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Early diagnosis in primary oral cancer: is it possible?

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Abstract

In this treatise oral carcinogenesis is briefly discussed, particularly with regard to the number of cell divisions that is required before cancer reaches a measurable size. At that stage, metastatic spread may have already taken place. Therefore, the term “early diagnosis” is somewhat misleading.

The delay in diagnosis of oral cancer is caused both by patients’ delay and doctors’ delay. The total delay, including scheduling delay, work-up delay and treatment planning delay, varies in different studies, but averages some six months. The total delay is more or less evenly distributed between patients’ and doctors’ delay and is partly due to the unawareness of oral cancer among the public and professionals, and partly to barriers in the health care system that may prevent patients from seeking dental and medical care. Due to the relatively low incidence of oral cancer it will be difficult to increase the awareness of this cancer type among the public, thereby reducing patients’ delay. However, it should be possible to considerably reduce doctors’ delay by increasing the awareness of oral cancer among professionals and by improving their diagnostic ability.

Population-based annual or semi-annual screening for oral cancer is not cost-effective, high-risk groups such as heavy smokers and drinkers perhaps excluded. Dentists and physicians, and also oral hygienists and nurse practitioners, may play a valuable role in such screening programs.

Key words: *Oral cancer, early detection of cancer, diagnostic cancer delay.*

Introduction

Oral cancer represents some 2 percent of all new cases worldwide that may arise in the body. (1) Approximately, 90% of all oral cancers consist of squamous cell carcinoma arising from the oral epithelium. The remaining 10% consist of malignant intraoral salivary gland tumors, melanomas, sarcomas of the soft tissues and the jaw bones, non-Hodgkin's lymphomas and the exceedingly rare malignant odontogenic tumors and metastatic tumors of primary cancers located elsewhere in the body.

The adjective "early" in relation to cancer can be used in three ways, being 1) early in the process of carcinogenesis, 2) early in the meaning of a relatively small size at the time of detection, and 3) early in the meaning of a short time interval, i.e. short delay, between the time of symptoms and the time of diagnosis.

Growth rates of malignant tumors; lead-time bias; length-time bias

In general, some 30 doublings (=10^9 cells) are required to reach a volume of 1 cubic centimeter, being the size that the first symptoms may become detectable on palpation. (2) The increase in the number of cancer cells and, thereby of the size of the tumor, depends on 1) cell cycle time of the proliferating cells, 2) the fraction of proliferating tumor cells, and 3) the amount of fraction of spontaneous cell loss. Head and neck tumors are a relatively rapidly proliferating group of tumors with a median potential doubling time of 6-7 days. (3) The median potential doubling time has been defined as the time within which the dimensions of a tumor would double if there were no cell loss. Tumor doubling time may be influenced by the immune system of the host and by micro-environmental factors, including the phenomenon of angiogenesis. Most human tumors are many months or even years old before they become clinically detectable and may have metastasized, regionally or to a distant site, long before the primary is detected. (2) Altogether, the term "early detection" is a somewhat questionable one.

Displacing a diagnosis of cancer to an earlier date may prolong the survival time without actually influencing the time of death of an untreated patient. This pitfall has been termed "lead-time bias" (Fig. 1). In view of the relatively high growth rate of squamous cell carcinomas, the lead-time bias in oral cancer is probably limited.

The probability of detecting cancer in an asymptomatic stage is related to the growth rate and the sensitivity of the detection technique used. Rapidly growing tumors have a short potential screening period, being the time interval between possible detection and the occurrence of symptoms, while slowly growing tumors have a longer potential screening period. As a result, a higher proportion of indolent tumors is found in a screened population, causing an apparent improvement in survival. This phenomenon has been referred to as length-time bias.

Early treatment of a primary tumor will lead to a reduction in mortality particularly if the primary tumor can be eliminated before dissemination, assuming that no treatment is available for such disseminated cancer type. Stage I (T1N0) oral squamous cell carcinomas have a high cure rate of some 80%, at least at the five-year-survival rate level, while stage IV carcinomas have a cure rate of a mere 20 percent. However, even in the example of the stage I tumor one faces the problem of second primaries of which many have been shown to be clonally related to the first primary. These second primaries are most likely the result of incomplete excision of a clinically invisible mucosal field at the time of removal of the primary tumor, being referred to as second "field" cancers. (4)

