve CME credits, both in compulsory and voluntary schemes. 19-21 However, when dealing with oral pathology, some surveys report journal reading to be the preferred continuing education activity by practitioners. Furthermore, dentists who read about oral cancer refer fewer difficulties in achieving a diagnosis of potentially malignant lesions.28 Our results show that one-fourth of the participants received information on oral cancer, for the first time since graduation, through reading activities. It is then important to promote strategies to increase reading activities.

Secondary prevention-related practices

Early diagnosis is critically essential and may have a dramatic impact on survival and curation.7,8 The standard diagnosis relies on detection during visual examination followed by tissue biopsy for histopathological diagnosis.5 However, other techniques may prove useful as complementary tools such as light-based detection systems,; specific blood tests (CEA, SCCAA, IAP, CY-FRA, ANXA1 and others); specific saliva tests, and imaging.37

Opportunistic screening (offering patients a screening test when they attend a clinic for some other unrelated reason) may be cost-effective particularly in general dental practice.38 However, including high-risk groups in this screening is not feasible as these groups do not attend dental practice on a regular basis.39 Selective opportunistic high-risk screening may be a more realistic and effective solution for areas with low incidence of oral cancer.40

When dealing with smokers or excessive alcohol consumers, it is advisable for the clinician to remain alert for signs of potentially malignant lesions or early-stage cancer during visual and tactile exploration of all patients.45

Most respondents (90.3%) declared to perform a systematic exploration of oral soft tissues to rule out oral cancer. This proportion is close to that found in former studies in Europe and the USA (83-86%) 41-42 but significantly higher than that described in a representative sample of Spanish GDPs (81.5%).15

The proportion of GDPs who perform biopsy tests is low in spite of existing recommendations.43 The number of primary care dentists who offer oral biopsy, either on a routine or on a selective basis, is scarce in Europe (12% in Northern Ireland;44 21% in UK45) probably due to the lack of specific training. However, recent reports show that this proportion is increasing.15,18 The fact that, in our study, men perform biopsies more frequently than women was already described in a former study. 46

From our study, we conclude that GDPs attending CME oral cancer courses show positive preventive attitudes in oral cancer, especially towards delivering counseling on alcohol consumption and performing routine exploration of the oral mucosa and biopsy. Reading scientific journals is the cornerstone of CME. Oral cancer prevention and detection should be periodically included in dental newsletters and journals.

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Table 1: Distribution of covariables by preventive attitudes among dentists

	Mean age (yrs)	Female (%)	Mean time of practice (yrs)	Mean nº of courses	Specific course		Total	
					Nº	%	Nº	%
Attitudes of the dentists								
Anti tobacco advice								
Yes	35.0	62.7	9.6	3.1	337	95.2	740	93.6
No	36.4	47.1	10.8	2.5	17	4.8	51	6.4
Advice on alcohol consumption								
Yes	36.0	60.0	10.3	3.4	241	68.1	527	66.6
No	33.3	65.2	8.4	2.5	113	31.9	264	33.4
Advice on fruit intake								
Yes	37.4	58.8	11.4	3.7	169	50.4	335	42.4
No	33.4	63.8	8.4	2.6	185	40.6	456	57.6
Routine mucosa exploration								
Yes	35.3	61.8	9.8	3.2	319	90.1	714	90.3
No	34.0	61.0	8.9	1.9	35	9.9	77	9.7
Biopsy								
Yes	36.7	48.0	10.7	4.3	126	35.6	227	28.7
No	34.5	67.2	9.3	2.5	228	64.4	564	71.3

Table 2: Odds ratios (OR) and 95% Confidence Intervals (95%CI) of dentists preventive attitudes according to Continuing Medical Education (CME) variables

CME variables	Anti tobacco advice*		Alcohol advice*		Fruit intake advice*		Mucosa exploration*		Biopsy*	
	OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
Total number of courses										
0-1	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2-3	1.96	0.84 – 4.58	1.11	0.73 – 1.70	0.96	0.62 – 1.47	2.02	1.04 – 3.93	1.32	0.82 – 2.11
≥ 4	2.18	0.76 – 6.22	1.95	1.12 – 3.40	1.37	0.82 – 2.29	10.6	2.90 – 38.41	3.48	2.01 – 6.02
Specific oral cancer course										
No	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Yes	1.05	0.50 – 2.19	1.00	0.70 – 1.43	1.33	0.94 – 1.88	0.62	0.34 – 1.16	1.48	1.02 – 2.14
Years of practice										
0-3	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
4-7	0.59	0.11 – 3.17	1.50	0.75 – 3.03	1.10	0.54 – 2.25	1.75	0.43 – 7.16	0.74	0.35 – 1.57
8-15	0.22	0.03 – 1.68	0.84	0.35 – 2.02	0.57	0.24 – 1.39	0.36	0.07 – 1.80	0.31	0.12 – 0.80
≥ 16	0.70	0.07 – 7.45	1.33	0.44 – 4.05	0.83	0.29 – 2.38	0.29	0.04 – 2.17	0.19	0.05 – 0.53
Age										
< 28	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
28-32	1.90	0.33 – 10.93	0.86	0.42 – 1.76	1.54	0.74 – 3.20	1.36	0.32 – 5.69	1.25	0.57 – 2.72
33-41	1.74	0.24 – 12.69	1.93	0.79 – 4.74	4.60	1.89 – 11.18	2.11	0.40 – 11.21	2.90	1.14 – 7.39
≥ 42	1.01	0.11 – 9.59	1.26	0.41 – 3.88	3.58	1.22 – 10.48	2.74	0.36 – 21.16	4.14	1.32 – 12.96
Sex										
Male	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Female	1.78	0.83 – 3.83	0.98	0.67 – 1.44	1.11	0.77 – 1.60	1.37	0.71 – 2.63	0.54	0.37 – 0.79

* Adjusted for sex, age, and years of practice.

FUTURE LINES OF INVESTIGATION

8. FUTURE LINES OF INVESTIGATION

Unfortunately, in the early detection of oral cancer studies, the variable "outcome" of late diagnosis is poorly defined, and the multiple authors use several different criteria and conceptual frame. Because of this, the different temporal sections that make the interval between the first body changes associated with the tumour and the treatment start date should be investigated. It should also be checked the clinical applicability of the "Aarhus Statement" in the different socio-cultural context.

Conversely, several research groups have studied the concept of delay in diagnosis of oral cancer, but using heterogeneous criteria such as different types of data collected (eg: continuous variables versus categorical, or diverse sources of information on patient delay (standard questionnaires, interviews, hospital records, etc.) than may –along with variations in tumour biology- explain the absence of a consistent relationship between diagnosis delay and stage at diagnosis in the literature. Despite these shortcomings, diagnostic delay has recently been relater to a worse survival rate in head and neck cancers3.

However, and due to the reported absence of an adequate conceptual frame for studying diagnostic delay in other tumours of the human body (little consistency of definitions of delay, different ways of measuring delays, and difficulties in comparing cancers with different biological behaviour), a guideline –The Aarhus Statement- has been proposed to improve the design and reporting studies on early cancer diagnosis4. This guideline recommends the substitution of the term "delay" (eg: "patient delay") by "intervals" or "time intervals". The aforementioned statement also suggests key time points (date of first symptom, date of first presentation, date of referral and date of diagnosis) and time intervals.

It is particularly relevant for GDPs the "date of first presentation" (time point at which, given the presenting signs, symptoms, history and other risk factors, it would be at least possible for the clinician seeing the patient to have started investigation or referral), and the date of referral (time at which there is a transfer of responsibility from one health care provider to another). This time period could be shortened using training as part of CPD for all members of the dental team1, and a variety of additional approaches.

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DISCUSSION

9. DISCUSSION

Many has been written on early diagnosis of oral cancer and much will be written as secondary prevention not only eases treatment but it is also widely reported to influence survival. However, when dealing with early diagnosis the question of when to consider a diagnosis delayed arises and then time-points become particularly important. Ideally, a non-delayed diagnosis (perfect early diagnosis) should be performed at the time of the cancer onset (at the very beginning of the preclinical phase), which is, obviously, not feasible. In turn, reports on this topic focus on the clinical phase of the disease and use the inception of signs and symptoms as the zero point to their researches. This approach is limited by an evident lack of precision, particularly when the sign/symptom onset is frequently retrospectively identified by the patient and, thus, prone to a recall bias. Conversely, it is a somehow identifiable time-point (although with a wide range of error tolerance) that can be used in different settings and permits investigations on this field which would not be possible otherwise.

Using the sign/symptom inception as a reference implies additional shortcomings, as not all areas of the oral cavity are equally accessible for self-exploration and similar lesions produce different symptoms in different oral sites (Wildt et al, 1995; O'Sullivan 2001; Tromp et al 2005), so some cancers may be more easily detected than others, which would be more prone to a late diagnosis due to this particularity. At this stage, some attention has to be paid to the psychosocial characteristics of the patient, who has to identify these sign/symptoms as abnormal and has to decide whether professional help is required for his/her problem. This decision will undeniably influence the time of diagnosis (Kumar et al 2001).

The mere idea of diagnostic delay entails that some time is needed to reach a diagnosis, so only cancers diagnosed beyond that time-frame could be considered delayed. This concept introduces more variability in research on this topic, as the time required to diagnose an oral neoplasm is not specifically defined in the literature and it is conditioned by a wide range of agents and situations (Gómez et al, 2010). This fact adds to the already mentioned limitations at identifying the initial event that defines the time lapse. In this sense, many research groups have used the mean or the median of the time distribution (considered since the sign/symptom onset to definitive diagnosis) to distinguish between non-delayed and delayed cases (those beyond the mean or the median); the median is more frequently used because it is not af-

fected by extreme values and these distributions usually have very wide ranges (Stroup et al, 2000).

As a result of the vagueness in the definition of the limits of the concept of diagnostic delay in oral cancer, the existing investigations do not always use homogeneous criteria (Yu et al, 2008; Gómez et al, 2009; Gómez et al, 2010) and thus comparative analysis are not always possible. However, it seems reasonable to assume that a cancer's stage at diagnosis is a function of the length of time it has been developing prior to diagnosis. Then, the longer the delay, the more advanced the disease would be and a worse prognosis should be expected (McGurk et al, 2005) but, although oral cancer main features (tumour size and nodal status) appear to correlate well with tumour growth chronology (Brown et al, 1989; Parker et al, 1996), many studies either failed to prove this association (Guggenheimer et al, 1989; Dimitroulis et al 1991; Kowalski et al 1994; Gorsky & Dayan, 1995; Wildt et al, 1995; Amir et al, 1999; Pitiphat et al, 2002; Kerdpon & Sriplung, 2001; Onizawa et al, 2003), or demonstrated and inverse relationship (shorter delays linked to more advanced stages) (Carvalho et al, 2002).

Theoretical tumour growth assumes no treatment and no cell lost, but cell loss increases when a tumour grows and outstrips its blood supply. Neoplasms typically grow progressively, but even with a single tumour type there are significant variations that lead to unpredictable differences in the pattern, speed of onset, and progression of patient symptoms than would definitively condition the moment of diagnosis (Neal, 2009). Studies involving tumours of different locations also distort this apparent relationship between diagnostic delay and tumour stage, as occurs with gingival locations which are associated advanced stages at diagnosis due to the early invasion of the adjacent bony tissue (T4 primary tumour), yet could present without time delay (Seoane et al, 2006).

Different velocities of tumour growth may well also explain why some tumours remain small in size in spite of delay. Even though some studies linked diagnostic delay and advanced tumour stage, it is possible that the relationship between delay and advanced tumour stage, it is possible that the relationship between delay and advanced tumour stage is veiled by the fact that certain cancers remain silent during the initial stage and induce symptoms only when they reach and advanced phase (silent tumour hypothesis) (Scott et al, 2005). This being, the tumour growth rate would act as a confounding factor in the relationship between diagnostic delay and tumour stage since patients with aggressive tumours and poor prognosis do not usually present diagnostic delay, while tumours with low proliferation rates demonstrate good prognosis

despite long diagnostic delays (Kaufmann 1980; Evans, 1982). In this sense, reports on tongue cancer are particularly interesting (Kantola et al, 2001; Teppo & Alho, 2008) because the impact of diagnostic delays on survival is apparently unreasonable: shorter delays impaired survival. This paradoxical circumstance, where diagnostic delay, tumour stage and tumour prognosis are inversely related, has been previously described in endometrial, cervix, lung, colon, renal and urethral cancer, and seems to suggest that stage at diagnosis and survival are strongly affected by the biological aggressiveness of the cancer (Crawford et al 2002; Neal 2009; Gómez et al, 2010).

Oral cancer is a relatively proliferating tumour with proven heterogeneity in its biological behaviour. Specifically HPV negative, aneuploid and TP53-mutated tumours have shown less favourable prognoses (Leemans et al, 2010). Moreover, the expression of different oncogenic markers including , p16, p21, p27, MDM2, MGMT, EGFR, ERBB2, RARB, MYC, BCR-ABL1, RAS, CCND1, STAT-3, and VEGF, induce a more rapid clinical course (da Silva et al, 2011) that considerably reduces the opportunities for a diagnosis at early stages of the disease. Alternatively, HPV positive oral cancers, mostly oropharyx, mainly wild-type TP-53 have demonstrated favourable prognosis (Leemans et al 2010).

The lack of sound scientific evidence supporting the traditional association between diagnostic delay and disease extension, together with the wide variability in the biological behaviour induced by different genetic profiles, may justify the hypothesis that biological heterogeneity may be more relevant than diagnostic delay in oral cancer. The corroboration of this hypothesis would have important implications in oral cancer and precancer screening strategies, reinforcing opportunistic screening in at-risk populations (as rapidly growing tumours –where the quickness in obtaining a diagnosis does not guarantee an early stage- have short periods for a potential screening, whereas slowly growing tumours permit a longer screening period).

In order to disentangle this apparently contradictory information, the second part of our investigation used meta-analytical tools on the existing literature on this topic. The initial systematic search identified 1016 relevant papers published since 1966, which were reduced to 10 after a more detailed review. This fact is a reflection of the heterogeneous criteria employed by the different research groups and frequent methodological flaws that impairs research in this field.

Globally, the results of this meta-analysis showed that diagnostic delay is moderately related to mortality of head and neck cancers. The association was stronger for pharynx cancer, a fact that may be due to the rapidity at which

pharyngeal cancers metastasize (Brouha et al 2005). Part of this observed effect may be caused by residual confounding, distortion due to incomplete adjustment for variables that could potentially alter the relationship between delay and mortality. Sex is one of those variables, as some studies included in our meta-analysis did not provide relative risk estimates adjusted for sex, and the pooled effect for sex adjusted studies was much smaller than that of unadjusted studies. The biological behaviour of the tumour is another of those variables, which was considered only by one of the studies included in our investigation (Seoane et al, 2010).

The already mentioned relationship between tumour site and perception of the symptoms and identification of the clinical signs may explain the different magnitudes of association observed between delay and survival in the meta-analytical study: our results show a strong association between the existence of diagnostic delay and worse survival to pharyngeal carcinomas. It is remarkable that most of these pharyngeal cancers were diagnosed at very advanced stages of the disease (stage IV) (Koivunen et al 2001; Ho et al 2004). On the contrary, the effect of diagnostic delay on mortality could not be proved for oral carcinomas, probably because 2 out of 4 studies considered restricted their analysis to tongue tumours (Kantola et al 2001), and existing reports on tongue cancers are particularly contradictory, as referral delays worsen survival (Kantola et al 2001), but professional delays do not (Sandoval et al 2009).

