Diagnostic delay of oral squamous cell carcinoma in a cohort of Bulgarian patients

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Abstract: *Oral squamous cell carcinoma is the most common malignancy of the oral cavity. Although oral cancers are usually visible and accessible, delays in diagnosis are not uncommon. The aim of the present study was to characterize diagnostic delay of oral cancers in a cohort of Bulgarian patients. The mean total delay of oral cancer diagnosis was found to be 7.3 months (median 4 months) in 288 patients included in the study. It was possible to determine patient and professional delay in 52 cases. The mean patient delay in diagnosis was 5.7 months (median 3 months) and the mean professional delay – 1.4 months (1 month). Diagnostic delay of oral cancer was found to be significantly associated with education levels of patients and with site of tumor within the oral cavity. In conclusion, a relatively long delay of oral cancer diagnosis was found possibly due to, among other factors, patients being less educated and tumors being less visible.*
Keywords: *oral cancer, diagnosis, delay*

I.   Introduction

Oral squamous cell carcinoma is the most common malignancy of the oral cavity [1]. It is the eighth most common cancer worldwide [2]. In spite of advances in both medicine and technology there has been no improvement of survival rates in patients with oral cancer. Five-year survival rate has remained at around 50 % [2]. With known risk factors such as smoking and alcohol consumption, efforts have been aimed at prevention and early diagnosis. Unlike other malignancies oral cancers are usually visible and accessible and making an early diagnosis should not be a problem. The literature however has consistently demonstrated proof of delays in diagnosis of OSCC. Many authors have tried to elucidate why such unacceptable delays exist and what factors are responsible for them - patient, clinician, tumor, or socioeconomic factors, the ultimate aim being timely diagnosis, treatment and subsequently improved survival[3].

Therefore, the aim of the present retrospective study was to determine if and how much diagnosis of oral cancer was delayed in a cohort of Bulgarian patients and try to shed more light on possible contributing factors.

II.   Material And Methods

The investigation was retrospective in nature. The clinical records of 16410 patients admitted to the Clinic of Maxillofacial surgery, University Hospital "St. George", Plovdiv, Bulgaria, from 2004 till 2013 were reviewed. Patients with histologically proven diagnosis of oral cancer were identified and included. Patients diagnosed with recurrent or second primary tumor or with history of pre-existing oral potentially malignant disorder were excluded. Cases with no record of time of onset of symptoms were also excluded. The principal outcome variables were recorded according to the following definitions:
-    patient delay - time from the moment the patient became aware of the lesion or its symptoms until first visit to doctor - general dental or medical practitioner, or specialist;
-    professional delay - time from patient's first visit to the doctor to the time definitive diagnosis was made;
-    total delay - time from patient's first becoming aware of signs or symptoms until definitive diagnosis was made.

Data was also collected about gender, age, level of education of patients ("secondary or higher" vs "no secondary or higher education"), marital status, smoking (smoker vs ex-smoker vs non-smoker) and alcohol consumption (yes vs no), site, size (T), stage and grade of differentiation of tumor, outpatient treatment of lesion before specialist referral.

Descriptive statistics were used to characterize the patients and tumors. Kolmogorov-Smirnov test was used to assess normality of distribution. As only age had normal distribution, non-parametric tests (Mann-Whitney U or Kruskal-Wallis H tests) were used for the other variables. Chi-square test was used to look for associations between delay variables and other factors, with level of significance at $p < 0.05$. SPSS statistics 22.0 (Chicago, IL) was used for analysis.

III.   Results

Patient characteristics

The total number of patients with histologically proven oral cancer for the 10-year period was 383. After applying the exclusion criteria there were 288 patients left and data about them analyzed.

The mean age of the patients was 62.06 +/- 12.20, the youngest being 13 and the oldest - 93 years.

Most of the patients were male - 80.2 % and only 19.8 % - female.

Slightly more than half of the patients (57 %) had secondary or higher education (Figure 1).

68.8 % of the patients were married.

Two thirds of the patients were smokers at the time of diagnosis (67.5 %) (Figure 2).

More than half confirmed regular intake of alcohol 63.6 %, compared to 36.4 % non-drinkers.

Tumor characteristics

The most commonly involved sites of oral cancer were lips and tongue, followed by floor of mouth, and gingiva (Figure 3).

There were 18.4 % patients with T1 tumours, 30.6 % of them had T2 lesions, 13.9 % - T3, and 36.8 % - T4. The distribution according to stage differs - almost 43 % of the patients presented with stage IV disease (Figure 4).

Most of the cancers were moderately (41.7 %) or well differentiated (31.6 %).