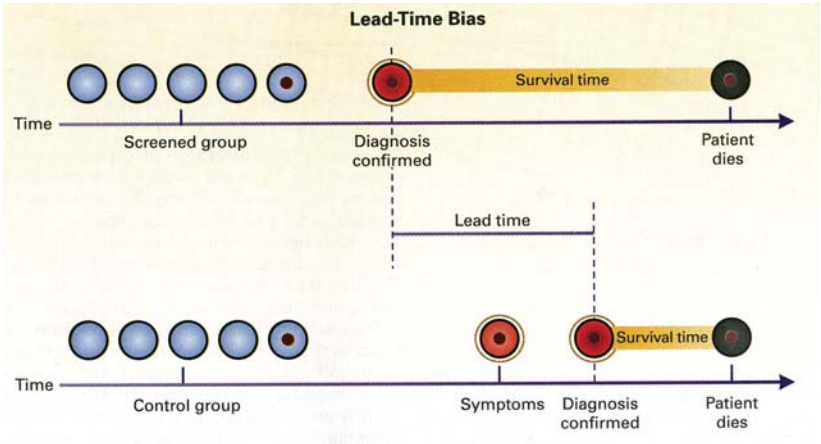

Fig. 1. Lead-time bias (With permission published from: Patz EF, Jr., Goodman PC, Bepler G. Screening for lung cancer. N Engl J Med 2000; 343: 1627-33. Copyright © (2000) Massachusetts Medical Society. All rights reserved.)

Signs and symptoms of oral cancer in a relatively early stage

The majority of oral cancers are diagnosed at the time that signs or symptoms have occurred (Figs. 2, 3). It is rather rare to diagnose oral cancer, particularly squamous cell carcinomas, in an asymptomatic stage. In Table 1 a summary is presented of the patients' profile, early symptoms, early signs and sites of predilection of the various oral cancer types. None of these signs and symptoms are pathognomonic of malignancy with the exception of halfsided anaesthesia or paraesthesia of the lower lip in case of cancer involvement of the mandibular bone. Remarkably, 13 (32%) out of 41 consecutive patients with oral squamous cell carcinoma presented with a T3 or T4 tumor at the time of diagnosis (Table 2). (5) It has been shown that almost half of the oral cancers, worldwide, are diagnosed at advanced stages III and IV. (6)

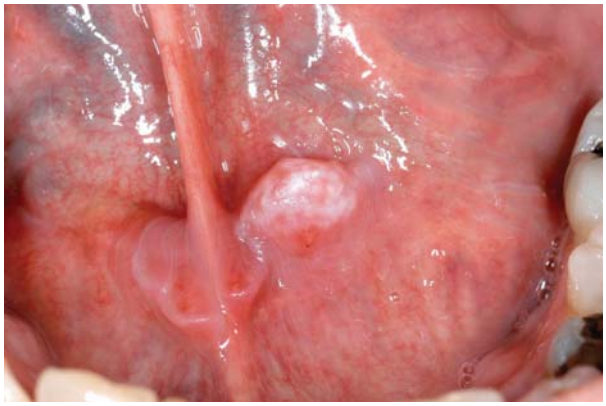

Fig. 2. Relatively small (T1) squamous cell carcinoma of the floor of the mouth.

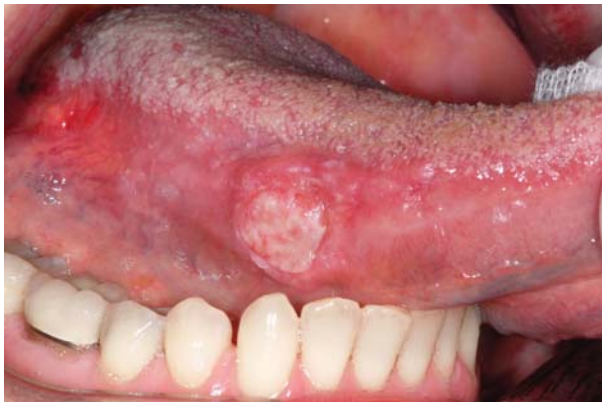

Fig. 3. Relatively small (T1) squamous cell carcinoma of the border of the tongue.

Table 1. Early signs and symptoms of the various types of oral cancer.