Taking into account the results obtained from the meta-analytical approach to the problem of the relationship between diagnostic delay and tumour stage and survival to oral cancer, the next step of this investigation had to be an ambispective cohort study on incident cancer patients. The study sample was made of 88 oral cancer patients whose lesions were unevenly distributed within the oral cavity: buccal mucosa (n=5), upper and lower gingival (n=15), hard palate (n=2), tongue (n=32), floor of the mouth (n=24) and retromolar trigone (n=10). To calculate diagnostic delay, and in order to diminish the recall bias inherent to this kind of studies, delay data collected from the patient was also validated by those obtained from close relatives. In both situations, identical structured interviews were undertaken for all cases.

Previous reports have described the association between primary tumour site and delayed diagnosis or diagnosis at advanced stages (Brouha et al, 2005)): tongue, buccal mucosa and lip have been recognised as locations that favour early-stage diagnosis (Gorsky & Dayan, 1995), whereas the floor of the mouth and the retromolar trigone have been linked to diagnosis at advanced stages; locations like palate or gingivae showed contradictory results (Gorsky & Dayan, 1995; Morelatto et al, 2007). Our data show that the floor of the mouth, gingivae

and retromolar trigone behaved as an independent prognostic factor for late stage at diagnosis. These findings may well be explained by the fact that patient's self-perception and self-exploration abilities depend on the site of the tumour (Andersen & Cacioppo, 1995), and also because gingival locations are associated to advanced stages at diagnosis (late diagnosis) due to the early invasion of the adjacent tissue (T4 primary tumour) (Seoane et al 2006).

Advanced-stage diagnosis in oral cancer has traditionally been attributed to delays in reaching a diagnosis, as patients at advance tumour stages are more likely to have longer patient and professional delays than those at early stages (Sargeran et al, 2009). However, the lack of sound scientific evidence supporting the existence of an association between diagnostic delay, extent of the disease (III-IV TNM stages) and lower survival rates is evident (Gómez et al 2009; Gómez et al 2010; Goy et al 2009). This fact is probably related to a series of limitations and methodological flaws identified in the published reports to date, mainly related to heterogeneity in both the definition and measurement of diagnostic delay, the retrospective nature of these studies and also to a memory bias of the patients (Gómez et al 2009; Gómez et al 2010).

In this study, diagnostic delay was not significantly linked to advanced stage at diagnosis; thus the quickness in obtaining a diagnosis does note guarantee an early-stage tumour, although delay in the diagnosis of a neoplasm is universally considered unacceptable.

On the other hand, poor differentiation of the tumour (biologically more aggressive) behaved as an independent risk factor for diagnosis at stages III-IV. The tumour growth rate may play the role of a confounding factor in the relationship between diagnostic delay and disease-stage or survival, as patients with aggressive tumours and bad prognosis do not usually present diagnostic delay whereas tumours with low proliferation rates elicit good prognosis despite long diagnostic delays (Seoane et al, 2010). Unfortunately, the evidence on tumour proliferation activity that could corroborate this hypothesis is scarce.

These results seem to suggest that the stage of oral cancer at the time of diagnosis is affected more by the biology of the cancer (degree of differentiation) than by diagnostic delay.

The corroboration of the above mentioned theory implies that the efforts aimed at early diagnosis of oral cancer should be prioritized towards screening programmes designed to detect the disease during its asymptomatic phase. Educational interventions on the population particularly focused on risk groups (self-exploration) and on the professionals (clinicians index of suspicion) should include a sound knowledge of the disease presentation, particularly on sites like the floor of the mouth, gingivae and retromolar trigone.

CONCLUSIONS

10. CONCLUSIONS

I. Advanced tumour stages in oral cancer have been conventionally ascribed to delays in reaching a diagnosis. Surprisingly, there is a lack of sound scientific evidence supporting this traditional association between diagnostic delay and disease extension and survival. However, different oral cancer genetic profiles result on a wide variability in the biological behavior of the tumour and may justify the hypothesis of the biological heterogeneity of diagnostic delay in oral cancer.

II. Diagnostic delay is a moderate risk factor of mortality from head and neck cancer. However, we cannot rule out that, at least, part of the effect observed may be due to residual confounding. We consider that new studies assessing the prognostic impact of diagnostic delay are necessary. These studies should have a sound epidemiologic design with a prospective component in the follow-up in order to minimise recall bias. It is of paramount importance that optimal adjustment for confounding variables be carried out. These future investigations would also benefit from considering the biological features of the tumour and the delay in the treatment.

III. Male gender, intraoral locations other than lingual cancer, and a poor or moderate tumour differentiation behave as risk factors for late-stage diagnosis. These characteristics should be considered when designing educational interventions for the population, which should be particularly focused on risk groups (self-exploration) and on the professionals (clinicians index of suspicion).

IV. The general dental practitioners attending oral cancer continuous medical education courses show positive preventive attitudes in the ambit of oral cancer, especially towards delivering counseling on alcohol consumption and performing routine esploration of the oral mucosa and biopsy.

RESUMEN

11. RESUMEN

El cáncer de cabeza y cuello es la octava causa de muerte por cáncer en el mundo, y prácticamente la mitad de los pacientes son diagnosticados con enfermedades avanzadas. Estos estadios avanzados se asocian a altas tasas de mortalidad, con supervivencias a los 5 años que van del 82% para enfermedades localizadas al 27.6% en los casos con metástasis a distancia, sin que esta tasa de mortalidad haya sufridos variaciones sensibles en las últimas décadas. De hecho, aproximadamente un 19% de todos los pacientes diagnosticados de cáncer oral fallecen en durante el primer año, independientemente de los tratamientos a los que hayan sido sometidos.

La relación entre el estadio en el momento del diagnóstico y la supervivencia concede a este parámetro un valor pronóstico intuitivo, corroborado por un ingente número de estudios que lo identifican como el más relevante de todas las variables implicadas en la supervivencia de estos pacientes. Sin embargo, es muy poco conocida la relación entre el retraso diagnóstico en cáncer oral y la extensión de la enfermedad diagnosticada en estadios avanzados (TMN III-IV) y una tasa de supervivencia baja.

Es por esto, por lo que el diagnóstico precoz (*Early detection*) parece ser la piedra angular para reducir el retraso diagnóstico y mejorar la supervivencia al tumor. Sin embargo, este término es confuso y admite al menos un doble significado. De una parte, "precoz" informa sobre un pequeño tamaño tumoral en el momento de la detección y de otra "precoz" se refiere a un corto intervalo de tiempo para el diagnóstico.

Diagnóstico de Carcinomas Orales de pequeño tamaño.

El tamaño tumoral condiciona aspectos terapéuticos y pronósticos en el cáncer oral. Específicamente, el diagnóstico de carcinomas orales de tamaños grandes se asocia a un riesgo incrementado de metástasis en ganglios linfáticos cervicales y pobre supervivencia. Más recientemente, se considera que el espesor tumoral o la profundidad de invasión constituye un factor pronóstico más relevante que el tamaño tumoral clínico o patológico. Además, esta variable ha demostrado capacidad predictiva, de forma independiente, del riesgo de metástasis ganglionares subclínica, de recidivas locales y de supervivencia al tumor. En este sentido, se ha propuesto un espesor "crítico" de 4 mm, por

encima del cual, el riesgo de metástasis tumoral es cuatro veces mayor a los tumores con menor profundidad de invasión. En términos generales, se consideran carcinomas orales de células escamosa (COCE) de pequeño tamaño a los menores de 2 cm. de diámetro, con menos de 4 mm de profundidad de invasión tumoral y generalmente asintomáticos.

11.1. Elaboración de una hipótesis biológica: El pronóstico del cáncer oral está más condicionado por el comportamiento biológico del tumor que por el retraso en el diagnóstico

Una revisión intensiva de la literatura nos ha permitido generar la hipótesis de la "Heterogeneidad biológica " del tumor para explicar la variabilidad del retraso diagnóstico como factor pronóstico de la supervivencia al COCE. Esto es, la inconsistencia de la asociación entre un mayor retraso en el diagnóstico del cáncer oral y el peor resultado en términos de extensión de la enfermedad y de supervivencia. La diferente agresividad tumoral determinaría el estadiaje en el momento del diagnóstico y la supervivencia del paciente, en mayor medida que la demora diagnóstica.

11.1.1. Bases de la hipótesis

Tumores de un mismo tipo de cáncer podrían tener una parecida agresividad clínica, sin embargo, diferentes carcinomas orales pueden presentar diferentes tasas de crecimiento y diferentes niveles de agresividad. Recientemente nuestro grupo, en un estudio multivariante, ha demostrado que la actividad proliferativa, cuando se ajusta el análisis por estadios del tumor (I-II vs. III-IV), resultó ser un factor pronóstico independiente para predecir la supervivencia . Sin embargo, el retraso diagnóstico no tuvo influencia significativa sobre esta variable. Estos resultados parecen sugerir que la supervivencia al cáncer oral se encuentra más afectada por el rápido crecimiento tumoral que por el retraso en el diagnóstico.

El cáncer oral es un tumor relativamente agresivo que ha demostrado heterogeneidad en su comportamiento biológico; específicamente los carcinomas orales papilomavirus negativo (HPV -), aneuploides, y con TP53 mutado, han mostrado un pronóstico más desfavorable. Además, la expresión de diferentes marcadores genéticos como el p16, p21, p27, MDM2, MGMT, EGFR,

ERBB2, RARB, MYC, BCR-ABL1, RAS, CCND1, STAT-3, VEGF, inducen un curso clínico más rápido de la enfermedad, lo que limita considerablemente el diagnóstico en estadios iniciales. Por el contrario, tumores HPV + de localización predominantemente en orofaringe han mostrado un pronóstico mas favorable.

11.1.2. ¿Como evaluar esta hipótesis?

Se ha sugerido que la biología del cáncer oral pudiese ser más decisiva en términos de supervivencia al tumor que el retraso diagnóstico. Con la finalidad de contrastar la veracidad de esta hipótesis parecen necesarios nuevos estudios, con un adecuado diseño metodológico y que controle todos los sesgos detectados en estudios previos (selección, información, confusión, y supervivencia). Sería también indispensable utilizar criterios estandarizados para medir el retraso diagnóstico y desarrollar protocolos que intenten minimizar el sesgo de memoria. El empleo de cuestionarios estructurados en atención primaria y la colaboración de los familiares del paciente, también podría incrementar la calidad de los datos sobre el retraso diagnóstico.

Además, parecen recomendables estudios con un importante componente prospectivo, de base poblacional, con un adecuado tamaño muestral que tan solo considere casos incidentes de cáncer oral, y que tengan como principal resultado la supervivencia del paciente. También, deben ser consideradas en el estudio otras variables pronósticas potencialmente confusoras como la edad, el sexo, la localización, la comorbilidad y el tratamiento, incluyendo el retraso generado hasta el tratamiento, dado que podría tener un impacto potencial en el resultado final. Un punto clave para evaluar la heterogeneidad del cáncer oral y su potencialidad biológica radica en la filiación histológica del tumor completo, en caso contrario podría generarse un sesgo asociado a la heterogeneidad del tumor, particularmente en tumores grandes. Estudios a desarrollar en el futuro podrían utilizar determinaciones cuantitativas del tipo de la citometría de flujo. Este procedimiento permite el estudio de la fracción de proliferación tumoral y de la apoptosis, lo que condiciona la tasa de crecimiento tumoral. Además, el empleo de tecnología de "*microarrays*" ha demostrado la posibilidad de análisis de perfiles genéticos con importantes implicaciones clínicas y pueden ser utilizados para predecir el comportamiento clínico del cáncer oral y de esta manera ajustar el verdadero peso del retraso diagnóstico en la supervivencia del paciente.

El diagnóstico de tumores de gran tamaño, o de enfermedad tumoral diseminada se ha asociado tradicionalmente al tiempo de retraso en alcanzar un diagnóstico definitivo. De forma sorprendente, parece existir una falta de evidencia que soporte esta asociación lógica entre retraso en el diagnóstico y la mayor extensión tumoral (peor supervivencia). De otra parte, diferentes perfiles genéticos, ya conocidos, del cáncer oral condicionan una amplia variabilidad en el comportamiento biológico del tumor y podrían justificar la hipótesis de la heterogeneidad biología del retraso diagnóstico del cáncer oral.

Un punto clave radica en la dificultad para comparar diferentes subtipos de cáncer oral con diferentes comportamientos biológicos. Así, tumores con tasas de crecimiento altas dificultarían el diagnóstico precoz, y el paciente dispondría de un corto periodo temporal para un potencial "screening" tumoral, mientras tumores de crecimiento muy lento proporcionarían al paciente un amplio periodo para "screening" y en consecuencia intervenciones destinadas a incrementar la proporción de tumores diagnosticados en estadios iniciales (TNM I-II) deberían considerar esta circunstancia. En este sentido, la asunción de la hipótesis implicaría favorecer estrategias de "screening" en cáncer y precáncer oral. Además, en base a este concepto debería fortalecerse el "screening" oportunista de esta patología en periodos asintomáticos, específicamente en pacientes con factores de riesgo.

11.2. Estudio de los factores asociados al diagnóstico en estados avanzados de la enfermedad.

Recientemente nuestro grupo ha demostrado mediante un estudio meta-analítico que el retraso diagnóstico está ampliamente asociado a carcinomas orofaringeos diagnosticados en estadios avanzados de la enfermedad (TNM III-IV). Esta asociación se mostró especialmente fuerte cuando el análisis fue acotado a localizaciones orales del cáncer (pooled RR, 1.47; 95% CI, 1.09-1.99) y cuando el retraso era mayor a un mes (pooled RR, 1.69; 95% CI, 1.26-2.77). Sin embargo, estos datos deben manejarse cautelosamente debido a que los 9 estudios incluidos en este análisis fueron de carácter transversal, con diseños retrospectivos y con un potencial sesgo de memoria. Además, una gran cantidad de estudios han evaluado los determinantes del retraso diagnóstico (periodo desde el primer síntoma o signo hasta conseguir el diagnóstico definitivo), sin embargo son muy escasos los estudios enfocados a determinar

los predictores de diagnóstico en estadios avanzados, lo que está directamente implicado en la mortalidad por este tumor

Es por ello, por lo que el presente estudio se fijó como objetivo analizar los potenciales factores relacionados con el diagnóstico de la enfermedad en estadios avanzados (III-IV), con la finalidad de identificar grupos de riesgo y facilitar estrategias de detección precoz. Para ello llevamos a cabo un estudio ambispectivo, considerando una muestra de 88 pacientes con diagnóstico histológico de cáncer oral procedentes del Servicio de Cirugía Maxilofacial del CHUAC que cumplían como criterio de inclusión en el estudio: El diagnóstico histológico de COCE (tumor primario) y cualquier localización anatómica oral (AJCS). Se consideraron las siguientes variables: la edad, el sexo, la localización clínica, el consumo de tabaco y/o alcohol, el patrón macroscópico, la presencia de lesiones premalignas asociada al tumor, y el grado de diferenciación tumoral. También se utilizaron estrategias encaminadas a minimizar el sesgo de memoria en la cuantificación del retraso diagnóstico. El estadio TNM fue considerado como variable dependiente (precoz: I o II; tardío = III o IV). Los datos se analizaron mediante un paquete estadístico SPSS 12.0 y se elaboró un modelo multivariante. El nivel de significación elegido para todas las pruebas fue $p<0.05$.