In 29 patients there was information on record about the lesions having been treated by general dentist before referral and final diagnosis. Similarly, 26 patients associated the lesion with wearing dentures.

Delay in treatment

All 288 patients had information about the duration of signs or symptoms and thus total delay was noted. However, data about the first time they sought professional help was found only in 52 cases, based on which more specific patient and professional delays were calculated. The results are presented in table 1.

All three variables (delays) were tested for associations with the different patient and tumour factors.

No significant associations were found between delays in diagnosis and sex, age, marital status, TNM stage, grade of differentiation, smoking and alcohol consumption and treatment by dentist.

Interestingly, there was significant difference in total delays of treatment between patients who had secondary or higher education and those who did not (5.3 months vs. 9 months). Besides, non-parametric testing revealed significant differences in delays of diagnosis depending on the site of the oral cancer (Table 2).

IV.   Discussion

The present study found relatively long mean total delay of oral cancer diagnosis - 7.3 months. It was longer than another study from Bulgaria by Stanimirov P (2013) where delay was 4 months[4]. Although the patient groups were similar, no explanations for the difference were obvious.

Numerous other studies have also reported on delays of diagnosis of oral cancer, all aimed at elucidating contributing factors and thus eventually facilitatingearly diagnosis of oral cancer (table 3). Many authors reported only mean time between first symptoms and final diagnosis[5-10],though it makes sense to also analyze median time due to the presence of outliers and skewness of data, as done by other authors[11-16]. Some authors have chosen an arbitrary time point after which diagnosis was considered delayed, usually three months[16,17].

On the other hand, most authors have differentiated between patient-related delays and clinician-related delays[5–8,11–13,15,16]. Such differentiation was considered important for better elucidation of contributing factors and was therefore used in the present study.

The present study found mean patient delay to be 5.7 months (median 3 months). The result compared unfavorably to most studies from countries such as Australia, the Netherlands, Denmark, UK, Thailand, USA, where mean patient delay was reported to be between 3 and 4.5 months[5,7–9,11,12]and in some other countries (Greece, Japan, China) even lower[13–15].In an attempt to explain the longer patient delay in diagnosis, associations with patient and tumor factors were tested statistically. Sex, age, marital status, TNM stage, grade of differentiation, smoking and alcohol consumption and treatment by dentist were not significantly associated with the patient delay. However, patients who had secondary or higher education level were diagnosed significantly earlier than patients who did not. In contrast, Guggenheimeret al (1989) did not find any correlation between the amount of education and delay in diagnosis[18]. In Pitiphat et al's study (2002) education carried risk for delayed diagnosis although it did not reach statistical significance [14]. Panzarella et al(2014) did not find significant correlation between education level and patient delay in diagnosis either[19]. However, they found that "Unawareness" and "Denial" were significant risk factors, which led them to conclude that educational interventions were needed to increase patient awareness and their role in early diagnosis of OSCC. Still, the association of diagnostic delay with education level in the present study implies the significanceof education about the level of self- and health-awareness among patients with oral cancer.

Although marital status was not found to be a significant factor for delay in diagnosis in this investigation, Pitiphat et al (2002) did find it to be associated with delay in diagnosis - unmarried patients were diagnosed significantly later, probably due to less favourable lifestylesand unhealthy behaviours[14].

Other interesting factors contributing to patient-related delay in diagnosis of oral cancer were found in a study from Thailand[8]. Kerdpon et al(2001) found that self-treatment - use of herbal medication by patients - was significantly associated with delay in treatment. Another significant factor was religion - Buddhist sought treatment earlier than Muslims [8].

On the other hand, Peacock et al (2003) commented that insurance status was an important predictor of tumor stage at first presentation – patients with no insurance were more likely to present with advanced stage tumor compared to patients with private insurance. In support of their claim they compared their median patient delay of 18.4 weeks to findings by Yu et al (2008) of 4.5 weeks of median patient delay in a Canadian cohort of oral and oropharyngeal cancer patients, noting that Canadian health care was publicly funded[9,20].

In summary, data from the literature about causes of patient delays in diagnosis of oral cancer and the results of the present study were inconclusive but pointed toward lower socio-economic status with lower level of education of patients and cultural characteristics as contributing factors for such delays.

Shafer (1975)reported that the blame for the mismanagement (delay in diagnosis of oral cancer) must be shared almost equally by the dentist (24% of cases), the physician (35% of cases), and the patient (20% of cases) in their cohort of mismanaged patients[21]. The general medical practitioners were far more prone to treat the oral lesions by some form of drug, whereas the dentists were more prone to blame the denture or the teeth.

