Early Diagnosis of Oral Cancer

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Core Message

The subject of detection and diagnosis timing for oral cancer has not been adequately studied and no robust conclusions can be reached with the current evidence. A majority of oral cancers are diagnosed in advanced stages (3 and 4) and have relatively poor prognosis. The reasons for this are not always clear but appear to be associated with low education levels about the disease in both populations at risk and primary care practitioners. Sets of heterogeneous data indicate that early diagnosis followed by swift implementation of therapy has superior outcomes and lower morbidity. Improved educational models may benefit future patients as well as the society at large.

15.1 Introduction

Despite increased governmental and educational efforts aimed at early diagnosis, oral cancer continues to be identified in advanced stages in a majority of the afflicted populations. The extant literature on reasons for this delayed diagnosis remains fragmented, and firm conclusions remain elusive. The consequences of this delay are also inconclusive, although in general, prognosis appears to be more guarded in patients with late-stage disease as compared to those diagnosed early. In this chapter, we will review the pertinent available information and propose avenues for the reduction of late diagnosis of oral cancer.

15.2 Diagnostic Delays

It has been generally accepted that the diagnosis of disease at an earlier stage is associated with better chances for cure or amelioration, with less complex and less costly treatment. It makes teleological sense that a treatment applied prior to a disease producing extensive damage has a better chance of being successful and has less morbidity. This theory may hold true for malignant diseases based upon staging of disease designed to reflect outcome of therapy/prognosis [1, 2]. The quest for early detection has led to implementation of screening programs, of which some have reported success while others remain controversial. Notable in the former categories, screening for colorectal, skin, cervical, and breast cancers has resulted in significant decreases in morbidity and mortality from the respective diseases [3]. However, there is growing concern that overdiagnosis and overtreatment have been occurring, with potential associated morbidity and increasing cost of care, which may be reflected in current reported outcomes [4]. Additionally, simplistic anatomical staging does not account for differences in biology of the tumor, tumor heterogeneity, and rate of progression of individual cases. An advanced-stage tumor could represent a minimally symptomatic and slow-growing lesion or a recent-onset lesion with rapid progression. Further, tumor behavior of regional spread (bone invasion, lymph node involvement) and metastatic spread is not predicted solely on anatomic criteria. Molecular study holds the promise to improve our ability to predict the future behavior of cancer and to assist in selecting specific therapies.

Definition

Diagnostic delay is the time lapse between patient arrival at different healthcare providers and the time lapse during healthcare utilization by the patients before a cancer diagnosis is made.

15.2.1 The Oral Cavity

The oral cavity is easily accessible for examination that can be completed in mere minutes. Nevertheless, more than half of oral malignancies are diagnosed in late stages [5]. To further complicate the discussion, tumor doubling time is highly variable, and that is not reflected in anatomical staging systems. We will discuss in this chapter the causes and consequences of late diagnosis together with some possible solutions.

Oral cancer is an umbrella word that encompasses several types of malignant diseases. Practically all tissues of the oral cavity (save the teeth) may undergo malignant transformation, and a number of malignant diseases from distant sites can metastasize to the mouth. Hence, a number of cancers have been diagnosed in the region: various sarcomas (e.g., osteo- and chondrosarcoma, Ewing's and Kaposi's sarcoma), lymphoma, leukemia, multiple myeloma, salivary gland cancers (e.g., mucoepidermoid, adenoid cystic), and basal cell carcinoma. However, by far the most common oral malignancy is squamous cell carcinoma (SCC), which accounts for over 90% of all diagnosed oral cancers. As all other entities are relatively rare, most reports on oral cancer in the literature concentrate on SCC, which is also the focus of this chapter.

The oral cavity is easily accessible to direct vision and palpation, which makes delays in diagnosing malignancy at the site somewhat puzzling. However, the oral cavity has complex and differing mucosal surfaces including keratinized and nonkeratinized mucosa, oropharyngeal lymphoid tissues, areas challenging to visualize in the posterior oral cavity, and oropharynx. Oral cancers have variable presentation from leukoerythroplakia, erythroplakia, leukoplakia, and homogeneous and non-homogeneous ulcerative lesions and masses, and presentations that can mimic much more common inflammatory and reactive oral conditions. Furthermore, many oral lesions with cancer risk or frank cancer are associated with minimal or no symptoms, thus limiting detection.