La edad media de la muestra fue de 60 años (DS=11.3), mayoritariamente varones (65.9%), fueron incluidos en el estudio. Las localizaciones preferentes fueron la lengua (36.4%), el suelo de boca (27.3%) y la encía (17%).

La mediana del intervalo entre el primer signo/síntoma y el diagnóstico histológico ha sido de 45 días, no sufrieron retraso diagnóstico el 54.5% de la muestra y solo el 45.5% de los carcinomas orales se diagnosticaron en estadios precoces de la enfermedad (I-II). Las formas de presentación clínica más frecuentes en el momento del diagnóstico han sido las ulceradas (70.5%) y en un 16.5% de los casos el carcinoma oral se encontraba asociado a una lesión precancerosa. La muestra estaba constituida fundamentalmente por carcinomas bien y moderadamente diferenciados (91%).

En el análisis univariante la edad (OR=1.0 ;CI95%=0.9-1.0), el hábito tabáquico (OR=1.4 ;CI95%=0.5-3.9), la ingesta de alcohol (OR=1.0 ;CI95%=0.4-2.6), la co-existencia de lesión precancerosa (OR=0.6 ;CI95%=0.2-2.1) y la forma clínica de presentación (ulcerada/mixta) del carcinoma oral (OR=2.7 ;CI95%=0.7-9.9) no se asociaron de forma significativa al diagnóstico en estados avanzados. Tampoco el retraso diagnóstico total se asoció al TNM-(III-IV) (OR=0.7 ;CI95%=0.3-1.6). Por el contrario, el sexo masculino se identificó como factor de riesgo de diagnóstico con enfermedad avanzada (OR=3.8 ;CI95%=1.4-9.6). También en el análisis univariante los

tumores moderada/ pobremente diferenciados (OR=4.2 ;CI95%=1.6-10.9), con localizaciones en suelo de boca (OR=3.6 ;CI95%=1.2-11.1), las encías (OR=8.8 ;CI95%=2.0-38.2) y el trígono retromolar (OR=8.8 ;CI95%=1.5-49.1) han mostrado una fuerte asociación con el diagnóstico en estadios avanzados de COCE. El análisis mediante regresión ha permitido excluir al sexo en el modelo multivariante permaneciendo como variables asociadas al riesgo de diagnóstico en estadios avanzados tanto la localización del tumor como el grado de diferenciación del mismo.

En la presente serie, hasta el 54.5% de los casos fueron diagnosticados en estadios avanzados. En este sentido, el conocimiento de predictores de diagnóstico en estadios avanzados permitiría el desarrollo de estrategias encaminadas a facilitar el diagnostico precoz.

La edad, el sexo, el consumo de tabaco y de alcohol no se han comportado como variables asociadas al diagnóstico tardío. Tampoco en estudios previos estas variables se han asociado de forma significativa al retraso diagnóstico asociado al paciente o al profesional. Las formas clínicas ulceradas del COCE han sido mayoritariamente diagnosticadas, hasta en el 60% de los casos, en estadios III-IV; sin embargo esta asociación no ha alcanzado significación estadística.

De otra parte, otros estudios han reflejado la existencia de asociación de localizaciones del carcinoma oral y retrasos diagnósticos ó diagnóstico en estadios avanzados. La lengua, la mucosa bucal y el labio aparecen como localizaciones que favorecen el diagnostico en estadios iniciales de la enfermedad. Por el contrario, la localización de COCE en el suelo de boca y el trígono retromolar facilitan los diagnósticos en estadios avanzados. Otras localizaciones como son el paladar o la encía han mostrado resultados contradictorios. En nuestro estudio, las localizaciones en suelo de boca, encia y trígono retromolar se han comportado como un factor de riesgo independiente para el retraso diagnóstico. Estos hallazgos podrían explicarse por la diferente percepción del paciente y la dificultad de observación clínica en dependencia de la localización tumoral.

La falta de consistencia que la literatura revela respecto a la asociación del retraso diagnóstico y la extensión tumoral, se encuentra probablemente ocasionada por problemas metodológicos, fundamentalmente relacionados con la heterogeneidad en la definición y el procedimiento de medida del retraso diagnóstico, la naturaleza retrospectiva de estos estudios y el sesgo de memoria. En el presente estudio, el retraso en el diagnóstico no se asoció de forma significativa a tumores en estados avanzados.

Por el contrario, tumores pobremente diferenciados, biológicamente más agresivos, se comportaron como un factor de riesgo independiente para diagnósticos en estadios III-IV. En este sentido, el crecimiento tumoral podría actuar como un factor confusor de la relación retraso diagnóstico y enfermedad avanzada. Además, las medidas educativas dirigidas sobre la población, particularmente a los grupos de riesgo (autoexploración), y sobre los profesionales para incrementar su grado de alerta en el diagnóstico del cáncer oral debe incluir información sobre los determinantes del diagnóstico tardío de la enfermedad. En esta línea, nuevos estudios deberían abordar aspectos de la biología tumoral en relación a la extensión de la enfermedad en el momento del diagnóstico.

11.3. Estudio del impacto del retraso en el diagnóstico sobre la supervivencia al cáncer oral

Diversos grupos de investigación han considerado criterios heterogéneos para definir el retraso diagnóstico en cáncer de cabeza y cuello, utilizando diferentes fuentes de información y no han aportado en sus trabajos datos sobre las características genéticas o biológicas de la enfermedad. A pesar de ello, y de la falta de resultados homogéneos, algunos investigadores consideran al retraso diagnóstico como un factor pronóstico independiente para la supervivencia en los carcinomas de cabeza y cuello.

En vista a esta paradójica situación, nos planteamos llevar a cabo un meta-análisis que permita evaluar el conocimiento existente sobre la potencial asociación del retraso en el diagnóstico y la supervivencia a este tipo de carcinomas

Se llevó a cabo una revisión sistemática con meta-análisis que incluyó las bases MEDLINE (1966-2010), EMBASE (1980-2011), y los "ISI proceedings" para artículos publicados en cualquier idioma. En la estrategia de búsqueda se utilizaron los términos ("Head and neck cancers") AND ("delay" OR "prognostic" OR "survival").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]. Los estudios fueron considerados si cumplían los criterios de elegibilidad.

I. Proporcionar datos originales de pacientes con carcinomas con diagnóstico histológico, con estudios multivariantes y curvas de supervivencia con al menos 2 años de seguimiento.

II. Que las muestras considerasen pacientes con carcinomas de cabeza y cuello (WHO-IARC), excluyendo tumores odontogénicos y de piel.

III. La exposición de interés fue el retraso en el diagnóstico, asignado a cualquiera de los agentes implicados.

La calidad de los estudios se evaluó siguiendo las recomendaciones (MOOSE) para meta-análisis de estudios observacionales, y la cuantificación se llevó a cabo por 2 observadores independientes. Todos los análisis se hicieron mediante el software HEPIMA, versión 2.1.3 .

Mediante esta estrategia de búsqueda se accedió a un total de 1016 artículos, que fueron mayoritariamente excluidos en base a una pobre definición de la variable de exposición o por la ausencia de información de otras variables de interés. Finalmente, fueron seleccionados 8 artículos, uno de los cuales proporcionó de forma independiente datos sobre carcinomas orales, de faringe y de laringe.

En términos generales, el riesgo relativo de mortalidad asociado al retraso diagnóstico en carcinomas de cabeza y cuello fue de 1.34 (1.12-1.61), con importante heterogeneidad (Ri=0.95). Cuando se estratificó el análisis atendiendo a los diferentes criterios de retraso diagnóstico, el retraso en la referencia del paciente mostró la mayor magnitud del efecto (RR fixed effects =2.72 (1.45-5.09)), mientras el retraso diagnóstico total mostró la menor magnitud en la asociación (RR fixed effects=1.04 (1.01-1.07). Los RR fueron 1.27 (0.81-1.98) para el cáncer oral y de 1.64 (0.91-2.96) para el cáncer de laringe.

Todos estos artículos reportan estudios de supervivencia de carácter retrospectivo lo que podría generar una sobreestimación del efecto. Además, todos los trabajos habían ajustado el análisis multivariante por el estadio tumoral (TNM), sin embargo tan solo 2 estudios aportan datos sobre las características biológicas de estos tumores. Cuando se consideraron los estudios de mayor calidad, estos proporcionaban un incremento del riesgo de mortalidad asociado al retraso en el diagnóstico en carcinomas de cabeza y cuello (RR= 1.77 (1.14-2.75)).

Entre las limitaciones de este estudio debemos advertir sobre la falta de consenso en la definición de retraso diagnóstico, la heterogeneidad de medidas que fueron utilizadas, la naturaleza retrospectiva de los estudios y el prob-

able sesgo de memoria de los pacientes y de sus familiares. Este meta-análisis ha mostrado una sobreestimación del efecto en los estudios retrospectivos frente a los prospectivos (RR (95%CI)=1.57 (1.11-2-24) vs. 1.04 (1.01-1.07)).

De otra parte, la inclusión de artículos publicados en cualquier idioma parece prevenir la aparición de un potencial sesgo de lenguaje en el proceso de revisión e inclusión de estudios.

El grado de malignidad podría entenderse como un confusor potencial de la asociación; esto es, tumores con mayor agresividad presentan un peor pronostico y no suelen sufrir retraso diagnóstico. La contrapartida serían los tumores menos agresivos con mejor pronóstico y cuya indolencia suele acarrear retrasos hasta alcanzar el diagnóstico definitivo.

Otra circunstancia que podría disturbar la asociación entre el retraso diagnóstico y la supervivencia es la influencia del retraso en el tratamiento. Esto ultimo muy dependiente del profesional y del sistema sanitario.

En conclusión, el retraso diagnóstico se comporta como un factor de riesgo moderado en la mortalidad por cáncer de cabeza y cuello.

11.4. Educación continuada mediante artículos científicos: Actitudes preventivas de los dentistas generales respecto al cáncer oral.

Las estrategias educativas de control de cáncer son poco conocidas, sin embargo, la educación médica continuada ha demostrado un alto impacto en las actitudes, el conocimiento y los comportamientos frente al cáncer oral.

En este sentido, la lectura de artículos científicos podría ser un componente clave en la educación médico-odontológica continuada.

Los dentistas juegan un papel fundamental en el diagnóstico precoz del cáncer oral. Diferentes autores han averiguado que entrenamientos específicos dirigidos a estudiantes de odontología y medicina pueden ser un componente crítico y efectivo dentro de las estrategias de control de cáncer. Estas estrategias incluyen consejos para reducir el consumo de tabaco, la promoción de dietas saludables, y lo mas importante, la detección precoz mediante programas de screening oportunista con un adecuado seguimiento de los pacientes. En esta línea parece de radical importancia desarrollar iniciativas apropiadas para incrementar los conocimientos y favorecer actitudes preventivas tanto a nivel universitario como profesional usando la vía de la formación continuada.

El consejo general de odontólogos y estomatólogos de España ha llevado a cabo recientemente una experiencia piloto en educación continuada en

cáncer oral por medio de la lectura de artículos científicos. El objetivo del estudio fue evaluar las actitudes preventivas y clínicas relacionadas con el cáncer oral entre los dentistas españoles.

Para ello diseñamos un estudio transversal entre los dentistas generalistas con ejercicio en el territorio español que participaron en el programa online de educación continua en base a la revista RECOE (Revista del Consejo de Odontólogos y Estomatólogos de España), distribuida de forma gratuita entre los 25000 dentistas miembros del consejo general.

La población de estudio estuvo formada por 791 dentistas con una media de edad de 35 ± 9,6 años, mayoritariamente mujeres (61,7%), de los cuales más de un tercio de ellos tenía más de 10 años de práctica profesional. En cerca de una cuarta parte de los participantes en el estudio, la lectura de artículos científicos de cáncer constituyó la única fuente de información sobre este tópico en el periodo de post-licenciatura.

La gran mayoría de los dentistas participantes proporcionan consejos sanitarios para abandonar el hábito tabáquico (96,6%), y dos tercios proporcionan este tipo de consejos para reducir el consumo de alcohol. Por el contrario, solo el 42% recomiendan a sus pacientes el consumir una cantidad adecuada de frutas y verduras. La revisión sistematizada de la mucosa oral constituye una práctica clínica de rutina entre el 90,3% de los dentistas, pero solo el 29% realizan biopsias ante lesiones sospechosas orales.

El análisis multivariante no permitió observar ninguna variable relacionada con el proporcionar consejos sanitarios anti-tabaco, lo que significa que este tipo de consejos se proporcionan con independencia del grado de entrenamiento posgraduado de los dentistas. También pudo observarse que las recomendaciones sobre la ingesta de frutas y verduras, son proporcionadas más frecuentemente por los dentistas de mayor edad, sin que esta actitud preventiva haya podido relacionarse con la formación posgraduada.

Por el contrario la exploración rutinaria de la mucosa oral y el biopsiar lesiones sospechosas de malignidad han resultado ser actitudes preventivas relacionadas con la formación continuada. Los dentistas que han recibido cuatro o más cursos de formación continuada sobre cáncer oral tienen dos veces más probabilidad de proporcionar consejos sanitarios acerca del alcohol, diez veces más probabilidad de explorar sistemáticamente la mucosa, y 3,5 veces más probabilidad de tomar biopsias ante lesiones sospechosas. Finalmente, una larga experiencia profesional medida en términos de años de práctica clínica, no ha resultado estar relacionada con la probabilidad de adoptar medidas preventivas contra el cáncer oral.

Estos resultados muestran que los cursos de formación continuada son útiles para incrementar las actitudes preven especialmente las relacionadas con la práctica clínica. Los cursos específicos parecen ser también útiles para incrementar la práctica de la biopsia oral.

Sin embargo, estos hallazgos están limitados por el hecho de que derivan de un estudio transversal basado en una muestra de convergencia. Particularmente, la principal desventaja de este tipo de diseños, es que no permite una adecuada inferencia causal dado que las variables de exposición y de resultados son medidas al mismo tiempo, y la temporalidad no puede ser claramente establecida. Por otra parte, este tipo de estudios han demostrado su utilidad en el manejo de servicios médicos para mejorar la práctica clínica y para identificar problemas educacionales.

Además, es necesario asumir un potencial sesgo de selección en nuestros datos, debido a la ausencia de randomización entre los participantes. En cualquier caso, la población de nuestro estudio es representativa de la población de dentistas generalistas de España en lo que concierne a la edad, años de experiencia profesional, distribución geográfica y actitudes preventivas frente al cáncer oral.

Para proporcionar robustez a los riesgos relativos estimados hemos ajustado nuestros resultados por factores que podrían estar relacionados con el "outcome" del estudio y con las variables de exposición.

Sin duda la prevención ofrece la mejor estrategia en términos de coste-efectividad para el control del cáncer.

A pesar de que los consejos sanitarios para la cesación tabáquica, el consumo moderado de alcohol y dietas saludables son una parte esencial de la ética en el papel del dentista, diversas deficiencias en su conocimiento han podido ser identificadas en nuestro estudio, específicamente en aspectos educacionales y prácticas de prevención primaria y secundaria frente al cáncer oral. Nuestro estudio ha concluido que los dentistas generalistas que acuden a cursos de formación continuada específicos sobre cáncer oral muestran actitudes preventivas positivas frente al mismo, específicamente en los consejos sanitarios para la cesación del consumo de alcohol, la exploración rutinaria de la mucosa oral y la biopsia.