The present investigation found the mean professional delay to be 1.4 months (median 1 month), which was not much longer than most studies in the literature (see table 3). In an attempt to analyze professional delay and recommend ways to eliminate it most authors have turned their attention toward specialist referral patterns. Hollows et al(2000) reported that the mean delay in referral for general dental practitioners (GDPs) was 14.5 days (sd = 32.3, range 0 to 176) and for general medical practitioners (GMPs)8.4 days (sd = 17.6, 0 to 90)[7]. Although both periods were relatively short, one of the possible explanations for the difference was that dentists might attempt local treatment of lesions that they did not consider malignant at first.

In Bulgaria,most patients are referred by dentists. Some dentists might attempt local treatment unlike medical doctors who would presumably refer the patient for treatment sooner. Similar explanation was offered by Kedpronet al(2001). In their study patients referred by GMPs were generally in earlier stages than patients referred by GDPs, probably due to medication, denture adjustment, extractions and reassurances[8].

Onizawa et al(2003) also found delay in referrals by dentists[13]. Therefore, they commented that dentists have been prone to adjust the dentures or the teeth close to the lesion as an initial mismanagement of oral cancer.

The case histories of 29 patients in the present study had information about the lesion getting local treatment, usually by a dentist before the patients were referred and final diagnosis made. No statistically significant difference was present between this group of patients and the rest in terms of delay of diagnosis. However, it is highly likely that for a number of cases such information was not recorded and therefore definite conclusions cannot be made.

Another possible explanation for delayed diagnosis was the site of tumor growth (table 2). The floor of the mouth, lower gingiva and retromolar area were associated with the longest diagnostic delays within the oral cavity possibly due to being less visible locations. Lips should be considered separately. Although they had the longest delays in diagnosis of all sites, it was probably due to their being less aggressive and their slow growth compared to proper oral cavity cancers. No other study was found,which reported on associations between site of cancer and delay in diagnosis.

One of the main reasons so many investigators have been searching for the most important factors contributing to diagnostic delays of oral cancer is the desire to increase the number of patients diagnosed at an early stage and thus improve the prognosis of the disease. Common sense would incline clinicians to think that delay in patients' seeking help and getting diagnosed with oral cancer would lead to their initial presentation with a higher staged disease. However, investigators have consistently failed to demonstrate such an association[12,16], as was the case with the present study. This fact would most probably be explained by the wide variation of tumor aggressiveness and growth rate among patients. If so, one could expect that delay in seeking help among patients with equally aggressive oral cancers could lead to more advanced tumor stages at presentation and subsequently worse survival. This, however, remains to be demonstrated.

In conclusion, the present study found relatively long patient and total delays of oral cancer diagnosis associated with lower level of education of the patients and with certain cancer sites within the oral cavity.

Reference

[1]. Lortet-Tieulent J, Renteria E, Sharp L, Weiderpass E, Comber H, Baas P, et al. Convergence of decreasing male and increasing female incidence rates in major tobacco-related cancers in Europe in 1988-2010. Eur J Cancer [Internet]. 2015 Nov 20 [cited 2014 Sep 7];51(9):1144–63. Available from: http://www.sciencedirect.com/science/article/pii/S0959804913009520

[2]. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol [Internet]. 2009 Jan [cited 2014 Jul 22];45(4–5):309–16. Available from: http://www.sciencedirect.com/science/article/pii/S1368837508001838

[3]. Varela-Centelles P, Seoane J, Lopez-Cedrun JL, Fernandez-Sanroman J, García-Martin JM, Takkouche B, et al. The length of patient and primary care time interval in the pathways to treatment in symptomatic oral cancer. A quantitative systematic review. Clin Otolaryngol [Internet]. 2017 Jul 24; Available from: http://doi.wiley.com/10.1111/coa.12919

[4]. Stanimirov P. Prognostic factors in squamous cell carcinoma of the oral cavity [PhD thesis], Sofia, Bulgaria, Medical university Sofia, 2013.

[5]. Dimitroulis G, Reade P, Wiesenfeld D. Referral patterns of patients with oral squamous cell carcinoma, Australia. Eur J Cancer B Oral Oncol [Internet]. 1992;28B(1):23–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1422466

[6]. Khoo S, Shanmuhasuntharam P, Mahadzir W, Tay K, Latif A, Nair S. Factors Involved In the Diagnosis of Oral Squamous Cell Carcinoma in Malaysia. Asia Pacific J Public Heal [Internet]. 1998 Jan 30;10(1):49–51. Available from: http://journals.sagepub.com/doi/10.1177/101053959801000111

[7]. Hollows P, McAndrew PG, Perini MG. Delays in the referral and treatment of oral squamous cell carcinoma. Br Dent J. 2000;188(5):262–5.