Important

Early detection is a goal of oral evaluation
Early detection may affect treatment required and predict outcome of treatment
Staging of cancer is designed to reflect outcomes of stages of cancer

Staging of cancer is used to assist in selection of cancer therapy

Potentially malignant lesions may mimic benign conditions and may be asymptomatic/minimally symptomatic

A number of researchers have studied this issue over the past few decades, yet the problem appears to persist. Initial efforts were hampered by heterogeneous definitions of delay and criteria for assessing timing of various steps in the diagnosing process. In response to these problems, an international panel of scientists has issued the Aarhus guidelines [6], in which standards for time intervals were proposed (Table 15.1). The framework thus created allowed for more consistency among studies and easier determination of specific barriers and consequences of delay. These studies then were able to show a clear association of late diagnosis/treatment of oral cancer with worse outcomes. [7]

15.3 The Patient Interval

The length of the patient interval and its exact causes have had limited evaluation. It appears that patient delay is on average 5–6 months [5] and is related to the lack of awareness of oral cancer in the general population and particularly among populations at high risk. This may certainly reflect the minimally symptomatic or asymptomatic nature of SCC, until advanced (Fig. 15.1). Even when noted, patients may assume the lesion would heal with time or attempt nonmedical treatment (Fig. 15.2). It is important to note that patients who have knowledge of oral cancer are more likely to seek medical evaluation [5, 7, 8]. A meta-analysis on this topic [9] included 16 pertinent publications. The populations, methodologies, and location of the studies were heterogeneous, which makes any firm conclusions difficult. The author concludes that sociodemographic variables were not associated with delay, as were the presence of oral habits such as smoking, quid or betel nut chewing, and alcohol consumption. A third category of reasons, the psychosocial factors, was too amorphous and inconsistent to permit any conclusions. A recent study of Indian patients reported a median patient interval of 30 days (range 4–365); lack of awareness and hope of spontaneous healing were the main reasons for delay in this population as well [10]. A similar study of 52 Bulgarian patients concluded with similar results, in terms of both duration and reasons for delay. In this latter study, an additional cause for diagnostic delay was the oral location of the tumor [11]. A typical initial presentation complaint is either an enlarging lump/swelling persistent ulcer or pain/other neurologic symptom. [12] It remains unclear whether demographic factors play a role in the patient interval [5], although it appears that being female or married was associated with earlier diagnosis, whereas being non-white was associated with later diagnosis [13]. In particular, African-American populations in the USA, with low education levels, have significantly less knowledge of oral cancer and its risk factors [14]. Additionally, there are large differences in access to and utilization of medical and dental care between rural and urban populations, ethnic minority and majority populations, and poorly educated and college degree populations

Fig. 15.1 Lateral tongue stage 1 SCC presenting as an ulcer on erythroleukoplakia. This lesion was asymptomatic and treated initially as a traumatic ulcer

Fig. 15.2 Stage 3 SCC on lateral border of the tongue. The patient waited for 6 months for the lesion to heal

Table 15.1 Time intervals according to the Aarhus guidelines

Interval	Definition
Patient interval	First symptom to first presentation to a health professional (HCP)
Primary care interval	First presentation to HCP to first referral to secondary care level
Diagnostic interval	First presentation to HCP to diagnosis
Pretreatment interval	Diagnosis to start of treatment

[15]. Where and to whom patients present may be a significant factor in dental providers identifying earlier-stage cancers identified on oral examination or with oral symptoms and physicians' diagnosis of advanced-stage disease associated with symptoms such as weight loss, sore throat, and blood in sputum [16].

A study of a younger group (age < 45) of 15 Scottish patients identified a diverse number of reasons for patient delay. This group was aware of oral cancer and its risk factors but thought it would not happen to them. Most considered their oral lesion innocuous and attempted self-treatment [17]. A similar study of 58 British patients under 45 years old confirmed the association of patient delay with lower education levels but also noted that stress and lower amounts of tobacco were associated with longer wait [18]. This may be further complicated in the USA related to "insurance delay."