La lectura de artículos científicos representa pues, un componente clave de la formación odontológica continuada. Además, la prevención del cáncer oral y su detección debería ser incluida periódicamente en las revistas dentales especializadas.

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Does Tumour Biological Behaviour Influence Prognosis More than Diagnostic Delay in Oral Cancer?

Juan Manuel Seoane-Romero, Pablo Ignacio Varela-Centelles, Pedro Diz-Dios, Isabel Ramos-Barbosa, Javier Fernández Feijoo and Juan Seoane*

Grupo de Investigación en Odontología Médico-Quirúrgica (OMEQUI), School of Medicine and Dentistry, Santiago de Compostela University, Spain

Abstract: Worldwide, oral cancer has one of the lowest survival rates (lethal disease for over 50% of cases diagnosed annually) and remains unaffected despite recent therapeutic advances.

Unfortunately, almost half of the oral cancers are diagnosed at stages III or IV, probably due to delays in reaching a definitive diagnosis. Many preventive approaches (secondary prevention) have been designed assuming the logical hypothesis that the longer the diagnostic delay, the more advanced the cancer and the worse the prognosis. However, a number of studies failed to prove this association or even found an inverse relationship.

We hypothesize that tumour's biological heterogeneity in terms of aggressiveness may explain shorter delays linked to advanced stages and bad prognosis. The assumption of this hypothesis would entail favouring oral cancer and precancer screening strategies at the preclinical stage of the disease, and therefore strategies of opportunistic screening for oral cancer and precancer on asymptomatic at risk population should be reinforced.

Keywords: Mouth neoplasms, prognosis, delayed diagnosis, biological behaviour, squamous cell carcinoma.

INTRODUCTION

Oral cancer is a worldwide public health issue [1,2] whose incidence and mortality rates are steadily growing in Europe (eg: France, Hungary, Spain and Croatia), Brazil and South-Eastern Asia (Sri Lanka, Pakistan, Bangladesh and India) [3].

This neoplasm retains one of the lowest survival rate (lethal disease for over 50% of cases diagnosed annually) which remains unaffected despite recent therapeutic advances. This is particularly worrying as rising trends in oral cancer incidence are being reported for young and middle-age men from Brazil, India, certain areas of Europe and the USA [3,4].

Tumour stage at diagnosis remains the most important prognostic marker for oral squamous cell carcinoma [5]. Unfortunately, almost half of the oral cancers are diagnosed at stages III or IV with poor 5-year survival rates (20% to 50%) depending upon tumour sites, probably due to delays in reaching a diagnosis [6-9]. It has been suggested that if these malignancies were diagnosed and treated at earlier stages, survival rates would exceed 80% [10].

A number of researchers have revised the concept of diagnostic delay in head and neck cancer, however these investigations do not use homogeneous criteria [8,9,11], and comparative analyses are not always possible [8,9]. Nowadays, the concept of delay in diagnosis is often broken into two categories, namely patient delay –the period between the patient first noticing a symptom or sign and the first consultation to a healthcare professional concerning that symptom or sign [8,9,12,13] and provider/professional delay –the period from the patient's first consultation with a healthcare provider and the definitive pathological diagnosis [12,13]. The overall diagnostic delay (total delay) would elapse from the first symptom or sign until the definitive histological diagnosis [8,9,12,13].

It seems reasonable to assume that a cancer's stage at diagnosis is a function of the length of time it had been developing prior to diagnosis (logical hypothesis). Thus the longer the delay, the more advanced the disease would be and a worse prognosis should be expected [14]. However, many studies either failed to prove this association [15-23,25] or demonstrated an inverse relationship (shorter delays linked to more advanced stages) [19,22,24,25]. Although methodological flaws could partially explain this paradox, new hypotheses seem to be necessary in this field.

THE HYPOTHESIS: BIOLOGICAL HETEROGENEITY OF ORAL CARCINOMAS

The inconsistencies observed in the association between longer delays in oral cancer diagnosis and worse outcome in terms of clinical stage and survival could be related to variability in the biological behaviour

*Address corresponding to this author at the Stomatology Department, School of Medicine and Dentistry, c/ Entrerríos sn. 15782 Santiago de Compostela (A Coruña), Spain; Tel: +34881812344; Fax: +34981562226;
E-mail: juanmanuel.seoane@usc.es

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of these tumours. Differences in tumour aggressiveness would explain tumour's stage at diagnosis and patient survival better than the mere length of the diagnostic delay (Figure **1**).

SUPPORTING THE HYPOTHESIS

Tumours of a single cancer type can appear to be similar but grow at very different rates and with different levels of aggressiveness [26]. Patients with fast-growing tumours may be diagnosed relatively rapidly, but often an advanced stage has already been reached, given the nature of the disease [24]. Shorter patient and professional delays have been associated to advanced stage at diagnosis in some oral cancer series [19,22,24,25,27,28].

We have recently demonstrated, by means of a multivariate study, that when the analysis is adjusted for tumour stage at diagnosis (I-II vs., III-IV), proliferative activity arises as an independent prognostic factor for survival and diagnostic delay does not influence this outcome [29]. These results seem to suggest that survival to oral cancer is affected more by the rapid tumour growth of the cancer than by delays in the diagnosis.

TESTING THE HYPOTHESIS

It has been suggested that cancer biology may be more important than diagnostic delay. In order to test the feasibility of this hypothesis and to assess the impact of diagnostic delay on the course of oral squamous cell carcinomas, new studies with sound epidemiologic design to minimize the biases identified in the existing reports (selection, information, confounding, survival and lead-time biases) are needed [15-25]. It is mandatory to utilize standardised criteria for measuring the diagnostic delay and to develop protocols to mitigate recall bias [8,9]. The use of structured questionnaires at the primary care level and the participation of patient relatives could increase the quality of the information on diagnostic delay [8,27,28].

It seems advisable to conduct population-based studies with an important prospective component and an adequate sample size that consider exclusively incident oral cancer cases using patient survival as the main outcome. These studies should also account for potential confounding variables, such as age, gender, tumour site, co-morbidity and treatment –including also delay during the treatment phase- because it can influence outcomes [13]. A key point to assess oral cancer heterogeneity and its biological potential is the

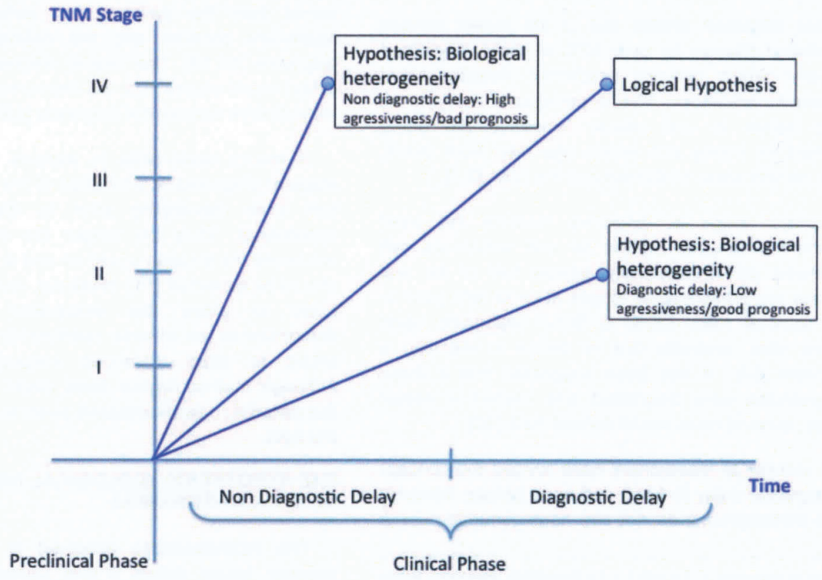

Figure 1: Hypotheses on the influence of tumour aggressiveness and diagnostic delay on disease stage at diagnosis.

histological analysis of the whole tumour, otherwise there could exist a bias, particularly in large tumours. Future studies would benefit from a quantitative analysis approach (i.e.: analysis by flow cytometry of larger tumour samples), as this procedure permits the study of the fraction of proliferating tumour cells and the amount of fraction of spontaneous cell loss, which influence the tumour's growth rate [51]. Moreover, gene expression signatures generated from DNA microarray analysis have proved to be predictive biomarkers for clinical outcome [52] and could be used to infer the clinical behaviour of the oral cancer and to adjust this way the actual weight of diagnostic delay on patient survival.

DISCUSSION

Oral cancer main features (tumour size and nodal status) appear to correlate well with tumour growth chronology [31,32]. This paradigm focused research on the possibility that diagnostic delay contributed to the spread of the disease. Despite this theory could be confirmed for a number of tumours, no definitive conclusions could be drawn for oral cancer [8,9,33-39].

Theoretical tumour growth assumes no treatment and no cell lost, but cell loss increases when a tumour grows and outstrips its blood supply. Neoplasms typically grow progressively, but even within a single tumour type there are significant variations that lead to unpredictable differences in the pattern, speed of onset, and progression of patient symptoms that would definitively condition the moment of the diagnosis [26].

When dealing with delays in diagnosis, the beginning of the study has to be the recognition of the signs and symptoms by the patient. This fact is critically affected by his/her psychosocial characteristics, some of them able to predict diagnostic delay and advanced tumour stage at diagnosis [30]. Similar findings were reported from a case-control study demonstrating that the length of diagnostic delay was significantly greater in patients with advanced tumour stages (TNM stage IV) [16].

However, there is no sound scientific evidence supporting an association between diagnostic delay in oral cancer, disease extension at diagnosis, and lower survival rates [15-25]. This fact may well be partially due to methodological flaws in the published reports to date [8,9,36,40,41].

These reports use different conceptions of diagnostic delay and are thus liable to misclassifications, utilize retrospective designs without strategies to diminishing patient's memory bias and often break down diagnostic delay classifications into subgroups with small sample sizes. Studies involving tumours of different locations introduce confounding factors in the analysis, as the patient self-perception and self-exploration abilities depend on the site of the tumour [19,37,42]. For example, gingival locations are associated to advanced stages at diagnosis due to the early invasion of the adjacent bone tissue (T4 primary tumour), yet could present without time delay [38]. Additional difficulties come from the type of data collected (e.g.: continuous variables [19,27,30] *versus* categorical [41,43]), from the different sources of patient data (questionnaires, interviews, clinical records) and also from the already mentioned patient memory bias.

Different velocities of tumour growth may well also explain why some tumours remain small in size in spite of delay. Even though some studies linked diagnostic delay and advanced tumour stage, it is possible that the relationship between delay and advanced tumour stage is veiled by the fact that certain cancers remain silent during the initial stages and induce symptoms only when they reach an advanced phase (silent tumour hypothesis) [7]. This being, the tumour growth rate would act as a confounding factor in the relationship between diagnostic delay and tumour stage since patients with aggressive tumours and poor prognosis do not usually present diagnostic delay, while tumours with low proliferation rates demonstrate good prognosis despite long diagnostic delays [44,45].

Despite the aforementioned, a recent meta-analytic study by our research group has shown that diagnostic delay is broadly associated to more advanced stages in oropharyngeal cancers. This association resulted to be especially strong when the analysis was restricted to oral cancer (pooled RR, 1.47; 95%CI: 1.09 – 1.99) and when the delay was longer than one month (pooled RR, 1.69 95%CI: 1.26 – 2.77) [9]. The probability for delayed patients to present an advanced-stage oral cancer at diagnosis in this report was 25% higher than that of a non-delayed patient. Nevertheless, these data should be interpreted with caution since all 9 studies considered in the meta-analysis were cross-sectional in nature, with retrospective designs and a potential for recall bias [9].

The number of studies focusing on the relationship between diagnostic delay and survival to oral cancer are scarce, and their results show substantial

discrepancies: on the one hand the strength of the association did not reach signification [46], but on the other hand there seem to exist a strong relationship when referral delay is considered [27,47]. More specifically: when longer than a month, these delays worsen survival to oral and oropharyngeal cancer [47]. However, when tumour aggressiveness is considered, the role of diagnostic delay could not be demonstrated [29]. Moreover, confounding effects of lead-time bias could condition the association between diagnostic delay and survival to the tumour [26].

Reports on tongue cancer are particularly interesting [27,28] because the impact of diagnostic delays on survival are apparently unreasonable: shorter delays impaired survival. This paradoxical circumstance, where diagnostic delay, tumour stage and tumour prognosis are inversely related, has been previously described in endometrial, cervix, lung, colon, renal and urethral cancer, and seems to suggest that stage at diagnosis and survival are strongly affected by the biological aggressiveness of the cancer [8, 26,48].

Oral cancer is a relatively proliferating tumour with proven heterogeneity in its biological behaviour. Specifically HPV negative, aneuploid and TP53-mutated tumours have shown less favourable prognoses [49]. Moreover, the expression of different oncogenic markers including , p16, p21, p27, MDM2, MGMT, EGFR, ERBB2, RARB, MYC, BCR-ABL1, RAS, CCND1, STAT-3, and VEGF, induce a more rapid clinical course [50] that considerably reduces the opportunities for a diagnosis at early stages of the disease. Alternatively, HPV positive oral cancers, mostly oropharyx, mainly wild-type TP-53 have demonstrated favourable prognosis [49].

CONCLUSION

Advanced tumour stages in oral cancer have been conventionally ascribed to delays in reaching a diagnosis. Surprisingly, there is a lack of sound scientific evidence supporting this traditional association between diagnostic delay and disease extension and survival. However, different oral cancer genetic profiles result on a wide variability in the biological behaviour of the tumour and may justify the hypothesis of the biological heterogeneity of diagnostic delay in oral cancer.

An important issue is the difficulty in comparing oral cancer subtypes with very different behaviours. Thus rapidly growing tumours –where the quickness in obtaining a diagnosis does not guarantee and early stage- have short periods for a potential screening, whereas slowly growing tumours permit a longer potential screening period. This circumstance should be taken into account when designing interventions aimed at reducing the duration of the diagnostic pathway.

In this sense, the corroboration of this hypothesis would imply favouring oral cancer and precancer screening strategies, and therefore opportunistic screening for oral cancer and precancer on asymptomatic, at-risk population should be reinforced.

POTENTIAL CONFLICTS OF INTEREST

None.

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Impact of delay in diagnosis on survival to head and neck carcinomas: a systematic review with meta-analysis

Seoane, J.,* Takkouche, B., Varela-Centelles, P.,* Tomás, I.* & Seoane-Romero, J.M.*

*Stomatology Department, School of Medicine and Dentistry, University of Santiago de Compostela, and Department of Preventive Medicine, School of Medicine and Dentistry, University of Santiago de Compostela, Spain

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Objective: To address the contradictory information on the role of delay in diagnosis on head and neck cancer survival.
Study design: Systematic review and meta-analysis.
Search strategy: Search on MEDLINE (1966 to March 2011), EMBASE (1980 to March 2011) and ISI proceedings (from inception to March 2011). The terms used were ('Head and neck cancers') AND ('delay' OR 'prognostic' OR 'survival') both in MeSH terms and free-text words. The reference lists of the retrieved articles were also revised manually to identify other potentially relevant papers. All searches were independently undertaken by two clinicians and one epidemiologist, and the results merged.
Setting: Primary and specialised care levels.
Participants: Meta-analysis of data from papers on the subject published from 1966 to 2011.
Main outcome measures: Survival.
Methods: After search in Medline and other databases, we computed pooled relative risks (RR) and 95% confidence interval (95%CI) from the 10 studies retrieved.
Results: The estimate of the relative risk of mortality related to any diagnostic delay (either patient or professional delay) was 1.34 (95%CI 1.12–1.61). Referral delay was associated with a three-fold increase in mortality. Total delay was marginally related to mortality (RR: 1.04, 95%CI: 1.01–1.07). By anatomic location, pharynx cancer shows the highest association (RR: 1.68, 95%CI: 1.22–2.31).
Conclusions: Diagnostic delay is a moderate risk factor of mortality from head and neck cancer. However, part of the effect observed may be due to residual confounding (confounding from unknown variables that are not eliminated by adjustment).