Cancer type	Patients' profile	Early symptoms	Early signs and possible precursor lesions	Sites of predilection
Squamous cell sarcinoma	Usually above 40 yrs Mainly tobacco/alcohol	Local discomfort or pain Referred pain (ear	Changes in color and/or texture (ulcer) Often precursor lesion (leukoplakia, erythroplakia)	Borders of the tongue, floor of mouth, lower lip
Malignant intraoral salivary gland tumor	Mainly in adults Unknown aetiology	Usually absent	Soft tissue swelling, sometimes asymptomatic otherwise	Palate and upper lip
Melanoma	Mainly in adults Unknown aetiology	Usually absent	Pigmented swelling with or without ulceration Often precursor lesion ("melanosis")	Palate and gingiva (upper and lower)
Sarcoma, soft tissues	All ages Unknown aetiology	Usually absent	Mucosal swelling	Not applicable
Sarcoma, jaw bones	All ages Unknown aetiology	An/paraesthesia lower lip (mandible)	Bony swelling Radiographic changes	Not applicable
Non-Hodgkin's lymphoma	Mainly in adults Unknown aetiology	Usually absent; occasionally an/paraesthesia lower lip, recurrent (mandible)	Mucosal swelling, with or without ulceration; radiographic changes in case of intraosseous location Occasionally precursor lesion (lymphoid hyperplasia)	Mandibular bone Maxillary soft tissue

Table 2. T classification in 41 oral consecutive SCC patients at the time of diagnosis (5).

Oral subsite*	T1	T2	T3	T4	All T's
Mobile tongue	8	5	-	1	14
Floor of mouth	4	2	5	1	12
Lower alveolar ridge	2	2	2	2	8
Buccal mucosa	2	3	1	-	6
Upper alveolar ridge	-	-	-	1	1

* Lower lip excluded

Diagnostic delay and treatment delay

It is well known that the prognosis of patients with oral squamous cell carcinomas largely depends on the stage of the disease at the time of diagnosis. The challenge, therefore, is to advance the diagnosis to an earlier stage which then would result in less morbidity of treatment and in an as yet unknown number of cases in a better prognosis. In general, it is accepted indeed that patients with a short diagnostic delay carry a better prognosis than those with a long diagnostic delay. However, some studies on oral cancer have not shown a better survival with early diagnosis. (7, 8) The discrepancy between the results of the various studies may, among others, be caused by the use of different definitions, study designs and patients' memory bias. (9, 10)

In the study by Peacock et al. (11) doctors' delay was extended with "scheduling delay" at primary health care centers, (12) work-up delay in the cancer center, and treatment planning delay (Table III).

Unfortunately, oral cancer population-based screening programs do not meet the epidemiological guidelines for a successful program and are not considered to be cost-effective in its current forms. (13) There may be some benefit when focusing screening programs on high-risk groups, such as heavy smokers and heavy drinkers, (14) patients with previous cancer in the head and neck area, (15) and patients with previous cancer outside the head and neck area. (16)

-Patients' delay

Considering the fact that oral cancer makes up some 2 percent of all cancer types that may arise in the body, it should be no surprise that the public awareness of oral cancer is limited. For probably only a few patients, at least in industrialized countries, fear of a diagnosis of cancer leads to considerable patients' delay, while the majority of patients has not even considered the possibility of a malignant disease in case of a symptomatic oral lesion. (17) This is particularly true in young patients. (18, 19) Other factors associated with patients' delay are heavy smoking and drinking, (20) low socioeconomic status, (11, 21) not being under the regular care of a dentist, (22) location on the tongue, (23) and limited accessibility of primary health care for patients with a low socioeconomic status.

The mean patients' delay in the two previously mentioned studies amounted approximately three months with a range of less than a week to more than two years. (5, 11)

Information campaigns in news programs and TV apparently have little effect on patients' delay (24); on the other hand, information leaflets for patients may be useful. (25)

-Doctors' delay

A general dentist will not see more than an estimated average of 10 oral cancer patients during his or her professional life; the same holds true for family doctors. Obviously, signs and symptoms of the various cancer types that may occur in the body vary widely. This is also true for the various types of oral cancers and even for the most common type of oral cancer, the squamous cell carcinoma. In view of the rarity of oral cancer and the diversity of signs and symptoms it is no surprise that there is sometimes a considerable doctors' delay before an oral cancer diagnosis is suspected. Therefore, the diagnostic ability of primary health care workers should be improved. (26)

In the previously mentioned studies from the Netherlands (5) and the U.S.A.11, the mean doctors' delay amounted 22 days and 36 days, respectively. In the study from the Netherlands there was no significant difference between dentists and medical general practitioners. Doctors' delay of more than five weeks occurred significantly more often in patients under the age of 40 years.