15.4 The Primary Care Interval

The primary care interval is largely dependent on the initial presentation of the patient (symptoms and lesion specifics) and examiner's training and comfort with diagnosing oral lesions. It is anticipated that most oral cancers are preceded by clinically visible lesions called "potentially malignant disorders (PMD)." [19] This is in contrast to oropharyngeal cancer, where potentially detectable precursor lesions may not occur and even when diagnosed due to neck mass, a primary cancer may never be identified [2].

Identification of an oral lesion by the examining clinician can lead to early diagnosis of dysplasia and/or incipient SCC of the oral mucosa. Most dentists are comfortable with performing oral cancer exams, and the vast majority of such exams are performed by dentists or dental hygienists [5, 20]. A Canadian study identified having a regular dentist and having a PMD to be associated with early-stage diagnosis [21]. However, only about 43% of the population of the USA visits a dentist on a given year [22], though that number is better when only adults are counted (64%) [23]. Nevertheless, even among dentists faced with a suspicious oral lesion, a significant number (18%) preferred to prescribe an antibiotic or antifungal agent, whereas only 13% considered that further investigation and referral to a specialist were necessary [5]. And the majority of practicing dentists would seek continuing education on detection. Furthermore, a study of graduating dental students showed that about three quarters did not think they were able to recognize (pre)malignant lesions [24]. The prescription of antibiotic in response to an oral lesion is a common initial management by physicians as well.

A study of the SEER database suggested that a large number of medical visits were associated with a reduced risk of advanced disease at diagnosis but only for nonsmokers/nondrinkers. For those in high-risk groups, this advantage disappeared: the cancer was diagnosed in stage 3 or 4 despite an average of 11 physician visits in the year preceding diagnosis [25]. These findings are both puzzling and concerning, as smokers/drinkers should elicit increased circumspection of head and neck malignancy and trigger a more thorough examination, and suggest potential of minor symptoms or rapid progression as possibly impacting detection. Since this was a data-based study, the reasons for the findings remain obscure. A later similar study by the same group of authors [26] also identified that continuity of care correlated with earlier diagnosis of oral cancer but only when the medical provider was an internist. The effect was lost for family doctors. Again, the reasons for these differences remain unknown.

Factors associated with an extended primary care interval have not been adequately explored. A small study from Japan suggested that having a small lesion, an ulcerative lesion, and/or no palpable lymph nodes correlated with delay of referral [27].

The consequences of an increased primary care interval have been studied in a Finnish population of 221 symptomatic head and neck cancer patients of whom 20% (n = 45) were not referred or followed up ("overlooked"). Survival at 3 years was significantly worse for those patients with tongue or glottic tumors, but not any other patients [28]. This was a cross-sectional study of medical records, and thus, this unusual finding remains unexplained.

15.5 The Diagnostic Interval

The diagnostic interval is in large part a measure of the healthcare system efficiency [5]. Once the true potential of the lesion is recognized, factors such as availability of specialized care and their accessibility and affordability become paramount. Evidence suggest that rural, minority, low-income, and uninsured patients have significantly lower utilization of healthcare services [15, 29]. Nevertheless, even specialists may add to the diagnostic delay, particularly if patients have negative clinical lymph nodes. [30]

Further diagnostic delay may come from utilization of diagnostic tests other than the gold standard biopsy. For example, a Cochrane systematic review on adjunctive aids reported that vital staining, cytology, or spectroscopy may miss up to 26%, 19%, and 23% of oral cancers, respectively [30]. Even when a biopsy is performed, a cancer diagnosis may be missed due to sampling error or pathological specimen handling problems and the experience of the pathologist. We have found no data describing the size of these potential problems.

A meta-analysis of the interval between the first symptom and diagnosis, which included data from ten studies performed in nine different countries, concluded that diagnostic delay was commensurate with either worse survival or more advanced stage at diagnosis [31]. These data are difficult to interpret due to heterogeneity of populations and variety of analyzed outcomes. Nevertheless, the fact that nine of the ten included studies reported consistent results suggests the unfavorable outcomes of extended diagnostic interval.