Head and neck cancer is ranked as the eighth leading cause of cancer death worldwide.[1–4] Several factors have been assessed as independent prognostic markers for head and neck cancer, but tumour stage at diagnosis is still recognised as the most important one.[3] Advanced stages are frequently associated with high mortality rates: the reported 5-year survival rate for patients with localised disease is 82%, that of patients diagnosed with regional disease is 51% and that of patients with distant metastasis only 27.6%.[4] This poor 5-year survival rate has remained unchanged for more than three decades.[3,4] Unfortunately, almost half of the head and neck cancers are diagnosed at advanced stages (III or IV), probably due to delays in reaching a diagnosis.[5,6]

Correspondence: J. Seoane, Stomatology Department, School of Medicine and Dentistry, University of Santiago de Compostela, Entrerrios s ⁄n 1782 Santiago de Compostela (A Coruña), Spain. Tel: +34 981 223 033; Fax: +34 981 223 033; e-mail: juanmanuel.seoane@usc.es

Nowadays, diagnostic delay is most often categorised as (i) patient delay – the period between the patient first noticing a symptom and their first consultation with a health care professional concerning that symptom;[6–8] and (ii) provider ⁄professional delay – the period elapsed between the patient's first consultation with a health care professional and the definitive pathological diagnosis.[6–8] The overall diagnostic delay (total delay) includes the period elapsed since the first symptom or sign until the definitive diagnosis.

Several research groups have assessed the role of diagnostic delay in the staging of the tumour, and by extension, in the survival from head and neck cancer. Heterogeneous criteria were used in this assessment. Different types of data were used (continuous[9] and categorical data[10,11]), and different sources of information on patient delay were collected (standard questionnaires, interviews, hospital records, etc.). This heterogeneity in the assessment, along with variations in tumour biology, may explain the absence of a consistent relationship

between diagnostic delay and stage of the tumour in the literature.[3,5,6] Whilst several research groups did not find sufficient evidence,[10,12,13] some others have recently described a significant relationship between advanced stages and diagnostic delay.[6,14,15] Despite these shortcomings, diagnostic delay has recently been recognised as an independent prognostic factor for survival to head and neck cancer.[3,9,12,15–17]

In view of this inconsistent data, we undertook a systematic review and meta-analysis to assess the relation between diagnostic delay and survival in head and neck cancer.

Material and methods

Literature search

We performed a systematic search on computerised databases including MEDLINE (1966 to March 2011), EMBASE (1980 to March 2011) and ISI proceedings (from inception to March 2011) for papers published in any language. The abstracts of the articles were screened to exclude irrelevant studies. The terms used were ('Head and neck cancers') AND ('delay' OR 'prognostic' OR 'survival') both in MeSH terms and free-text words. The reference lists of the retrieved articles were also revised manually to identify other potentially relevant papers. All searches were independently undertaken by two clinicians and one epidemiologist, and the results merged.

Studies were included if they fulfilled the following criteria:

1 Presented original data from survival studies with a survival follow-up of at least 24 months, starting from the date of the histological diagnosis of a squamous cell carcinoma.

2 The sample was made of patients with head and neck cancer, excluding odontogenic, ear, skin and salivary glands tumours.

3 The exposure of interest in the study was patient delay (the time from the patient's first awareness of symptom or sign to the first consultation with a physician or dentist); or professional delay (PDI – presentation to diagnosis interval – the time from the patient's first consultation with a physician or a dentist to the date of final histological diagnosis); or total diagnostic delay (the sum of the patient and professional delay); or referral delay (difference between the date of first symptom and the date of the referral letter transferring the patient to the secondary care level).

Quality assessment

We assessed study quality by use of a five-point binary scale (yes ⁄ no) that we specifically developed for this study. The scale is based on the Newcastle–Ottawa scale[18] with modifications in view of standard guidelines.[19] Throughout this assessment, when the information on a specific item was not provided by the authors, we graded this item as 'no'. The quality scoring was independently undertaken by two researchers (BT and JS). The first item assessed the source of the outcome date. One point was given if the date of death was ascertained through clinical history or death certificate and zero point if otherwise. The second item assessed the cause of death (one point if it was clearly due to the cancer diagnosed previously, including metastasis, and zero point if non-specific mortality was measured). The third item assessed the follow-up time (one point if follow-up was 4 years or more and zero if <4 years). The fourth item assessed the definition of delay. One point was given if inception was clearly defined and zero if not. The last item concerned adjustment for confounding factors. One point was given if the analysis was adjusted for sex, age and other factors and zero if not.

Statistical analysis

The study-specific adjusted log relative risks (RR) were weighted by the inverse of their variance to compute a pooled RR and its 95% CI. We computed both fixed-effects and random-effects pooled estimates. The fixed-effects model assumes that there is no between-study variance (i.e. that the results of the studies used in the meta-analysis are homogeneous and their variation is a result of sampling only). The random-effects model, by contrast, assumes that study results are heterogeneous. The random-effects model yields pooled results that are less precise (have wider CIs) but are closer to the true value in the event that heterogeneity exists. To quantify the heterogeneity, the proportion of the total variance because of between-study variance (the R_i statistic) was calculated.[20] For each analysis, we used random-effects results whenever the test statistic for heterogeneity was significant, and fixed-effects estimates otherwise. For each study, we estimated the relative risk of mortality for 'any delay' by pooling the estimates of each category of delay presented by the authors of the study. When only one category of delay was presented, we used its estimate and included it in the category 'any delay'.

To assess publication bias visually, a funnel plot was used.[21] Because funnel plots have several limitations and represent only an informal way to detect publication bias,[20] the test suggested by Egger et al.[22] was also applied. All analyses were performed using the HEpiMA software, version 2.1.3.[23]

Table 1. Summary of the 10 studies included in the meta-analysis

Study	Country	Period of data collection	Site of tumour	Sample size	Average delay (days)	TNM at diagnosis n (%)	Patient delay RR (95%CI)	Professional delay RR (95%CI)	Referral delay RR (95%CI)	Total delay RR (95%CI)	Any delay RR (95%CI)	Quality score
Kantola et al.[9]	Finland	1974–1994	Tongue	75	72 days (referral delay) 21 days (professional delay	I 9 (12%) II 22 (29.3%) III 33 (44%) IV 11 (14.7%)	–	–	6.3 (1.7–22.9)	–	6.3 (1.7–22.9)	3
Teppo and Alho[31]	Finland	1986–1996	Tongue	62	42 days (median) (Patient delay) 21 days (median) (Professional delay)	I 8 (13%) II 22 (35%) III 25 (40%) IV 7 (11%)	0.58 (0.36–0.93)	1.07 (0.68–1.70)	–	–	0.79 (0.57–1.1)	4
Seoane et al.[33]	Spain	1997–2002	Oral	63	108 days (total delay)	I 9 (14.3%) II 20 (31.7%) III 10 (15.9%) IV 24 (38.1%)	–	–	–	1.0 (0.9–1.1)	1.0 (0.9–1.1)	3
Sandoval et al.[32]	Spain	1996–1999	Oral and oropharynx	146	N.A.	I 15 (10.3%) II 30 (20.5%) III 35 (24%) IV 66 (45.2%)	–	–	2.1 (1.0–4.3)	–	2.1 (1.0–4.3)	4
Ho et al.[14]	USA	1994–2001	Oropharynx	87	106 days (Professional delay)	I 3 (3%) II 5 (6%) III 15(17%) IV 59 (68%)	–	1.09 (0.64–1.87)	–	–	1.09 (0.64–1.87)	1
Koivunen et al.[13]	Finland	1986–1996	Pharynx	84	108 (median) Total delay	I 3 (4%) II 17 (20%) III 16 (19%) IV 46 (55%)	2.5 (1.39–4.38)	Erroneous	–	–	2.5 (1.39–4.38)	4
Teppo and Alho[31]	Finland	1986–1999	Pharynx	66	30 days (median) (Patient delay) 33 days (median) (Professional delay)	I 1 (2%) II 10 (15%) III 12 (18%) IV 41(62%)	3.33 (1.76–6.32)	0.24 (0.07–0.76)	–	–	1.79 (1.02–3.13)	4

Table 1. (Continued)

Study	Country	Period of data collection	Site of tumour	Sample size	Average delay (days)	TNM at diagnosis n (%)	Patient delay RR (95%CI)	Professional delay RR (95%CI)	Referral delay RR (95%CI)	Total delay RR (95%CI)	Any delay RR (95%CI)	Quality score
Teppo and Alho[31]	Finland	1986–1999	Larynx	93	60 days (median) (Patient delay) 63 days (Professional delay)	I 30 (45%) II 8 (12%) III 21 (32%) IV 7 (11%)	1.73 1.20–2.51	3.5 (1.8–6.9)	–	–	2.04 (1.47–2.82)	4
Teppo and Alho[12]	Finland	1990–1995	Larynx	66	180 (median) (Total delay)	I 37 (40%) II 15 (16%) III 29 (31%) IV 12 (13%)	1.73 (0.48–6.21)	3.07 (1.20–7.88)	–	–	2.51 (1.17–5.36)	4
Hansen et al.[17]	Denmark	1995–1997	Glottis	544	108 days (1965–1979) 100.5 days (1980–1989) 115 days (1990–1997)	I 270 (49.6%) II 204 (37.5%) III 70 (12.9%) IV 0 (0%)	–	–	–	1.04 (1.02–1.07)	1.04 (1.02–1.07)	3

N.A., Not available; RR, relative risks.

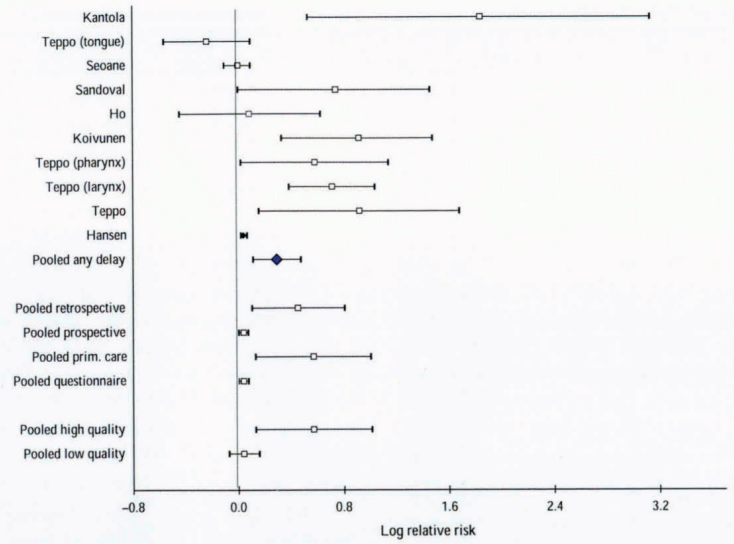

Fig. 1. Study-specific and pooled relative risks from studies of diagnosis delay and head and neck cancer.

Ethical considerations

None.

Results

A total of 1016 articles were accessed through the literature search strategy. Review of the titles, abstract, and in some cases the full text, excluded 1001 articles. We further excluded seven studies because of either unclear or arbitrary definition of diagnostic delay,[24] or lack of information on any of the variables of interest.[24–30] We finally included 10 studies that were published in eight different articles between 2001 and 2010 (Table 1 and Fig. 1). The period of data collection spanned between 1974 and 2002. The anatomic location of the tumours varied widely between studies: two studies presented data on tongue tumours, three on oral or oropharynx cancer, two on pharynx, two on larynx and one on glottis tumours. The sample size varied between 66 and 544 patients. All studies but one were carried out in European countries.[9,12–14,17,31–33] One article provided independent data for oral, pharynx and larynx cancers.[31] Five studies presented data on patient delay, five on professional delay, two on referral delay and two on total delay. One study presented data on professional delay that were clearly erroneous (point estimate of the relative risk out of the range of the confidence interval).[13] This erroneous estimate was not included in our meta-analysis. Distribution by tumour stage varied widely between studies: from 2% to 50% for TNM stage I and from 0% to 68% for TNM stage IV.

Table 2 lists the pooled effect estimates for all 10 studies and diverse subgroups. The random-effects pooled estimate from all studies was 1.34 (95%CI 1.12–1.61) with substantial heterogeneity (R_i = 0.95). Although patient and professional delays were associated with increased risk of mortality, both estimates did not reach statistical significance. Referral delay estimate, although based on two studies only, is associated with a statistically significant three-fold increase in mortality. On the contrary, total delay is apparently not related to the outcome (pooled RR: 1.04, 95%CI: 1.01–1.07).

Although the funnel plot (Fig. 2) indicates a slight skewness to the right, the asymmetry test yielded a P-value of 0.83 indicating absence of asymmetry. Publication bias is then unlikely to occur with the data at hand.

By anatomic location, pharynx cancer shows the highest association between delay and mortality (Pooled RR: 1.68; 95%CI: 1.22–2.31, low heterogeneity).

To assess the possible confounding effect because of the stage of the tumour, we stratified our analysis into two subgroups: studies that included 60% or more of advanced stages (TNM III and IV) and studies with <60% of advanced stages. The pooled RR in the first group was 1.74 (95% CI: 1.30–2.33) with no heterogeneity, and in the second group 1.19 (0.99–1.44) with considerable heterogeneity.

