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# Total Diagnostic Delay in Oral Cancer may be Related to Advanced Disease Stage at Diagnosis

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## Summary

### Selection Criteria

The investigators conducted a systematic search of MEDLINE (1966 to December 2008), EMBASE (1974 to 2008), and ISI proceedings (from inception to 2008) for both English and non-English articles using a predefined list of search terms. Two clinicians and 1 epidemiologist independently screened all abstracts to exclude unrelated studies. Only articles that presented original data from observational studies were considered. Studies were included if they met the following criteria: (1) included patients with confirmed pathological diagnosis of oral or oropharyngeal squamous cell carcinoma; (2) the outcome of interest was clearly defined as disease stage (TNM classification); (3) the exposure of interest was total diagnostic delay defined as the period between the patient noticing either the first sign or symptom and definitive diagnosis; and (4) provided relative risks and 95% confidence intervals (CIs).

### Key Study Factor

Review of studies assessing diagnostic delay in oral cancer. Quality scoring was conducted by 2 independent reviewers using the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) methodology.[1] Three key criteria were assessed: (1) if the follow-up time was 10 years or longer; (2) if critical confounding factors, such as tobacco and alcohol use, were measured; and (3) if results were ascertained by anatomic location of oral and pharyngeal cancer. Studies were classified as “yes” or “no” for each of these criteria.

**Purpose/Question**: To assess whether total diagnostic delay in oral cancer is related to advanced stages of the disease at diagnosis

**Type of Study/Design**: Systematic review with meta-analysis of data

**Level of Evidence**: Level 2: Limited–quality patient-oriented evidence

**Strength of Recommendation Grade**: Grade B: Inconsistent or limited-quality patient-oriented evidence

### Main Outcome Measure

The primary outcome was stage at diagnosis (TNM classification).[2] The authors classified stage at diagnosis in 2 groups: early stage (T1 or T2 and N0) or advanced stage (T3, T4 or N > 0). Outcomes of the meta-analysis were expressed as odds ratios (ORs). Two pooled ORs were calculated within each key criterion: one for studies that scored “yes” and one for those that scored “no”.

### Main Results

Nine studies conducted in 9 different countries met the inclusion criteria and were included in the analysis. These studies, involving 934 early cases and 961 advanced cases, were published between 1989 and 2005.

When compared with the absence of diagnostic delay, patients with diagnostic delay were significantly more likely to present at an advanced stage of the disease (fixed effects pooled OR 1.32 [95% CI: 1.07-1.62]). The association was stronger when limited to oral versus pharyngeal sites (pooled OR 1.47 [95% CI: 1.09-1.99]) and when diagnostic delay was longer than 1 month (pooled OR 1.69 [95% CI: 1.26-2.77]). However, the Forest plot showed that only pooled fixed effects were significant, not the pooled random effects: only 3 of the 9 study-specific ORs indicated a significant association.

### Conclusions

The analysis estimated that patients with delayed diagnosis had a higher probability of presenting with advanced stage oral cancer compared with those without delayed diagnosis, particularly among those with oral cancer and those with a delay longer than 1 month. Based on the limited quality of the data, however, better evidence about the relationship between diagnostic delay and disease progression or disease outcomes is needed.


## Commentary and analysis

Stage at diagnosis is an important predictor of survival for patients with oral and pharyngeal cancers. Unfortunately, about 60% of these cancers are detected at advanced stages (regional or distant) and although improving, 5-year relative survival is poor.[3] Regional stage survival for 2001 to 2007 was 55% and for distant stage, 33%.[3] Therefore, it is important to identify strategies to detect these cancers at earlier stages of disease.

This study's objective was to perform a systematic review and meta-analysis to investigate whether total diagnostic delay was associated with advanced disease stages.[4] Total diagnostic delay refers to the period elapsed between the first symptom or sign and the definitive diagnosis. There are generally 2 to 3 stages of total diagnostic delay. *Patient delay* refers to the period between when the patient first notices a symptom and the first contact with a health care provider. *Provider delay* is the period between when a patient first contacts a health care provider and a specialist's definitive diagnosis. The Gomez study included a third stage, *scheduling delay*, which is the period between the scheduling of the appointment and the actual visit to the health care provider. The study had clearly defined inclusion criteria, was not limited to the English language, and included both MESH terms

and text words. All searches were conducted independently by 2 clinicians and 1 epidemiologist; however, the steps in the identification of eligible studies was lacking. Nine observational studies met the inclusion criteria (randomized controls have not been conducted owing to ethical considerations) and differed by period of data collection, anatomic site, age range, samples size, and sex. Authors note that the study was limited by recall bias and the lack of information on tumor growth rate.