[8]. Kerdpon D, Sriplung H. Factors related to delay in diagnosis of oral squamous cell carcinoma in southern Thailand. Oral Oncol. 2001;37(2):127–31.

[9]. Peacock ZS, Pogrel MA, Schmidt BL. Exploring the reasons for delay in treatment of oral cancer. J Am Dent Assoc [Internet]. 2008 Oct;139(10):1346–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18832270

[10]. Sargeran K. Treatment delay among oral cancer patients in Tehran, Iran. Media. 2016;28(1):19107.

[11]. Jovanovic A, Kostense PJ, Schulten EA, Snow GB, van der Waal I. Delay in diagnosis of oral squamous cell carcinoma; a report from The Netherlands. Eur J Cancer B Oral Oncol [Internet]. 1992 Jul;28B(1):37–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1422468

[12]. Wildt J, Bundgaard T, Bentzen SM. Delay in the diagnosis of oral squamous cell carcinoma. Clin Otolaryngol Allied Sci [Internet]. 1995;20(1):21–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7788928

[13]. Onizawa K, Nishihara K, Yamagata K, Yusa H, Yanagawa T, Yoshida H. Factors associated with diagnostic delay of oral squamous cell carcinoma. Oral Oncol. 2003;39(8):781–8.

[14]. Pitiphat W, Diehl SR, Laskaris G, Cartsos V, Douglass CW, Zavras AI. Factors associated with delay in the diagnosis of oral cancer. J Dent Res [Internet]. 2002;81(3):192–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11876274

[15]. Gao W, Guo C-B. Factors related to delay in diagnosis of oral squamous cell carcinoma. J Oral Maxillofac Surg [Internet]. American Association of Oral and Maxillofacial Surgeons; 2009;67(5):1015–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19375011

[16]. Kaing L, Manchella S, Love C, Nastri A, Wiesenfeld D. Referral patterns for oral squamous cell carcinoma in Australia: 20 Years progress. Aust Dent J. 2016;61(1):29–34.

[17]. Scott SE, Grunfeld EA, McGurk M. The idiosyncratic relationship between diagnostic delay and stage of oral squamous cell carcinoma. Oral Oncol. 2005;41(4):396–403.

[18]. Guggenheimer J, Verbin RS, Johnson JT, Horkowitz CA, Myers EN. Factors delaying the diagnosis of oral and oropharyngeal carcinomas. Cancer. 1989;64(4):932–5.

[19]. Panzarella V, Pizzo G, Calvino F, Compilato D, Colella G, Campisi G. Diagnostic delay in oral squamous cell carcinoma: the role of cognitive and psychological variables. Int J Oral Sci [Internet]. 2014;6(1):39–45. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3967306&tool=pmcentrez&rendertype=abstract

[20]. Yu T, Wood RE, Tenenbaum HC. Delays in diagnosis of head and neck cancers. J Can Dent Assoc (Tor). 2008;74(1).

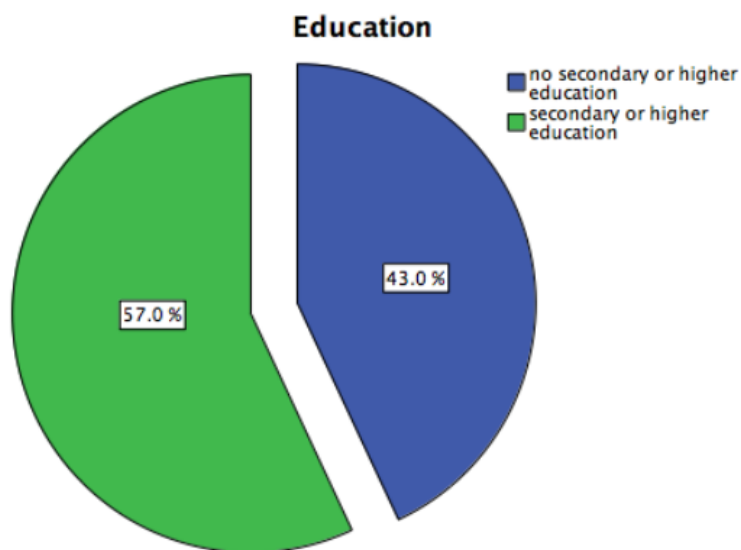[21]. Shafer WG. Initial mismanagement and delay in diagnosis of oral cancer. J Am Dent Assoc [Internet]. Elsevier; 1975;90(6):1262–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1095626