Table 2. Pooled relative risks (RR) and 95% confidence intervals (CI) of mortality because of delay in head and neck cancers

Item	Number of studies	RR (95% CI) fixed effects	RR (95% CI) random effects	R_i*	Q test P-value
Any delay (all studies)	10	1.05 (1.02–1.07)	1.34 (1.12–1.61)	0.95	0.00005
Patient delay	5	1.54 (1.21–1.94)	1.67 (0.88–3.19)	0.85	0.00005
Professional delay	5	1.34 (1.00–1.78)	1.32 (0.66–2.66)	0.82	0.0004
Referral delay	2	2.72 (1.45–5.09)	3.17 (1.12–9.00)	0.61	0.15
Total delay	2	1.04 (1.01–1.07)	1.04 (1.01–1.07)	0.00	0.44
Oral cancer	4	1.00 (0.92–1.10)	1.27 (0.81–1.98)	0.94	0.003
Pharynx cancer	3	1.68 (1.22–2.31)	1.69 (1.05–2.72)	0.55	0.11
Larynx cancer	3	1.05 (1.02–1.08)	1.64 (0.91–2.96)	1.00	0.00005
ï 60% of stages III and IV	4	1.74 (1.30–2.33)	1.76 (1.21–2.54)	0.37	0.19
<60% of stages III and IV	6	1.04 (1.01–1.07)	1.19 (0.99–1.44)	0.96	0.00001
Retrospective studies	8	1.09 (1.00–1.19)	1.57 (1.11–2.24)	0.92	0.00005
Partially prospective studies	2	1.04 (1.01–1.07)	1.34 (0.69–2.61)	1.00	0.05
Primary care centres	7	1.50 (1.25–1.79)	1.77 (1.14–2.73)	0.81	0.0001
Questionnaires	3	1.04 (1.01–1.07)	1.04 (0.95–1.13)	0.84	0.11
Population-based studies	3	1.02 (0.92–1.11)	1.16 (0.82–1.65)	0.89	0.13
Hospital-based studies	7	1.05 (1.02–1.08)	1.67 (1.14–2.44)	0.99	0.00005
Source of mortality data known	7	1.09 (1.00–1.19)	1.68 (1.13–2.49)	0.94	0.00005
Source of data unknown	3	1.04 (1.01–1.07)	1.17 (0.85–1.60)	0.99	0.15
Sex adjusted	7	1.04 (1.01–1.07)	1.16 (0.99–1.36)	0.94	0.0001
Sex non-adjusted	3	2.77 (1.81–4.24)	2.77 (1.81–4.24)	0.00	0.42
Quality score <4	4	1.04 (1.01–1.07)	1.04 (0.93–1.17)	0.89	0.04
Quality score ï4	6	1.54 (1.28–1.86)	1.77 (1.14–2.75)	0.81	0.0002

RR, Relative Risk; CI, confidence interval.
*Proportion of total variance because of between-study variance.

When we restricted the analysis to retrospective studies, we obtained a pooled estimate that showed an increase in the risk of about 60%. The risk increase for partially prospective studies was substantially lower.

The data of the studies included in this meta-analysis were collected either through questionnaires or by reviewing clinical records from primary care centres. The latter yielded a statistically significant pooled estimate of 1.77 (95% CI: 1.14–2.73).On the contrary, no increase in the risk was observed for those studies that collected the data through questionnaires.

Adjustment for potential confounding factors, such as sex, was not performed systematically in the studies retrieved. Those studies that adjusted for sex showed a minute increase in the risk of mortality that was non-significant, unlike unadjusted studies the pooled estimate of which showed substantial risk increase.

After scoring the quality of the studies on a five point scale, we divided the studies in two groups: those that scored 4 or more points out of five and those that scored less. The high quality studies showed a pooled estimate of 1.77 (95% CI 1.14–2.75) whilst low quality studies showed no increase in the risk of mortality. Related to this issue, those studies that provided details on the source of mortality data yielded a higher risk increase than those with unknown data source.

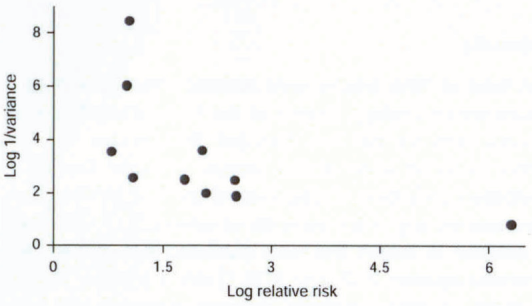

Fig. 2. Funnel plot of relative risk versus log inverse variance of relative risk for any delay.

Discussion

Globally, the results of this meta-analysis showed that diagnostic delay is moderately related to mortality of head and neck cancers. The association was stronger for referral delay and for pharynx cancer, a fact that may be due to the rapidity at which pharyngeal cancers metastasise.[15] In addition to the effect exerted by the stage of the tumour, part of the effect of delay on mortality may be caused by residual confounding, distortion because of incomplete adjustment for variables that could potentially

distort the relation between delay and mortality. Sex is one of those variables. We observed that some of the studies included in our meta-analysis did not provide relative risk estimates adjusted for sex and that the pooled effect for sex adjusted studies was much smaller than that of unadjusted studies. Also, the biological behaviour of the tumour may play the role of a confounding factor in the relation between diagnostic delay and survival, as patients with aggressive tumours and bad prognosis do not usually present diagnostic delay whereas less aggressive tumours elicit good prognosis despite a long diagnostic delay.[11] Unfortunately, only one of the studies included in our review took the tumour proliferation activity into account.[33]

Other limitations of this systematic review and meta-analysis include the lack of consensus in the literature about the period beyond which the diagnosis of a head and neck cancer should be considered delayed: whilst some authors have used the mean or the median of the time distribution to describe and categorise the diagnostic delay,[11] the latter being more frequently used because it is not affected by extreme values and the distributions usually have very wide ranges; other authors divide diagnostic delay into arbitrary intervals[12,13,31,32] or define it as continuous variable without a specific time point.[9] Further, the large majority of the studies included in this meta-analysis were retrospective in nature. Their data are probably less accurate, because of the difficulties encountered by patients in remembering the exact date of the onset of symptoms. These data are prone to recall bias. In our study, we observed that the results from retrospective studies are overestimated. The reports from Finland[9,12,13,31] are probably less exposed to this bias, as primary care physicians recorded each visit on a specific sheet that included the reason for attendance, the diagnosis and the treatment given to the patient; and all new patients received at the tertiary care centres had to have a referral letter from their primary care physician.

Further, key data to establish diagnostic delay, as perception of the symptoms and identification of the clinical signs, are clearly dependent on the specific location of the tumour and may explain the different magnitudes of association. Our results show a strong association between the existence of diagnostic delay and worse survival to pharyngeal carcinomas. It is remarkable that most of these pharyngeal cancers were diagnosed at very advanced stages of the disease (stage IV).[13,14,20]

On the contrary, the effect of diagnostic delay and mortality could not be proved for oral carcinomas, probably because two of the four studies considered restricted their analysis to tongue tumours.[9,20] Existing reports on tongue cancer are particularly contradictory, as referral delays worsen survival,[9] but professional delays do not.[32] This paradoxical circumstance, where diagnostic delay, tumour stage and tumour prognosis are not related, was previously described in breast, cervix, lung, colon, renal and urethral cancer and seems to suggest that stage at diagnosis and survival are affected more by the biology of the cancer (rapid tumour growth) than by diagnostic delay.[34]

Although all three reports on larynx cancer show an effect of diagnostic delay and poor survival rates, the investigation that reported the weakest association did not include stage IV carcinomas in its study sample.[17] This fact may modify the final results by showing a weaker association than it actually exists for laryngeal carcinomas. Despite the fact that all reports on laryngeal cancer come from a specific geographical area (Finland and Denmark), it does not seem likely that it might compromise the generalisability of the results.

Conclusions

In view of the results obtained, we conclude that diagnostic delay is a moderate risk factor of mortality from head and neck cancer. However, we cannot rule out that, at least, part of the effect observed may be due to residual confounding (confounding from unknown variables that is not eliminated by adjustment). We consider that new studies assessing the prognostic impact of diagnostic delay are necessary. It is of paramount importance that optimal adjustment for confounding variables be carried out. These future investigations would also benefit from considering the biological features of the tumour and the delay in the treatment.

Conflict of interest

The authors declare no conflict of interest.

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Factors related to late stage diagnosis of oral squamous cell carcinoma

Juan-Manuel Seoane-Romero [1], Inés Vázquez-Mahía [2], Juan Seoane [1], Pablo Varela-Centelles [1], Inmaculada Tomás [1], José-Luis López-Cedrún [2]

[1] Stomatology Department. School of Medicine and Dentistry. University of Santiago de Compostela. Spain
[2] Oral and Maxillofacial Surgery. CHUAC. A Coruña. Spain

Correspondence:
Cantón Grande 5, Apt 1ºE
15003 A Coruña
Spain
juanmanuel.seoane@usc.es

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Abstract

Aims: To identify factors related to advanced-stage diagnosis of oral cancer to disclose high-risk groups and facilitate early detection strategies.

Study design: An ambispective cohort study on 88 consecutive patients treated from January 1998 to December 2003. Inclusion criteria: pathological diagnosis of OSCC (primary tumour) at any oral site and suffering from a tumour at any TNM stage. Variables considered: age, gender, smoking history, alcohol usage, tumour site, macroscopic pattern of the lesion, co-existing precancerous lesion, degree of differentiation, diagnostic delay and TNM stage.

Results: A total of 88 patients (mean age 60±11.3; 65.9% males) entered the study. Most patients (54.5%) suffered no delayed diagnosis and 45.5% of the carcinomas were diagnosed at early stages (I-II). The most frequent clinical lesions were ulcers (70.5%). Most cases were well- and moderately-differentiated (91%). Univariate analyses revealed strong associations between advanced stages and moderate-poor differentiation (OR=4.2; 95%CI=1.6-10.9) or tumour site (floor of the mouth (OR=3.6; 95%CI=1.2-11.1); gingivae (OR=8.8; 95%CI=2.0-38.2); and retromolar trigone (OR=8.8; 95%CI=1.5-49.1)).

Regression analysis recognised the site of the tumour and the degree of differentiation as significantly associated to high risk of late-stage diagnosis.

Conclusions: Screening programmes designed to detect asymptomatic oral cancers should be prioritized. Educational interventions on the population and on the professionals should include a sound knowledge of the disease presentation, specifically on sites like floor of the mouth, gingivae and retromolar trigone. More studies are needed in order to analyse the part of tumour biology on the extension of the disease at the time of diagnosis.

Key words: *Oral cancer, advanced-stage, diagnosis, cohort study .*

Introduction

Survival rates for oral cancer are very poor (around 50% overall), and no remarkable improvements have occurred in recent decades despite advances in therapeutic interventions (1). Variables like age, co-morbidity, immunological or nutritional status, size and location of the tumour, nodal status, oncogene expression, proliferation markers, or DNA content have been assessed as independent prognostic markers for oral cancer (2), but stage at diagnosis remains as the most important prognostic indicator for oral and oropharyngeal squamous cell cancers (SCCs) in such a way that advanced stages are frequently associated with high mortality rates (3-5).

Advances in therapy and standards of care are likely to have played a role in the moderate increase of survival trends, particularly for females and tongue cancer (6, 7).

Detecting oral cancer at an early stage is believed to be the most effective means of reducing rates of death, morbidity and disfigurement from this disease (1), but progression in this field is slow: late-stage presentation is commonplace despite the existing evidence supporting that visual and tactile exploration may ease detection of oral cancer at early stages (8-10). Evidence also suggests that an oral examination of high risk individuals may be a cost-effective screening strategy (11).

An important number of studies have assessed the determinants for diagnostic delay (period elapsed since the first sign or symptom until definitive diagnosis) despite its controversial part in oral cancer (12-14), but the reports aimed at identifying predictors for diagnosis at advanced stages are very scarce though tumour stage is directly related to mortality by oral cancer.

This study was designed to analyse the hypothetical factors related to diagnosis of oral cancer at advanced stages (III-IV) in order to identify high-risk groups for late-stage diagnosis and facilitate early detection strategies.

Materials and Methods

An ambispective cohort study was designed to analyse those factors related to late-stage oral cancer diagnosis. The study sample was made of 88 patients treated at the Oral and Maxillofacial Surgery Service of the CHUAC from January 1998 to December 2003 that met the following inclusion criteria: pathological diagnosis of OSCC (primary tumour) at any oral site and suffering from a tumour at any TNM stage.

The primary sites of oral cancer were: buccal mucosa (n=5), upper and lower gingiva (n=15), hard palate (n=2), tongue (n=32), floor of the mouth (n=24) and retromolar trigone (n=10).

The variables considered included age, gender, smoking history, alcohol usage, tumour site, macroscopic pattern of the lesion (ulcerated, exophytic or mixed), co-existing precancerous lesion, and degree of differentiation. The time interval from the self-reported date when oral cancer signs and/or symptoms were first noted by the patient to the date of definitive pathological diagnosis was defined as the total diagnostic delay. In order to limit the recall bias inherent to this kind of studies, delay data collected from the patient was also validated by those obtained from close relatives. In both situations, identical structured interviews were undertaken for all cases. The median of total diagnostic times has been used as a cut-off point to distinguish between delayed and non-delayed cases in a more objective way.

TNM stage was considered as the dependent variable (early = tumour-node-metastasis [TNM] stage I or II; advanced = TNM stage III or IV). Early stages include a variety of tumour sizes (<4 cm) without invasion of adjacent structures, and no lymph node or distant metastases. Advanced stages include tumours invading adjacent structures, e.g., through cortical bone, into deep (extrinsic) muscle of tongue, maxillary sinus, and skin, or a more advanced node status than early stages' or display distant metastases (15).

-Statistical analysis

Data were entered on the PASW statics18 statistical package and the sample characterized by the variables of interest. A descriptive study was conducted where quantitative variables were expressed as mean ± standard deviation; and qualitative ones as absolute frequency and percentage.

Means were compared using the Student's t test after assessing their normality with the Kolmogorov-Smirnov test. Those variables that are clinically relevant or were significantly related to advanced TNM-stage after univariate analysis (simple logistic regression) were included in a multivariate model (multiple logistic regression). The significance level chosen for all tests was $p<0.05$.

Results

A total of 88 patients (mean age 60±11.3), mostly males (65.9%) entered the study. The most frequent tumour sites were tongue (36.4%), floor of the mouth (27.3%) and gingivae (17%).

The median for the interval between the first sign/symptom to pathological diagnosis was 45 days, and most patients (54.5%) suffered no delayed diagnosis. A 45.5% of the oral carcinomas were diagnosed at early stages (I-II). The most frequent clinical lesions were ulcers (70.5%), being the cancer associated to a precancerous lesion in a 16.5% of the cases.

Most cases were well- and moderately-differentiated (91%) (Table 1).

Univariate analyses revealed that age (OR=1.0; 95%CI=0.9-1.0), smoking habit (OR=1.4; 95%CI=0.5-

3.9), alcohol usage (OR=1.0; 95%CI=0.4-2.6), co-existence of a precancerous lesion (OR=0.6; 95%CI=0.2-2.1) and the clinical presentation (ulcerated/mixed) of the oral carcinoma (OR=2.7; 95%CI=0.7-9.9) were neither significantly associated to diagnosis at advanced-stages, nor to TNM-advanced stage (OR=0.7; 95%CI=0.3-1.6). On the other hand, male gender was identified as a risk factor for late TNM stage at diagnosis (OR=3.8; 95%CI=1.4-9.6). Strong associations between advanced stages and moderate-poor differentiation (OR=4.2; 95%CI=1.6-10.9) or tumour site (floor of the mouth (OR=3.6; 95%CI=1.2-11.1); gingivae (OR=8.8; 95%CI=2.0-38.2); and retromolar trigone (OR=8.8; 95%CI=1.5-49.1)) have also been identified by univariate analysis (Table 2)

Regression analysis excluded "gender" from the multivariate model, remaining tumour site and degree of differentiation significantly associated to high risk of late-stage diagnosis (Table 3).

Table 1. Description of the sample (n=88) .