Warning

Staging of cancer is currently anatomical (size, nodes, metastasis). Staging of cancer alone does not reflect behavior of all cancers. Future staging may include biologic (molecular) differences in cancer improving prediction of outcomes. Cancers are not homogeneous and may change over time and with treatment.

15.6 The Pretreatment Interval

Once an oral cancer diagnosis has been made, preparation for definitive therapy is initiated. The time to the beginning of treatment constitutes the pretreatment interval. While patients may contribute to the extension of this period, that is unusual, as the vast majority understand the gravity of the situation and the urgency of the issue. Here again, the availability of specialists and access to care may be the driving factors influencing the expediency of the process. This is particularly true for patients with advanced disease for whom multispecialty treatment is indicated.

A Canadian group reported the effect of operating room closures on prognosis of oral cancer and found that longer waits due to summer month slowdowns resulted in greater numbers of recurrence and earlier death [32]. Similar findings were reported in Italy where treatment delay was associated with worse 5-year survival, particularly in patients with early-stage and laryngeal disease [33]. The same conclusion was reached for inoperable patients treated with radiation +/− chemotherapy: prolonged waiting time for treatment resulted in worse survival [34]. In a recent study of the SEER database, the most important interval statistically associated with outcomes was the time delay between surgery and radiation therapy [35].

15.7 Medicolegal Aspects of Diagnostic Delay

Among the most common legal implications in oncology care is the potential of failure to diagnose and diagnostic delay in oncology outcome [36]. As described above, the issue is complex due to either none or mild and nonspecific symptoms of HNC until advanced stage of disease, the clinical presentation of early stage lesions may mimic more common inflammatory conditions, and the variable biology of cancers between patients, and the unpredictable progression of potentially malignant lesions to cancer that may be sudden. Medicolegal risk must also address the response of individual cancers to treatment, and it is important to note that the most significant time interval is interval delay between surgery and radiation therapy/chemotherapy (when indicated) as the most impactful time affecting outcome.

Risk management includes thorough patient evaluation (history, head and neck and oral exam), record keeping, and patient information, with appropriate testing and consultation as indicated [37]. Risk may be reduced by professional education (undergraduate and postgraduate curriculum) and professional continuing education [38]. A survey of dentists identified barriers of providing dental care prior to cancer therapy as lack of time for consultation, poor communication between healthcare providers, and that 55% felt inadequately trained in dental school, and more than 2/3 were interested in continuing education [39].

Eyecatcher

Available web-based teaching resources for healthcare professionals on screening for oral cancer:

Organizations/websites: American Academy of Oral Medicine, American Head and Neck Society; Head and Neck Cancer Alliance; Oral Cancer Foundation; NCI Clearinghouse: Oral cancer resources; SPONHC; American Dental Association; Leonardo Lifelong Learning Program: ► www.oralcancerldv.org

15.8 Conclusion

It remains clear that mortality from oral cancer remains unacceptably high and advanced disease at diagnosis is a potential factor in determining the risk [5, 32–34, 40–42]. A majority of patients are diagnosed with stage 3 to 4 disease, more likely when symptoms develop, and carry a poor prognosis. This situation is hard to accept, particularly since the oral cavity is accessible for visual exam and palpation. Such exam can have high sensitivity (85%) and specificity (97%) if performed regularly in high-risk patients [42]. While there is scant evidence that screening programs can lead to early diagnosis and reduce mortality even in high-risk groups [30], such programs are not cost-effective due to oral cancer and OPC representing relatively rare conditions [43]. Nevertheless, there is general agreement that opportunistic screening by primary healthcare providers, particularly dentists, should be undertaken regularly, as part of routine healthcare visits [42–44]. As risk factors for oral cancer are shifting from mostly tobacco and alcohol consumption to a more heterogeneous palette of factors, including viral pathogens, high-risk groups are becoming harder to define. Thus, opportunistic screening or case finding is recommended for all comers. Increased educational efforts should be undertaken to familiarize primary care providers with the signs and symptoms of oral (pre)malignancy to enhance the potential value of opportunistic screening for this condition in primary care settings.

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