Figure 1. Distribution of patients according to level of education.
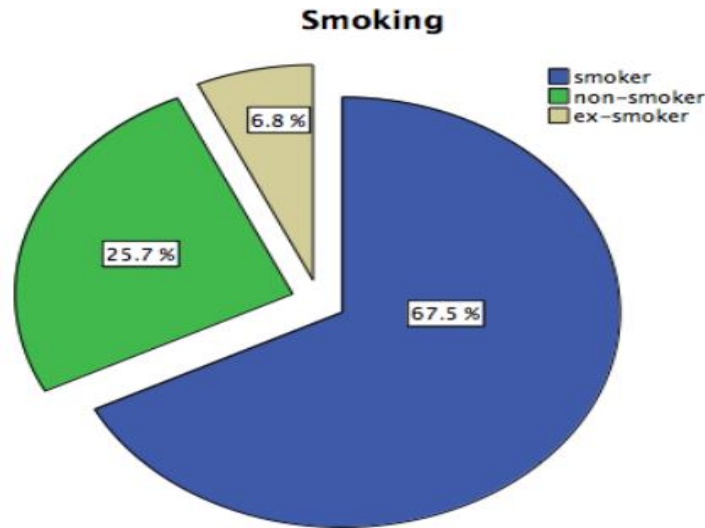
Smoking

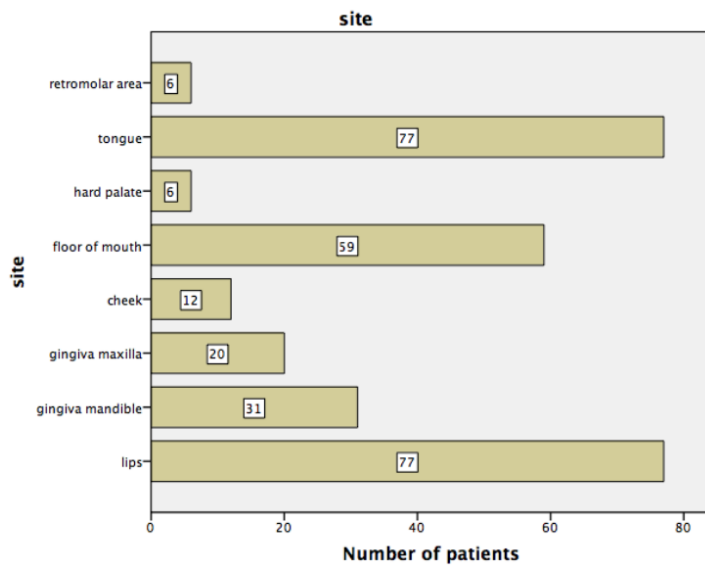**Figure 2**. Distribution of patients according to smoking habits.

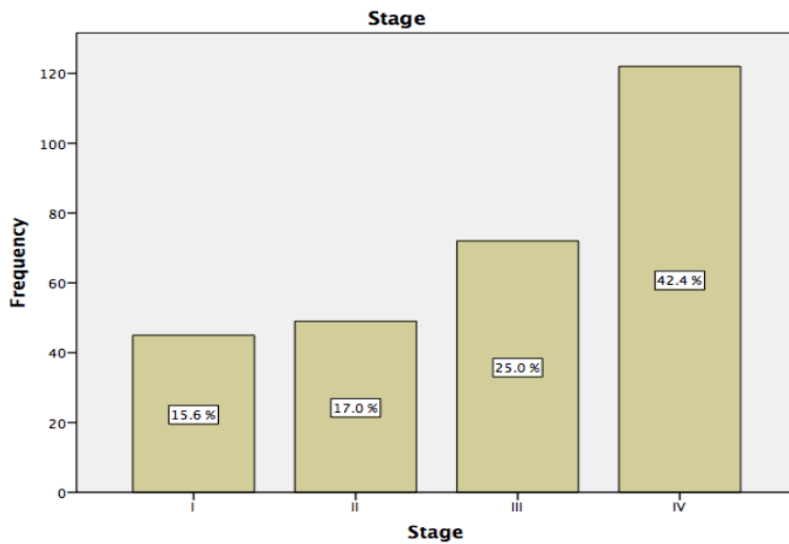**Figure 3**. Distribution of patients according to site of oral cancer.

Figure 4. Distribution of patients according to TNM stage.

Table 1. Delays in diagnosis of oral cancer (in months).
Table 2. Total delay in diagnosis according to site of tumour.
Table 3. Studies on patient and professional delay of oral cancer diagnosis.

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