In some countries, dental and perhaps also medical practitioners are encouraged to establish a diagnosis of oral cancer in their practice. A diagnosis of oral cancer requires a biopsy for histopathological assessment. Although the technique for an oral biopsy is rather simple, it is somewhat uncomfortable for the patient. Understandingly, there is a search for more convenient diagnostic techniques, such as vital staining, fluorescence visualization and fresh biopsy. (27) Salivary analysis may become a valuable diagnostic tool in oral cancer in the near future. (28) Optical techniques have been developed to identify more specific areas at risk for harboring carcinoma. Among these optical techniques are autofluoresence imaging, (29) narrow band imaging, (30) and optical coherence tomography. (31) The true additional value of these techniques is not clear yet. At present, histopathologic examination is still the gold standard. Nevertheless, the use of adjunctive techniques may increase the awareness of oral cancer among the medical and dental profession and may shorten doctors' delay.

If no biopsy is taken by the primary health care worker, timely referral is strongly recommended not so much because of a medical urgency, considering the life time of the tumor at diagnosis, but mainly because of psychological reasons. In this respect a maximum of 2-3 weeks seems an acceptable waiting-time. (32)

-Other sources of delay

As has been shown in Table III there are a few causes of delay other than patients' delay, doctors' delay, and scheduling delay. In the study of Brouha et al. (33) the interval between the time of the first visit to a general hospital and the time of the final diagnosis by a multidisciplinary tumor board in a cancer center has been referred to as specialists' delay. The median time in that study amounted 47 days, while the ideal standard was set at 30 days.

Waiting-time for surgery and radiotherapy may be a

problem. In a study from Denmark the average waiting-time for radiotherapy in head and neck cancer amounted four weeks; (34) 16 percent of the patients progressed in tumor stage.

Table 3. Delay in oral cancer treatment in 50 patients (slightly modified) (11).

Length of time (LOT), in days	
1. Time between first symptoms to first visit to primary care clinician ("Patients' delay", including "Scheduling delay")	range: 0-730 mean: 104 median: 129
Time between first visit to the primary care clinician and the time of a biopsy or referral ("Doctors' delay")	range: 0-280 mean: 36 median: n.m.*
Time between biopsy or referral and the time when the patient	range: 0-240 mean: 18 median: n.m.*
Time between first visit to the specialist and the completion of appropriate investigations ("Work-up delay")	range: 0-33 mean: 10 median: n.m.*
Time between completion of investigations and presentation to the head and neck board meeting ("Work-up delay")	range: 1-208 mean: 21 median: n.m.*
Time between presentation to the head and neck board meeting and the time of definitive treatment (day of surgery or first day of radiation therapy) ("Treatment planning delay")	range: 0-33 mean: 10 median: n.m.*
Total time	range: 52-786 mean: 206 median: n.m.*

* n.m. – not mentioned

Discussion

At present, there are no serological markers available that would be helpful in detecting primary oral squamous cell carcinomas in a stage that there is no measurable tumor yet. (35) There might be some benefit in screening for oral cancer in high-risk groups in order to detect oral cancer and precancerous lesions in a relatively early clinical stage. Treatment would then result in less morbidity and probably in most patients in improved overall survival time. It is a challenge for the dental and medical profession to define the high-risk groups and to explore the feasibility of an annual or semi-annual screening program, preferably combined with a program on tobacco and alcohol cessation and improvement of oral hygiene. Such programs can probably be performed by oral hygienists or nurse practitioners. A quick scan type of oral examination directed at the detection of oral cancer and precancer would take only a few minutes.

Dental and medical health care workers should receive continuous postgraduate training in the detection of oral cancer and precancer. Such professional training program might shorten doctors' delay with at least several weeks.

In most studies, patients' delay makes up a substantial part of diagnostic delay. In the study from the Netherlands the median patients' delay was 35 days, (5) while in the study from the U.S.A. this delay was more than 100 days. (11) Patients' delay may be partly related to financial barriers for some patients to seek dental or medical help. Another important reason of patients' delay lies in the unawareness among the public at large. Programs on mass media, including TV, focused on oral cancer have apparently not been effective.

In summary, it should be possible to advance the diagnosis of oral cancer into an earlier stage by trying to shorten both patients' delay and doctors' delay. Such earlier diagnosis will result in less treatment morbidity and probably in many patients in true longer survival. Since oral cancer, particularly squamous cell car-

cinoma, is largely a preventable disease, the emphasis should also, or perhaps even more so, be on cessation of tobacco and alcohol habits.

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