Variables	Mean	SD	Minimum	Maximum
Age	60.3	11.3	38.8	88.1
	n	%	95% CI	
Gender				
Female	30	34.1	23.6-44.5	
Male	58	65.9	55.4-76.3	
Smoking				
Non-Smoker	22	27.2	16.8-37.4	
Former-Smoker	16	19.7	10.4-29.0	
Current-Smoker	43	53.0	41.6-64.5	
Alcohol usage				
Non drinker	51	65.4	54.1-76.5	
Drinker	27	34.6	23.4-45.8	
Tumour site				
Tongue	32	36.4	25.7-46.9	
Floor of the mouth	24	27.3	17.3-37.1	
Gingivae	15	17.0	8.6-25.4	
Buccal Mucosa	5	5.7	1.8-12.7	
Retromolar trigone	10	11.4	4.1-18.5	
Hard palate	2	2.3	0.2-7.9	
TNM Stage				
Stage I	10	11.4	4.1-18.5	
Stage II	30	34.1	23.6-44.5	
Stage III	14	15.9	7.6-24.1	
Stage IV	34	38.6	27.8-49.3	
Tumour size				
T_1	12	13.6	5.8-21.3	
T_2	43	48.9	37.8-59.8	
T_3	10	11.4	4.1-18.5	
T_4	23	26.1	16.3-35.8	
Neck node status				
Negative (N_0)	61	69.3	59.1-79.5	
Positive($N_{1,2,3}$)	27	30.7	20.4-40.8	
Macroscopic features				
Exophytic	12	15.3	6.7-24.0	
Mixed	11	14.1	5.7-22.4	
Ulcerated	55	70.5	59.7-81.2	
Degree of differentiation				
Well	29	33.0	22.8-43.8	
Moderate	51	58.0	47.6-69.5	
Poor	7	8.0	1.7-14.3	

Table 2. Patient characteristics distribution according to TNM-stage at diagnosis. Simple logistic regression analysis.

Variables	Early stage (I-II) n=40 (45.5%)	Advanced stage (III-IV) n=48 (54.5%)	p-value	Odds Ratio (95%CI)
Age (yrs)				
Mean ±SD	59.4±11.0	61.1± 11.6	0.5	1.0 (0.9-1.0)
Gender				
Female	20 (66.7)	10 (33.3)		1.0 (Referent)
Male	20 (34.5)	38 (65.5)	0.005	3.8 (1.4-9.6)
Tobacco use				
Non-smoker	11 (50.0)	11 (50.0)		1.0 (Referent)
Smoker	24 (40.7)	35 (59.3)	0.4	1.4 (0.5-3.9)
Alcohol Use				
Non-drinker	12 (44.4)	15 (55.6)		1.0 (Referent)
Drinker	22 (43.1)	29 (56.9)	0.9	1.0 (0.4-2.6)
Associated precancerous lesion				
No	28 (43.1)	37 (56.9)		1.0 (Referent)
Yes	7 (53.8)	6 (46.2)	0.5	0.6 (0.2-2.1)
Macroscopic features				
Exophytic	8 (66.7)	4 (33.3)		1.0 (Referent)
Mixed+Ulcerated	28 (42.4)	38 (57.6)	0.1	2.7 (0.7-9.9)
Location				
Tongue	22 (68.8)	10 (31.1)		1.0 (Referent)
Floor of the mouth	9 (37.5)	15 (62.5)	0.02	3.6 (1.2-11.1)
Gingivae	3 (20.0)	12 (80.0)	0.004	8.8 (2.0-38.2)
Buccal mucosa	3 (60.0)	2 (40.0)	0.7	1.4 (0.2-10.1)
Retromolar trigone	2 (20.0)	8 (80.0)	0.01	8.8 (1.5-49.1)
Hard palate	1 (50.0)	1 (50.0)	0.6	2.2 (0.1-38.8)
Diagnostic delay				
No	20 (41.7)	28 (58.3)		1.0 (Referent)
Yes	20 (50.0)	20 (50.0)	0.4	0.7 (0.3-1.6)
Degree of differentiation				
Well	20 (69.0)	9 (31.0)		1.0 (Referent)
Moderate	19 (37.3)	32 (62.7)	0.008	3.7 (1.4-9.8)
Poor	1 (14.3)	6 (85.7)	0.02	13.3 (1.3-127.5)

Table 3. Multiple logistic regression analysis of the association between advanced staged and patients/tumours characteristics.

Characteristics	B	S.E.	Wald	p-value	Odds Ratio (95%CI)
Constant	-2.88	0.7	14.4	0.000	0.056
Gender					
Female					
Male	0.98	0.58	2.82	0.09	2.6 (0.8-8.4)
Location of the tumour					
Tongue					
Floor of the mouth	1.57	0.71	4.8	0.028	4.8 (1.1-19.5)
Other	2.37	0.68	11.9	0.001	10.7 (2.8-41.3)
Degree of differentiation					
Well					
Moderate	1.32	0.58	5.2	0.022	3.7 (1.2-11.7)
Poor	4.11	1.30	9.9	0.002	61.1 (4.7-786.7)

Discussion

The current recommendations to screen for oral cancer at every routine check-up is not practical and has not produced the intended results. Selective opportunistic screening may be a more realistic and effective solution. Detection of oral and oropharyngeal SCCs during a non-symptom-driven examination has proved an association to lower stage at diagnosis, in the same way as patients with a regular primary care dentist are significantly more likely to be diagnosed at early stages (4, 16).

Unfortunately, about a 60% of cancers are identified late (stages III or IV) with survival rates ranging from 10% to 40% after 5 years (17, 18). Up to a 54.5% of the patients in this series were diagnosed at late stages, and recognition of predictors for advanced-stage diagnosis could permit the development of strategies aimed at improving this percentage.

Age, gender, and tobacco and alcohol consumption did not behaved as variables linked to late-stage diagnosis; as were not previously associated to professional or patient-related diagnostic delays (19, 20). The existence of precancerous lesions associated to the tumour did not seem to modify the extension of the disease at the moment of diagnosis, despite that proliferative verrucous leukoplakia or the presence of mild or moderate epithelial dysplasia at the margins of a surgically removed OSCC carries a significant risk of local recurrence and modifying prognosis (21).

Ulcerated-type OSCC were diagnosed mostly (up to a 60%) at stages III-IV, but this association did not reach statistical signification. Moreover, the predictive value for survival of the lesion clinical appearance is controversial, although it is accepted that ulcerated lesions imply poorer survival rates (22).

Previous reports have described the association between primary tumour site and delayed diagnosis or diagnosis at advanced stages (23): tongue, buccal mucosa and lip have been recognised as locations that favour early-stage diagnosis (18), whereas the floor of the mouth and the retromolar trigone have been linked to diagnosis at advanced stages; locations like palate or gingivae showed contradictory results (18, 24). Our data show that the floor of the mouth, gingivae and retromolar trigone behaved as an independent prognostic factor for late stage at diagnosis. These findings may well be explained by the fact that patient's self-perception and self-exploration abilities depend on the site of the tumour (25), and also because gingival locations are associated to advanced stages at diagnosis (late diagnosis) due to the early invasion of the adjacent tissue (T4 primary tumour) (26).

Advanced-stage diagnosis in oral cancer has traditionally been attributed to delays in reaching a diagnosis,

as patients at advance tumour stages are more likely to have longer patient and professional delays than those at early stages (27). However, the lack of sound scientific evidence supporting the existence of an association between diagnostic delay, extent of the disease (III-IV TNM stages) and lower survival rates is evident (12-14). This fact is probably related to a series of limitations and methodological flaws identified in the published reports to date, mainly related to heterogeneity in both the definition and measurement of diagnostic delay, the retrospective nature of these studies and also to a memory bias of the patients (12, 13).

In this study, diagnostic delay was not significantly linked to advanced stage at diagnosis; thus the quickness in obtaining a diagnosis does not guarantee an early-stage tumour, although delay in the diagnosis of a neoplasm is universally considered unacceptable.

On the other hand, poor differentiation of the tumour (biologically more aggressive) behaved as an independent risk factor for diagnosis at stages III-IV. The tumour growth rate may play the role of a confounding factor in the relationship between diagnostic delay and disease-stage or survival, as patients with aggressive tumours and bad prognosis do not usually present diagnostic delay whereas tumours with low proliferation rates elicit good prognosis despite long diagnostic delays (28). Unfortunately, the evidence on tumour proliferation activity that could corroborate this hypothesis is scarce.

This paradoxical circumstance has previously been described in breast, cervix, lung, colon, renal, and urethral cancers and seems to suggest that stage at diagnosis is affected more by the biology of the cancer (rapid tumour growth) than by diagnostic delay (28, 29). These results seem to suggest that the stage of oral cancer at the time of diagnosis is affected more by the biology of the cancer (degree of differentiation) than by diagnostic delay.

Taking into account that early diagnosis is a foremost step for reducing cancer mortality, it is concluded that the efforts aimed at early diagnosis of oral cancer should be prioritized towards screening programmes designed to detect the disease during its asymptomatic phases. Educational interventions on the population, particularly focused on risk groups (self-exploration) and on the professionals (clinician's index of suspicion) should include a sound knowledge of the disease presentation, specifically on sites like floor of the mouth, gingivae and retromolar trigone. More studies are needed in order to analyse the part of tumour biology on the extension of the disease at the time of diagnosis.

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Continuing Education in Oral Cancer Prevention for Dentists in Spain

Juan Seoane, M.D., D.D.S., M.P.D.H., Ph.D.; Pablo Varela-Centelles, D.D.S., M.Med.Sci., M.P.D.H., Ph.D.; Inmaculada Tomás, D.D.S., Ph.D.; Juan Seoane-Romero, D.D.S., M.Sc.; Pedro Diz, M.D., D.D.S., Ph.D.; Bahi Takkouche, M.D., Ph.D.

Abstract: Continuing education (CE) can have a large impact on dentists' oral cancer attitudes, knowledge, and behavior. Reading scientific journals is a key component of CE. The objective of this study was to assess preventive and clinical attitudes of the participants in an educational intervention on oral cancer in Spain based on scientific journals. Members of the Spanish Board of Dentists and Stomatologists participated in an online, cross-sectional study, using an anonymous, self-administered questionnaire. There were 791 general dental practitioners (GDPs) invited to participate in the study. The large majority reported that they deliver tobacco-cessation counseling (93.6 percent) as well as advice on alcohol consumption (66.6 percent), but advice on vegetable intake was less frequently provided (42.4 percent). Alcohol intake advice, routine mucosa exploration, and biopsy performance on lesions suspicious of malignancy are preventive attitudes related to training. Compared with those who did not benefit from CE courses or did so only once, the GDPs who took four or more CE courses showed a doubling in the odds of giving alcohol advice to their patients and a tenfold increased odds of performing mucosa check on a routine basis; they were 3.5 times as likely to take biopsies of suspicious lesions. A longer experience as a GDP did not increase the probability of adopting preventive attitudes. In addition to presenting the results of this study, the article also discusses the general usefulness of other preventive measures in oral cancer.

Dr. Seoane is Senior Lecturer and Head, Stomatology Department, School of Medicine and Dentistry, University of Santiago de Compostela, Santiago de Compostela (A Coruña), Spain and Head of Continuing Education, Spanish General Dental Council, Madrid; Dr. Varela-Centelles is Lecturer, Stomatology Department, School of Medicine and Dentistry, University of Santiago de Compostela, Santiago de Compostela (A Coruña), Spain; Dr. Tomás is Senior Lecturer and Dentistry Dean, Stomatology Department, School of Medicine and Dentistry, University of Santiago de Compostela, Santiago de Compostela (A Coruña), Spain; Dr. Seoane-Romero is a Ph.D. student, University of Santiago de Compostela, Santiago de Compostela (A Coruña), Spain; Dr. Diz is Senior Lecturer, Stomatology Department, School of Medicine and Dentistry, University of Santiago de Compostela, Santiago de Compostela (A Coruña), Spain; and Dr. Takkouche is Senior Lecturer, Department of Preventive Medicine, University of Santiago de Compostela, Santiago de Compostela (A Coruña), Spain. Direct correspondence and requests for reprints to Dr. Juan Seoane, Cantón Grande 5, Apt. 1º E, 15003 A Coruña, Spain; 34-981223033 phone; juanmanuel.seoane@usc.es.

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Oral and pharyngeal cancer is the sixth leading cancer in the world and ranks in the top three cancers in high incidence areas.[1] Furthermore, with a worldwide incidence of 3.8 cases per 100,000 person-years and a mortality rate of 1.9 cases per 100,000 person-years, oral cancer accounts for 1.7 percent of all cancer deaths, according to 2010 data from the International Agency for Research on Cancer.[2] This disorder was the seventh most prevalent malignancy in Europe in 2004.[1,3] Survival remains unaffected despite recent therapeutic advances,[1-4] mainly due to delay in the diagnosis.[4,5] However, if this malignancy were diagnosed and treated at early stages, survival rates would probably exceed 80 percent.[5]

Professional diagnostic delay is strongly related to tumor stage at the time of diagnosis.[6] Determinants of professional diagnostic delay include lack of knowledge about oral cancer, lack of experience in the disease, absence of full clinical examination, and presence of comorbidity.[7,8] Dentists play a critical role in the early diagnosis of oral cancer.[5] Many authors have identified specific training in medical and dental students as a key means of reducing the incidence and mortality of oral cancer through effective cancer control strategies. These strategies include advice on reducing tobacco consumption, promotion of healthier diet and lifestyle, and, most importantly, early detection through screening examinations and adequate follow-up.[9-16] It is then of paramount importance to develop appropriate initiatives to increase dentists' knowledge and favor preventive attitudes both at the university and the professional level, using continuing education (CE) in the latter.[17]

CE courses have a positive influence on oral cancer attitudes, knowledge, and behavior of the attendees, which are key needs for oral cancer control.[5,18] Reading scientific journals is often a key

component of CE.[19-22] In this regard, professional dental organizations in the United States (the American Dental Association) and the United Kingdom (the British Dental Association) have implemented CE initiatives aimed at providing training on new treatments, recent research advances, and business practices, using their newsletters or journals. However, we are not aware of any oral cancer-related CE effort using scientific journals aimed at general dental practitioners (GDPs).

The Spanish Board of Dentists and Stomatologists (SBDE; COE in Spanish) recently carried out a pilot experience in CE in oral cancer by means of scientific journals. The objective of this study was to assess preventive and clinical attitudes related to oral cancer among GDPs.

Methods

We carried out a cross-sectional study in January and December 2009 among GDPs affiliated with the SBDE (affiliation is compulsory for dental practice) who accessed an online CE program based on the board's journal (*Revista del Consejo de Odontólogos y Estomatólogos, RCOE*). This journal is distributed to or freely accessed every trimester by the 25,000 members of the board.

As a special collaboration with our study, the *RCOE* published in April 2009 a monograph on oral cancer written by a panel of experts, which focused on early detection of lesions suspicious of malignancy.[23] A customized platform was designed to host an anonymous and confidential self-administered questionnaire designed for our study, as well as an online exam on the content of the monograph that had to be submitted to the accreditation board in order to pass the CE course.

The questionnaire was a modified version of previous survey instruments.[14,15] To ensure feasibility, we carried out a pilot study among a small sample of the participants. The questions were broadly grouped into three sections: GDP profiling questions (demographics and practice), questions on preventive attitudes towards oral cancer, and specific questions about clinical practice oriented towards early detection (systematic examination of the oral cavity and biopsy of suspicious oral lesions). Ethical approval was granted by the Bioethical Committee of the University of Santiago de Compostela.

Statistical analysis was performed using SPSS+ 11.0 statistical package (Chicago, IL, USA). To determine which factors were related to preventive attitudes, we used a multiple logistic regression analysis to obtain odds ratios (ORs) and their 95 percent confidence intervals (95 percent CI). The outcome was one of the following preventive attitudes: anti-tobacco advice, alcohol advice, fruit intake advice, routine mucosa check, or biopsy performance. The exposure variables were those related to training, such as the number of CE courses or the amount of professional experience. The estimates were adjusted by age, gender, and the rest of the exposure variables. Hence, each of our OR estimates is free of potential confounding due to personal variables or to other variables related to training.