Gomez et al found that the probability for people with delayed diagnosis to present at an advance stage of disease was 30% higher than for those without diagnostic de-lay.[4] These findings are in contrast to a systematic review of 27 studies by Goy et al,[5] also published in 2009, which found no consistent positive association between diagnostic delay in any of the head and neck cancer sites analyzed (all head and neck sites combined, oral cavity, pharynx, and larynx) and advanced-stage disease. Goy et al[5] decided that a quantitative synthesis using meta-analysis could not be conducted because of the heterogeneity of the studies. Inaccurate measurement of delay, masking of symptoms owing to the effects of smoking or alcohol use, recall bias, and variations in the aggressiveness of tumors may have accounted for the lack of an observed effect between patient delay and stage.[5,6] The latter is an important factor because tumor growth rate has been shown to affect stage at diagnosis and survival more than diagnostic delay and should be included in studies examining the relationship between delay and stage of disease.[7,8] Similar to the Goy et al[5] study, a recent analysis of 88 consecutive patients from 2003 to 2008 also failed to find a relationship between diagnostic delay and stage of diagnosis of oral cancer, whereas the site of the cancer (floor of the mouth, gingiva, and retromolar area) and degree of differentiation (moderate-poor) were significantly associated with high risk of late-stage diagnosis.[8] Because of the heterogeneity of the data and inherent biases, the Gomez et al study and others exploring the relationship of delayed diagnosis and stage of disease should be interpreted with caution; however, future analyses that include larger numbers of quality studies, limit recall bias, and stratify by anatomical site may shed more light on the relationship between diagnostic delay and disease stage. These studies also should focus on better measurement of delay duration, include tumor growth rate, and relate delay to disease outcomes, such as survival and mortality.

Traditionally, visual and tactile screenings as a preventive measure to promote early detection and diagnosis of oral cancer lesions are commonly included in cancer control programs.[9,10] A recent Cochrane review[9] concluded, based on one 9-year randomized controlled trial with high risk for bias, that there was not enough evidence to support or refute the use of visual examination in screening for oral cancer in the general population. There was some evidence that visual examination may have helped reduce death rates in high-risk patients, such as tobacco and heavy alcohol users.[9,10] The American Dental Association (ADA) developed clinical recommendations regarding screening for oral squamous cell carcinomas during routine examinations, encouraging practitioners to “remain alert for signs of potentially malignant lesions or early stage cancers while performing routine visual and tactile examinations,” particularly among tobacco and alcohol users.[11] In addition, neither the Cochrane review nor the ADA recommendations found sufficient evidence to recommend adjunctive technologies, such as toluidine blue, fluorescence imaging, or brush biopsy in screening for oral cancer.[9,11]

This study showed that patients with delayed diagnosis were significantly more likely to present with an advanced-stage cancer at diagnosis compared with those with no delay in diagnosis. The Healthy People 2020 initiative for the United States includes overall goals to reduce health disparities in the general population, which includes individuals at higher risk and those who suffer from a greater burden of oral diseases, such as oral and pharyngeal cancer.[12] These goals include primary and secondary prevention strategies. For example, 3 developmental objectives focus on screening and counseling patients on tobacco use and cessation from the perspective of both the provider and the patient.[12] Secondary prevention strategies include an objective that focuses on increasing the proportion of oral and pharyngeal cancers detected at the earliest stage.[12] These objectives validate the role of dental practitioners in the primary and secondary prevention of oral cancer through screening and counseling patients for tobacco and alcohol use, evaluation that includes obtaining a medical history and screening for oral cancer as a component of a thorough head and neck examination, especially among patients who use tobacco and alcohol.

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