Results

Our study population consisted of 791 GDPs with a mean age of 35±9.6 years, most of whom were females (61.7 percent) and more than one-third of whom had ten years or more of practice. About one-fourth of the participants acknowledged that their only postgraduate training on oral cancer was reading the issue of the newsletter used in this study, while 36.3 percent had attended more than two courses on oral malignancies. Table 1 summarizes the distribution of key variables in the study population. The large majority (93.6 percent) said they deliver anti-tobacco advice to their patients, and two-thirds reported advising their patients to reduce alcohol intake. However, only 42.4 percent said they recommend that their patients have an adequate intake of fruit and vegetables. As for routine clinical attitude, 90.3 percent reported checking their patients' oral mucosa, but only 28.7 percent said they perform biopsies on suspicious oral lesions.

From the multivariate analysis (Table 2), we observed that no variable was significantly related to anti-tobacco advice delivery. This means that advice was given independently of the background or training of the GDPs. We also observed that recommendations on fruit intake were significantly more frequent among older GDPs, but no other factor, especially those referring to training, was related to this preventive attitude.

Alcohol intake advice, routine mucosa exploration, and biopsy performance on lesions suspicious of malignancy are preventive attitudes related to training factors. Compared to those who did not benefit from CE courses or did so only once, the GDPs who took four or more CE courses showed a

Table 1. Distribution of covariables by preventive attitudes among dentists in study

	Mean Age (years)	Female (%)	Mean Time of Practice (years)	Mean Number of Courses	Specific Course Number	Specific Course %	Total Number	Total %
Anti-tobacco advice								
Yes	35.0	62.7%	9.6	3.1	337	95.2%	740	93.6%
No	36.4	47.1%	10.8	2.5	17	4.8%	51	6.4%
Advice on alcohol consumption								
Yes	36.0	60.0%	10.3	3.4	241	68.1%	527	66.6%
No	33.3	65.2%	8.4	2.5	113	31.9%	264	33.4%
Advice on fruit intake								
Yes	37.4	58.8%	11.4	3.7	169	50.4%	335	42.4%
No	33.4	63.8%	8.4	2.6	185	40.6%	456	57.6%
Routine mucosa exploration								
Yes	35.3	61.8%	9.8	3.2	319	90.1%	714	90.3%
No	34.0	61.0%	8.9	1.9	35	9.9%	77	9.7%
Biopsy								
Yes	36.7	48.0%	10.7	4.3	126	35.6%	227	28.7%
No	34.5	67.2%	9.3	2.5	228	64.4%	564	71.3%

doubling in the odds of giving alcohol advice to their patients and a tenfold increased odds of performing mucosa checks on a routine basis. They were 3.5 times as likely to take biopsies of suspicious lesions and twice as likely to give alcohol advice to their patients. Also, those who had taken two or three CE courses doubled their odds of performing mucosa checks. Having taken specific oral cancer courses increased by 50 percent the likelihood of performing biopsies when indicated. Finally, a longer experience as a GDP (measured by years of practice in the field) did not seem to increase the probability of adopting preventive attitudes. On the contrary, experienced doctors were less likely to take biopsies. However, older GDPs were found to perform more biopsies on suspicious lesions.

Discussion

Whereas continuing education is compulsory for dentists in the United States, this requirement is not uniform in the European countries, where, in general, it is considered a moral duty for each dentist. Such countries as Austria, Cyprus, Estonia, Finland, The Netherlands, Norway, Sweden, and Spain maintain a voluntary scheme for their CE system.[24] Therefore, the results of our study cannot be compared directly with those countries where CE is mandatory for dentists.

Our results found that CE courses are useful to increase GDPs' preventive attitudes about oral cancer, especially those related to clinical practice (routine mucosa exploration and biopsy performance). Specific courses were found to be useful to increase biopsy-taking but do not seem to improve other preventive attitudes. The paradoxical association between a decrease in mucosal exam and biopsy-taking and an increase in years in practice could well be explained by the fact that less experienced GDPs (<10 years) have benefited from improved CE and have received undergraduate training entirely at dental schools. Similar findings have been reported from Italy, where the school of graduation (dental school vs. medical school) seems to influence these preventive practices.[18]

Our study is limited by the fact that it is a cross-sectional study based on a convenience sample. In particular, the main disadvantage of this design is that it does not allow for proper causal inference as exposure and outcome are measured at the same time and temporality is not firmly established. However, this type of study has proved useful for health services management to improve clinical practice and to identify educational problems. There is a potential for selection bias in our data due the absence of randomization of the participants. However, the population of our study is representative of the Spanish general population of GDPs as far as age, years of professional experience, geographic distribution, and

Table 2. Odds ratios (OR) and 95 percent confidence intervals (95% CI) of dentists' preventive attitudes according to continuing education variables

	Anti-Tobacco Advice		Alcohol Advice		Fruit Intake Advice		Mucosa Exploration		Biopsy	
Variables	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Total number of courses										
0–1	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2–3	1.96	0.84–4.58	1.11	0.73–1.70	0.96	0.62–1.47	2.02	1.04–3.93	1.32	0.82–2.11
≥4	2.18	0.76–6.22	1.95	1.12–3.40	1.37	0.82–2.29	10.6	2.90–38.41	3.48	2.01–6.02
Specific oral cancer course										
No	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Yes	1.05	0.50–2.19	1.00	0.70–1.43	1.33	0.94–1.88	0.62	0.34–1.16	1.48	1.02–2.14
Years of practice										
0–3	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
4–7	0.59	0.11–3.17	1.50	0.75–3.03	1.10	0.54–2.25	1.75	0.43–7.16	0.74	0.35–1.57
8–15	0.22	0.03–1.68	0.84	0.35–2.02	0.57	0.24–1.39	0.36	0.07–1.80	0.31	0.12–0.80
≥16	0.70	0.07–7.45	1.33	0.44–4.05	0.83	0.29–2.38	0.29	0.04–2.17	0.19	0.05–0.53
Age										
<28	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
28–32	1.90	0.33–10.93	0.86	0.42–1.76	1.54	0.74–3.20	1.36	0.32–5.69	1.25	0.57–2.72
33–41	1.74	0.24–12.69	1.93	0.79–4.74	4.60	1.89–11.18	2.11	0.40–11.21	2.90	1.14–7.39
≥42	1.01	0.11–9.59	1.26	0.41–3.88	3.58	1.22–10.48	2.74	0.36–21.16	4.14	1.32–12.96
Gender										
Male	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Female	1.78	0.83–3.83	0.98	0.67–1.44	1.11	0.77–1.60	1.37	0.71–2.63	0.54	0.37–0.79

Note: Data in all columns adjusted for gender, age, and years of practice.

preventive attitudes about oral cancer.[15] Confounding by other variables cannot explain our results. We have adjusted our results by those factors that may be related to the outcome and the main exposure (preventive attitudes and training). The relative risk estimates are robust to this adjustment. However, as in any observational study, we cannot rule out the presence of residual confounding due to unknown or unmeasured variables.[25-28]

Prevention offers the most cost-effective strategy for cancer control.[29,30] Despite the fact that advice on smoking cessation, alcohol intake moderation, and healthy eating is an essential and ethical part of the dentist's role, gaps in knowledge have been described previously.[31] Regarding smoking, previous studies found a significant reduction in the risk of oral cancer among quitters, which approximates that of never smokers approximately ten years after cessation.[32] Our study found that a high proportion of the GDPs reported using their position to advise patients on tobacco cessation. A similar proportion has been reported in the United Kingdom.[33] Alcohol consumption is considered excessive when it exceeds an average of one (for females) or two (for males) drinks per day.[34] Recommendations to reduce alcohol intake have the potential to reduce the incidence of oral cancer and oral premalignant lesions in nonsmokers and smokers alike. However, only two-thirds of our population advised their patients on alcohol consumption. Contrary to earlier impressions, it has been found that patients do accept alcohol screening and alcohol counseling by the dentist.[35] Finally, regardless of the existence of studies that support the beneficial effects of high intake of vegetables and fruits on the risk of developing cancers of the oral cavity and on reducing recurrences and mortality (overall and specific),[36] the lower consumption of fruits and vegetables is a less-known risk factor for oral cancer both in Europe and the United States.[9-16] Our study's findings agree: only 42.4 percent of the participants reported providing dietary recommendations to prevent this disease.

Reading scientific journals is an accepted method of continuous scientific training, and there is a growing awareness of the need of any clinician to devote a certain amount of time to this activity.[25-27] Some studies have found that clinicians favor enrollment in educational courses over reading activities to earn CE credits, both in compulsory and voluntary schemes.[19-21] However, when dealing with oral pathology, some surveys have found journal reading to be the preferred CE activity by practitioners. Furthermore, dentists who read about oral cancer have been found to refer fewer difficulties in achieving a diagnosis of potentially malignant lesions.[28] In our study, one-fourth of the participants said they received information on oral cancer, for the first time since graduation, through reading activities. It is therefore important to promote strategies to increase reading activities.

Early diagnosis of oral cancer is critically essential and may have a dramatic impact on survival rates and cures.[7,8] The standard diagnosis relies on detection during visual examination followed by tissue biopsy for histopathological diagnosis.[5] However, other techniques may prove useful as complementary tools such as light-based detection systems, specific blood tests (CEA, SCCAA, IAP, CYFRA, ANXA1, and others), specific saliva tests, and imaging.[37] Opportunistic screening (offering patients a screening test when they attend a clinic for some other unrelated reason) may be cost-effective particularly in general dental practice.[38] However, including high-risk groups in this screening is not feasible as these groups do not visit a dental practice on a regular basis.[39] Selective opportunistic high-risk screening may be a more realistic and effective solution for areas with low incidence of oral cancer.[40]

When dealing with smokers or excessive alcohol consumers, it is advisable for the clinician to remain alert for signs of potentially malignant lesions or early-stage cancer during visual and tactile exploration of all patients.[41] A large majority of respondents (90.3 percent) in our study said they perform a systematic exploration of oral soft tissues to rule out oral cancer. This proportion is close to that found in previous studies in Europe and the United States (83 to 86 percent).[42,43] The proportion of GDPs who perform biopsy tests is low, however, in spite of existing recommendations.[44] The number of primary care dentists who offer oral biopsies, either on a routine or on a selective basis, has been found to be low in some countries (e.g., 12 percent in Northern Ireland[45] and 21 percent in the United Kingdom[41]), probably due to the lack of specific training. However, recent reports have found that this proportion is increasing.[15,18] The fact that, in our study, men were found to perform biopsies more frequently than women is consistent with the findings in an earlier study.[46]

Our study found that the GDPs taking CE oral cancer courses had positive preventive attitudes in oral cancer, especially about delivering counseling on alcohol consumption and performing routine exploration of the oral mucosa and biopsy. Reading

scientific journals is the cornerstone of CE, so oral cancer prevention and detection should be periodically included in dental newsletters and journals.

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DIAGNOSTIC DELAY

Sir, we have read with great interest the article by Dave,[1] where the author warns about diagnostic delay in oral cancer and makes patients (patient delay), healthcare professionals (doctor delay) and the healthcare system (system delay) responsible for it. The paper also highlights the importance of reducing delayed diagnosis in order to ensure cancer treatment at an early stage. However, when the question 'Why is reducing delayed diagnosis important?' arises, the only answer in the manuscript is that 'the most important prognostic factor in oral cancer is the stage of the tumour at the time of diagnosis', without considering that it has been proved that diagnostic delay is broadly associated with more advanced stage oral cancer (pooled RR: 1.47; 95% CI: 1.09-1.99), particularly when the delay is longer than one month (pooled RR: 1.69; 95% CI: 1.26-2.77).[2] Moreover, the estimation of the relative risk of mortality for head and neck carcinomas related to any diagnostic delay (either patient or professional delay) is 1.34 (95% CI: 1.12-1.61), and specifically referral delay is associated with a three-fold increase in mortality.[3]

Conversely, several research groups have studied the concept of delay in diagnosis of oral cancer but using heterogeneous criteria such as different types of data collected (eg continuous variables versus categorical), or diverse sources of information on patient delay (standard questionnaires, interviews, hospital records, etc) that may – along with variations in tumour biology - explain the absence of a consistent relationship between diagnosis delay and stage at diagnosis in the literature. Despite these shortcomings, diagnostic delay has recently been related to a poorer survival rate in head and neck carcinomas.[3]

However, The Aarhus Statement has been proposed to improve the design and reporting of studies on early cancer diagnosis.[4] This guideline recommends the substitution of the term 'delay' (eg 'patient delay') for 'intervals' or 'time intervals'. The aforementioned statement also suggests key time points (dates of first symptom; first presentation, referral and diagnosis) and time intervals.

Particularly relevant for GDPs are the date of first presentation and the date of referral. This time period could be shortened, as Dave accurately suggests, by using training as part of CPD for all members of the dental team, and a variety of additional approaches.

J. M. Seoane-Romero, P. Varela-Centelles, J. Seoane, Spain

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WHITENING ADVOCATE

Sir, as most readers will be aware, the law regarding tooth whitening products containing more than 0.1% hydrogen peroxide changed on 1/10/12 making the use of such products illegal in anyone under 18 years.

I had orthodontic treatment from an early age and the appearance of my teeth clearly improved, however, I was still extremely dissatisfied with opacities present on the central incisors. I would never smile exposing my teeth; I was extremely self-conscious and embarrassed if they were noticed. After talking to my dentist about this I was referred to the Charles Clifford Dental Hospital at 15 years of age.

During the teenage years appearance is crucially important. Secondary school can be a cruel place if you do not fit into the 'norm'. Teenage years are a time of growth in confidence and of building self-esteem and the impact of the appearance of the teeth can be grossly underestimated unless you have experienced having a cosmetic defect.

I was very fortunate in that the staff of the Paediatric Dentistry Department, Charles Clifford Dental Hospital had a keen understanding of the personal impact on me. We discussed the possibility of tooth whitening and assessing the results before we seriously considered the more invasive treatment options. From my perspective, it was the ideal solution, being non-invasive with the potential for excellent results that could be easily maintained. I was able to undertake the whitening at home over a two-week period. The results were astonishing; the opacities were no longer visible and I encountered no side effects. The boost to my confidence cannot be underestimated. The results from the whitening treatment definitely had the greatest positive impact out of all the treatment I'd had carried out over the years.

I have recently undertaken another brief course of whitening treatment as the opacities were becoming visible again but this has resolved successfully after treatment. Now aged 20 and studying dentistry at Sheffield myself, I understand fully the impact that both cosmetic and pathological defects of the teeth have on an individual and this is partly the reason why I have chosen to train in the profession.

I am a strong advocate of this treatment in the type of circumstances I have described and find it difficult to believe that if I were in the same situation now it would not be possible to have this treatment. I cannot see any viable reason why a fully qualified dental professional could not carry out whitening treatment for patients with cosmetic defects that are clearly affecting their mental wellbeing.

A. Coulby
By email

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LONG IN THE TOOTH TECHNIQUE

Sir, with reference to osteo-odonto keratoprosthesis (*Tooth in eye surgery*; *BDJ* 2013; **214:** 373), this technique was reported in this journal as long ago as 1966.[1]